# SYNTHETIC STUDIES IN SALAMANDER ALKALOIDS

by

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# ABSTRACT

Part I, describes an efficient four step method to effect an unsymmetric ring cleavage between carbons 2 and 3 in the A ring of 17β-acetoxy-5β-androstan-3-one (81b).

Bromination of 81b followed by treatment with sodium acetate in refluxing acetic acid gave 2β,17β-diacetoxy-5β-androstan-3-one (159) in good yield. Subjecting 159 to hydroxylamine hydrochloride-sodium acetate in refluxing methanol afforded anti 17β-acetoxy-2β-hydroxy-5β-androstan-3-one oxime (187) in 75-85% crude yield. Beckmann fragmentation of 187 by employing thionyl chloride furnished 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195) in over 80% purified yield.

Mechanistic studies on the formation of 159 from 17β-acetoxy-4β-bromo-5β-androstan-3-one (158) indicated that neither 4α,17β-diacetoxy-5β-androstan-3-one (175a) or 4β,17β-diacetoxy-5β-androstan-3-one (175b) can be intermediates and that the intermediate isolated by Satoh and Takahashi must be 2α-acetoxy-5β-cholestan-3-one (174).

Part II, describes attempts to elaborate 195 to the 17β-hydroxy isomer of samandarine 47b.

Treatment of 195 with refluxing isopropenyl acetate in the presence of concentrated sulphuric acid yielded a mixture of cis and trans 2,17β-diacetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (223a) and (223b) in 62-68% purified yield. Ozonization of this mixture followed by reduction gave 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile

(262) in 86% yield. A Wittig reaction on 262 with subsequent acetylation afforded 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a) in ca. 65% purified yield. Attempts to construct 47b from 57a proved unrewarding. However, most recently, Shimizu has converted 57a to 47b in three steps.

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# INTRODUCTION

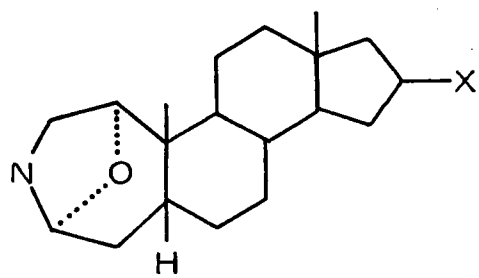
## 1. General

The domain of natural product synthesis has provided an excellent testing ground for the development of the fundamental principles of organic chemistry. Each synthetic endeavour usually brings to light a new principle and extends the boundaries of existing chemical knowledge.

In general, synthetic studies in the field of natural product chemistry have played a key role in the advancement and shaping of organic chemistry, especially, in terms of reaction mechanisms, stereochemistry, and synthetic methods.[1] For example, synthetic studies directed towards the synthesis of vitamin $B_{12}$ have led directly to the development of the principle of conservation of orbital symmetry.[2]

These facts coupled with the increasing demand for more effective therapeutic agents provided the driving force to tackle a synthetic problem. It was felt that the salamander alkaloids, a unique class of steroidal alkaloids[3], would provide a testing ground for new synthetic reactions and they could possess therapeutic potential.

These steroidal alkaloids are divided into three groups according to their skeletal features. Group one possess a bicyclooxazolidine skeleton. Six alkaloids; samandarine (1), samandarone (2), samandaridine (3),

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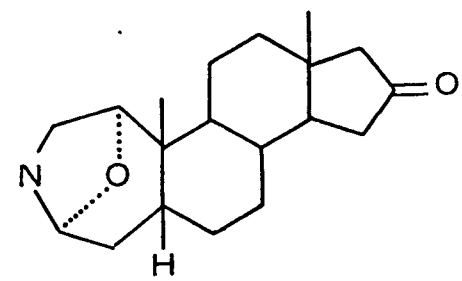
4, X = OAc

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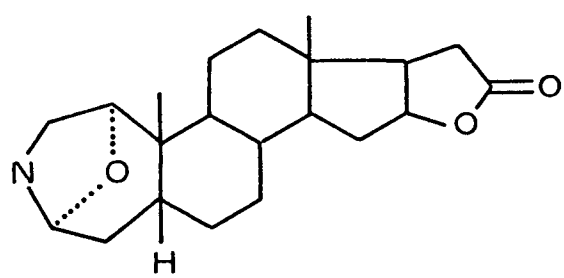


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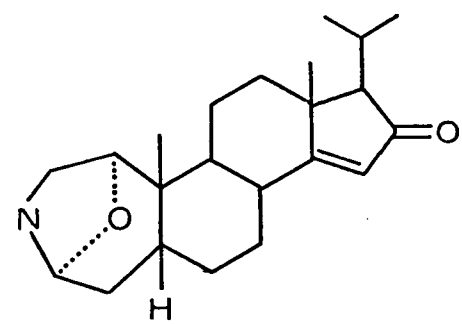


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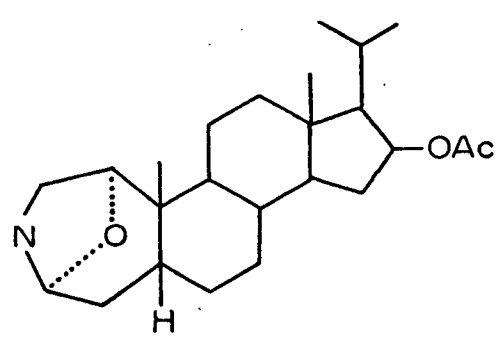


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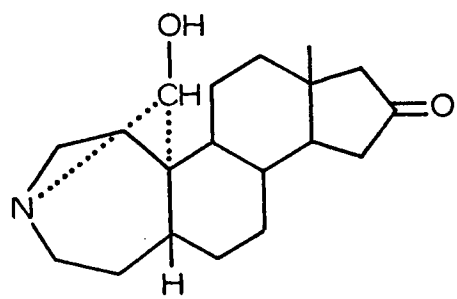


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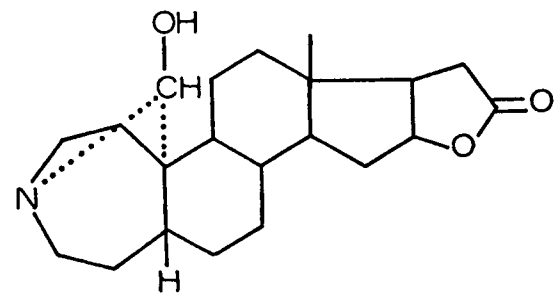


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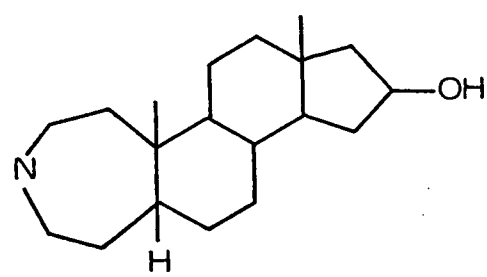


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O-acetyl-samandarine (4), samandenone (5), and samandinine (6) exhibit this novel constitution. Group two contain a carbinolamine skeleton. Two alkaloids; cycloneosamandione (7a) and cycloneosamandaridine (7b) display this type of skeleton. Samanine (8) constitutes group three. It is worthy of mention that there is a difference in alkaloid content between the two subspecies of Salamandra, namely, S. maculosa taeniata (S.m.t.) endemic to western Europe and S. maculosa maculosa (S.m.m.) endemic to south-eastern Europe. An outline of the alkaloids and their occurrence in the two subspecies are presented in Table I (see Page 5 ); the table shows the three groups of alkaloids within the salamander family. The work described herein is concerned with the alkaloids in group one.

Despite their apparent simplicity the elaboration of the steroidal framework to the bicyclooxazolidine skeleton offers a challenging synthetic problem. Hara and Oka[4] have described the total synthesis of samandarone (2) and this constituted a formal synthesis of samandarine (1) and samandaridine (3). However, it was recognized that their synthetic approach had limitations, for example, their synthesis yielded only milligram quantities of samandarone (2) and their overall synthetic sequence was rather lengthy.

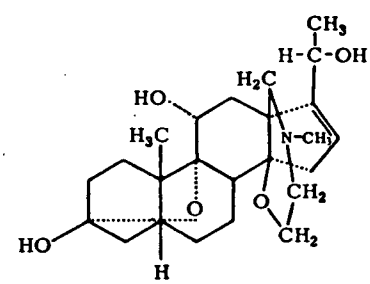
The work presented herein describes several approaches directed towards gaining a general method of entry into the bicyclooxazolidine skeleton of general type 1. It was hoped that the limitations of the Hara - Oka synthesis would be overcome by developing a new synthetic approach which would be both efficient and short.

Since these alkaloids occupy such a conspicuous position among the naturally occurring steroidal alkaloids it is in order to indicate a

Table I. Salamandra Alkaloids

| Group | Name | Formula | m.p. | Occurrence |
|---|---|---|---|---|
| 1. | Samandarine | $C_{19}H_{31}NO_2$ | 188° | S.m.t. |
| | Samandarone | $C_{19}H_{29}NO_2$ | 190° | S.m.t.; S.m.m. |
| | Samandaridine | $C_{21}H_{31}NO_3$ | 290° | S.m.t.; S.m.m. |
| | O-Acetyl-Samandarine | $C_{21}H_{33}NO_3$ | 159° | S.m.m.; S.m.t. |
| | Samandenone | $C_{22}H_{31}NO_2$ | 191° | S.m.t.; S.m.m. |
| | Samandinine | $C_{24}H_{39}NO_3$ | 170° | S.m.m. |
| 2. | Cycloneosamandione | $C_{19}H_{29}NO_2$ | 119° | S.m.t.; S.m.m. |
| | Cycloneosamandaridine | $C_{24}H_{31}NO_3$ | 282° | S.m.t.; S.m.m. |
| 3. | Samanine | $C_{19}H_{33}NO$ | 197° | S.m.t. |

general type of classification. Heterosteroids may be divided into nuclear and extranuclear categories.[5] The former contain heteroatoms like nitrogen, oxygen, and sulphur in the basic steroidal nucleus, and in the latter, the heteroatom forms part of a ring system, groups or a side chain attached to the nucleus. Steroids possessing nitrogen are designated azasteroids. The number of naturally occurring extranuclear azasteroids are considerable. Several categories of steroidal alkaloids belonging to this group are well known. These include alkaloids present in Solanum[6], Veratrum[7], Holarrhena[8], Buxus[8], Sarcococca[8], and Pachysandra[8]. Martin-Smith et al.,[9-11] have reviewed the literature concerning the steroid alkaloids of Funtumia, Paravallaris, Chonemorpha, Fritilaria, and Malouetia. Recently, Witkop and coworkers[12] have investigated the venom of the Columbian arrow poison frog, Phyllobates aurotaenia. They isolated batrachotoxinin A (9) which retained only 1/500 of the toxicity of the original venom. Nevertheless, it is still as toxic

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as strychnine. It is very unusual for a steroidal alkaloid to be so extremely toxic. From the pharmaceutical viewpoint, batrachotoxin and the related congeners in the venom are interesting because they or a

synthetic variation could have medicinal applications. For example, structurally modified compounds of batrachotoxinin A (9) could have lower toxicity and increased biological activity. These possibilities and facts provided impetus to work with heterosteroids. In addition, the structure of batrachotoxinin A (9) is strikingly novel. Wehrli and coworkers[13] have recently reported the partial synthesis of batrachotoxinin A (9).

With regards to naturally occurring nuclear azasteroids, the only example where nitrogen forms an integral part of the steroid nuclear skeleton is of the compounds obtained from the parotid and skin glands of salamanders.[3] It has been known since antiquity that salamanders are venomous animals. Over a century ago Zalesky[14] isolated a poisonous substance from the skin glands of salamanders which he designated samandarine though it is now known to be a mixture of alkaloids. Schöpf and Braun[15] examined the alkaloid mixture and in 1930 they isolated the major alkaloids presented in Table I (see Page 5). The skeletal features of these alkaloids coupled with their animal origin made them strikingly unique. These were the first of a very small number of alkaloids found in animals to date.

Interestingly, several toxins; bufotalin, pumiliotoxin C, dehydrobufotenine, tetradotoxin, batrachotoxin, and samandarine have attracted attention because of their diverse chemical, toxicological and pharmacological properties.[16] In particular, Faust[17] and Gessner[18-22] have examined the toxicology and pharmacology of samandarine (1). Poisoning with samandarine first causes convulsions followed by irregular palpitation and finally paralysis. Death occurs very quickly because of

TABLE II. Toxic substances with their $LD_{50}$

| Substance | $LD_{50}$ (µg/kg.) |
|---|---|
| Batrachotoxin | 2 |
| Tetradotoxin | 8 |
| Bufotalin | 400 |
| Curare | 500 |
| Strychnine | 500 |
| Samandarine | <3400 ($LD_{100}$)* |
| Sodium Cyanide | 10,000 |

*$LD_{100}$ is greater than a $LD_{50}$

primary respiratory paralysis without damaging the heart. Samandarine is toxic to all higher animals, fish, birds, and mammals. Even the salamanders die if their own venom enters their blood. The lethal dose is 19 mg/kg. for the frog, 3.4 mg/kg. for the mouse and 1 mg/kg. for the rabbit. The relative toxicity of samandarine is outlined in Table II (see Page 8 ).

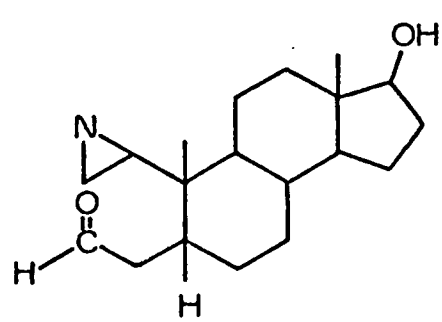
Ch'an su, the dried venom of a common Chinese toad, and extracts of the Mediterranean plant Scilla maritima have received varied application in primitive medical practice. The latter has been used from ca. 3500 B.C. principally for its diuretic and heart effects[23]. In 1785, Withering recognized the therapeutic effect of the cardiac glycosides obtained from Digitalis species. Wieland et al.,[24] investigated the extracts from the European toad Bufo vulgaris which led to the isolation of bufotalin and bufalin. The cardiac action of bufalin has been found almost equal to that of digitoxigenin. It is interesting to mention that extensive studies of Ch'an su, particularly by Meyer[25] and his colleagues, has led to the identification of a number of related bufadienolides in this material. Faust[17] and Gessner[18-22] have reported that the cardiac action of the Salamandra and the Digitalis toxins are similar. In view of the increase of cardiovascular diseases this result could have considerable importance in therapeutic treatment of these diseases. It is noteworthy that there is a difference between the Salamandra and the Digitalis toxins insofar as the arrest of the heart in diastole is not compensated for by atropine in the administration of samandarone but is for digitalis. However, the Salamandra toxins are not used in medical practice because of their unavailability and the lack of data on their biological activity.

## 2. Therapeutic Potential

Having selected a synthetic target which appears to demonstrate therapeutic potential it is now in order to consider the general principles of such a program.

In retrospect, there are two governing principles which determine the therapeutic potential of a synthetic endeavour. Firstly, the prerequisite of clinical evaluation is availability of testing material. To the synthetic chemist it is, therefore, important to develop high over-all efficiency in the synthetic sequence. Consequently, each synthetic operation must be assessed with regard to economy of effort. Samandarone (2) is neither readily available by synthesis (*vide supra*) nor from the natural source. Secondly, it is through the technique of molecular modification in drug design that the full potential of any system can be realized. These two general principles, therefore, directed the approach to the synthetic problem.

In order to gain a method of entry into the bicyclooxazolidine system it was planned to utilize aziridine aldehyde 10 as a "key" intermediate (*vide infra*). It was hoped that a common precursor could serve

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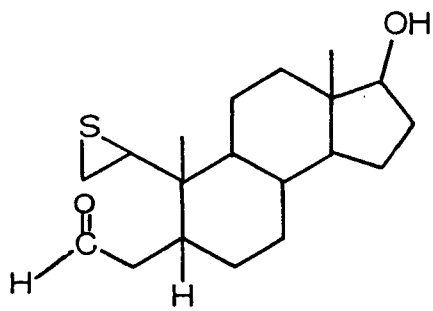
for the elaboration to the sulphur and oxygen analogues 11 and 12 respectively, to give the sulphur and oxygen analogues of samandarone (2).

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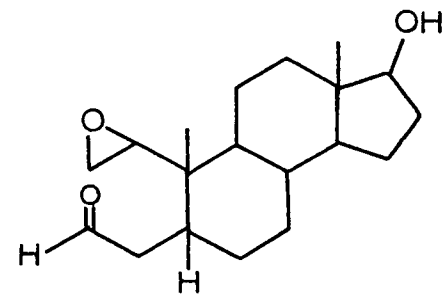


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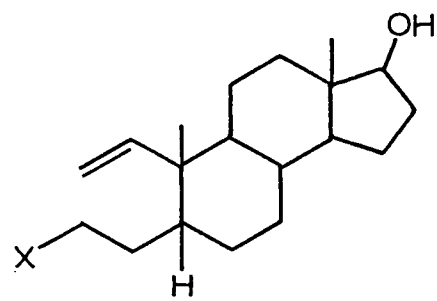
From a logistic viewpoint the ideal precursor would be an olefin of general type 13, since there are numerous, efficient, methods for converting an olefin to the appropriate three membered heterocycles. By

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this approach it is easy to conceive a wide range of plausible nuclear analogues and structurally modified compounds related to samandarone (2). In addition, manipulating and transforming the inherent functional group in the D ring gives further freedom for structural variance.

Once a versatile, practical, method of synthesis has been realized it would be instructive to ascertain if the activity is dependent upon the maintenance of the stereochemical integrity of various asymmetric centres in these alkaloids. If the toxicity is lowered or the activity increased by altering their stereochemical features or functional groups then they could have medicinal value in the treatment of cardiovascular diseases. Similarly, the various nuclear analogues may manifest low toxicity or increased activity and thus have therapeutic potential as well.

## 3. Chemical History

The formulation of a synthetic plan constitutes a prominent role in the successful synthesis of a natural product. The first step focuses on simplifying the synthetic problem with respect to the structural and stereochemical features in the target molecule. In general, there are three sources which can provide valuable knowledge for this solution. Firstly, details regarding the isolation and structural elucidation. Secondly, studies on the mode of biosynthesis and finally, if available, a description of previous synthesis of the target molecule or related molecules.

### Structure Determination

Schöpf and his colleagues, in the 1930's, reported the isolation, separation, and purification of several alkaloids (Table I, Page 5 )

from the toxic skin gland secretions of the alpine salamander.[3] The gross structure 1 was determined for samandarine in 1963 through chemical, spectroscopic, and X-ray crystallographic studies.[3]

Structural investigations of a newly isolated natural product begin with the determination of the elementary composition. The composition of samandarine was $C_{19}H_{31}No_2$. Samandarine (1) is a colourless, crystalline, saturated secondary amine containing a secondary hydroxy group which upon chromic acid oxidation affords samandarone (2).[15,26] The second oxygen occurs in an ether linkage and there are two C-methyl groups. Hofmann degradation of N-methylsamandarine methiodide (14) provided the first insight into the structural framework of these alkaloids (CHART I, Page 14).[15,26] This degradative reaction yielded 15 which possesses all the carbon atoms of the methiodide, thus proving that the nitrogen atom of samandarine (1) is present in a ring. Catalytic hydrogenation of 15 afforded 16. Compound 15 exhibited stability towards alkali but on warming with dilute sulphuric acid it adds one molecule of water forming 17. Chromic acid oxidation of 17 furnished the lactone samandesone (18). Furthermore, warming 17 with acetic anhydride yielded the quaternary acetate 20 of the starting material and 15. This result can be rationalized as an alkylation of the tertiary amine by an intermediate acetate 19. These results established that the nitrogen and the ether oxygen atom are joined to the same carbon atom in samandarine.

A series of chemical reactions provided for the elaboration of partial formula 14 to formula 24 (CHART II, Page 15 ). Treatment of samandarine (1) with lithium aluminum hydride yielded samandiol 21. While samandarine (1) is stable towards lead tetraacetate, samandiol 21

CHART I. Structure Elucidation of the Alkaloids

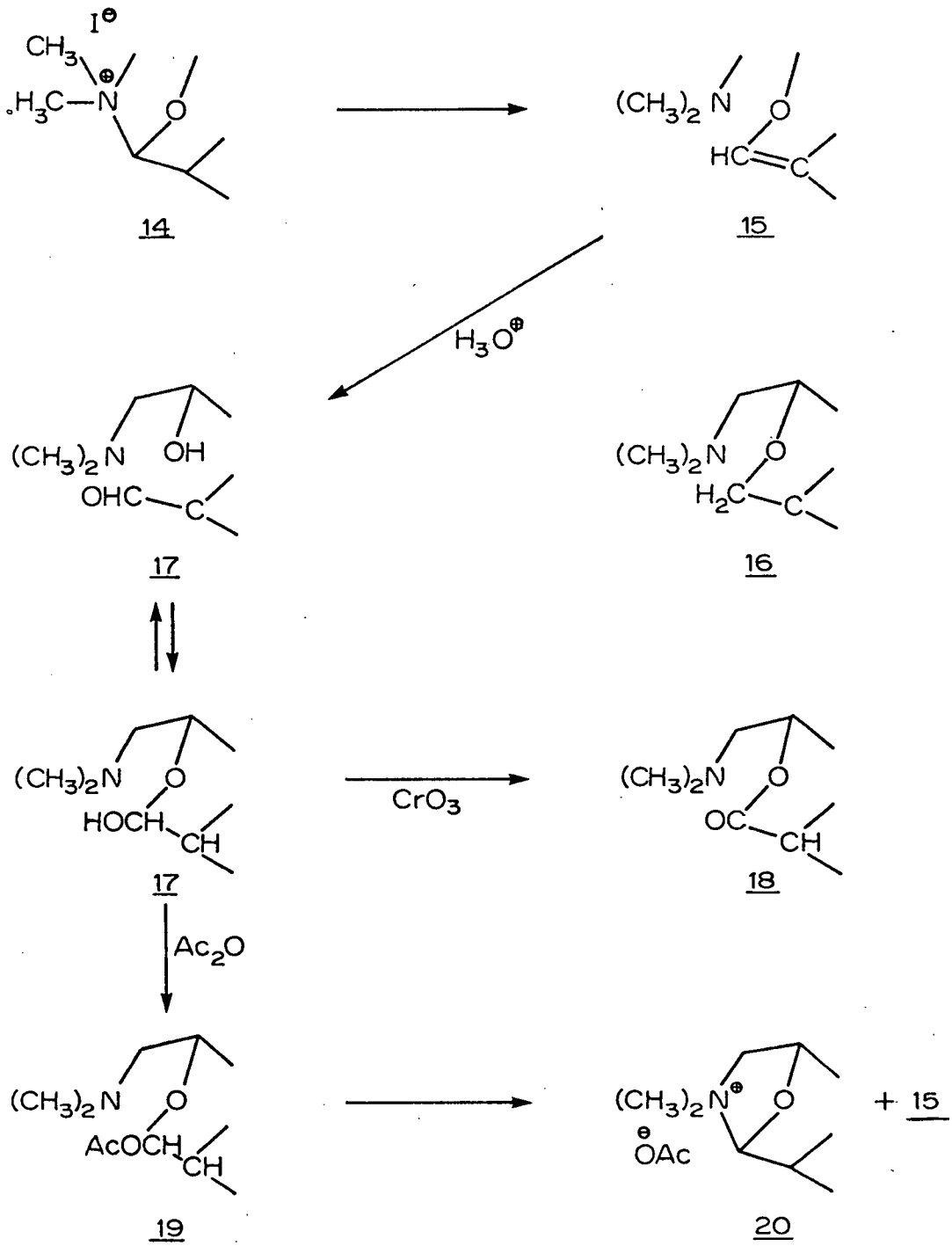
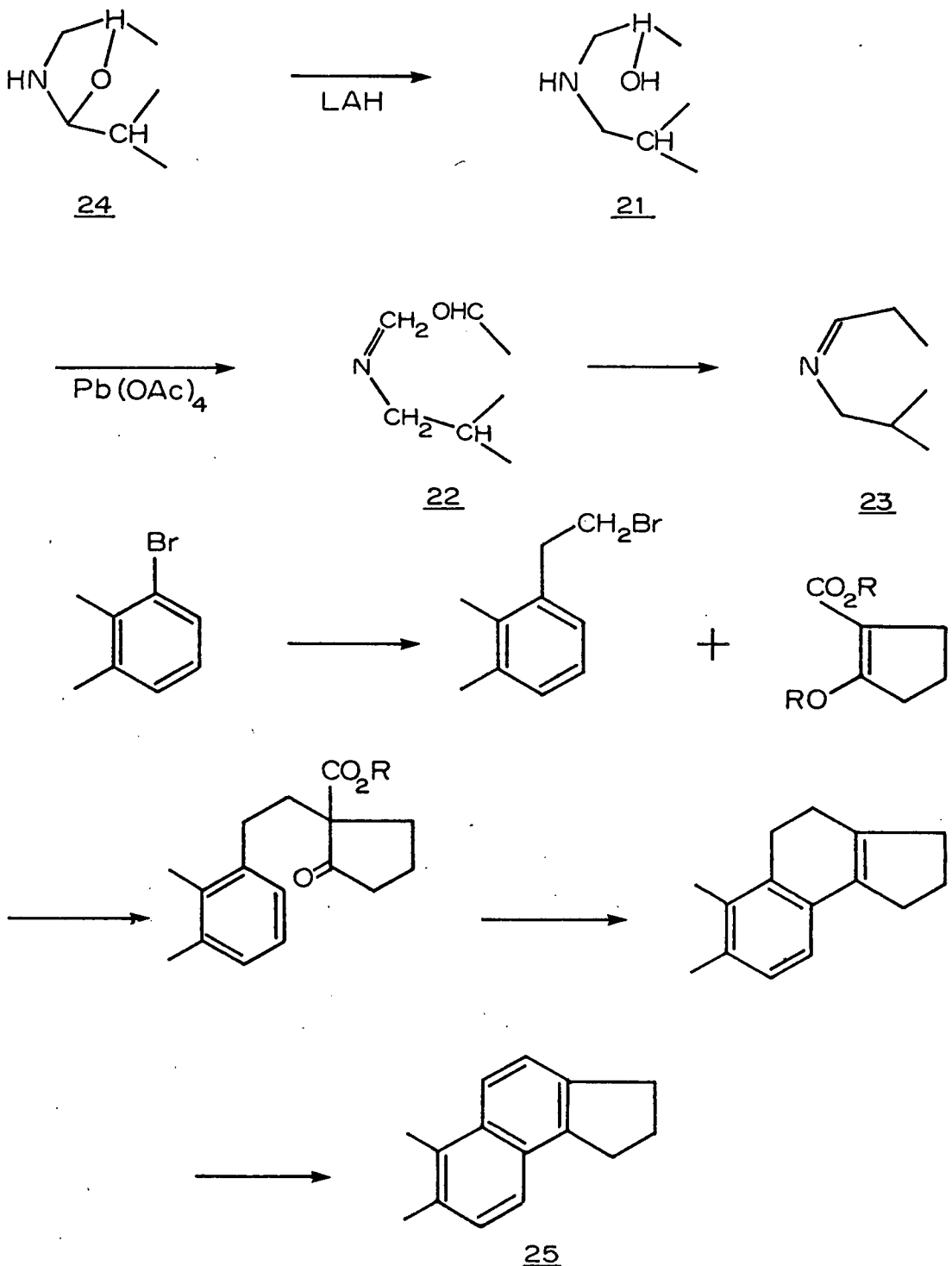


CHART II. Structure Elucidation of the Alkaloids

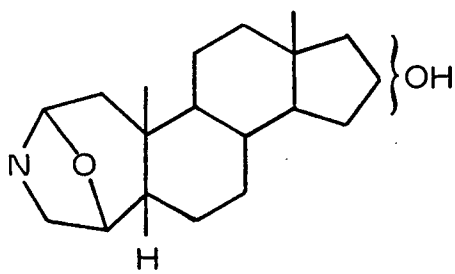


reacts with 1 mole of the reagent with formation of 1 mole of formaldehyde. Thus, samandiol 21 must possess a —NH—$CH_2$—CHOH— grouping as samandiol 21 does not contain a primary hydroxy group. In this reaction the Schiff base 22 which is first formed eliminates 1 mole of formaldehyde and undergoes ring closure to 23. Combining all these results finally led to partial formula 21 for samandiol and 24 for samandarine.[27]

The next major phase in the elucidation of the carbon skeleton of samandarine entailed dehydrogenation of samandiol with selenium at 320-340°.[28] The main product was isolated as a crystalline compound, $C_{15}H_{16}$. The ultra-violet spectrum of this showed it to be a 1,2-dimethyl-5,6-cyclopentenonaphthalene (25) which was synthesized by the method shown in Chart II (see Page 15 ).

From the partial formulae 24 and 25 one could deduce for samandarine a steroid skeleton with ring A containing an oxazolidine system. On this basis it is possible to write down three trial structures (26,27,28) in which the position of the secondary hydroxy group is still uncertain (see Page 17 ). The infrared spectrum of samandarone, however, revealed that the keto group formed by oxidation of the hydroxy group is in a five membered ring (band at 1740 $cm^{-1}$). Hence ring D contains the hydroxyl functionality.

X-ray analysis of samandarine hydrobromide, by the heavy atom method, gave the structure 1 corresponding to partial structure 27.[3] In addition, it was apparent that samandarine (1) has the same stereochemical configuration as the cholic acids. The salamander alkaloids are the first and only representatives with such a skeleton in the steroid alkaloids.[29] It is thus instructive to consider the distinctive features of the related compounds.

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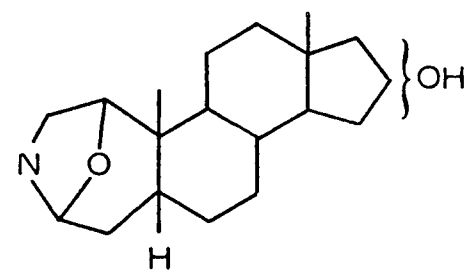


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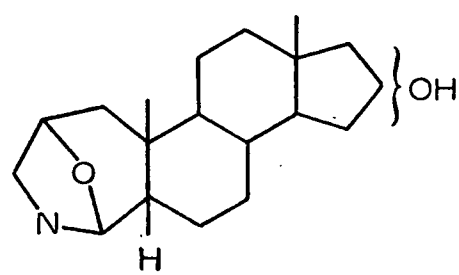


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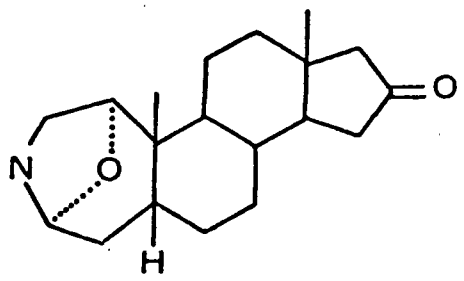
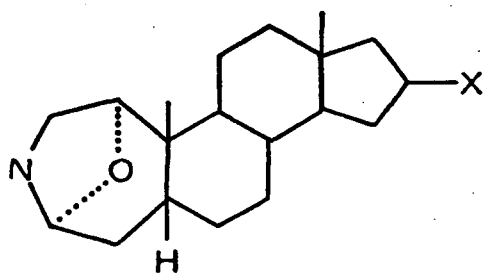



2

Samandarone (2)

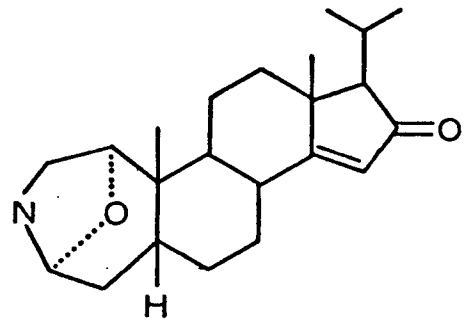
Samandarone is the main alkaloid in S. maculosa maculosa; in S. maculosa taeniata it is one of the minor alkaloids. Chromic acid oxidation of samandarine (1) affords samandarone; conversely, it is reduced stereospecifically by sodium and alcohol to samandarine (1).




4, X = OAc

O-acetyl-samandarine (4)

The structure of O-acetyl-samandarine was elucidated from the infrared spectrum and from chemical investigations. On saponification it affords samandarine (1) and acetylation of the latter forms O-acetyl-samandarine.[30]

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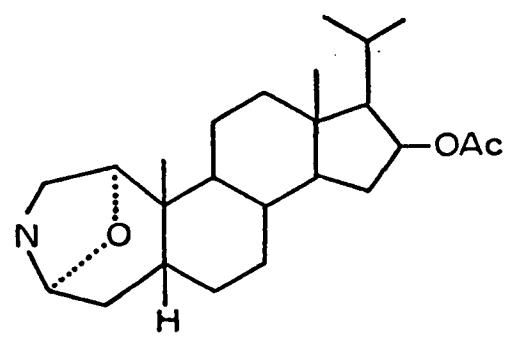
Samandenone (5)

The infrared indicated the presence of an oxazolidine system. Elemental analysis and spectroscopic methods gave structure 5.[31]

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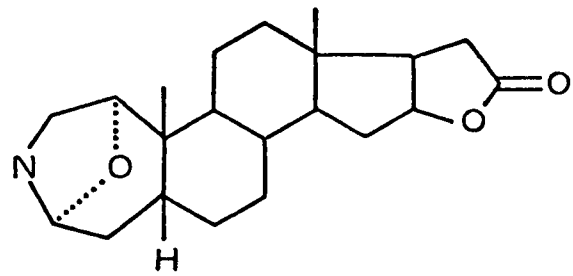
Samandinine (6)

The structure of this base results from infrared and mass spectral data.[32]



3

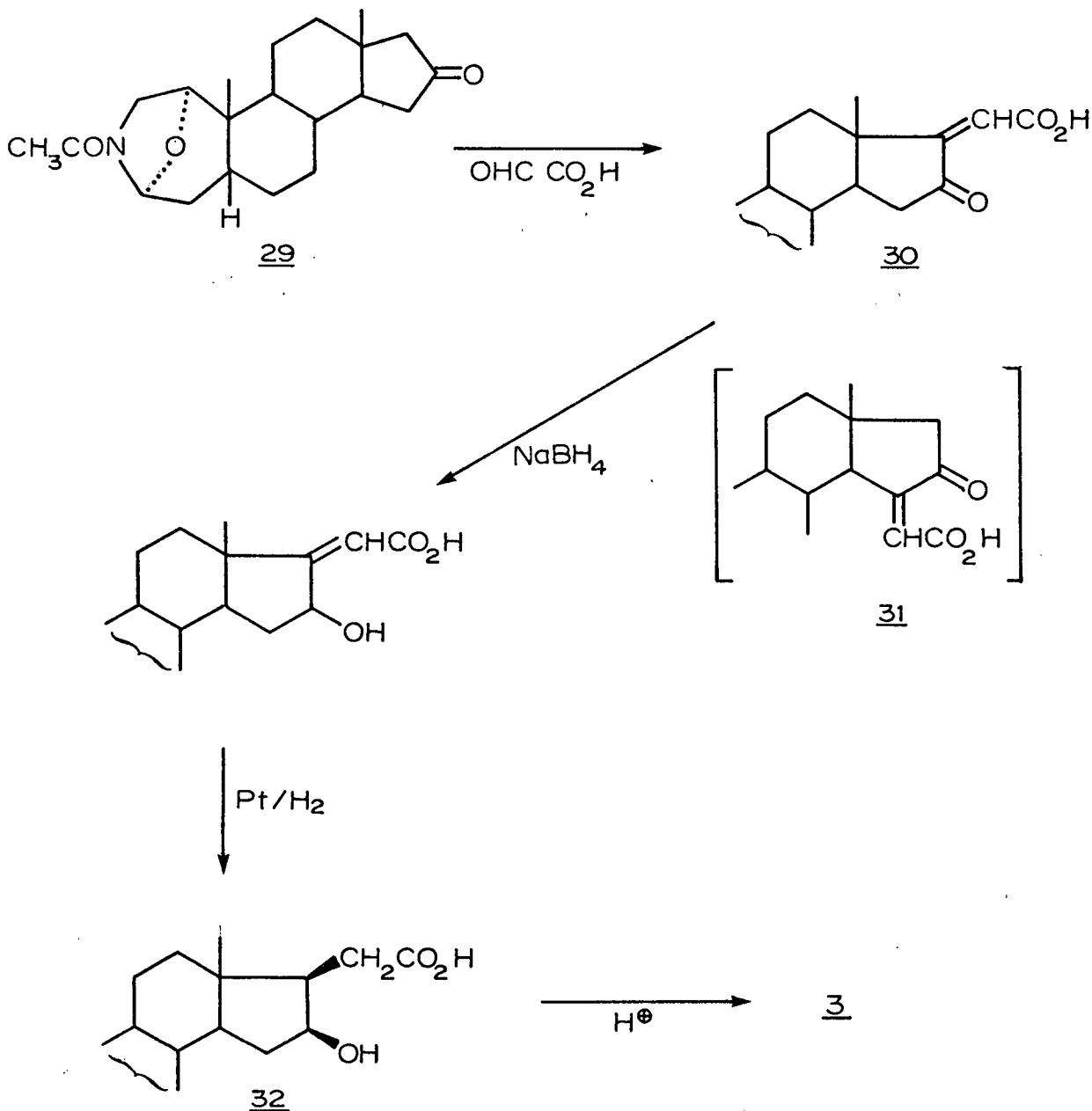
Samandaridine (3)

Chemical investigations and the infrared spectrum revealed the presence of a five membered lactone ring.[26] The structure was elucidated by X-ray analysis of the hydrobromide. The stereochemistry of samandaridine was confirmed by partial synthesis (CHART III, Page 21).[33] N-acetylsamandarone 29 was condensed with glyoxylic acid to give a mixture of two carboxylic acids 30 and 31. Reduction of 30 with sodium borohydride followed by catalytic hydrogenation proceeded stereospecifically to yield samandaric acid (32). Dilute mineral acid lactonises 32 to afford samandaridine (3).

Biosynthesis

Insight into the biogenesis of natural products has led to the development of "biogenetic-type" synthesis. Probably, the most outstanding case in the field of alkaloids is the famous Robinson tropinone synthesis which demonstrated to the synthetic chemist that complex molecules could be constructed by utilizing simple synthetic methods

CHART III. Partial Synthesis of Samandaridine



under very mild conditions. Furthermore, biogenetic synthesis are usually very short and efficient. This provides impetus to pattern a synthetic program along biogenetic lines. Consequently, the mode of biosynthesis of the salamander alkaloids could guide the direction of the synthetic approach.

The biosynthesis of the salamander alkaloids has attracted considerable attention since their structure was fully elucidated in 1963. It has been well documented that cholesterol serves as a common precursor in steroid metabolism.[34] For instance, cholesterol is a key intermediate in the formation of testosterone, a steroid sex hormone.

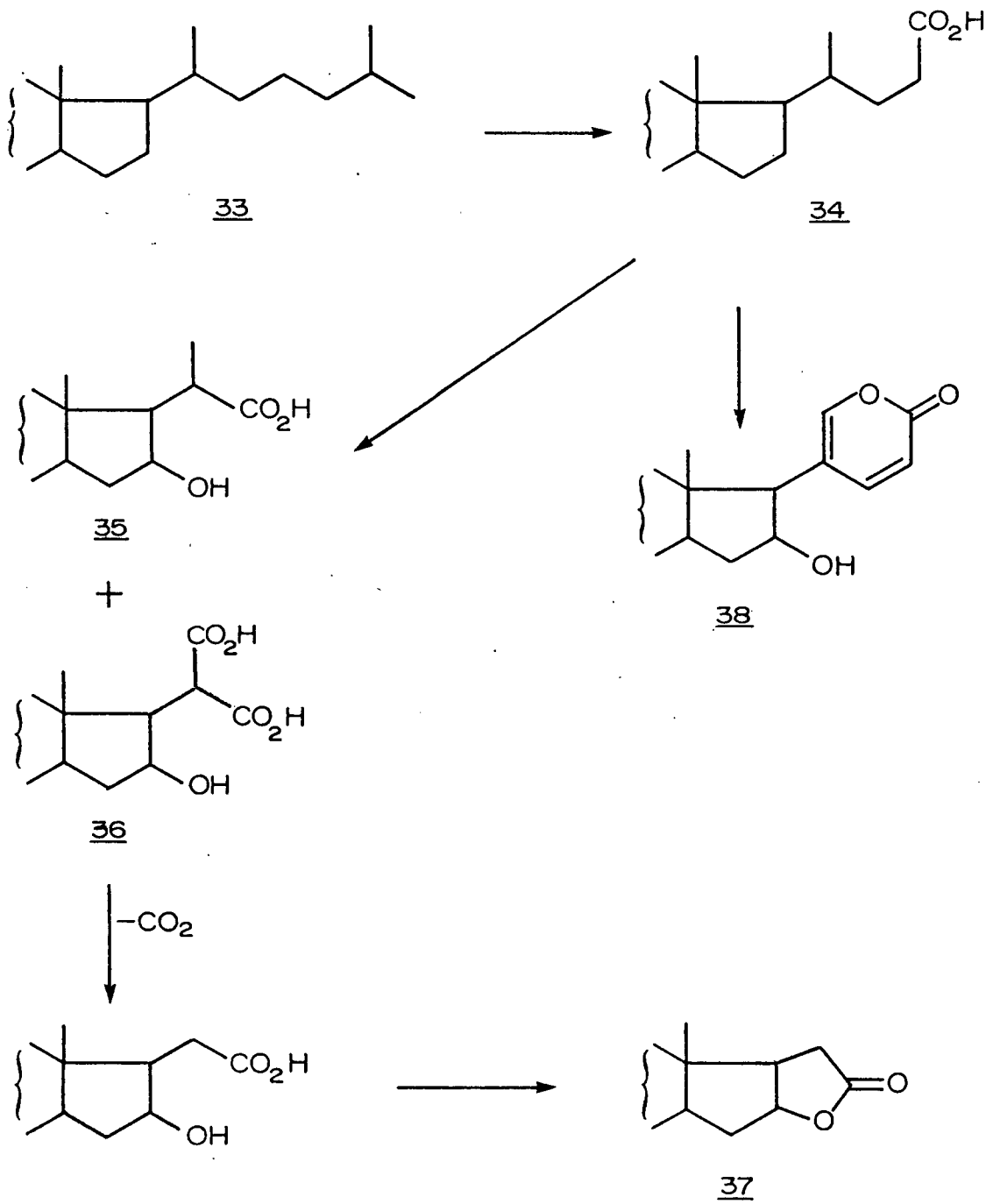
Structural analysis of the alkaloids revealed that they possess a steroid nucleus. In addition, it is apparent that structural variations in these compounds are due to the C-17 substitution pattern. Accordingly, they can be classified into three categories as illustrated in Table III (see Page 23). Further, the skin gland secretion has been found to contain considerable quantities of cholesterol.[35] As a result of these considerations it was proposed that cholesterol 33 could be a key biosynthetic intermediate.[35] Since samandenone (5) and samandaridine (3) bear substituents at C-17 they could represent intermediate stages in the biosynthetic pathway from cholesterol to the alkaloids without a side chain functionality at C-17.

Indeed, Habermehl *et al.*,[36] used $^{14}C$ labelled acetate and cholesterol to demonstrate that the salamander alkaloids originate from acetate *via* cholesterol. Hence, it seems attractive to conjecture that a cholic acid intermediate 34 (CHART IV, Page 24) is degraded by oxidation to the isopropyl group which is characteristic of samandenine (5)

Table III. C-17 Substitution Pattern in Salamandra Alkaloids

| |
|---|
| Carbon-17 having 2 H's<br>Samandarine (1)<br>Samandarone (2)<br>O-acetyl-samandarine (4) |
| Carbon-17 having —CH(CH$_3$)$_2$<br>Samandinine (6)<br>Samandenone (5) |
| Carbon-17 having —CH$_2$—C(=O)—O—<br>Samandaridine (3) |

CHART IV. Biosynthesis of the Side Chain in *Salamandra* Alkaloids



and samandinine (6). The formation of samandaridine (3) could be envisaged by further oxidation of 34 to a malonic acid 36 followed by decarboxylation and ring closure to generate the appropriate lactone 37. It should be noted that in a similar fashion the skin glands of Bufo (toad) could generate the bufotaline dienolide ring 38 from carboxylic acid 34 without loss of carbon atoms.[37] These concepts are portrayed in Chart IV (see Page 24).

The other interesting biosynthetic feature, which is at a speculative level, embodies the elaboration of the 5β-steroid A ring to the characteristic bicyclooxazolidine system. This entails the reduction of the $\Delta^5$ double bond, and insertion of nitrogen between carbons 2 and 3 with the appropriate introduction of an ether linkage between carbons 1 and 4. In this regard one can envisage a ring fission between carbons 2 and 3 followed by oxidation at the appropriate reactive sites which sets the stage for an enzyme catalysed ring closure to the natural skeleton. On the basis of this conjecture it, therefore, becomes apparent that the first major synthetic hurdle would be to effect an unsymmetric ring cleavage between carbons 2 and 3 in the A-ring of 5β-steroids. Assuming the foregoing, the task of differentiating the chemical reactivity at carbons 2 and 3 should be workable. Hence, there is now the possibility of performing the required types of transformations at specific centres with ordinary chemical reagents. In fact, this general behaviour was simulated by developing a method to effect an unsymmetric ring cleavage between carbons 2 and 3 in the A ring of 17β-acetoxy-5β-androstan-3-one.[38] In summary, the biosynthetic map, although speculative, directed the approach to the synthetic problem on hand.

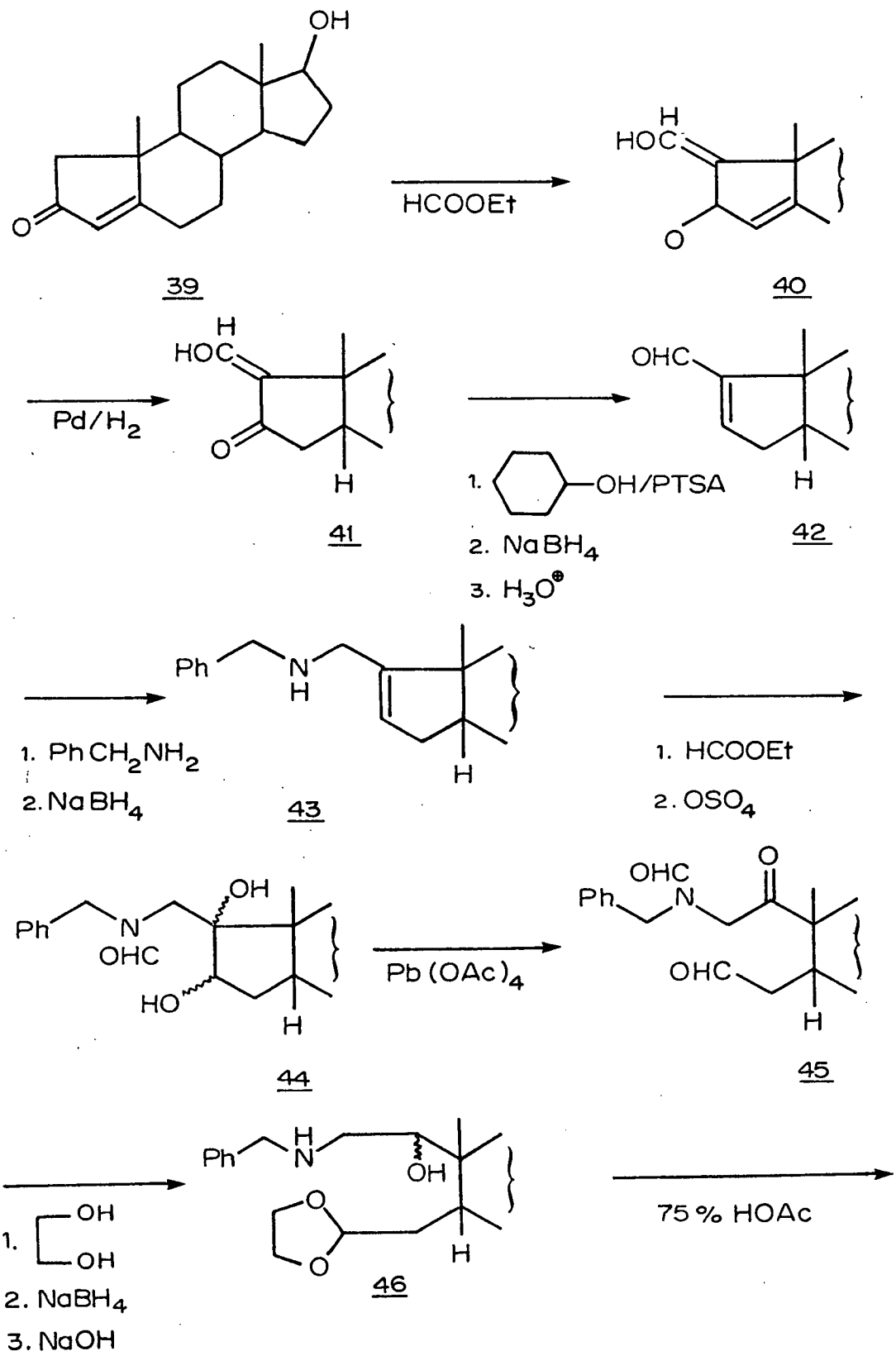
Synthesis

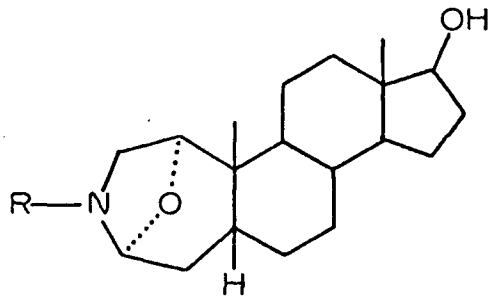
In 1967, Hara and Oka[4] reported the total synthesis of samadarone (2). This represented the first synthesis in the area of salamander alkaloids. In their synthesis they adopted the strategy of constructing a "key" intermediate 46 from compound 39 via 1-formyl-5β-A-norandrost-1-en-17β-ol (42) (CHART V, Page 27). They found that treatment of 46 with 75% acetic acid at 100° afforded compounds 47a and 48. Compound 47a was transformed to samandarone (2) by the sequence of reactions depicted in Chart V (see Page 27). As noted earlier, the Hara-Oka synthesis had limitations. For example, their synthesis yielded only milligram quantities of samandarone (2). However, the impractical nature of their synthesis does not detract from their achievement but emphasizes the need for further work in this area.

Most recently, Shimizu[39] has reported a new synthetic approach to samadarine-type alkaloids as depicted in Chart VI (see Page 29). The hydroxymethylene derivative of 17β-hydroxy-5β-androstan-3-one (53) was elaborated to compound 57a by utilizing the procedure of Autrey and Scullard[40]. The "key" reaction involved the conversion of 58 to the 17β-hydroxy isomer of samandarine 47b in ca 60% yield by employing sodium borohydride in refluxing isopropanol. Since a nitrile group is not a normal target of sodium borohydride reduction, Shimizu speculated that this reaction proceeded via formation of the cyclic amidine 59 or iminoester 60, which would then undergo sodium borohydride reduction with concomittant cyclization to compound 47b.

It is worthy of note that Eggart, Pascual, and Wehrli[41] have reported the synthesis of the 5α-isomer of 47b in another attempt to make the similar ring system.

CHART V. Hara - Oka Synthesis [4]

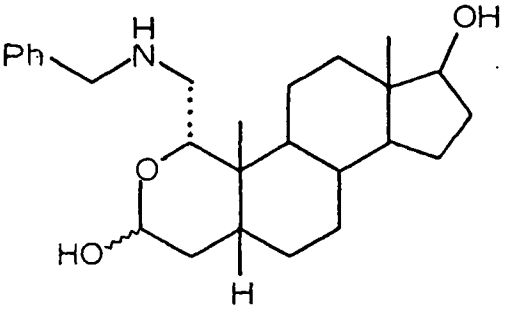




47a, R = $PhCH_2$

47b, R = H

+



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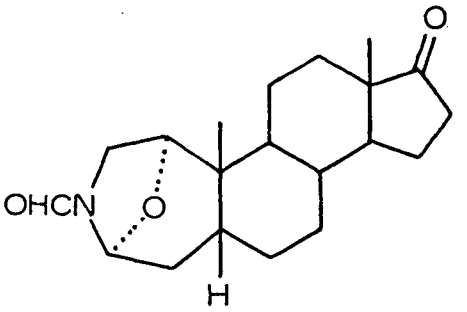
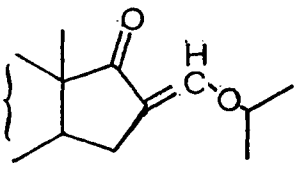
47a ⟶ (1. Jones oxid; 2. Cat/$H_2$; 3. HCOOEt)



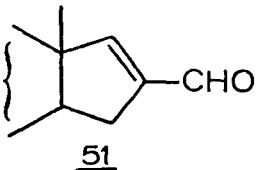
49

⟶ (1. HCOOEt/NaH; 2. HO–CH(CH$_3$)$_2$ /PTSA)



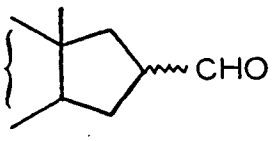
50

⟶ (1. $NaBH_4$; 2. $H_3O^{\oplus}$)



51

⟶ (1. [OH, OH]; 2. cat/$H_2$; 3. $H_3O^{\oplus}$)



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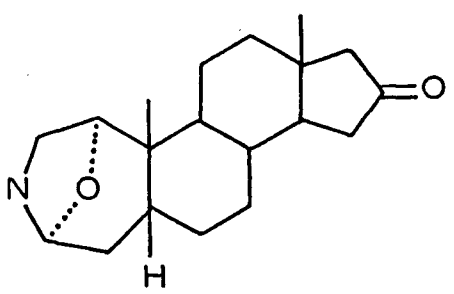
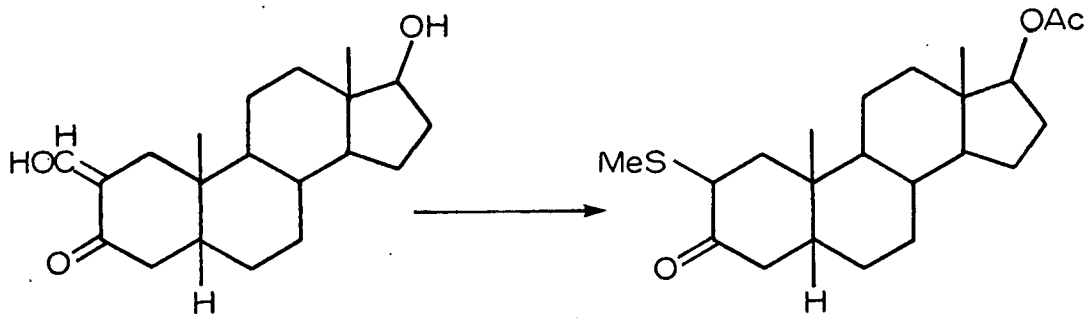
⟶ (1. i PA/conc $H_2SO_4$; 2. $O_3$; 3. HCl)

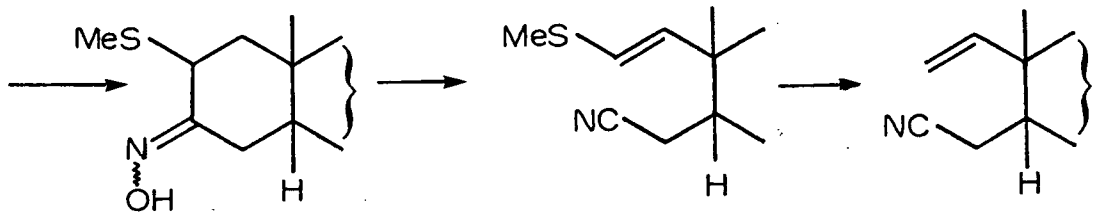


2

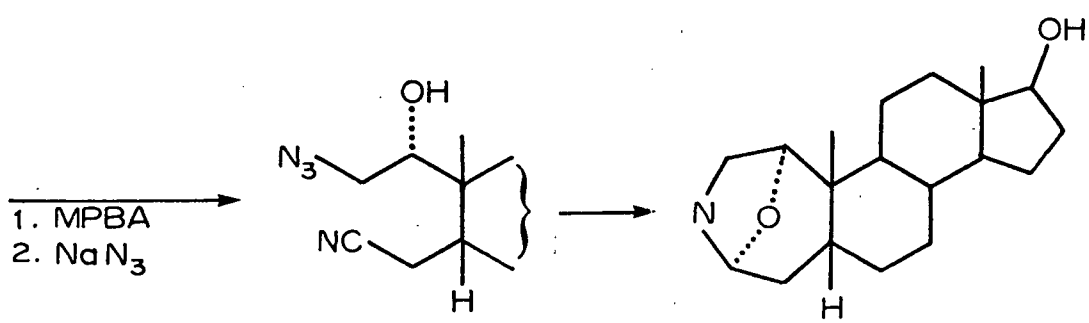
CHART VI. Shimizu Synthesis [39]



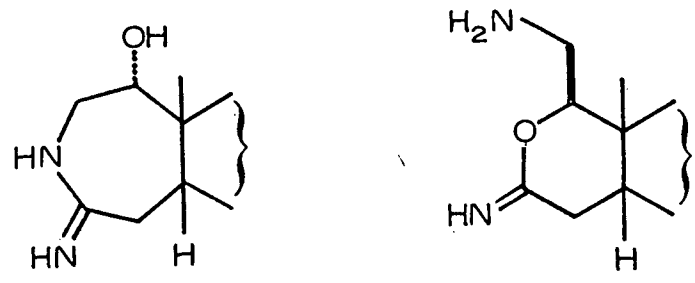

53 54




55 56 57a




58 47b

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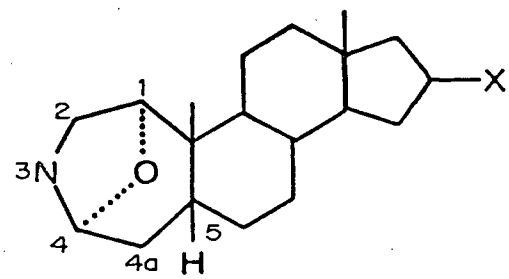
# DISCUSSION

## 1. General Plan

As previously mentioned, this thesis describes several attempts to gain a general method of entry into the bicyclooxazolidine skeleton of general type I. It was hoped that an efficient method of synthesis




1, X = OH

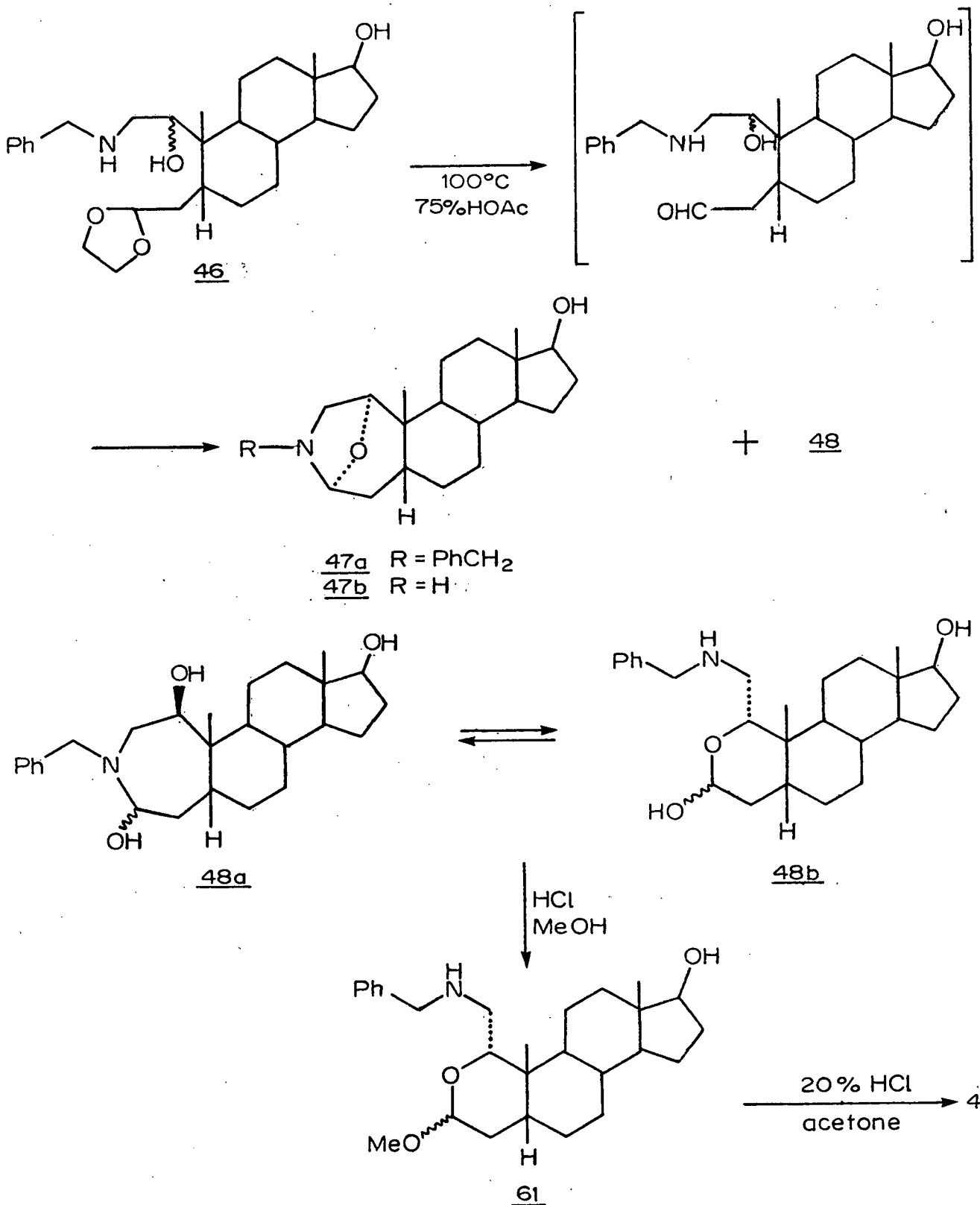
would be developed which would provide material for biological studies and that new synthetic reactions would be tested.

Compound 1 poses a structural and stereochemical problem which is concentrated in the A ring of the steroidal framework. The synthetic problem constitutes the elaboration of the steroidal A ring to the bicyclooxazolidine skeleton. The desired substitution pattern in the D ring could be achieved by employing appropriate synthetic procedures.[4]

Interestingly, structure 1 possesses nine asymmetric centres. Of these, seven are contiguous and range over the A, B, C, and D rings. In planning the synthesis testosterone was chosen as the starting material since it is a readily available steroid with a versatile D ring substituent. Thus, the stereochemical problem associated with a synthesis of the bicyclooxazolidine system reduces to fixing the relative stereochemistry at carbons 1, 4, and 5 (Structure I) with respect to the existing centres. The close proximity of carbons 1, 4, and 5 offers the opportunity to create these new centres, with the desired stereochemistry, under the influence of chiral factors present in the precursors.

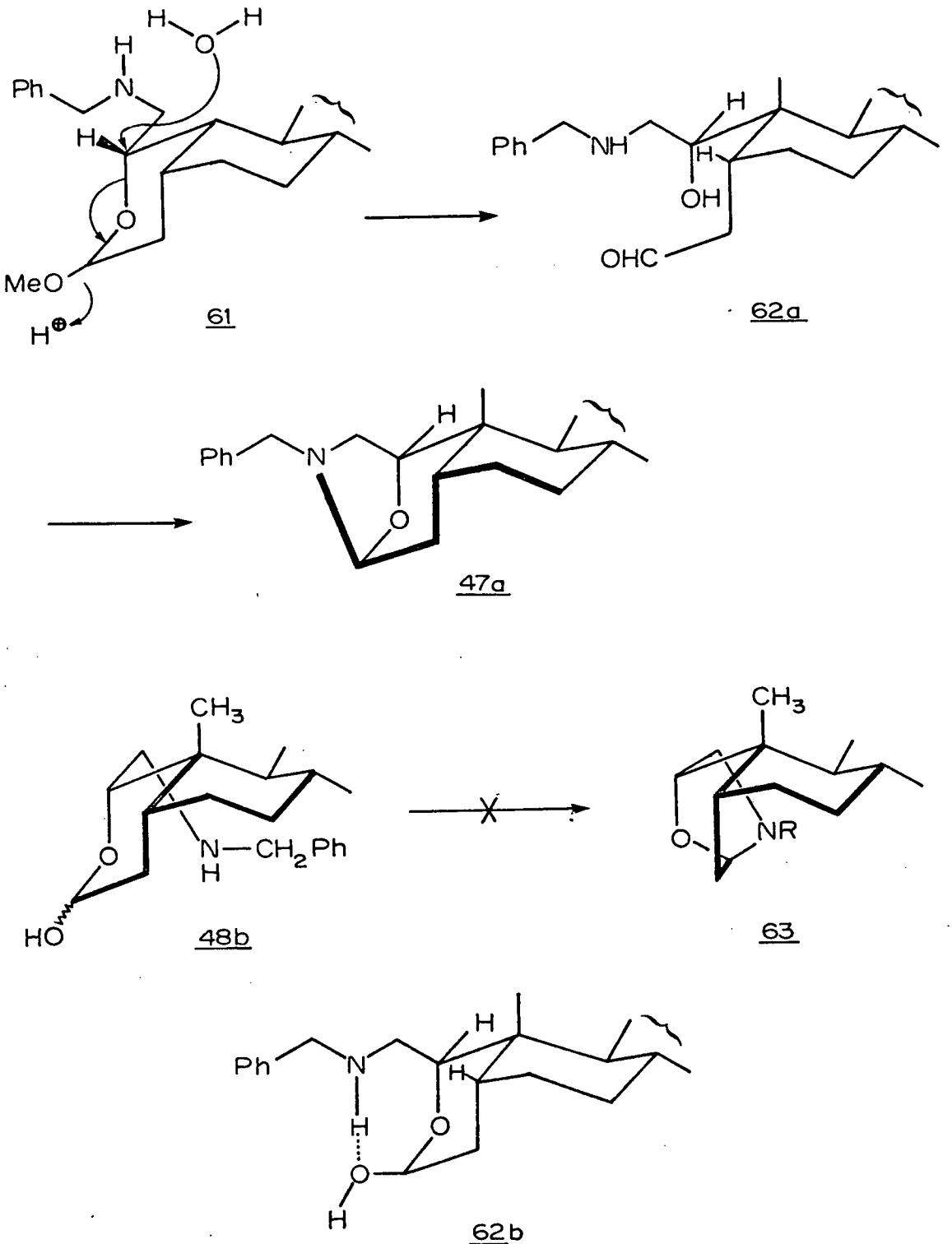
Firstly, the cis relationship between the carbon-10 methyl and carbon-5 hydrogen was established at the outset of the synthesis by employing Liston's procedure to hydrogenate testosterone[42]. Secondly, it was hoped that the stereochemistry of the ether bridge between carbons 1 and 4 in the final product would be fixed in the final stages of the synthetic pathway. With regard to the stereochemical problem on hand it is pertinent to examine the work of Hara and Oka[43]. In 1969, they reported the stereoselective conversion of 46 to 47a as illustrated in Chart VII (see Page 32).[43] In summary, they accomplished the construction of the bicyclooxazolidine skeleton by mild hydrolysis of a one to one mixture of the epimers, 2-benzylamino-3,3-ethylenedioxy-2,3-seco-5β-androstane-1, 17β-diol (46) with 75% acetic acid. This reaction gave 3-benzyl-3-aza-1α,4 α-oxido-A-homo-5β-androstan-17β-ol (47a) and another substance 48 which was subsequently found to be a mixture of compounds 48a and 48b. Treatment of compounds 48a and 48b with hydrogen chloride-methanol yielded the methoxy acetal 61. The action of 20% hydrochloric

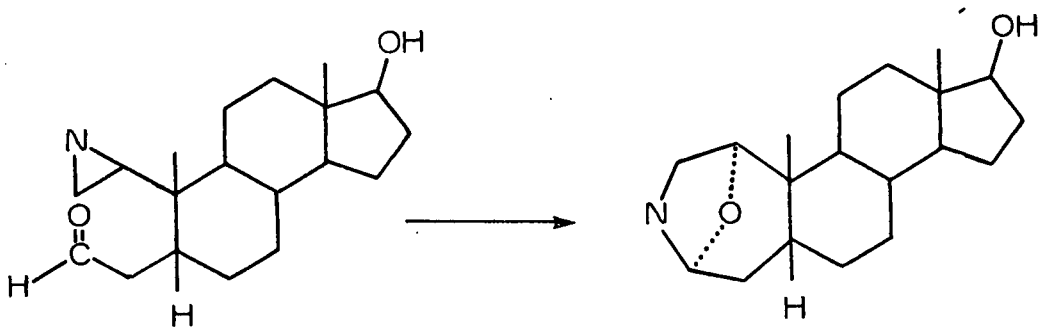
CHART VII. Stereoselective synthesis of the bicyclooxazolidine 47a from intermediate 46 [43]



acid in aqueous acetone on compound 61 afforded 47a. The reaction mechanism (CHART VIII, Page 34 ) which they invoked for this latter conversion involved the elimination of the methoxy group and the concerted attack of a water molecule at the electron-deficient carbon-1 atom, giving rise to inversion at the carbon-1 position of compound 61, followed by bicyclization of the resultant seco-oxy-aldehyde 62a to produce the thermodynamically stable system 47a. It is worthy of mention that compound 48b did not undergo bicyclization to give compound 63. In order for this to occur it would be necessary for the "A" ring of 48b to be in a boat conformation. On the other hand inversion at carbon-1 position with formation of compound 47a presumably occurs due to the following thermodynamic factors. In compound 48b there is a severe non-bonded interaction between the equatorial side chain and the carbon-11 making it thermodynamically less stable than compound 62b. In addition, the side chain in compound 62b is axial and the opportunity exists for intramolecular hydrogen bonding between the primary amine and the hydroxy group of the hemiacetal. The energy gained in the formation of this type of hydrogen bond could be as strong as 5kcal/mole. With the formation of compound 62b a favourable situation has been reached for cyclization. Removal of the benzyl group from 47a was achieved by catalytic hydrogenation which gave 47b in quantitative yield. In view of the foregoing results it was plausible to conceive the stereoselective synthesis of the samandarine nucleus via an intermediate closely analagous to 46. From the outset, the hypothetical intramolecular cyclization (eq. I, Page 35) constituted the central feature of the projected synthesis. There is analogy for this type of intramolecular cyclization. In 1969, Wasserman

CHART VIII. Mechanism for the formation of the bicyclooxazolidine 47a from acetal 61 [43]

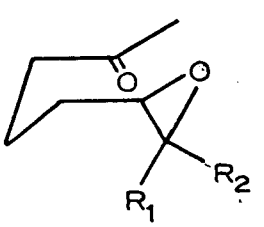





(1)

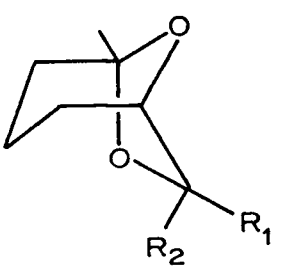
10 47b

and Barber[44] described the thermal rearrangement of δ,ε-epoxy ketones to the [3.2.1] bicyclic system. Thus, 6,7-epoxy-2 heptanone (64) may be thermally transformed into 1-methyl-7,8-dioxabicyclo [3.2.1] octane (65) in 75% yield. They extended and used this general type of thermal




64, $R_1 = R_2 = H$

66, $R_1 = C_2H_5$; $R_2 = H$

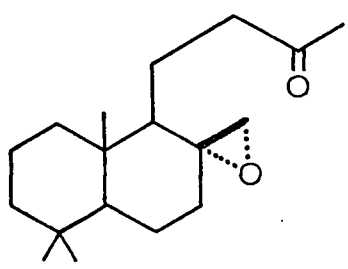



65, $R_1 = R_2 = H$

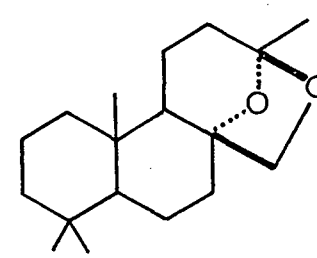
67, $R_1 = C_2H_5$; $R_2 = H$

68, $R_1 = H$; $R_2 = C_2H_5$

rearrangement to synthesis brevicomin, the principle sex attract of the western pine beetle. Thus, cis-6,7-epoxy-nonan-2-one (66) could be thermally transformed into a mixture of exo-6-ethyl-1-methyl-7-dioxa-bicyclo-[3.2.1] octane (67) (90%) and the corresponding endo isomer 68 (10%). The exo isomer was identical with brevicomin. Although the mechanistic details of this carbonyl epoxide rearrangement remain to be explored, it seems clear from the above results that during thermolysis of the δ,ε-epoxy ketones the epoxide ring undergoes ring opening predominantly with inversion of configuration. In addition, Demole and Wuest[45], and others[46,47] have reported the acid catalysed cyclization of δ,ε-epoxy ketones. For example, epoxy ketone 69 is converted to a 1:9 mixture of 70 and 71 in the presence of p-toluenesulphonic acid while with silicic acid 70 and 71 are formed in the ratio of 3:1.



69



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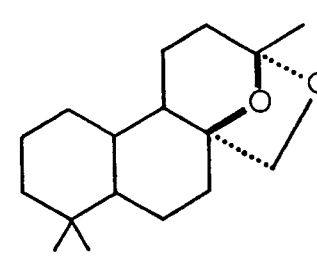
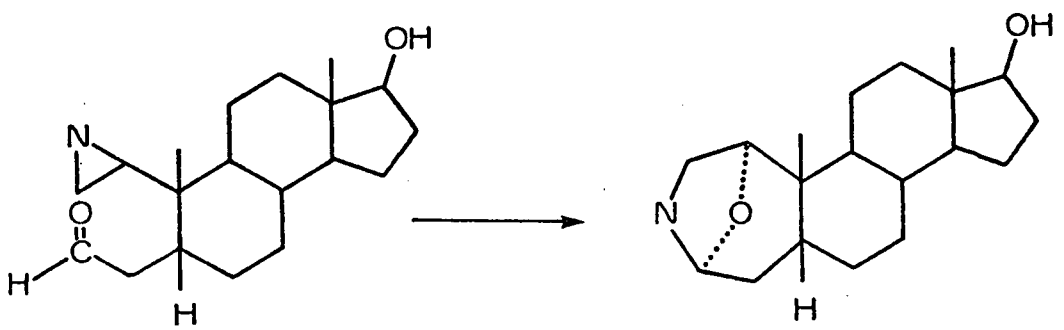


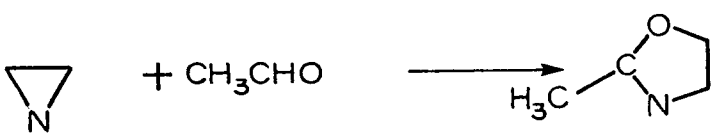
71

The distinctive features of the thermal epoxy ketone rearrangement are the efficiency and stereoselectivity of the conversion. Consequently, the aziridine aldehyde 10 was proposed as a possible "key" intermediate for gaining a method of entry into the bicyclooxazolidine skeleton. The scheme is portrayed, in general terms, by the hypothetical



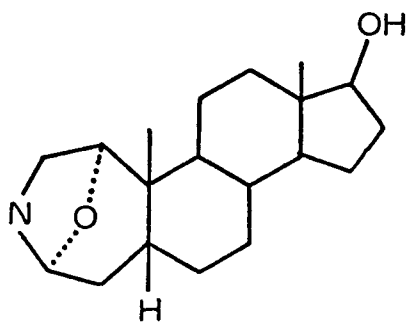

10 47b (I)

cyclization of 10 to 47b (eq. I). In principle, this transformation represents the nitrogen analogue of the δ,ε-epoxy ketone rearrangement. Doughty and his colleagues[48] have prepared oxazolidines by an intermolecular reaction in fair yield. For example, aziridine 72 reacted with acetaldehyde (73) to afford oxazolidine 74. It is well authenticated

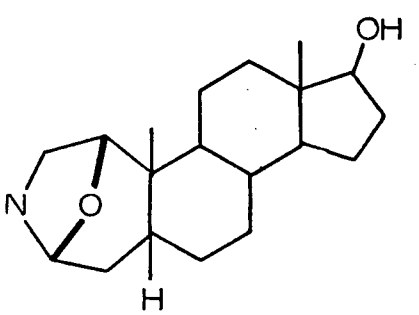



72 73 74

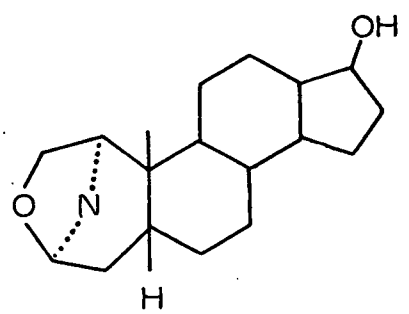
that intramolecular cyclizations are energetically more favourable than intermolecular cyclizations. Hence reaction I appeared attractive and potentially efficient. However, four products, 47b, c, d, and e, could be formed. In view of the work of Hara and Oka,[43] and others[45,46,47] it



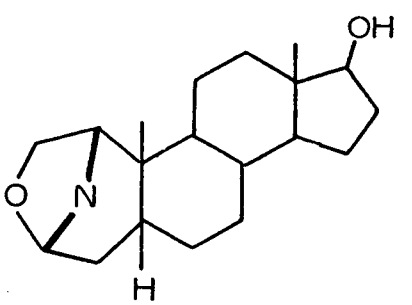

47b




47c




47d



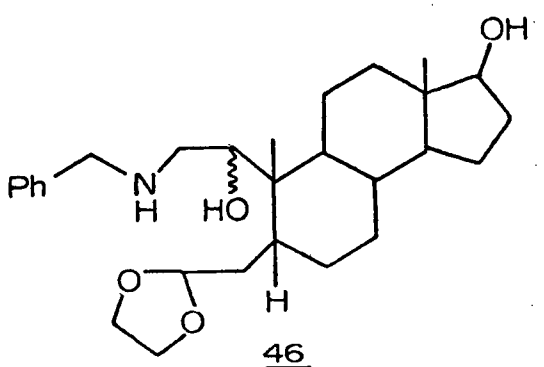

47e

was felt that if structural isomerism or stereochemistry proved to be a problem, control could be introduced by varying the reaction conditions or, ultimately, by modifying the "key" intermediate 10.

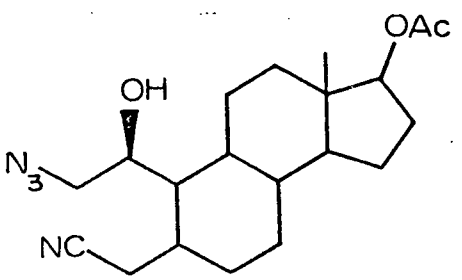
The theoretical cleavage of several bonds of the target molecule with appropriate functionalization afforded four probable candidates 75, 76, 77, and 78, for eventual cyclization to the bicyclooxazolidine

system 47b (CHART IX, Page 40). Several other intermediates were discarded because of structural and chemical complexities. It was hoped that aziridine 75, bearing the appropriate functionality X, could give rise to the intermediate 10. As a result aziridine 75 was recognized as an important structural unit through which our pathway could pass.

It is worthy to note that compounds 77 and 78 are closely analogous to the "key" intermediates 46 and 58 employed in the Hara - Oka and Shimizu syntheses, respectively. If the aziridine cyclization




46

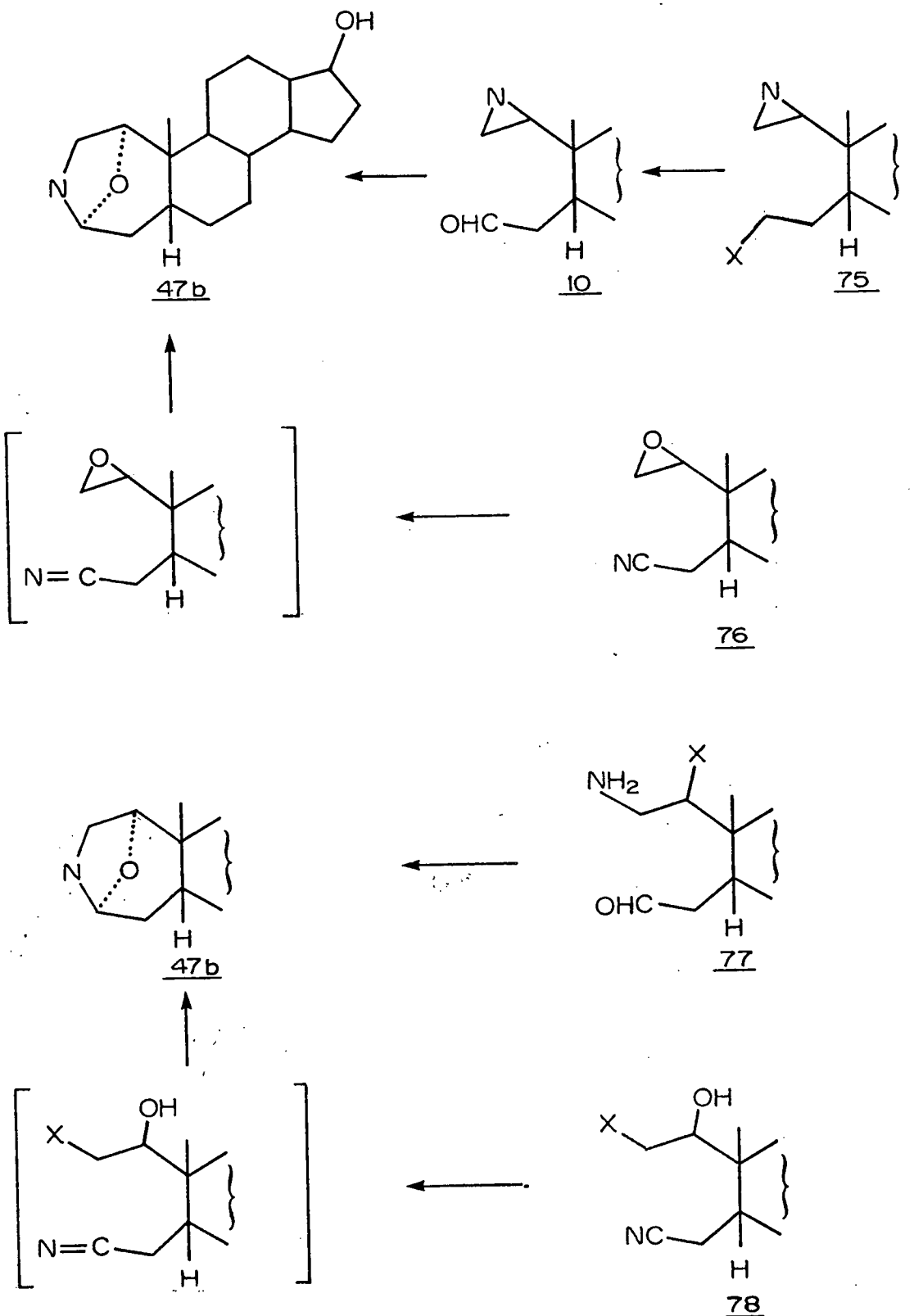


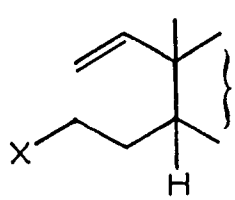

58

approach failed it could possibly be modified to embody an intermediate similar to either compounds 76, 77 or 78. In actuality, the original strategy did suffer a reversal in this direction.

One approach to the synthesis of aziridine 75 involved the formation of precursor 79 with the appropriate functionality X. It was planned to construct olefin 79 from an intermediate of general type 80 which could be derived from 17β-acetoxy-5β-androstan-3-one (81b) by effecting an unsymmetric cleavage between carbons 2 and 3 in the A ring. It is particularly important that the functionalities X and Y would set the stage for incorporating the olefinic bond of 79 in an efficient manner.

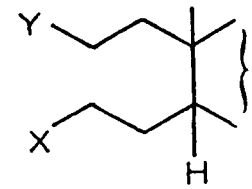
CHART IX. Possible synthetic pathways to the bicyclooxazolidine 47b





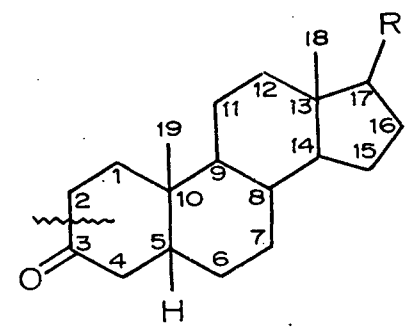

79






80



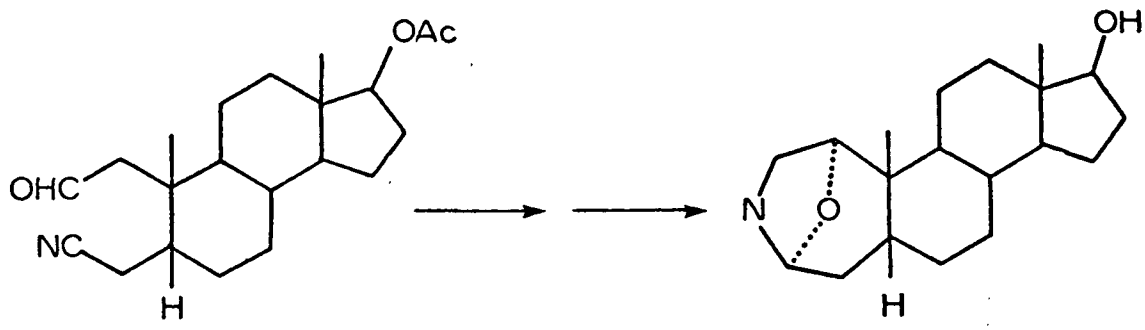



81a, R = OH
81b, R = OAc

This prospective synthetic plan, therefore, was concerned with two major objectives. The first objective would be to develop a method to effect an unsymmetric cleavage between carbons 2 and 3 in the A ring of 5β-steroids. The second major phase of the program would constitute the elaboration of the ring cleavage product to the bicyclooxazolidine skeleton *via* one of the "key" intermediates which have been alluded to.

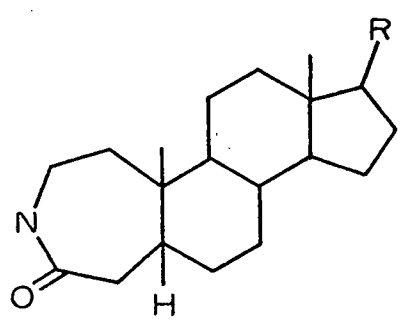
Accordingly, this thesis is divided into two parts. Part I, describes three general approaches directed towards effecting the desired ring cleavage reaction. The third approach which was investigated proved to be the method of choice. Part II, describes attempts to elaborate

cyanoaldehyde 195 to the 17β-hydroxy isomer of samandarine 47b.

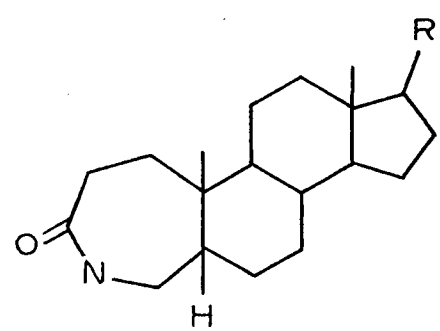



195 47b (1)

It is now in order to turn from the foregoing general analysis to specific synthetic detail and development. A review of the literature revealed that two general methods could be employed to effect cleavage of the 2,3 bond in the A ring of 5β-steroids. Firstly, Schmidt reaction of ketone 81b and Beckmann rearrangement of the oximes of ketone 81b effected ring expansion with incorporation of nitrogen to furnish two isomeric lactams 82c and 83c in a ratio of ca. 1:1.[49] Unfortunately,

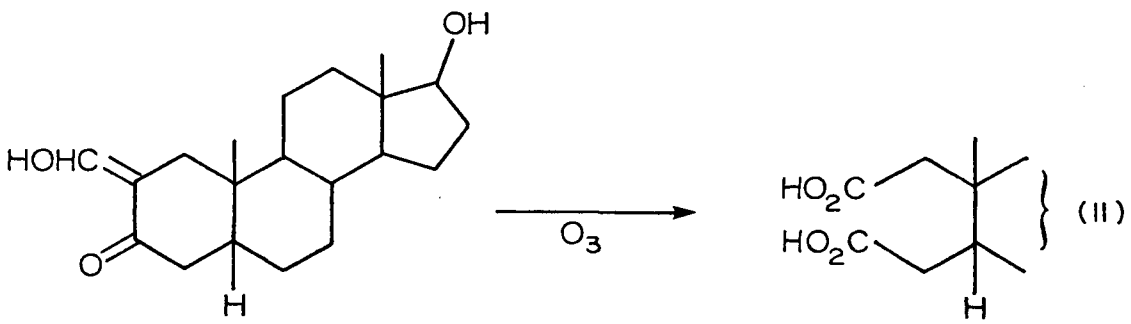



82a, R = OH
82b, R = OTS
82c, R = OAc



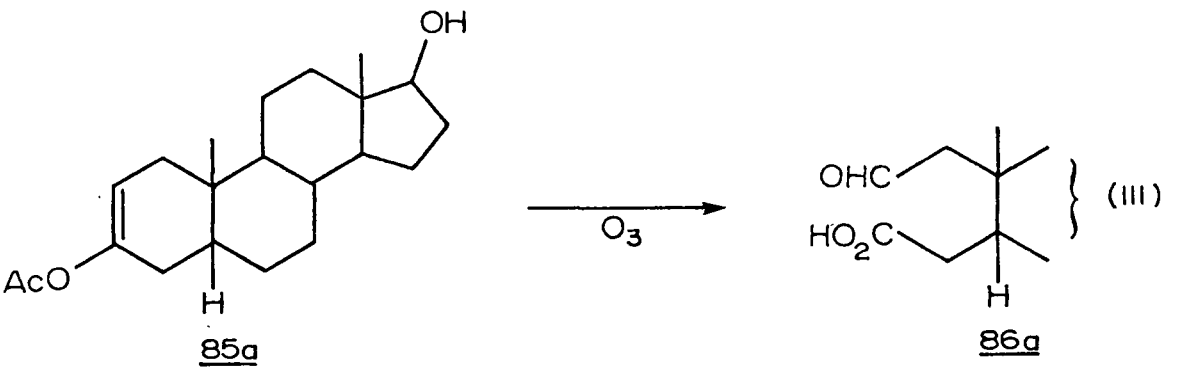

83a, R = OH
83b, R = OTS
83c, R = OAc

the separation of lactams 82c and 83c is a most difficult task.[50] Even if separation could be effectively achieved the required lactam can only be procured in less than 50% yield. In short, this does not represent an efficient process. Similarly Baeyer-Villiger oxidation of 3-oxo-steroids gave a mixture of lactones.[61] Secondly, ozonolysis of 2-hydroxy-methylene 53 led to a symmetric cleavage of ring A, equation II.[51]




53 84 (II)

Clearly, neither of these general procedures were compatible with the present needs. However, three general principles embedded within these transformations were recognized. First, with regards to the Beckmann rearrangement and the Baeyer-Villiger reaction, the insertion of a hetero atom between carbons 2 and 3 sets the stage for a facile unsymmetric ring opening. Second, after considering transformation II it was decided to effect an oxidative cleavage between carbons 2 and 3. Again, the stage would be set for unsymmetric ring cleavage as depicted in equation III. Finally, functionalization of carbon-2 with subsequent introduction of a convenient "handle" at carbon-2 could lead to ring cleavage in the desired fashion.[52]




85a 86a

Accordingly, these three general concepts set the course in the first phase of the projected synthesis. The third concept, namely, the functionalization of carbon-2 proved to be the method of choice.

## Part I

### a. Insertion of a hetero atom between carbons 2 and 3

Oka and Hara[50a,53] in 1968 reported the separation of syn and anti isomers of several steroidal 3-ketoximes and succeeded in differentiating between the geometrical isomers by means of n.m.r. spectroscopy using chemical shifts of the protons attached to the α-carbon atoms.[53a] Analysis of the methylene protons adjacent to the oximino carbon atom in cyclic ketoximes had not been demonstrated except for a few cases of simple derivatives of cyclohexanone and cyclohexenone. These signals, in the region of τ8.2 to τ7.5, are not clearly separated from the signals of other methylene or methine protons. In the case of α,β-unsaturated steroidal ketoximes, the assignment was due to the chemical shift of the olefinic proton rather than the methylene protons. In 1968, Oka and Hara[53a] reported the analysis of the 100 MHz n.m.r. spectra of the methylene protons adjacent to the oximino carbon atom of 3-oxosteroid oxime derivatives. The compounds used were pure isomeric forms of oximes and O-methyloximes of testosterone, 17α-methyl-testosterone, 19-nortestosterone, 17α-ethyl-19-nortestosterone, A-nortestosterone, and 5α- and 5β-androstanolones.

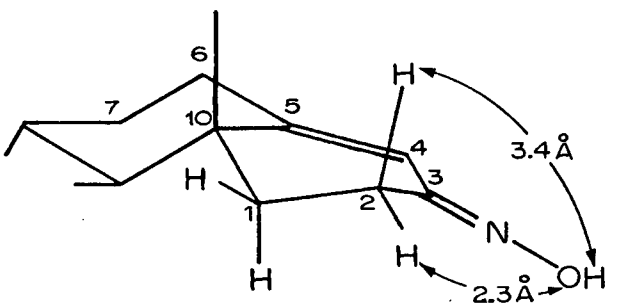
Firstly, the syn isomers of six-membered unsaturated 3-oxosteroid oximes had a four proton unresolved multiplet at τ7.9 to τ7.6 which was assigned to C-2 and C-6 methylene hydrogen atoms. On the other hand, the corresponding anti isomers showed one proton shifted downfield from the three-proton unresolved multiplet by 90 Hz. Its coupling pattern,

doublet (J = 18.5 Hz, centred at $\tau$7.0) of triplet (J = 4.8 Hz) indicated the signal to be due to the C-2$\alpha$ (equatorial) hydrogen atom. Consequently, the three proton multiplet at $\tau$8.0 to $\tau$7.6 was assigned to C-2$\beta$ (axial) and C-6 methylene hydrogen atoms.

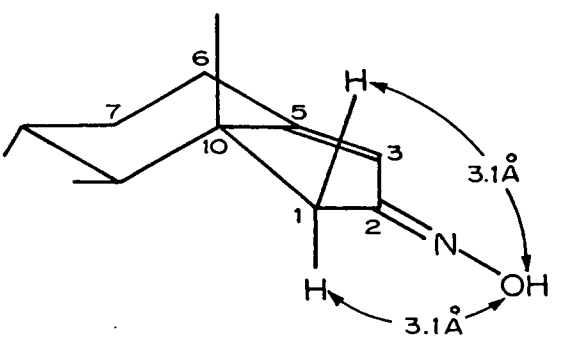
In contrast, the C-1 methylene hydrogens of the five membered unsaturated steroids, for example, A-nortestosterone were observed as a two proton singlet at ca. $\tau$7.5 for either syn or anti isomers, and only a 3 Hz downfield shift was found for the anti isomer. The C-6 allylic methylene hydrogens ($\tau$7.74 and $\tau$7.52) are coupled to one another (J = 13 Hz) and show further splitting from the olefinic and the C-7 methylene hydrogens. Hara and Oka[53a] considered the difference between six- and five-membered ring systems to be due to a different anisotropic effect of the oxygen atom, as is readily understood when molecular models are constructed (CHART X, Page 47). A C-2$\alpha$ (equatorial) hydrogen of a six-membered ring may be influenced strongly by the anisotropic effect because of its shorter distance (ca. 2.3Å) from the oxygen atom than that of the C-2$\beta$ (axial) one (ca. 3.4Å). For the five-membered ring, C-1$\alpha$ and $\beta$ hydrogens may be equidistant from the oxygen atom (ca. 3.1Å) and no difference in chemical shift between these two hydrogens is observed.

Hara and Oka[53a] applied these observations to the assignment of the geometrical isomers of unsymmetrical saturated oxime derivatives. They quantitatively separated 17$\beta$-hydroxy-5$\beta$-androstan-3-one oximes into the syn and anti isomers 87 and 88, respectively. The n.m.r. spectrum of pure syn oxime 87 displayed a pair of doublets at about $\tau$7 (intensity one proton) assigned to carbon-4 equatorial hydrogen from the AMX coupling pattern. The n.m.r. spectrum of the anti oxime 88 had a pair of triplets at about $\tau$7 (intensity one proton) assigned to carbon-2 equatorial hydrogen

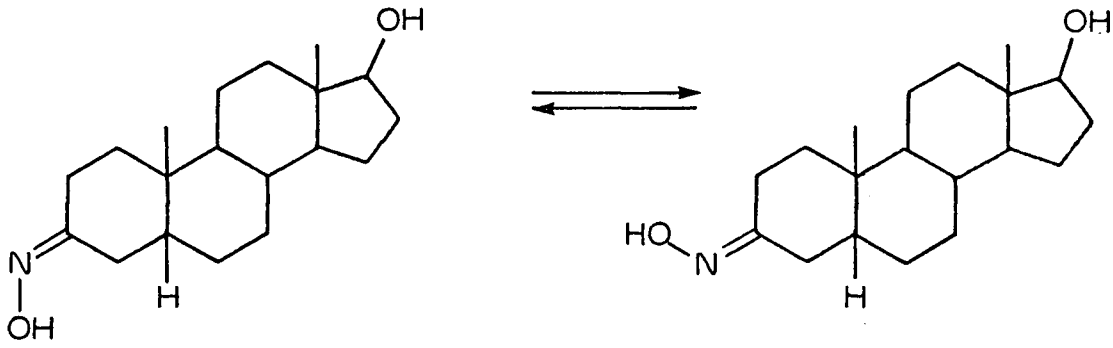
CHART X. Structural Aspects of anti-form oximes




anti-form

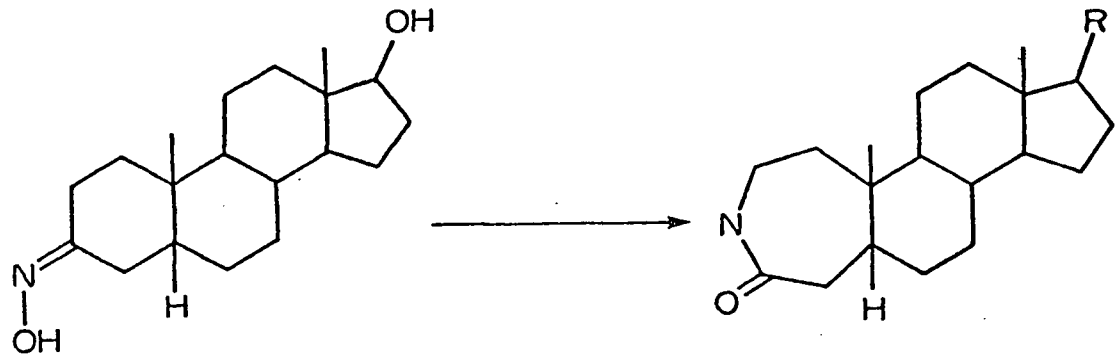



anti-form



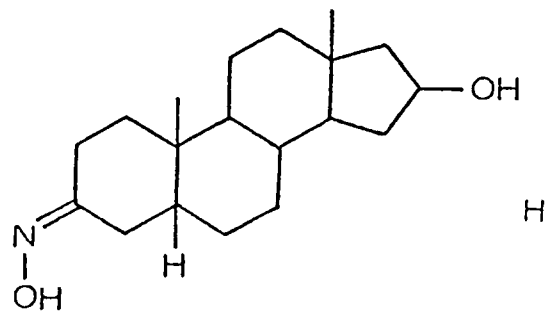

syn 87 anti 88

from the $AMX_2$ coupling pattern. The n.m.r. spectrum of the initial mixture indicated that the syn-anti composition was in accord with the yields obtained after chromatography. Interestingly, the pure syn or anti oxime, 87 or 88, was transformed into a mixture of oximes by heating to their melting points or warming in polar solvents. Furthermore,

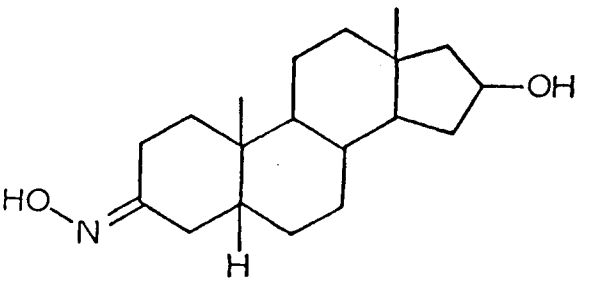



syn 87 82a, R = OH

they effected the stereoselective synthesis of 17β-hydroxyl-3-aza-A-homo-5β-androstan-4-one (82a) via specific Beckmann rearrangement of the pure syn oxime 87 in almost quantiative yield.[53b] Oka and Hara[50a] utilized these results to effect the total synthesis of samanine (8) as




syn 89

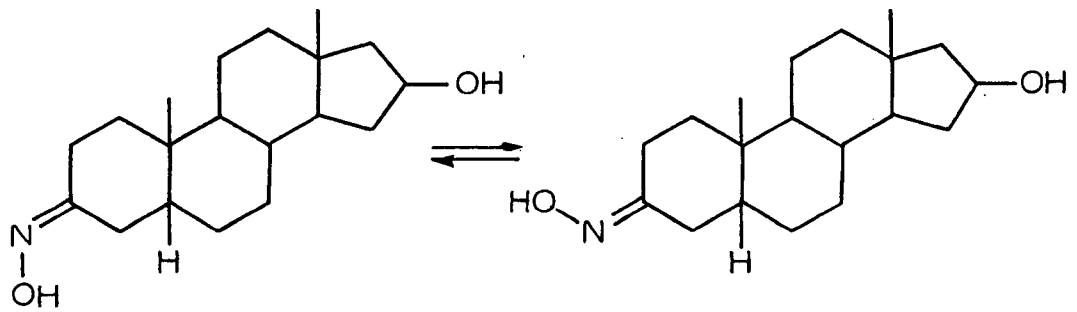



anti 90

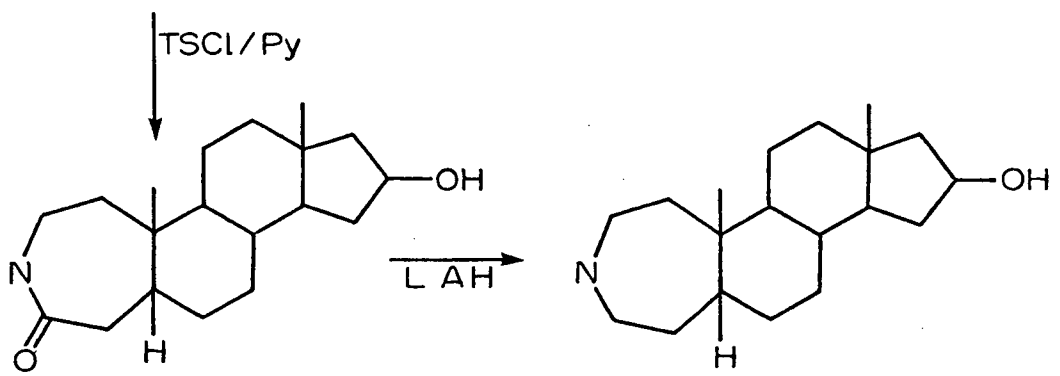
represented in CHART XI (see Page 50). After separation of the oximes 89 and 90 they converted the anti oxime 90 into an equilibrium mixture of syn and anti forms. The syn oxime 89 was obtained in almost quantitative yield from the anti isomer 90 by repetition of this procedure followed by silica gel column chromatography. In contrast, the mixture of lactams 91 and 92 prepared from the oximes 89 and 90 gave a single product on t.l.c. The separation of lactams 91 and 92 proved so difficult that it was not applicable to the specific synthesis of samanine (8). However, Habermehl et al.,[50b] in 1969 reported the separation of both isomers in gram amounts by using alumina. Nevertheless, these results were encouraging insofar as they suggested that the separation of the syn and anti oximes 89 and 90 could be utilized in developing an efficient method to effect ring cleavage in the required fashion. Since Hara and Oka[53a] did not report quantities of material, the reliability and efficiency of their approach was tested on a large scale.

To this end, hydrogenation of testosterone (93) under acidic conditions gave ketones 81a and 94 in ca. a 3:1 ratio as indicated by

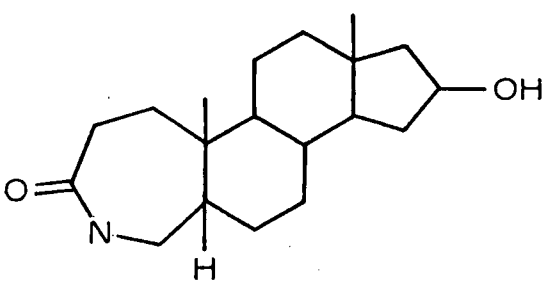
CHART XI. Total synthesis of Samanine (8) [50a]




syn 89 anti 90

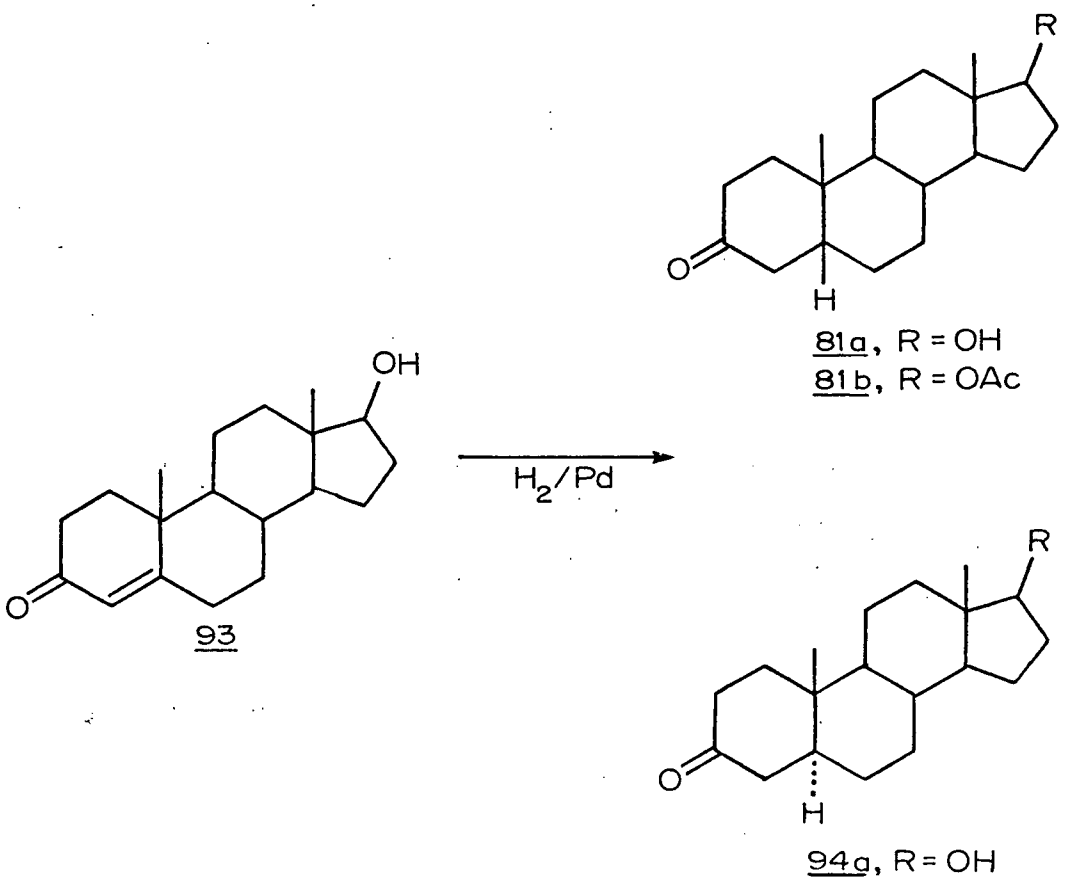



91 8




92

vapour phase chromatography of the acetylated mixture.[42] Several

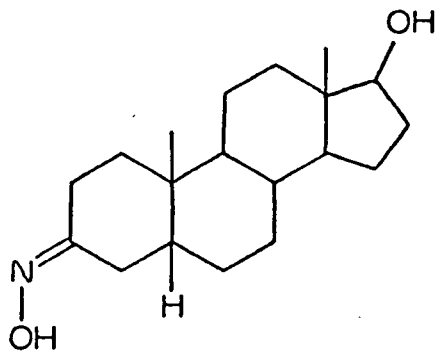



81a, R = OH
81b, R = OAc

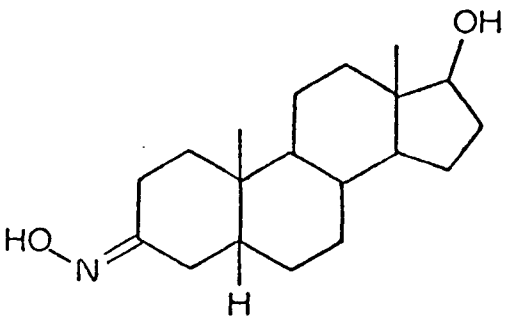
94a, R = OH

recrystallizations afforded ketone 81a in 22% yield as a white crystalline solid, m.p. 138-140° (lit.[54] m.p. 139-140°).

Treatment of ketone 81a with hydroxylamine hydrochloride[49a] and sodium acetate in refluxing methanol for three hours afforded a mixture of oximes 87 and 88, in 60% yield, as a white crystalline solid, m.p. 210-214° (lit.[53a] m.p. 211-213°). Of note was the disappearance in the infrared spectrum of the saturated carbonyl absorption at 1708 $cm^{-1}$ and the appearance of a weak absorption at 1650 $cm^{-1}$




syn 87




anti 88

due to the oxime functionality. The n.m.r. spectrum of the mixture of oximes 87 and 88 had signals at τ9.03 and τ9.27 as two three-proton singlets due to the carbon-19 and carbon-18 tertiary methyl groups, respectively. A one-proton triplet at τ6.35 (J = 9 Hz) was assigned to the proton adjacent to the 17β- hydroxy group and a one-proton multiplet appearing at ca. τ7 could be assigned to the carbon-4 and carbon-2 equatorial hydrogens of the syn and anti isomers 87 and 88, respectively.

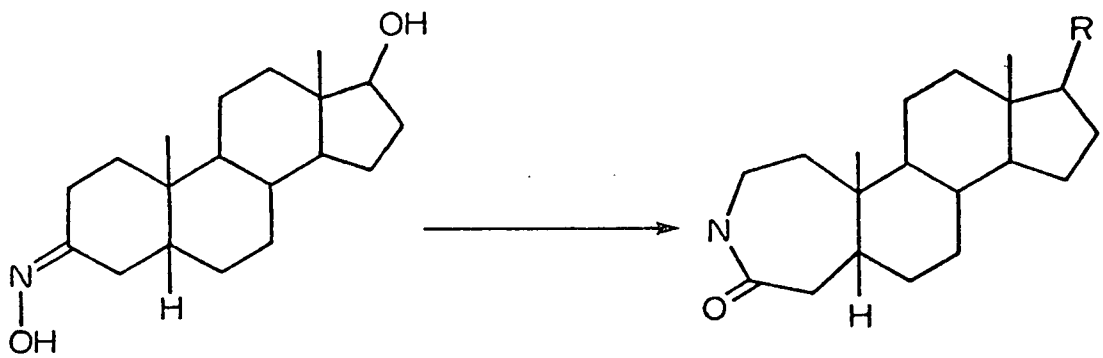
T.L.C. analysis of the reaction product with a variety of solvent systems showed a single spot. However, t.l.c. examination of the product on silica gel with benzene/ethyl acetate (4/1) as the solvent system revealed the presence of two components. Presumably, the syn and anti oximes 87 and 88 had been separated as in accordance with the work of Oka and Hara[53a]. The isolation of the syn and anti oximes was achieved by employing preparative t.l.c. on silica gel. The isolated yields in this case were very low. Attempts were made to separate the oximes 87 and 88 by column chromatography on silica gel.

Elution with benzene/ethyl acetate (4/1) gave a crystalline solid, m.p. 211-213° (lit. [53a] m.p. 211-212°), and a slower moving compound, m.p. 210-213° (lit. [53a] m.p. 211-213°) in ca. a 1:1 ratio.[50a]

However, the n.m.r. spectrum of the first fraction had a one proton unresolved multiplet at ca. $\tau$7 which did not appear to be characteristic of either the syn or anti oximes. In addition, the C-19 and C-18 tertiary methyl groups were clearly evident at $\tau$9.05 and $\tau$9.28, respectively, as two sharp three-proton singlets and a triplet at $\tau$6.40 (J = 9 Hz) was assigned to the proton adjacent to the 17$\beta$- hydroxy group. Similarly, the n.m.r. spectrum of the second fraction displayed a one proton multiplet at ca. $\tau$7 which was not characteristic of either the syn or anti oximes. Further, the n.m.r. spectrum had two sharp three-proton singlets at $\tau$9.05 and $\tau$9.27 due to the C-19 and C-18 tertiary methyl groups, respectively. Hence, n.m.r. spectroscopy indicated that both deuterochloroform solutions contained a mixture of the syn and anti oximes 87 and 88. It appeared that isomerization had taken place in the n.m.r. tube. Even more annoying was the knowledge that they were insoluble in carbon tetrachloride, benzene,and other non-polar solvents in which isomerization would not be expected to occur. At this stage, it appeared that n.m.r. spectroscopy was not an effective means to distinguish between the syn and anti oximes 87 and 88. In summary, our results indicated that the chromatographic separation of the syn and anti oximes 87 and 88 was not amenable to large scale preparations.

However, since about 200 mg. of the separated syn and anti oximes 87 and 88 had been obtained by small scale column chromatography, it was decided to attempt the Beckmann rearrangement of the syn oxime 87.[50a,53b]

Toward this end, treatment of syn oxime 87 with three molar equivalents of p-toluenesulphonyl chloride in about 200 molar equivalents of dry pyridine at room temperature for two days afforded lactam 82a in 65% yield. A small sample was recrystallized to constant m.p. 241-242°




syn 87 — 82a, R = OH

(lit. [53b] m.p. 242-244°). The crude reaction product was homogeneous on t.l.c. (silica gel and alumina). The infrared spectrum of the crude product indicated that the Beckmann rearrangement had indeed occurred. Thus, the infrared spectrum of 82a had a strong absorption at 1660 $cm^{-1}$ due to the lactam carbonyl and a broad absorption at 3440 $cm^{-1}$ due to the 17β- hydroxy group and the NH stretching vibration of the lactam group. Anti oxime 88 in acetone at room temperature was converted into an equilibrium mixture of syn and anti forms as evidenced by t.l.c. on silica gel with the appropriate solvent system. Because of the difficult chromatographic separation of the syn and anti oximes 87 and 88 no attempt was made to recover the syn oxime 87 from the anti oxime 88 by using silica gel chromatrography. Although the Beckmann rearrangement had been effected this particular type of approach was rejected because of the poor overall yield of lactam 82a based on ketone 81a,

coupled with the difficult chromatographic separation of the syn and anti oximes 87 and 88, respectively,

At this point, Uskoković and his colleagues[55] reported a new and highly promising fragmentation reaction (see CHART XII, Page 56 ). They found that pyrolysis of N-nitrosolactam 96 at 125° afforded the diazolactone 97,[56] which fragmented with extrusion of nitrogen to give a mixture of compounds 98 and 99 in 50 and 30% yield, respectively, Uskoković and his colleagues[55] rationalized the formation of these products by invoking two different concerted fragmentation paths a and b. Path a, could probably be initiated by abstraction of the C-11 hydrogen by either one of the ester oxygens which could afford acid 98 (R = H). Path b, could be envisaged as a nucleophilic attack of one of the ester oxygens on the C-10 carbon to give lactone 99. They proceeded to transform lactone 99 to ester 98 (R = OMe) via the hydroxy acid 100 in five simple steps.

Consequently, it was hoped that lactam 82a could be converted into olefinic ester 104a as depicted in Chart XIIIa (see Page 57 ). Such a sequel represents the unsymmetric cleavage of the 2,3 bond with incorporation of an olefinic bond as in accordance with the general plan. The first problem associated with such a sequel involved the separation of lactams 82a and 83a. However, separation of the isomeric lactams on silica gel proved futile. Only partial separation could be achieved by using alumina.[50b,57] Others have found difficulties with the separation of 4-aza- and 3-aza-lactams.[50a] This

CHART XII. Pyrolysis of N-nitrosolactam 96 [55]

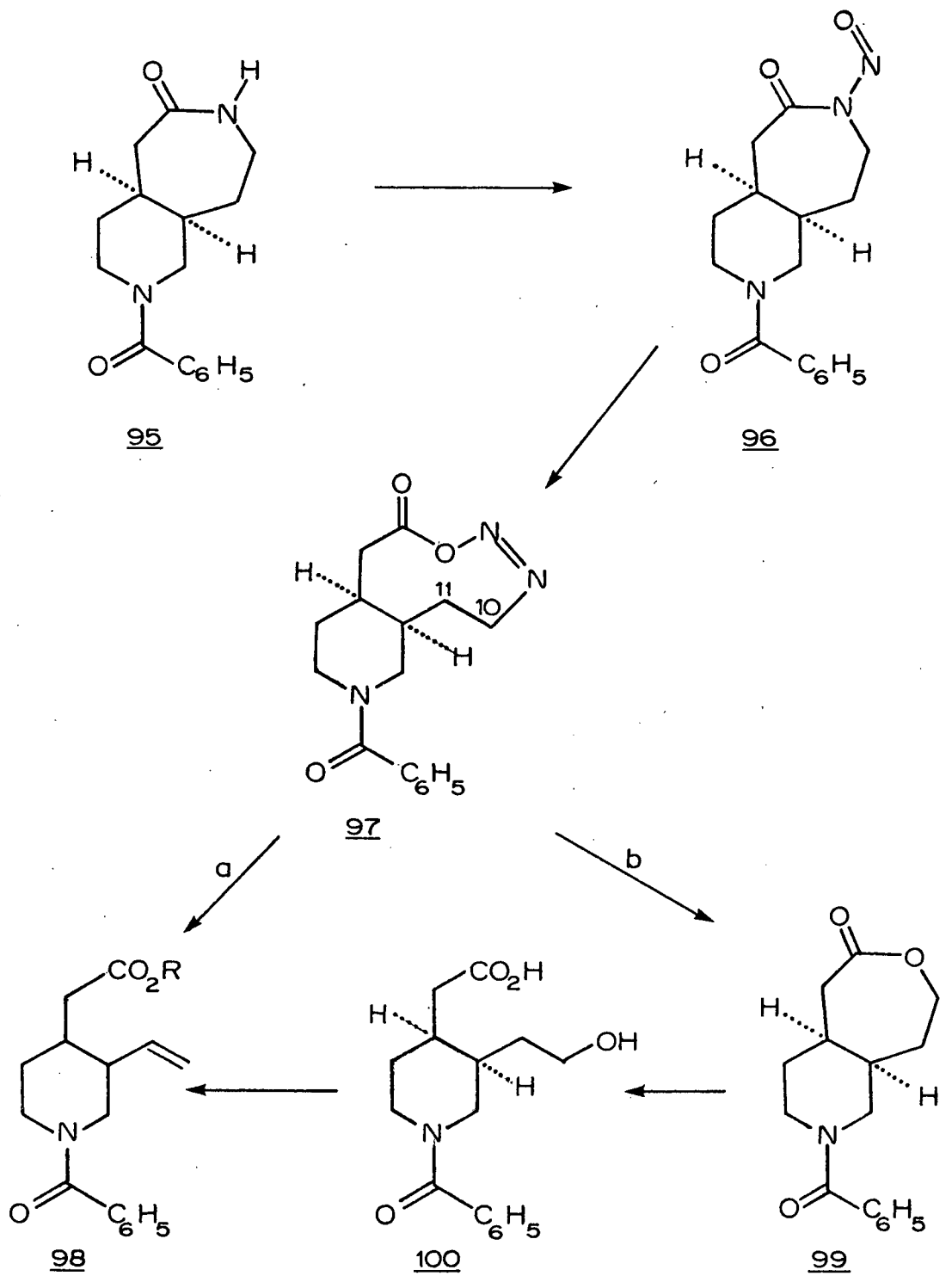
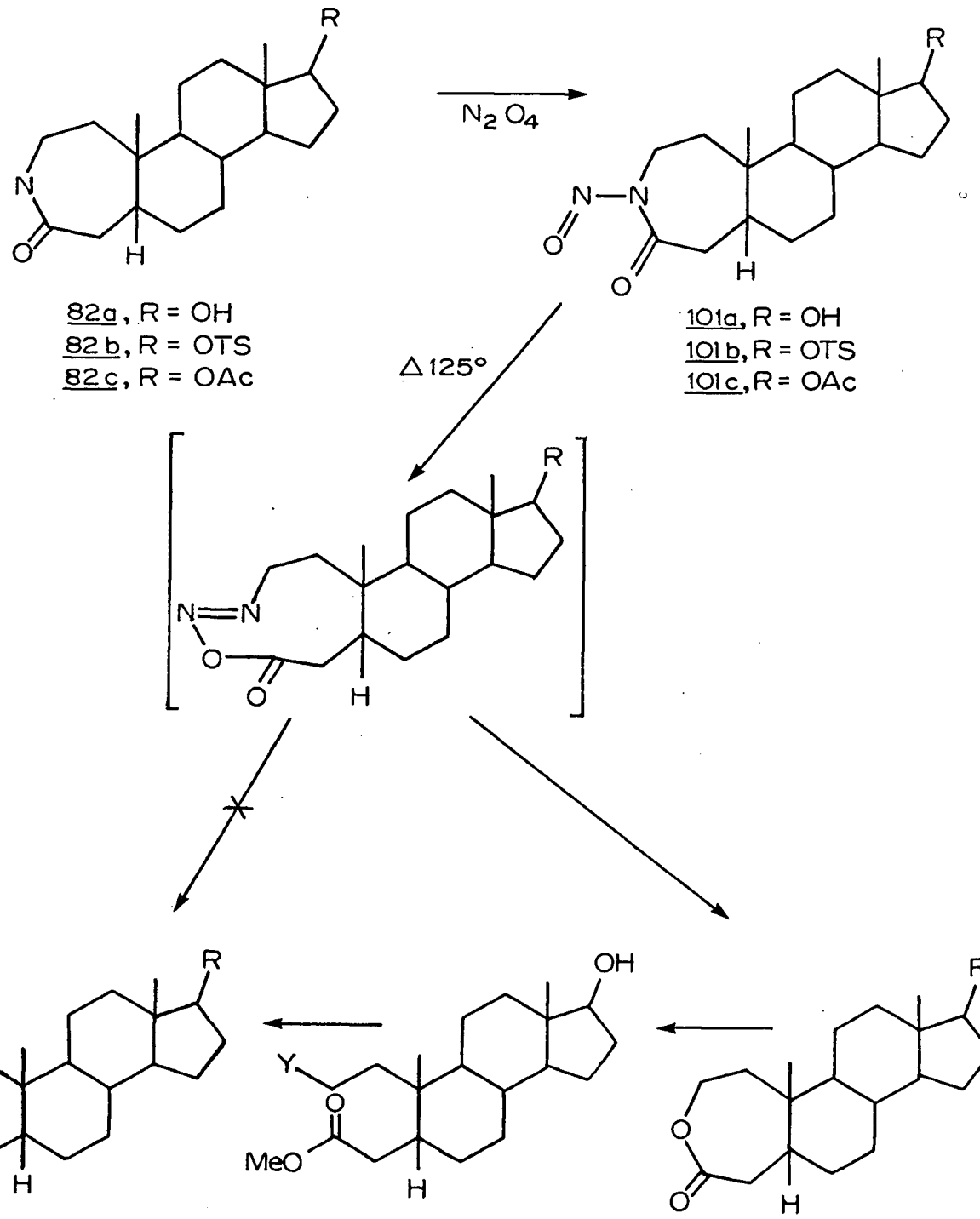
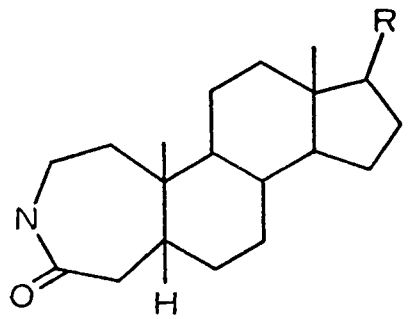
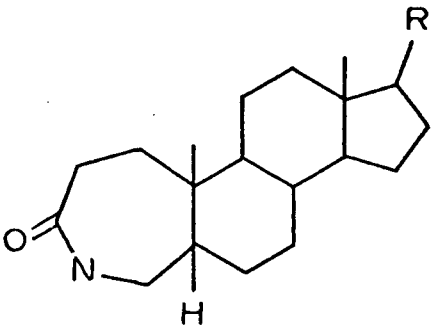


CHART XIIIa. N-nitrosolactam Investigations





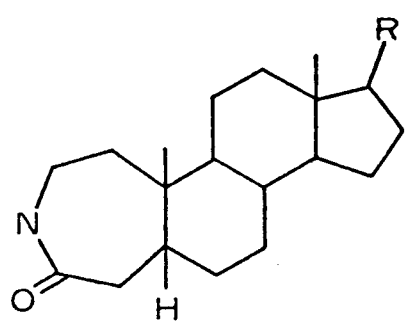
82a, R = OH



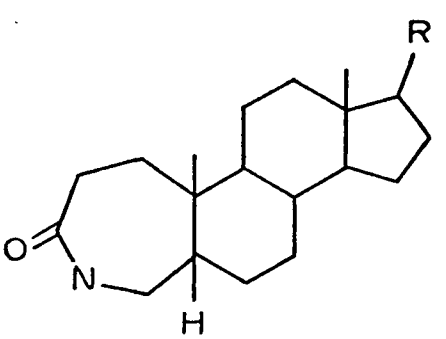
83a, R = OH

chromatographic study was not pursued any further since the thermal fragmentation reaction was the "key" feature of this approach.

It was decided to launch synthetic investigations with the mixture of lactams 82a and 83a and it was felt that if a suitable route was established by utilizing the mixture of lactams 82a and 83a it would be applicable to lactam 82a. Treatment of the mixture of oximes 87 and 88 with three molar equivalents of p-toluenesulphonyl chloride in about 200 molar equivalents of dry pyridine at room temperature for five days afforded lactams 82b and 83b, in 65% yield, as a white crystalline solid, m.p. 200-202°. The product was homogeneous on t.l.c. (silica gel).



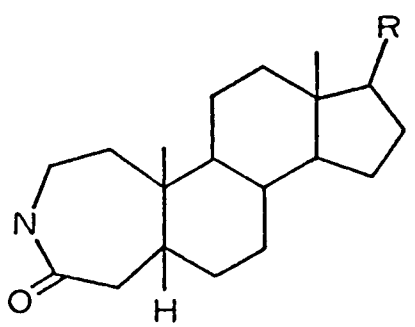
82b, R = OTS



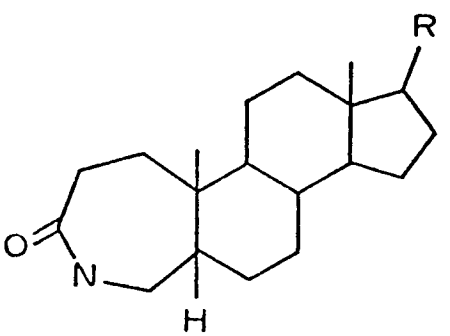
83b, R = OTS

In addition, the spectral properties of the mixture of lactams 82b and 83b were in accord with the assigned structures. Thus, the infrared spectrum of compounds 82b and 83b showed strong absorptions at 1190 $cm^{-1}$ (doublet) due to the tosylate group and at 1660 $cm^{-1}$ due to the lactam carbonyl. A weak absorption was evident at 3400 $cm^{-1}$ due to the N-H stretching vibration of the secondary amide. The n.m.r. spectrum of the mixture of lactams had three three-proton singlets at τ9.20, τ9.0, and τ7.53 due to the C-18, C-19 tertiary methyl groups, and the 17β-tosyl methyl group, respectively. Other assignable signals in the n.m.r. spectrum appeared at τ5.70 as a one-proton triplet (J = 10 Hz) due to the C-17 proton and at τ3.50 one exchangeable proton. A AB pair of doublets (J = 8 Hz) appeared at τ2.64 and τ2.17 due to the four aromatic protons of the 17β-tosylate group. Finally, the mass spectrum had a molecular ion peak at $\frac{m}{e}$ 459.

In view of the previous work it was annoying and somewhat surprising to realize that the 17β- hydroxy functionality had been converted into a tosylate group.[50a] Repeating the Beckmann rearrangement several times under various conditions revealed that tosylation always occurred when working with greater than 200 mg quantities of oximes 87 and 88. With considerable quantities of lactams 82b and 83b on hand, it

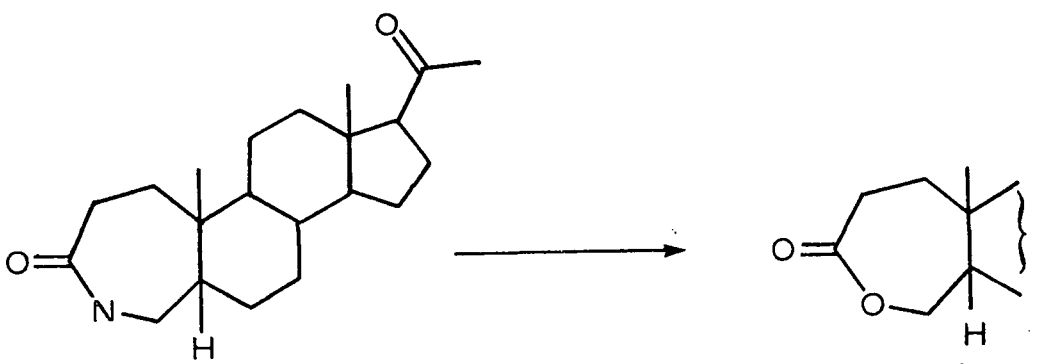



82b, R = OTS



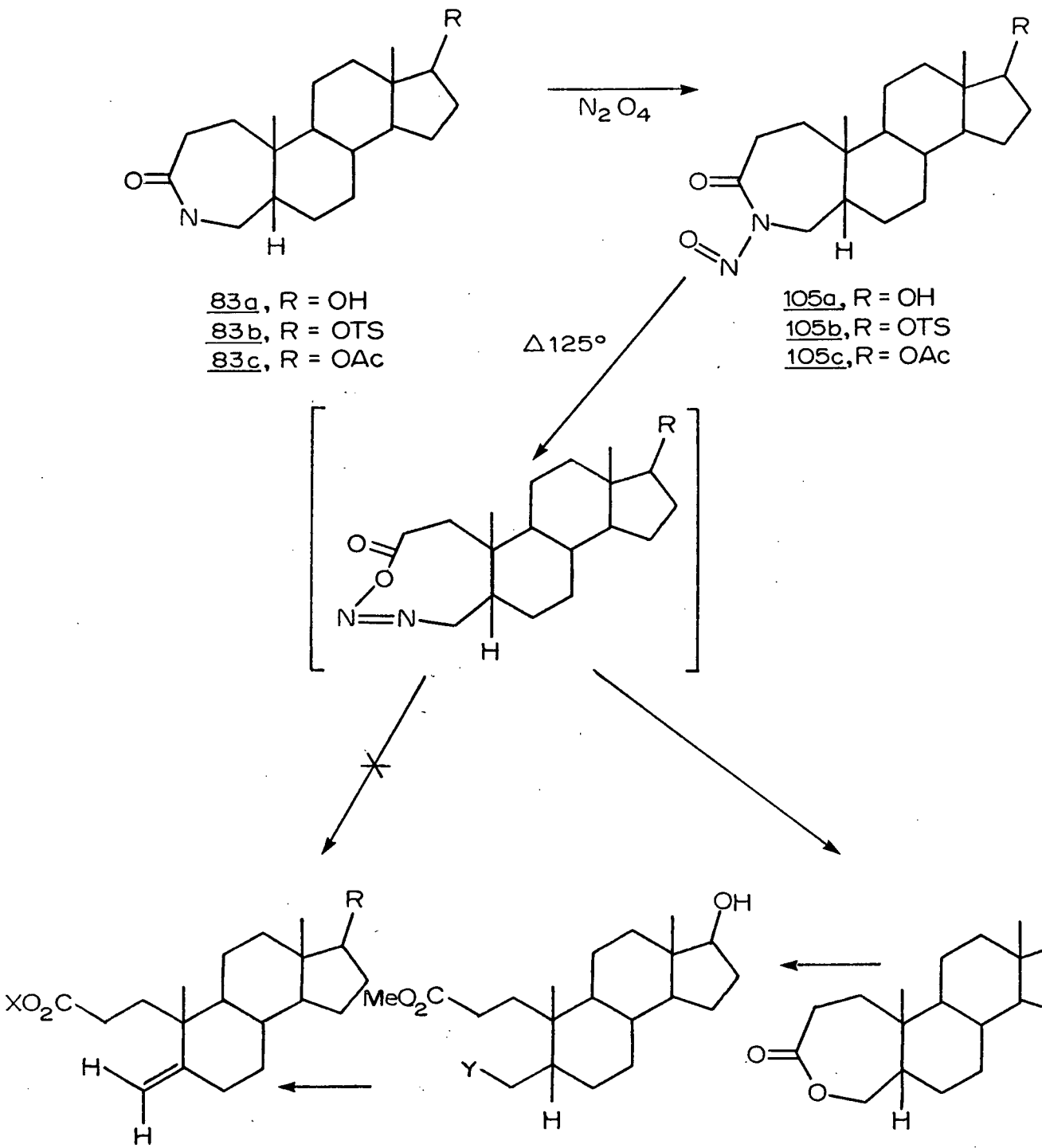

83b, R = OTS

was decided to continue our studies with these substances hoping at a later stage to reintroduce the 17β- hydroxy group. Thus, treatment of lactams 82b and 83b with dinitrogen tetroxide afforded in quantiative yield a mixture of N-nitrosolactams 101b and 105b as an unstable yellow powder (CHARTS XIIIa and XIIIb, Pages 57 and 61).[58] Of note was the disappearance in the infrared spectrum of the weak band at 3400 $cm^{-1}$ and the appearance of strong absorptions at 1720 $cm^{-1}$ (N-nitrosolactam) and 1415 $cm^{-1}$ (Nitroso). T.L.C. analysis of the crude reaction product revealed the presence of one broad spot. The time was now at hand to test the feasibility of the anticipated fragmentation reaction. In the event, pyrolysis of a small sample of the mixture of N-nitrosolactams 101b and 105b at 125° for two minutes afforded two major products as indicated by t.l.c. analysis. When the pyrolysis was carried out with larger amounts of material the results were quite reproducible. The infrared spectrum of the crude reaction product displayed a strong absorption at 1720 $cm^{-1}$. The n.m.r. spectrum of the crude product indicated the absence of olefinic protons. Finally, the mass spectrum showed a molecular ion peak at $\frac{m}{e}$ 460. This spectroscopic data coupled with previous work in this area, tended to suggest that lactones 102b and 106b were being formed.[56,59,60] For example, Nace et al.,[60] converted lactam 109 to lactone 110 by employing a procedure analagous to that used by White.[59a] The formation of the




109 110

CHART XIIIb. N-nitrosolactam Investigations




83a, R = OH
83b, R = OTS
83c, R = OAc

105a, R = OH
105b, R = OTS
105c, R = OAc

108a, R = H; X = Me
108b, R = OTS; X = Me
108c, R = OAc; X = Me
108d, R = OTS; X = H

107a, Y = OH
107b, Y = OTS
107c, Y = I

106a, R = OH
106b, R = OTS
106c, R = OAc

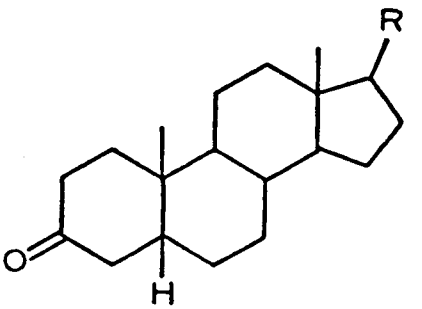
lactones 102b and 106b was confirmed by the fact that the products from the pyrolysis reaction could be correlated with the lactones derived from the Baeyer-Villiger oxidation of the appropriate 3-oxo-5β-steroid.[51,61]

Since the olefinic acids 104d and 108d (CHARTS XIIIa and XIIIb, Page 57 and 61) were not being generated it was decided to study the fragmentation reaction under various conditions in order to suppress the formation of the lactones and induce the desired fragmentation. At lower temperatures the reaction was too slow to be of any utility. At elevated temperatures several side products emerged which thwarted the isolation of the major components in a high state of purity. After trying several chromatographic systems two side products were isolated which did not display any olefinic character. In addition, the fragmentation reaction was effected in various solvents, for example, toluene, dimethylformamide, and hexamethylphosphoramide. The addition of acid to the reaction medium did not alter the mode of fragmentation but tended to furnish more undesirable contaminants. In summary, by varying reaction conditions attempts to produce olefinic acids 104d and 108d were to no avail. Essentially the reaction products always consisted of lactones 102b and 106b. It became clearly apparent that the most efficient method to obtain these type of compounds would be via the Baeyer-Villiger oxidation[62] of the appropriate 3-oxo 5β-steroid. Lactone 102c could then be converted to the olefinic ester 104a by employing procedures analogous to the work of Uskoković and his colleagues.[55]

Before proceeding to investigate the Baeyer-Villiger approach, experiments were carried out to convert the 17β-tosylate group into the 17β- hydroxy functionality in order to perform the necessary chemical correlation. However, the removal of the tosylate group was found to be

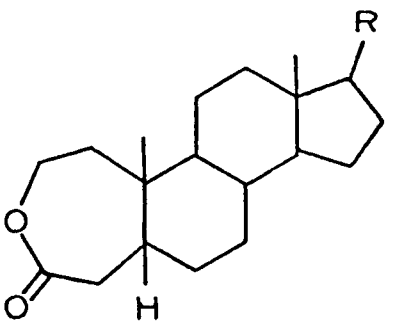
a formidable task. Under mildly basic conditions, for example, the lactones suffered ring opening. Unfortunately, attempts to remove the tosylate group by employing more drastic methods only led to ill-defined products bearing a tosylate group. In order to circumvent these difficulties it was proposed to mask the 17β- hydroxy group as an acetate functionality at the beginning of the sequence. As a result, N-nitrosolactam acetates 101c and 105c were prepared (CHARTS XIIIa and XIIIb, Pages 57 and 61 ). The infrared spectrum of 101c and 105c had strong absorption bands at 1720 $cm^{-1}$ due to the N-nitrosolactam carbonyl and the 17β- acetate functionality. The nitroso bands were evident between 1385 and 1360 $cm^{-1}$. As before, the thermal fragmentation of compounds 101c and 105c gave the mixture of lactones 102c and 106c. The infrared spectrum of 102c and 106c had a band at 1720 $cm^{-1}$ due to the lactone carbonyl and the 17β- acetoxy group. Of note was the disappearance of the nitroso bands at 1385 $cm^{-1}$ and 1360 $cm^{-1}$. The n.m.r. of 102c and 106c had two three-proton singlets at τ9.20 and τ8.97 due to the carbon-18 and carbon-19 tertiary methyl groups, respectively, and a three proton multiplet (between τ6.20 - τ5.20) could be attributed to the proton adjacent to the 17β- acetoxy group and the methylene protons adjacent to the lactone oxygen atom in the "A" ring. The mass spectrum of the mixture of lactones 102c and 106c had a molecular ion peak at $\frac{m}{e}$ 348.

Having obtained lactones 102c and 106c the Baeyer-Villiger oxidation of ketone 81b was carried out. Burckhaldt and Reichstein[61c] reported that Baeyer-Villiger oxidation of 3-oxo 5β-steroids gave a single lactone, namely, a 3-oxo-4-oxa-A-homo compound. On the other hand Hara and his colleagues[61b] re-examined the Baeyer-Villiger oxidation

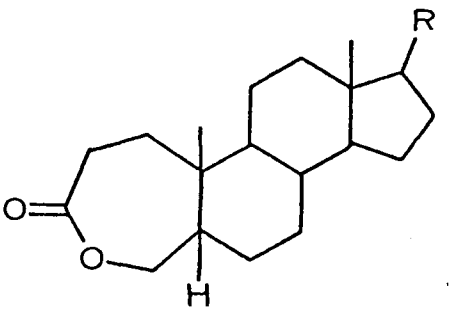



81b, R = OAc

of 3-oxo 5β-steroids and showed that the resulting product was a mixture of lactones although the infrared spectrum and other physical constants of the product seemed to suggest it to be a single compound. Evidence for it being a mixture were provided by the hydrolysis of the lactone, esterification with diazomethane, oxidation with chromium trioxide and separation of the diacid by partial esterification in the presence of a dilute acid. They studied the action of perbenzoic acid on 17β-acetoxy-5β-androstan-3-one (81b) and found that both lactones 102c and 106c were formed but they did not report yields (CHART XIV, Page 65 ). Reinvestigating the Baeyer-Villiger oxidation of ketoacetate 81b with m-chloroperbenzoic acid in chloroform for two days at room temperature gave a mixture of lactones 102c and 106c in 85% yield as a white crystalline solid, m.p. 118-125°. A small sample was recrystallized from methanol

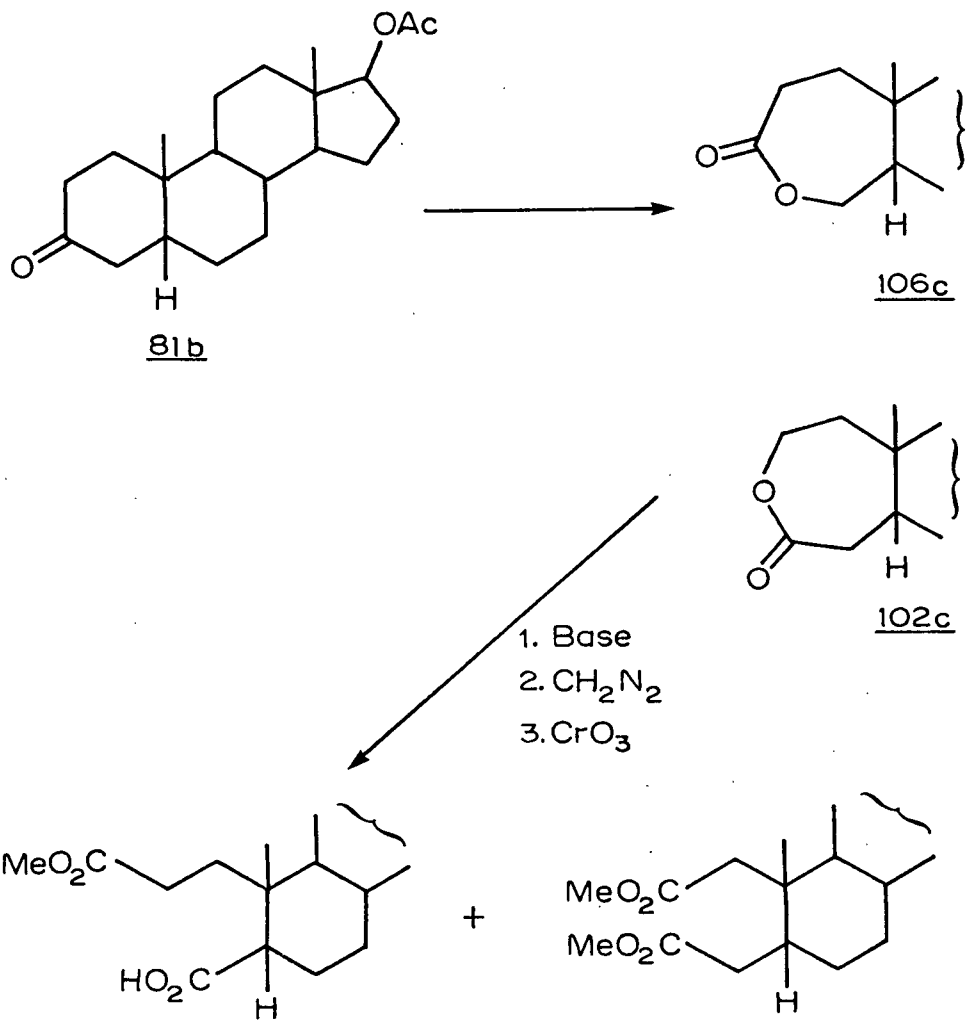



102c, R = OAc

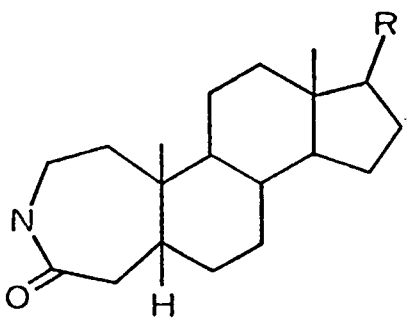



106c, R = OAc

CHART XIV. Baeyer-Villiger Investigations [61b]



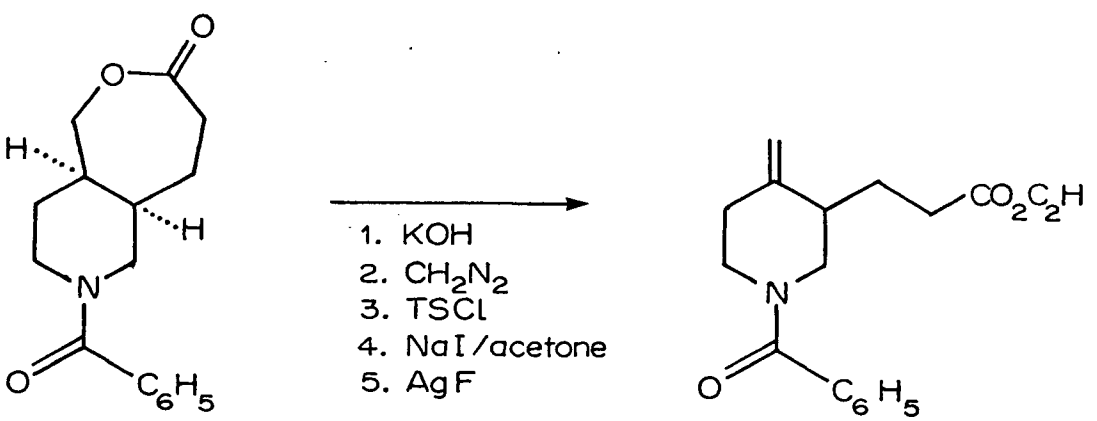
m.p. 207-208°, for analysis. The infrared and n.m.r. spectral properties of the crude lactones were identical with the products derived from the thermal fragmentation reaction (CHART XIIIa and XIIIb, Pages 57 and 61 ). In addition, their thin layer and vapour phase chromatographic behaviour were identical. The v.p.c. showed that the Baeyer-Villiger oxidation product was a mixture of lactones in ca. a 4:1 ratio,[61b] while the corresponding mixture from the fragmentation reaction exhibited ca. a 2:3 ratio.[53a] Thus, these results indicated that the proposed synthetic scheme as outlined in CHART XIIIa had proved unproductive. The synthetic pathway suffers from two major drawbacks. Firstly, the availability of pure lactam 82a appeared to offer a difficult problem. The economy of




82a, R = OH

this process was not attractive. Secondly, the central feature of the sequel proved unpromising since the olefinic esters 104c and 108c were not formed by the thermal fragmentation reaction and instead only lactones 102c and 106c were obtained (CHARTS XIIIa and XIIIb, Pages 57 and 61 ). It was, therefore, decided to abandon this type of approach. As previously noted, however, an alternate method evolved from these studies, namely, the possibility of utilizing lactone 102c. In view of the distribution

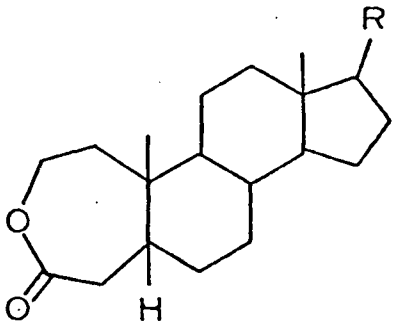
of the isomeric lactones in the crude Baeyer-Villiger oxidation product the most pressing problem was to ascertain the structure of the major lactone. Undoubtedly, this result would determine the validity of the Baeyer-Villiger approach. In fact, the structural problem was solved by taking advantage of part of the synthetic plan (CHART XIIIa, 102c → 104a, Page 57). This also provided the opportunity to test part of the proposed synthetic pathway. Uskoković and his colleagues[55] proved structure 111 by the degradation into the olefinic ester 112. In the



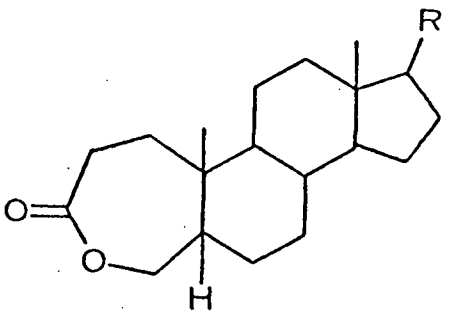

111 112

sequel (CHART XIIIa, Page 57), lactone 102c would afford 104a. On the other hand lactone 106c would furnish 108a (CHART XIIIb, Page 61). Attempts to develop a practical chromatographic method for effecting

the separation of lactones 102c and 106c proved unrewarding. For example,



102c, R = OAc



106c, R = OAc

separation by preparative t.l.c. on silica gel or alumina with various solvent systems gave at the very best only partial separation. Similarly, with lactones 102a and 106a only partial separation could be achieved. However, after several fractional crystallizations separation of 102c and 106c was achieved as evidenced by t.l.c. and v.p.c. examination, but this method was rejected because of poor yields. Inevitably, the proposed chemical operations would have to be performed on the mixture of lactones 102c and 106c. It was now hoped that the resulting mixture of olefinic esters 104a and 108a would be more amenable to chromatographic separation.

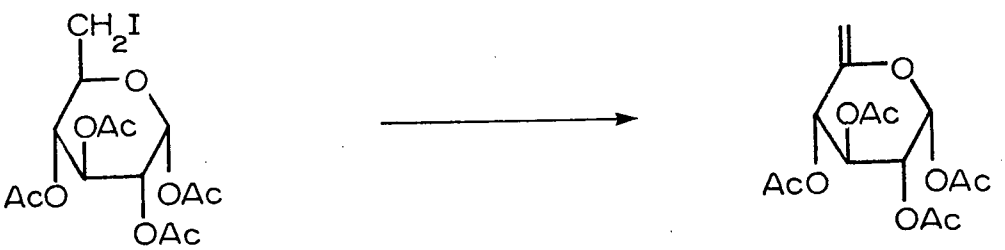
Ring opening of the lactones 102c and 106c was effected by treating the mixture with 5% sodium hydroxide in refluxing methanol for two hours. The reaction mixture, after work up, was esterified with diazomethane to afford the hydroxy methyl esters 103a and 107a, in 75% yield, as an oil (CHARTS XIIIa and XIIIb, Pages 57 and 61 ). The spectroscopic data of this material were in accord with the assigned structures. The pertinent spectral features in the n.m.r. were as follows: singlets were evident at $\tau$9.02 and $\tau$8.93 due to the C-19

tertiary methyl groups of hydroxy methyl esters 103a and 107a, respectively, in an approximate ratio of 1:3. In contrast, the C-18 tertiary methyl groups appeared as a singlet at τ9.27 for each compound. In addition, a singlet and multiplet at τ6.32 and τ6.35 (totalling six protons) could be attributed to the methyl ester functionality and the protons adjacent to the hydroxy groups, respectively, in compounds 103a and 107a. Finally, the mass spectrum indicated a molecular ion peak at $\frac{m}{e}$ 338.

Tosylation of the crude hydroxy methyl esters 103a and 107a with tosyl chloride in pyridine, at room temperature,[64] afforded the tosyloxy esters 103b and 107b (CHARTS XIIIa and XIIIb, Pages 57 and 61). The spectral data of 103b and 107b were in agreement with the assigned structures. Thus, the infrared spectrum of 103b and 107b displayed an absorption band at 1190 $cm^{-1}$ (doublet) due to the tosylate functionality and a broad absorption band was evident at 3400 $cm^{-1}$ due to the 17β-hydroxy group. The n.m.r. spectrum of 103b and 107b exhibited a four-proton AB pair of doublets at τ2.68 and τ2.20 (J = 9 Hz) and a three-proton singlet at τ7.55 which could be attributed to the tosylate functionality. In addition, the methylene protons adjacent to the tosylate group was evident as a two-proton multiplet at τ5.90. Finally, the mass spectrum indicated a molecular ion peak at $\frac{m}{e}$ 492.

The next step in the projected synthesis involved the substitution of the tosylate group with iodide[65]. However, this reaction proved more difficult than had been anticipated. Treatment of the tosyoxy esters 103b and 107b with 5% sodium iodide in acetone at room temperature for twenty-four hours under $N_2$ returned copious amounts of starting material. After considerable experimentation it was found that the

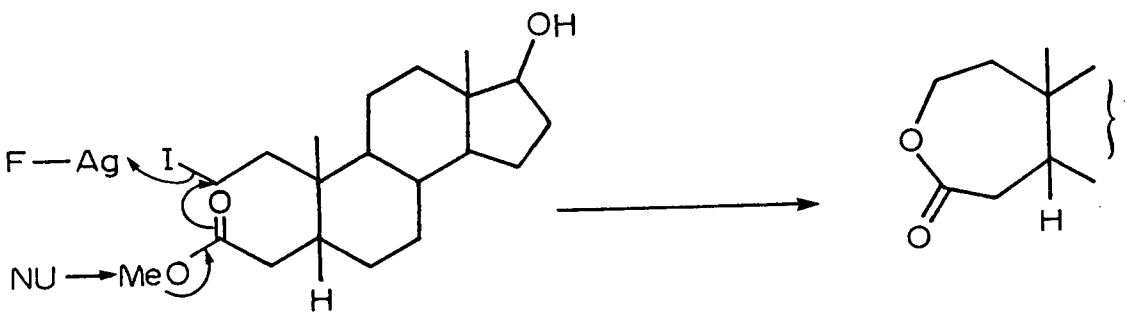
reaction time, temperature, and concentration of sodium iodide were most critical in this reaction. Thus, treatment of tosyloxy esters 103b and 107b with 10% sodium iodide in refluxing acetone for sixty hours under $N_2$ and protected from light furnished the iodo esters 103c and 107c as a yellow oil in fair yield (CHARTS XIIIa and XIIIb, Pages 57 and 61). T.L.C. examination of the crude reaction product revealed one broad spot with baseline contaminants. The mass spectrum indicated a molecular ion peak at $\frac{m}{e}$ 464 and a prominent peak at $\frac{m}{e}$ 337. Hence, the introduction of iodide has been achieved. Uskoković and his colleagues,[55] and others[66] have found that the action of silver fluoride in pyridine on primary iodides effects the elimination of hydrogen iodide. For example, treatment of iodide 113 with silver fluoride in pyridine affords olefin 114 in good yield.[66b]




113 114

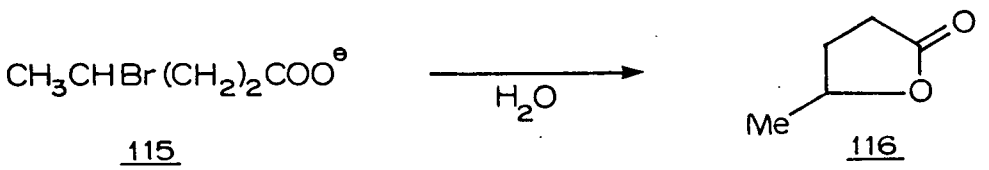
Experiments were carried out to generate the olefinic esters 104a and 108a from iodo esters 103c and 107c by employing silver fluoride in pyridine. This reaction, however, took an unexpected course which was in marked contrast to the work of Uskoković and his colleagues.[55] The olefinic esters 104a and 108a were not isolated but an isomeric mixture of

lactones which was chromatographically and spectroscopically identical with lactones 102a and 106a (CHARTS XIIIa and XIIIb, Pages 57 and 61 ). Presumably, a nucleophilic attack by one of the ester oxygens had occurred on carbon 2 with displacement of iodide in a $S_N2$ type fashion to afford lactones 102a and 106a. Furthermore, silver



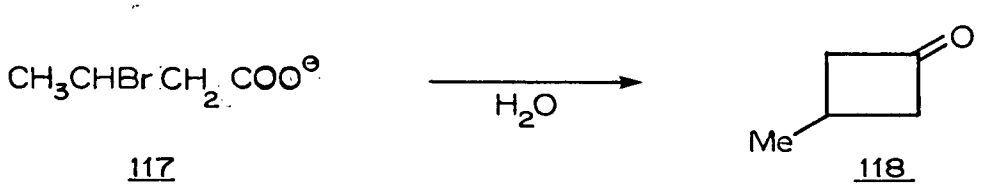

103c 102a

fluoride could facilitate in the removal of the iodide. It is noteworthy that the nature of neighbouring group reactions was first elucidated through experiments involving participation of the carboxylate groups, particularly through studies of the hydrolysis and alcoholysis of the anions derived from α-halocarboxylic acids.[67] As the distance between the halogen atom and the carboxylate group is increased, the cyclic structure involved in direct intramolecular displacement becomes much less strained and reaction by displacement becomes favoured. Thus the conversion of γ-bromovalerate 115 in water to the five-membered ring lactone 116 proceeds by direct displacement,[68a] and the same is probably true for the formation of β-butyrolactone 118.[68b] Interestingly, as is the case with other types of cyclization, formation of rings of seven or more members entails some difficulty, due to the low probability

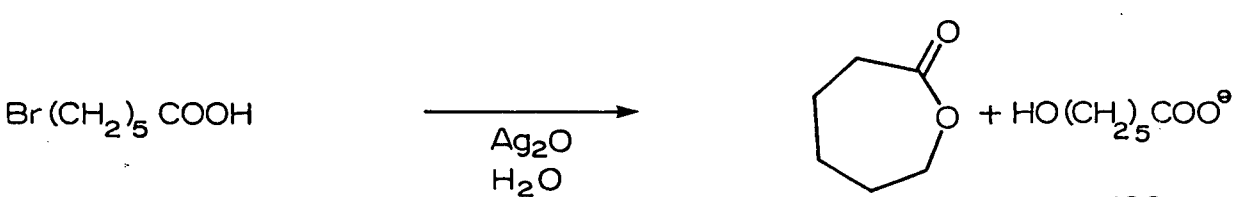



115 116

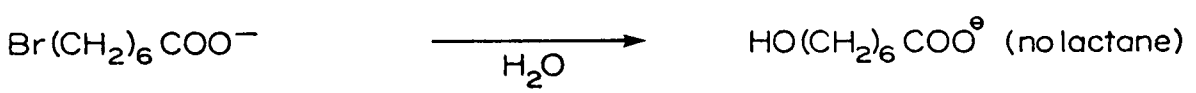
for collision between the opposite ends of a long chainlike molecule. When ε-bromocaproic acid (119) is treated with $Ag_2O$ in water, ordinary solvolysis to give the ε-hydroxy acid 120 competes with neighbouring-group participation.[68c] Anion 121 gives only a hydroxy acid.[68d] Whether




117 118




119 120



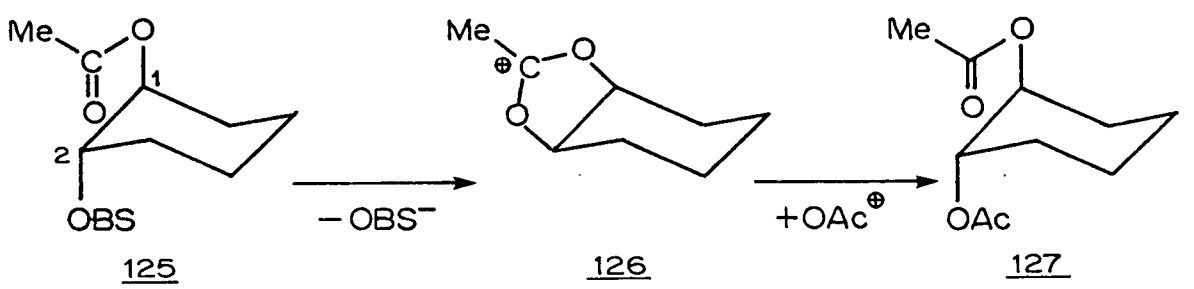

121 122

or not an ester linkage functions as a neighbouring group depends largely upon how it is situated with respect to the reaction centre in the substrate. The solvolysis of bromo ester 123 and the deamination of amino ester 124 result in inversion of configuration about the α-carbon, suggesting that there is negligible participation by the ester group when the reaction centre is alpha to the carbonyl of the ester. On the other hand,

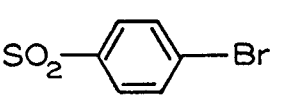
$CH_3CHBrCOOEt$ — 123

$CH_3CH(NH_2)COOEt$ — 124

ester participation has been observed in a number of substitutions in which the reaction centre gives rise to an intermediate containing a five-membered ring . For example, the reaction of trans-2-acetoxycyclohexyl tosylate (125) with acetate in glacial acetic acid gives trans-1,2-diacetoxycyclohexane (127). The product is not the cis-diacetate which



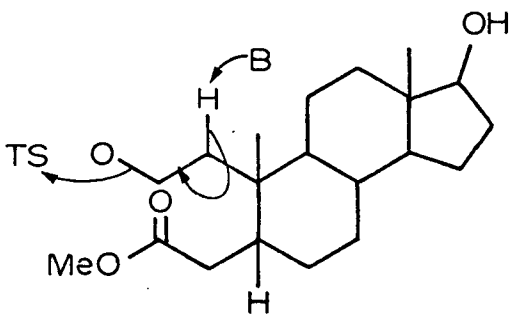

125 126 127

BS = 

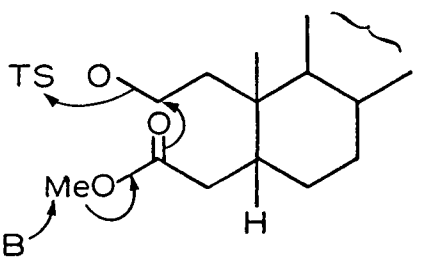
would be expected if acetate ion attacked the ring on one side while the tosylate ion departed from the other. The predominant product is the trans-diacetate 127, indicating that the acetoxy group is capable of preserving the configuration about a carbon atom 2 while this centre is subject to nucleophilic attack.[69] The proposed intermediate is the cyclic carbonium ion 126 which may suffer attack at carbon-1 or carbon-2. In either case, the trans diacetate 127 should result. On the basis of these results it appeared reasonable to presume that the seven membered lactones 102a and 106a (CHARTS XIIIa and XIIIb, Pages 57 and 61 ) had been formed by intramolecular displacement of iodide by one of the oxygens of the ester group.

By utilizing the tosyloxy esters 103b and 107b (CHARTS XIIIa and XIIIb, Pages 57 and 61 ) in a base catalyzed elimination it was hoped that the difficulties attendant with iodides 103c and 107c would be overcome. However, it is possible that a base catalyzed ring closure as outlined in CHART XV (see Page 75 ) or the displacement of the tosylate functionality by a nucleophilic reagent could occur. With regard to this latter reaction it is in order to consider the effects of changes in the base and medium on elimination versus substitution.[70] Strong bases benefit elimination as against substitution. With a high concentration of strong base in a nonionizing solvent, bimolecular mechanisms are favoured, and E2 predominates over $S_N2$. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favoured, and the $S_N1$ mechanism predominates over the E1. Some anions which do not promote elimination in protic solvents, where they are surrounded by a solvent shell, do so in aprotic solvents,

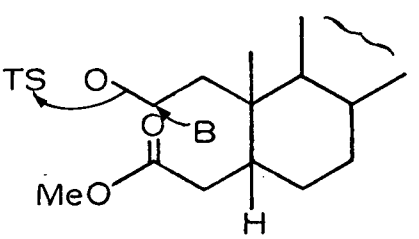
CHART XV. Possible effects of a base on tosyloxy ester 103b




103b'

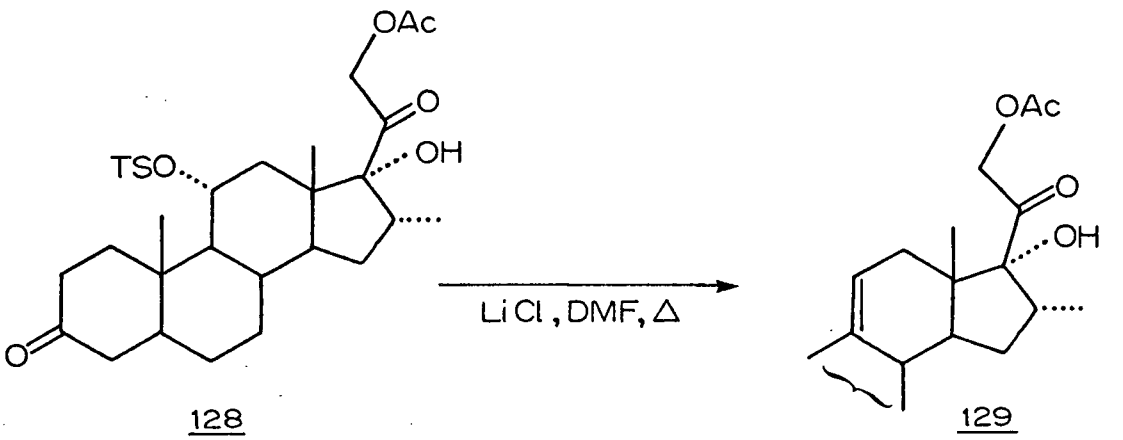



103b''



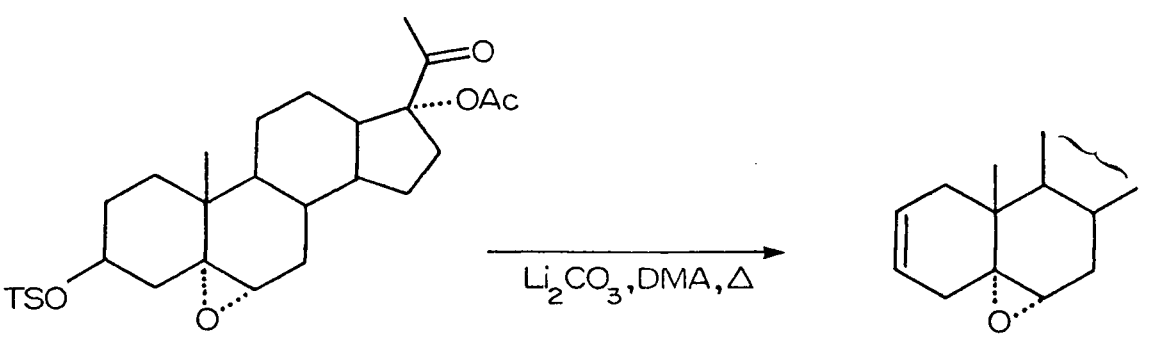

103b'''

where their affinity for protons is not satisfied by the solvent. For example, lithium chloride in dimethylformamide dehydrohalogenates many compounds. Ehmann and his colleagues[71] found that treatment of tosylate 128 with lithium chloride in dimethylformamide afforded olefin 129 in good yield. In addition, Berkoz and his colleagues[72] demonstrated that



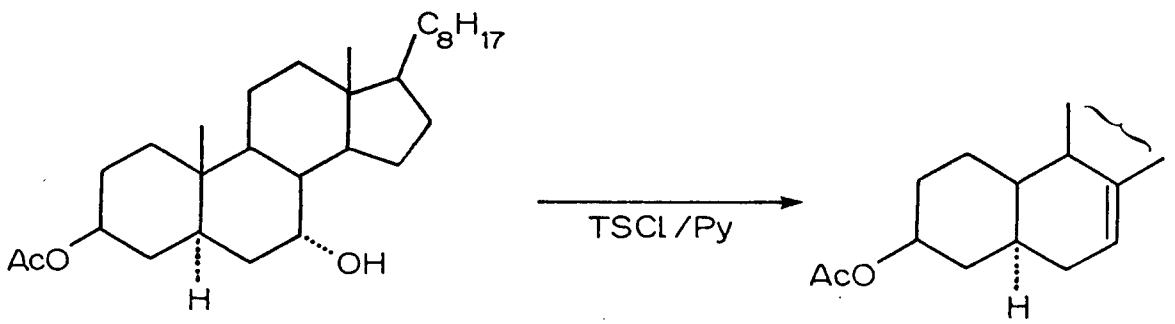

128 129

treatment of tosylate 130 with lithium carbonate in dimethylacetamide gave olefin 131 in low yield. The reaction of tosyloxy esters 103b and



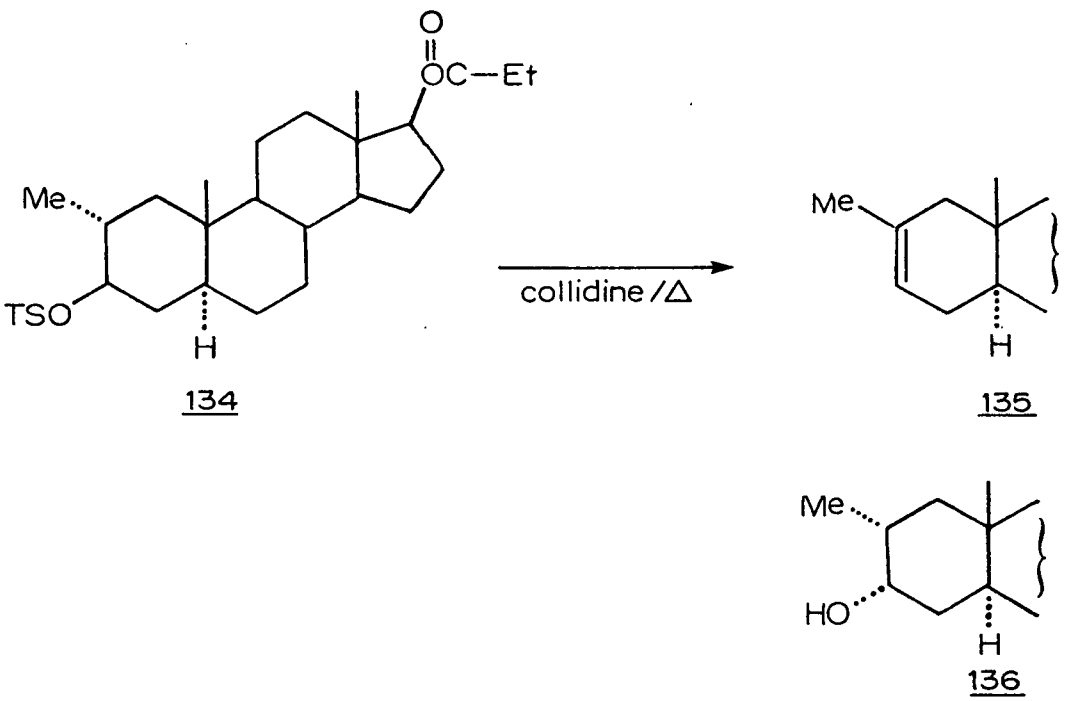

130 131

and 107b with lithium chloride and lithium carbonate in dimethylformamide and dimethylacetamide, respectively, led only to recovered starting material and diverse minor products. Wintersteiner and Moore[73] effected dehydration of 3β-acetoxy-cholestane-7α-ol (132) by reaction with tosyl chloride in refluxing pyridine and obtained olefin 133 in good yield.



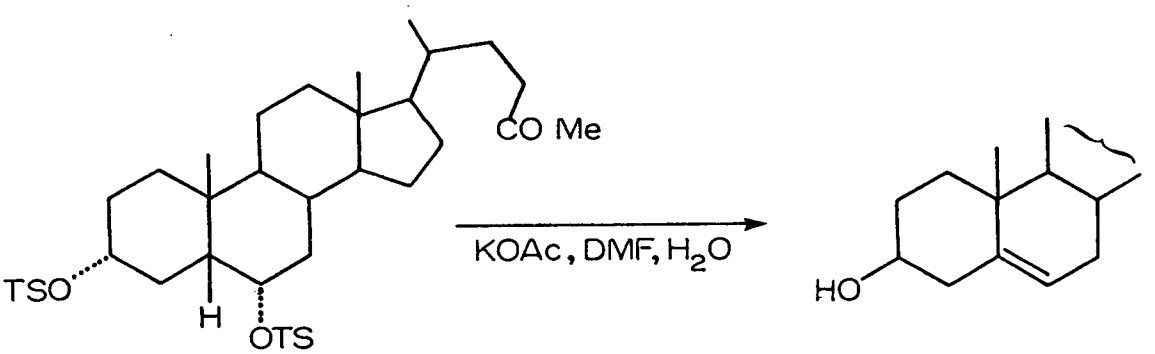

132 133

Treatment of tosyloxy esters 103b and 107b with refluxing pyridine for three hours under nitrogen afforded compounds 103a and 107a (CHARTS XIIIa and XIIIb, Pages 57 and 61 ) in ca. 50% yield and recovered starting material. This result could be interpreted if one assumed that the pyridinium tosylates were formed which on work up gave the appropriate alcohols or there was a nucleophilic attack on sulphur. Several other workers have observed the formation of alcohols in dehydrotosylation reactions. For example, the action of refluxing collidine on tosylate 134 affords olefin 135 and small amounts of alcohol 136.[74] Ziegler and Bharucha[75] reported that treatment of ditosylate 137 with potassium



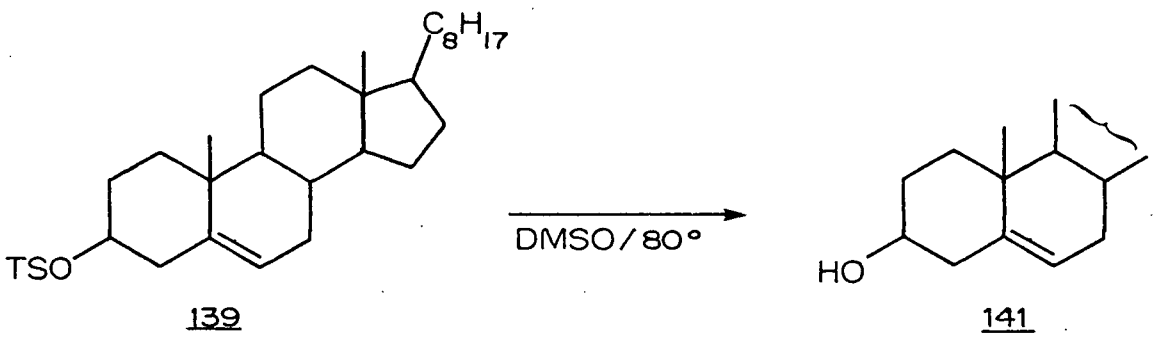

134 135 136

acetate in aqueous dimethylformamide gave olefinic alcohol 138. As a



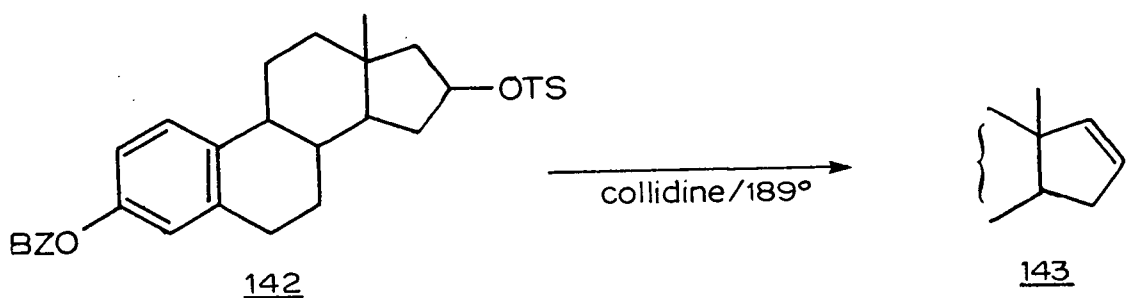

137 138

result very dry pyridine was used in the above reaction. It is noteworthy that tosylate 139 in dimethylsulphoxide at 80° affords alcohol 141 in 38% yield.[76] In order to prevent either a nucleophilic attack on sulphur or the direct displacement of the tosylate functionality it would be necessary to employ a hindered base. It has been shown that



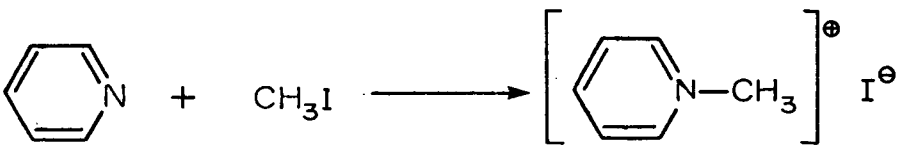

139 141

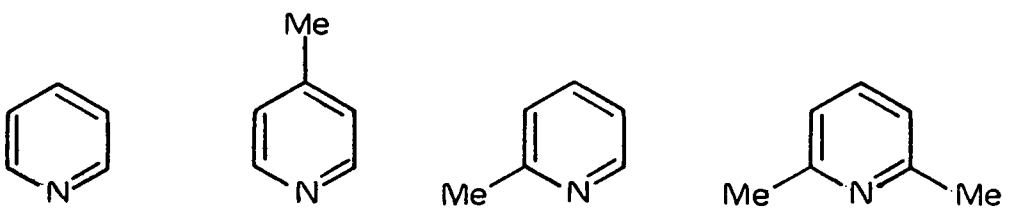
bimolecular substitutions may be retarded when the steric requirements of the attacking reagent become excessive. For instance, in CHART XVI (see Page 80) are listed the relative rates for the reaction of some substituted pyridines with methyl iodide.[77] Indeed, refluxing collidine has been employed to effect dehydrotosylation in good yield.[78] Elimination is favoured over substitution by increasing the temperature. Huffman and his colleagues[78a] converted compound 142 into olefin 143 by employing collidine at 189° for four hours. The action of refluxing collidine



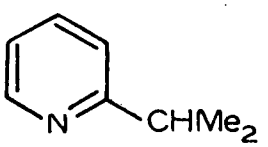

142 143

CHART XVI. Relative rates for the reaction of some substituted pyridines with methyl iodide

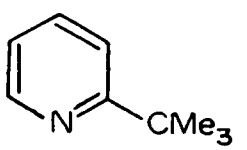



$\frac{k}{kpy}$ 1.00 2.27 0.47 .042

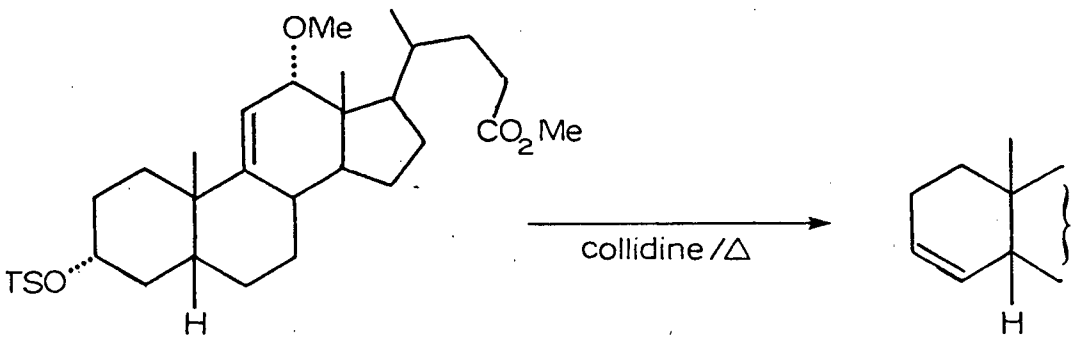



.072




.0002

on tosylate 144 for two hours afforded olefin 145 in 65% yield.[78b]

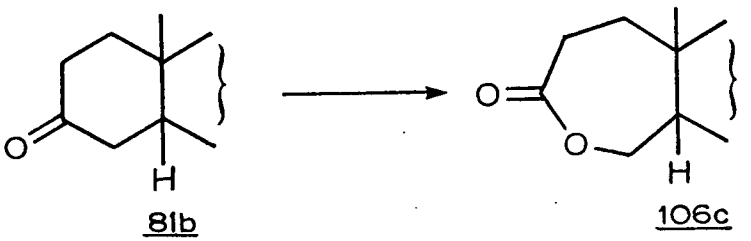



144 145

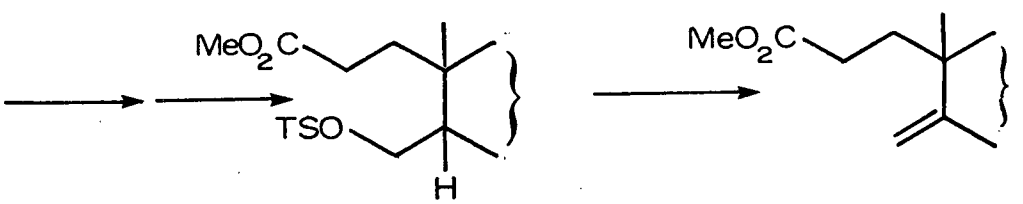
Thus, exposure of a mixture of tosyloxyesters 103b and 107b (CHART XVII, Page 82) to refluxing collidine for four hours under nitrogen afforded only olefin 108a in ca. 30% isolated yield as a clear oil. This reaction was monitored by t.l.c. on silica gel. Four hours represented the minimum time for complete consumption of starting material. Incomplete reaction gave lower yields of 108a and led to isolation difficulties. Olefin 108a was isolated by preparative t.l.c. on silica gel. The spectroscopic properties of 108a were in agreement with the assigned structure. The infrared spectrum of 108a had absorption bands at 900 $cm^{-1}$ and 1630 $cm^{-1}$ attributed to the methylene exocyclic double band. The salient feature in the n.m.r. of 108a was a broad two-proton doublet (J = 4 Hz) at $\tau$5.35 due to the vinyl protons on carbon 4. The mass spectrum of 108a indicated a molecular ion peak at $\frac{m}{e}$ 320. Various other products and insoluble solids were isolated from the reaction mixture. However, the infrared spectrum of these products did not display any olefinic features and they were not further characterized.

From this series of reactions it appeared that Baeyer-Villiger oxidation of ketoacetate 81b gave predominantly lactone 106c. Thus,

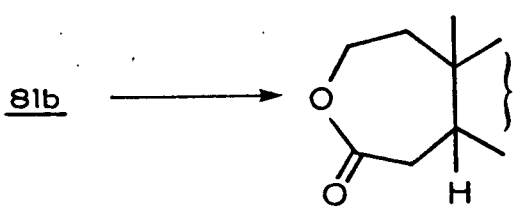
CHART XVII. Baeyer-Villiger Oxidation Studies



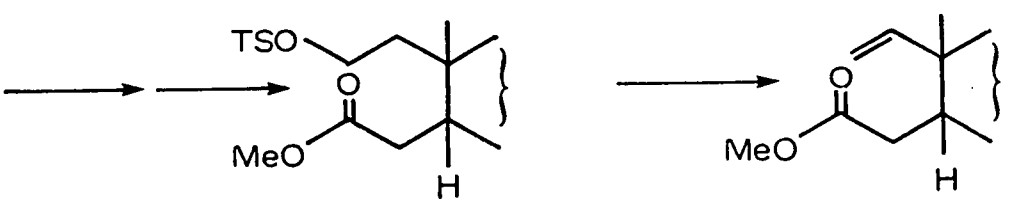
81b 106c



107b 108a



81b 102c

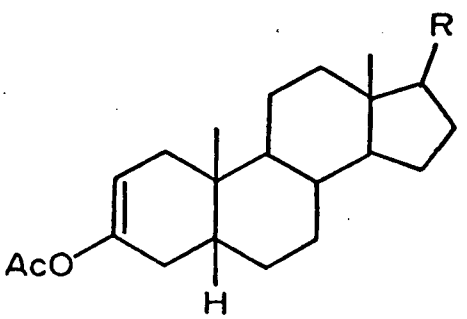


103b 104a

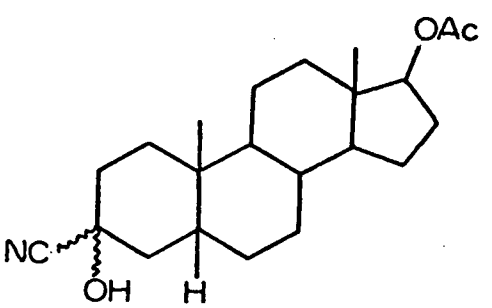
sequel 81b to 104a (CHART XVII, Page 82) did not demonstrate promise. This precluded making further explorations with the Baeyer-Villiger approach. From the practical aspect, the general plan involving the insertion of a hetero atom proved unfruitful since at each synthetic step isomeric mixtures were encountered, which were either inseparable or difficult to separate, and low yields were encountered in several instances.

b. Incorporation of Unsaturation Between Carbons 2 and 3

It was next planned to investigate the second approach, namely, the preparation of a $\Delta^2$ steroid of type 85. Prior to this investigation the only preparation of $\Delta^2$-5β-steroid free from the $\Delta^3$ isomer involved dehydration of the cyanohydrin 147.[79] Normally, the formation of $\Delta^3$



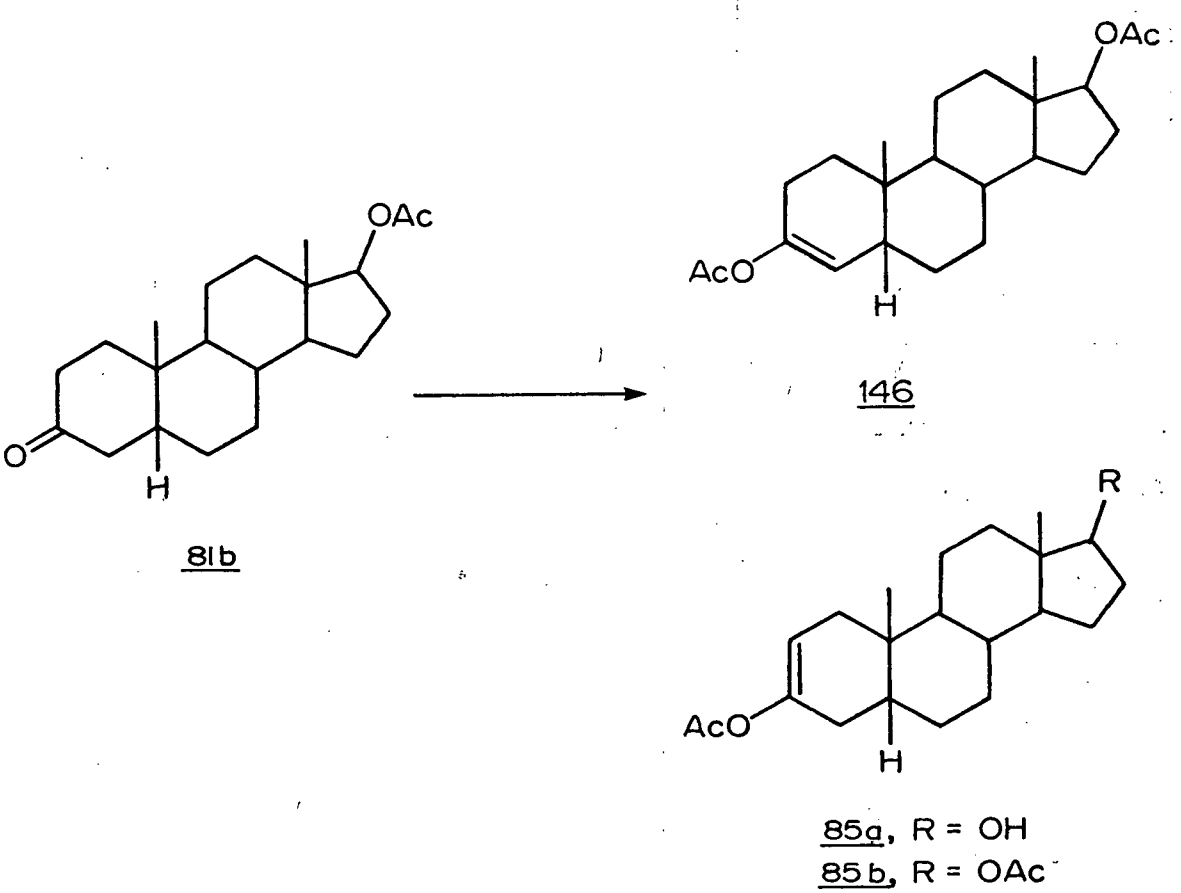

85a, R = OH
85b, R = OAc




147

products from 3-oxo 5β-steroids could be attributed to the preferential enolisation of these ketones towards carbon-4.[42,51,80] For example, Liston[42] found that under enol acetylating conditions 17β-acetoxy-5β-androstan-3-one (81b) afforded a mixture of enol acetates 85b and

146 in ca. a 1:3 ratio. When this mixture was subjected to equilibrating

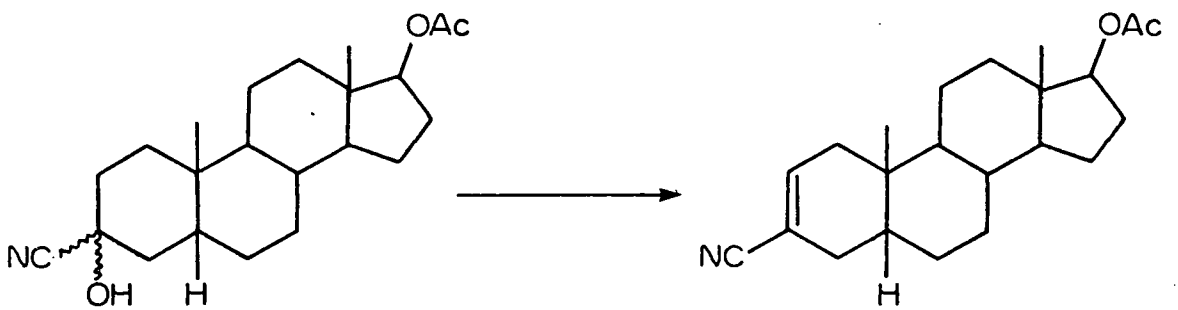



conditions enol acetate 146 was formed exclusively.[42] Djerassi[81] has suggested that two main factors operate in determining the direction of enol acetylation and probably enolisation in 3-oxo 5α-steroids. The first is steric and involves angular methyl group interactions while the second is hyperconjugative. Liston[42] utilized Hill's method[82] of calculating H-H and $CH_3$-H non-bonded interactions to demonstrate that the direction of enolisation of the 3-oxo 5β-steroids is governed by steric forces in the absence of any hyperconjugative effect. In calculating the relative stabilities of the two enolic forms of 17β-acetoxy-5β-androstan-3-one (81b) a number of assumptions were made:

(1) the A ring of the 3-oxo 5β-steroid assumes the classical half-chair conformation in the enolic form; (2) the B ring of the steroid assumes a geometrically perfect chair form; (3) nonbonded interactions are additive; and (4) the acetate group has no influence on the relative stability of the two enol acetates. None of the first three assumptions would be expected to hold in all cases since large nonbonded interactions could cause skeletal deformations; however, the interactions involved in these cases are relatively small and the distortions are considered minimal. Using Hill's procedure the calculated difference between the two enols is 1.91 k cal/mole, which corresponds to an equilibrium mixture of 96% $\Delta^3$-enol and 4% $\Delta^2$-enol at room temperature. Experimentally, 93.5% $\Delta^3$-and 6.5% $\Delta^2$-enol were found under equilibrating conditions at room temperature. These results suggest that steric forces are the dominant factors which govern enol acetylation and enolisation.

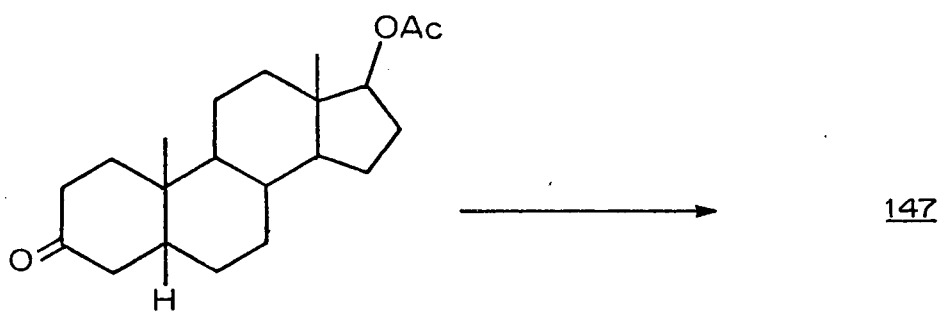
Under kinetically controlled conditions it may be possible to trap enol acetate 85b as the major product.[83] Attempts to trap enol acetate 85b by quenching a mixture of the enolate anions with acetyl chloride proved unfruitful. The n.m.r. spectrum of the resulting crude product indicated that enol acetate 146 had been formed.

At this stage, it was decided to study the synthesis of nitrile 148 as reported by Nathansohn.[79] Exposure of cyanohydrin 147 to phosphorus oxychloride in refluxing pyridine effected dehydration to afford olefin 148 in good yield.[79] Thus, cyanohydrin 147 was prepared



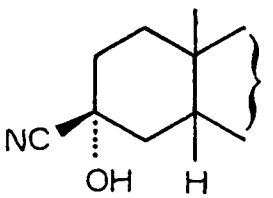

147 148

by treatment of ketoacetate 81b with acetonecyanohydrin at room temperature for thirty hours. However, in our hands it was found that the



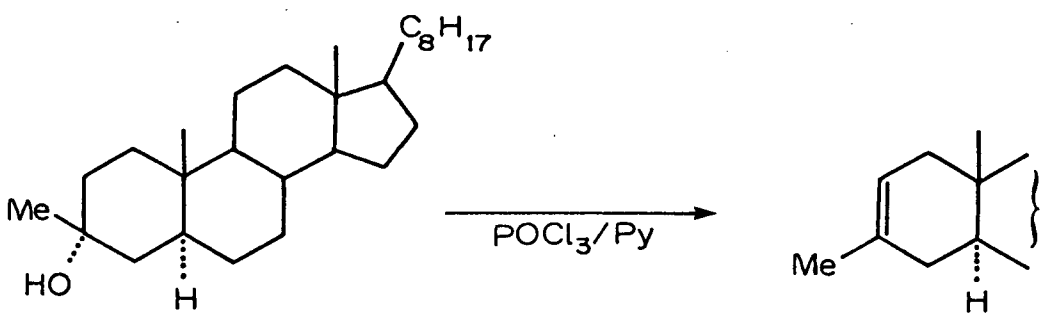

81b 147

action of phosphorus oxychloride on cyanohydrin 147 in refluxing pyridine afforded insoluble material and several minor compounds. As a result, the stereochemical features of the addition and dehydration reactions were examined. In the addition reaction the steric factor, which is connected with the accessibility of the carbonyl centre, would indicate that the cyanide nucleophile would approach from the β face to give cyanohydrin 147a. Furthermore, the reaction is carried out under equilibrating conditions (room temperature for thirty hours) and, therefore,



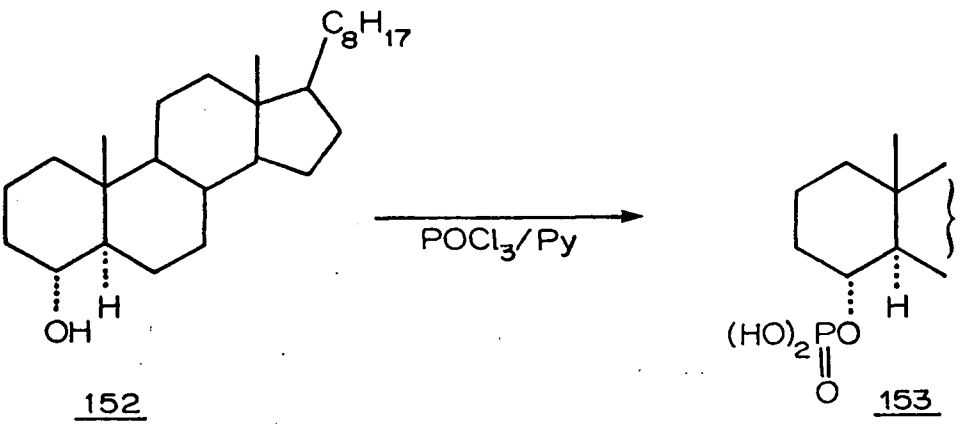

147a

the thermodynamically more stable product will be formed. The conformational free energy differences for cyclohexanol and cyanocyclohexane are 0.52 (pyridine) and 0.25 (tetrahydrofuran) k cal/mole, respectively.[84] These values and the above considerations tend to suggest that cyanohydrin 147a would be the predominant product in the reaction of acetonecyanohydrin with ketoacetate 81b. In the dehydration reaction the stereoelectronic factor requires trans-diaxial elimination. For example, the action of phosphorus oxychloride on compound 150 in pyridine gives olefin 151 in quantitative yield.[85a] On the other hand, the equatorial



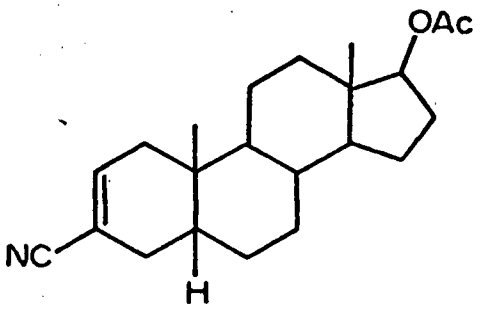

150 151

alcohol 152 forms the phosphate ester 153 when subjected to phosphorus oxychloride in pyridine.[85b] Hence, cyanohydrin 147a would not be expected to readily undergo dehydration. If the 3-hydroxy group of

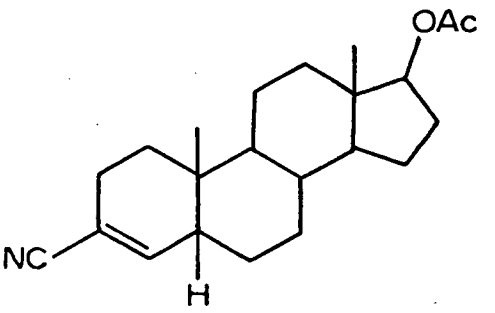



152 153

compound 147 has the β configuration, it appears that two trans-diaxial eliminations are possible; namely, dehydration of 147 to afford 148 and 149.



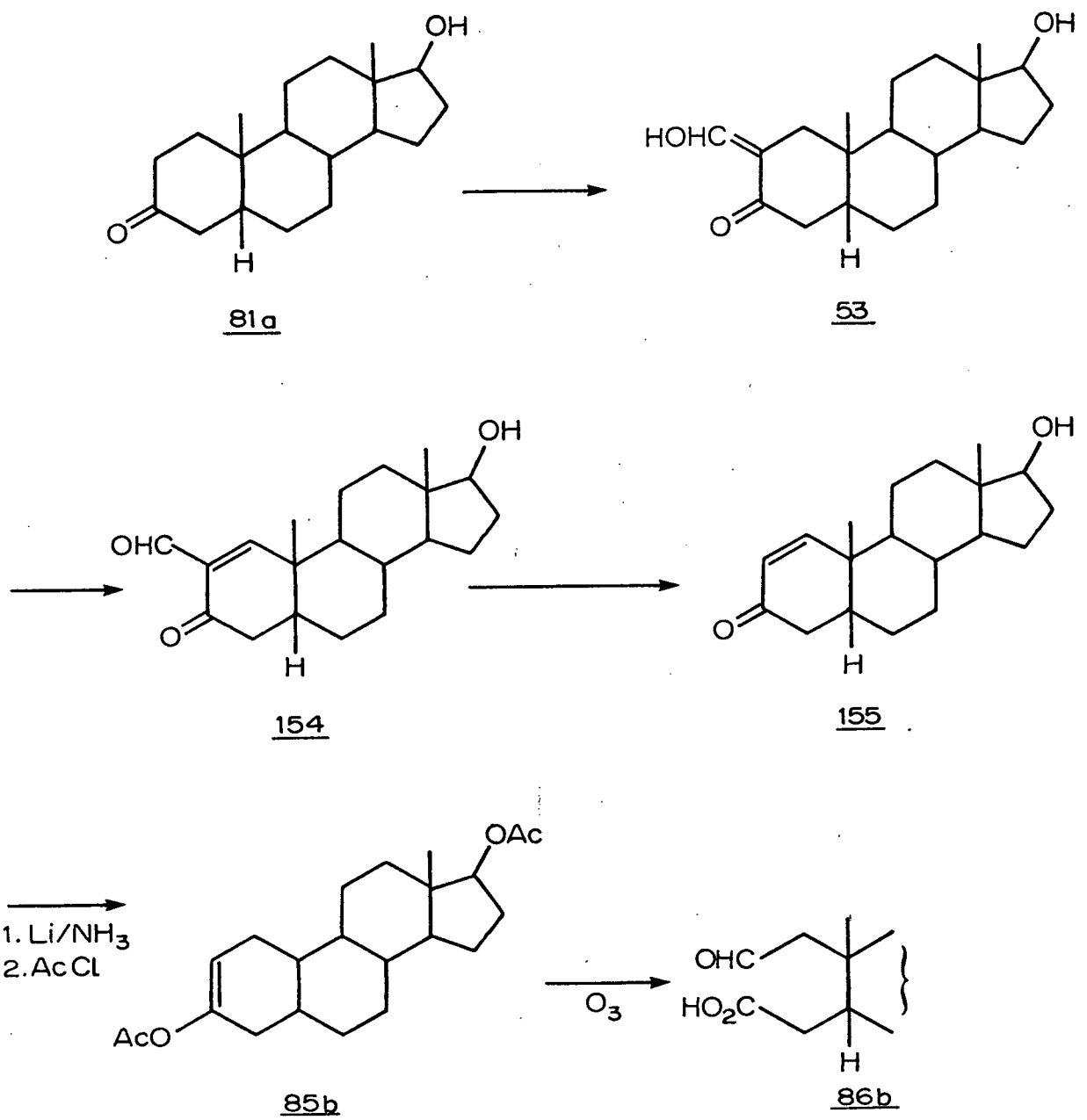

148




149

Next, attention was focused on a communication by Caspi et al.,[86] which described a convenient and practical method for the introduction of unsaturation at carbon 1 in 3-oxo 5β-steroids (CHART XVIII, 81a→155, Page 89). Birch reduction[87] of ketone 155 and subsequent trapping of the enolate anion with acetyl chloride might be expected to furnish enol acetate 85b (CHART XVIII, Page 89 ).[83c, 83d] Condensation of ketone 81a with ethyl formate in dry benzene at room temperature for thirty hours yielded the hydroxymethylene derivative 53 in 60% yield as a white

CHART XVIII. Proposed synthesis of compound 86b




81a 53 154 155 85b 86b

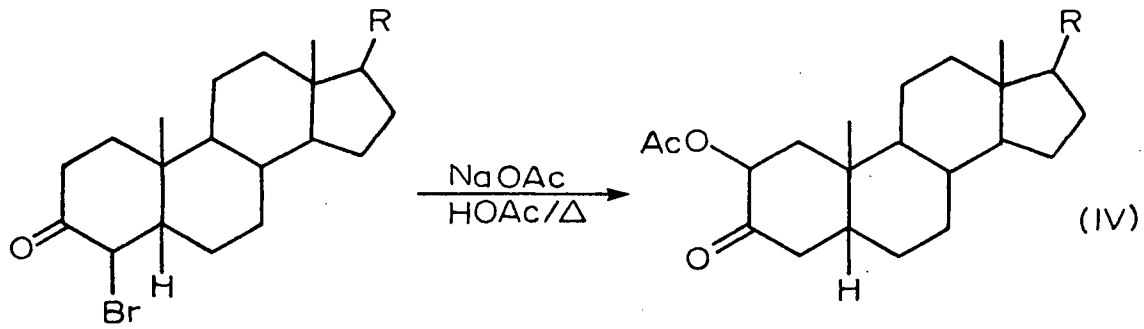
crystalline solid, m.p. 153-159° (lit.[80e] m.p. 157-163°). Exposure of hydroxymethylene 53 to dichlorodicyanoquinone in refluxing benzene for thirty hours yielded 2-formyl-17β-hydroxy-5β-androst-1-en-3-one (154) in ca. 30% purified yield as a clear oil. Several attempts to induce crystallization failed. It is worthy of mention that the introduction of unsaturation between carbons 1 and 2 has been achieved in 2-hydroxymethylenes of the A/B trans series by the action of dichlorodicyanoquinone.[88] The spectroscopic data of 154 were in accord with the assigned structure. For example, the infrared spectrum of 154 had absorption bands at 1720 $cm^{-1}$ and 2750 $cm^{-1}$ due to the aldehyde functionality. The α,β-unsaturated carbonyl was evident at 1670 $cm^{-1}$. Although the required degree of unsaturation in the A ring had been achieved and some of the difficulties associated with this transformation had been unravelled the purified yields were still poor even when operating on a small scale. This is in sharp contrast to the work of Caspi and his colleagues.[86] For example, they recorded a 60% yield of 154 in large scale preparative work. The next step demanded the removal of the formyl group. In a series of small scale trial experiments it was found that treatment of aldehyde 154 with chlorotris(triphenylphosphine)rhodium in refluxing benzene for three hours gave after work up a clear oil which consisted of trace amounts of starting material and two new compounds as evidenced by t.l.c. on silica gel. The infrared spectrum of the crude material tended to suggest the presence of an α,β unstaurated carbonyl compound. Thus, the reaction was carried out on a larger scale and ketone 155 was isolated by chromatographic means. However, after trying various chromatographic systems it was found that the isolated ketone

155 was always contaminated with triphenylphosphine oxide. In addition, all attempts to induce crystallization failed. From the spectroscopic data there is little doubt that this substance had structure 155. Thus, the infrared spectrum displayed absorptions at 1660 $cm^{-1}$ due to the $\alpha,\beta$ unsaturated carbonyl and at 840 $cm^{-1}$ which could be attributed to the carbon-1 carbon-2 double bond. The pertinent spectral features in the n.m.r. of 155 were an AB pair of doublets at $\tau$4.14 and $\tau$3.15 (J = 10 Hz) due to the carbon-1 and carbon-2 olefinic protons.

Although this synthetic route (CHART XVIII, Page 89 ) had presented several obstacles it appeared likely that intensive further investigations could have rendered a practical synthetic sequence. However, this approach was abandoned because of the low overall yield and the cumbersome methods of purification which had been realized.

c. Functionalization of Carbon-2

It is well documentated that reactions of 3-oxo 5$\beta$-steroids afford predominantly carbon-4 functionalized products except for the formation of the 2-hydroxymethylene derivative.[42,51,80] The 2-hydroxymethylene derivative was not directly applicable to the present design since ozonolysis leads to ring cleavage between carbons 2 and 3 in a symmetric manner, equation II.[51] Clearly, a method to differentiate carbons 2 and 3 would have to be found. As noted earlier, the formation of 4-substituted compounds can be rationalized by the preferential enolization of 3-oxo 5$\beta$-steroids towards carbon-4.[42,51,80] It appeared highly probable that this general principle could serve indirectly to



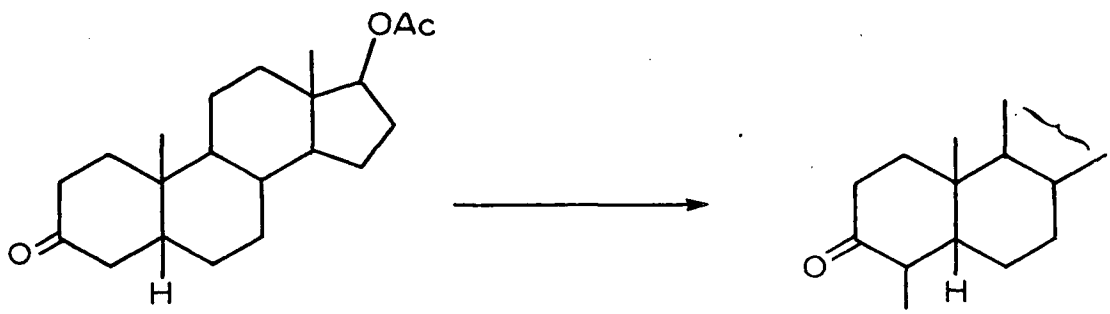

(IV)

156, R = $C_8H_{17}$
158, R = OAc

157, R = $C_8H_{17}$
159, R = OAc

functionalize carbon-2 in the required manner.

Takahashi et al.,[89] found that treatment of 4β-bromo-5β-cholestan-3-one (156) with sodium acetate in refluxing acetic acid afforded 2β-acetoxy-5β-cholestan-3-one (157) in good yield. Thus,

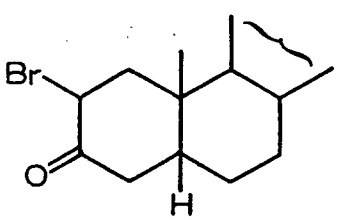



81b

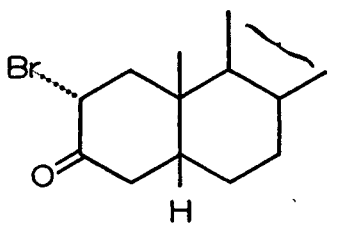
158

this reaction was extended to bromoketone 158. 17β-Acetoxy-5β-androstan-3-one (81b) was brominated by employing a procedure similar to that used by Fieser et al.,[90] Bromination of compound 81b in glacial acetic acid gave, after work up, a white crystalline solid m.p. 135-151°. A small

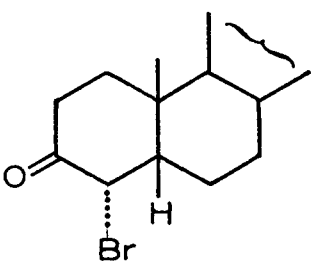
sample was recrystallized from ether to afford cubes m.p. 174-175° (lit.,[90] m.p. 174-175°). The v.p.c. of the crude reaction product indicated the presence of two compounds in ca. a 1:4 ratio. The infrared spectrum of the crude material had a broad carbonyl band at 1720 $cm^{-1}$. The salient feature in the n.m.r. spectrum of the crude product was a one-proton doublet (J = 12 Hz) at τ5.00 due to the carbon-4 axial proton of 158. Finally, the mass spectrum indicated a molecular ion peak at $\frac{m}{e}$ 410 and a P+2 peak almost equal in intensity to the parent peak because of the presence of molecular ions containing the $^{81}Br$ isotope. These results suggested that bromoketone 158 was the major product. The other compound present in the crude reaction product is presumably either bromoketone 160a, 160b or 160c. However, the




160a




160b

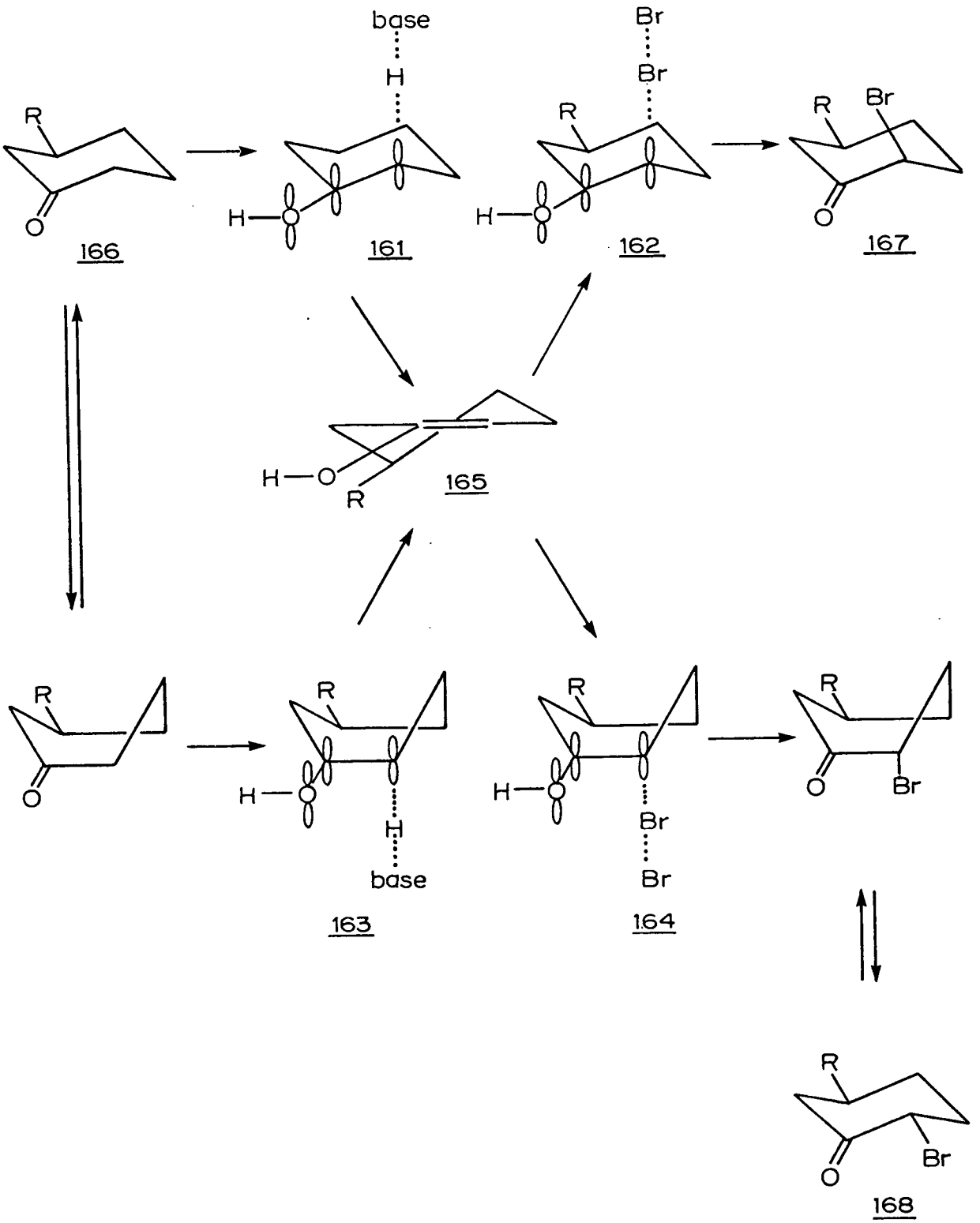



160c

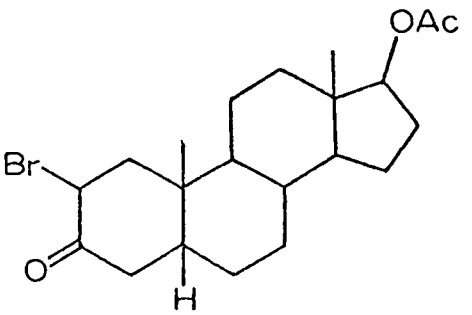
isolation of pure bromoketone 158 was not necessary for the next step in sequence. It is worthy to comment on the mechanistic aspects of the above bromination reaction. The stereochemistry of bromination of enols appears to be controlled by two factors that may either oppose or reinforce one another. The stereoelectronic factor,[91] which is applicable to cyclohexanone derivatives may be illustrated by the

accompanying equations (CHART XIX, Page 95 ). The energetically most favourable transition states for removal of an alpha proton, for example, 161 and 163 to form the enol 165 and for addition of a bromine atom (162 and 164) to form the product are those in which continuous overlap of the p orbitals involved is possible. If the chair forms 161 and 162 are considered it is clear that there should be preference for the removal of an axial proton and addition of bromine at an axial bond. However, the importance of this preference should diminish in proportion to the degree to which the transition states 161 and 162 resemble the planar enol 165 rather than the ketones 166 and 167. The second factor of concern is the steric interference that exists in the transition states for proton removal and bromine addition. It is apparent that if serious steric interactions exist in the chairlike transition states 161 and 162, the enolization and bromination may proceed via the boat-like transition states 163 and 164 and still allow continuous p-orbital overlap. In the bromination of ketoacetate 81b there would be a severe non-bonded interaction between bromine and the axial protons at carbons 7 and 9 in the chairlike transition state. Presumably, this is sufficient to cause the enol to react with bromine via the boat-like transition state, leading to the equatorial bromoketone 158. In view of these considerations the axial bromoketone 160c would not be expected to form. Djerassi and his colleagues[92] have demonstrated that bromination of the enol acetates derived from steroidal A ring ketones results in virtually the same product mixtures as are obtained from the ketones themselves. Since Liston[42] reported that enol acetylation of keto-acetate 81b gave rise to enol acetates 146 and 85b in ca. a 3:1 ratio, and bromination of enol acetate 85b gave bromoketone 160a, the bromination

CHART XIX. Mechanistic aspects of the bromination of ketones



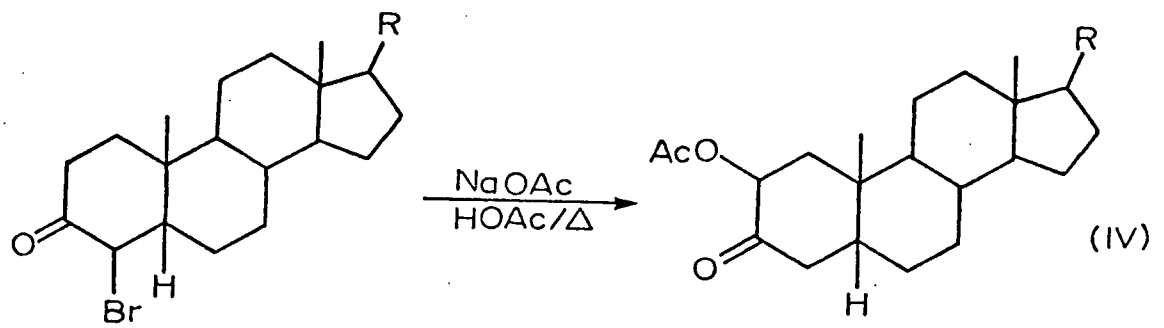
of ketoacetate 81b would be expected to afford bromoketones 158 and 160a in ca. a 3:1 ratio, respectively. It is, therefore, highly probable




160a

that bromoketone 160a is present in the crude reaction product.

Treatment of the crude bromination product with sodium acetate in refluxing acetic acid afforded 2β, 17β-diacetoxy-5β-androstan-3-one (159) in ca. 70% purified yield as a white crystalline solid, m.p.




158, R = OAc

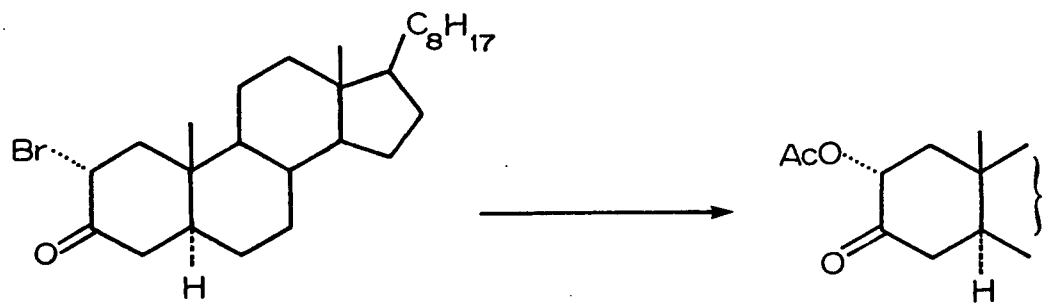
159, R = OAc

(IV)

170-173°. This material was homogeneous on silica gel t.l.c. A small sample was recrystallized from methanol, m.p. 161-162°, for analysis. The spectroscopic data of this material were in complete accord with

the assigned structure. The infrared spectrum of 159 had an intense carbonyl band at 1720 $cm^{-1}$ due to the 2β- and 17β- acetoxy groups and the 3-oxo group. An intense broad band at 1150-1200 $cm^{-1}$ was evident for the C-O stretching vibrations. The pertinent spectral features in the n.m.r. spectrum of 159 were a double doublet (J = 5 and 13 Hz) at ca. τ7.8 attributable to the 4β-hydrogen, a broad triplet (J = 9 Hz) at τ7.19 due to the 4α-hydrogen, and a double doublet (J = 6 and 14 Hz) at τ4.85 which could be assigned to the 2α-hydrogen. It is very important to realize that the splittings of the four intense lines of the X portion of an ABX spectrum do not necessarily represent the coupling constants $J_{AX}$ and $J_{BX}$, although frequently this may be a good approximation if the chemical shift between A and B is larger than $J_{AB}$.[93] This can pose a serious problem in conformational analysis, especially in steroids because the resonances due to both A and B may lie within the bounds of the methylene envelope and hence cannot readily be located. It has been observed that as the chemical shift between A and B is increased, the splittings of the X resonance correspond more closely to the coupling constants $J_{AX}$ and $J_{BX}$. Therefore, if a spectrum is determined at both 60 MC and 100 MC without observing any change in the pattern due to the X proton, it is probable that the splittings are good approximations to the coupling constants. This follows since the chemical shift between A and B has been increased by a factor of 1.67 in passing from the 60 MC to the 100 MC determination. The method, of course, fails if δAB=0 and is of dubious value if the chemical shift between A and B is only a few cycles.[93] This treatment was applied to compound 159. No change in the ABX pattern of the 2α-proton was observed.

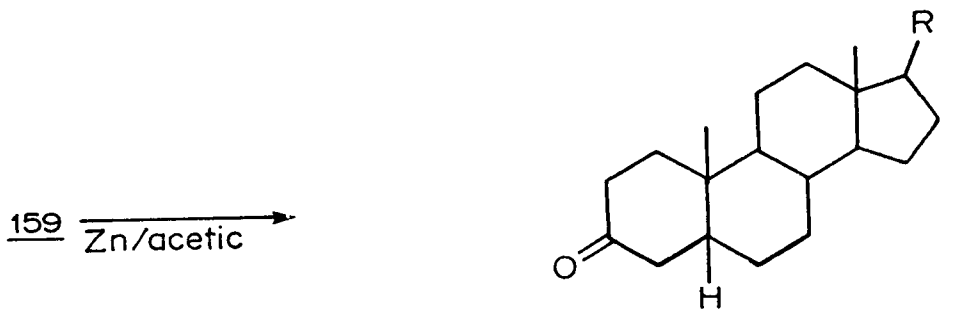
The probability that the chemical shift between the 1α- and 1β- protons in this compound is only a few cycles seems small since axial and equatorial protons are usually separated by at least 0.5 ppm.[93b] Therefore, it appears likely that the splittings are good approximations to the coupling constants. Finally, the mass spectrum of 159 indicated a molecular ion peak at $\frac{m}{e}$ 390. This product was not unexpected in light of previous substitution reactions of steroidal bromoketones.[89,90] For example, Fieser et al.,[90] found that treatment of the bromoketone 169 with potassium acetate in refluxing glacial acetic acid gave a 1:1 mixture of acetoxyketones 170 and 171. It is worthy of mention that




169 170 171

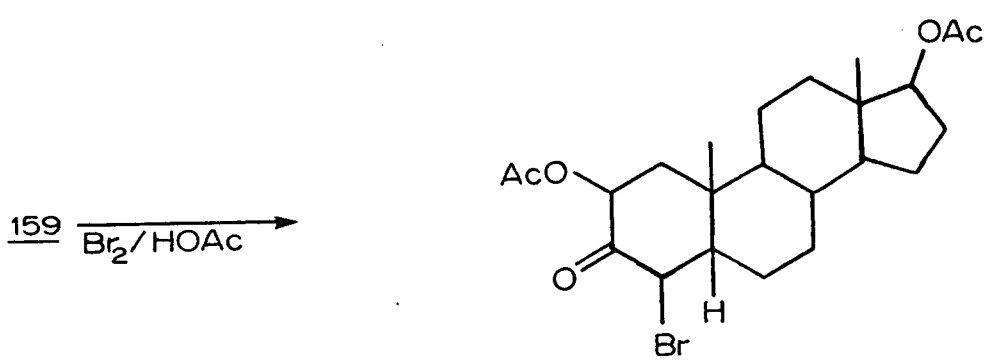
Zinc-acetic acid reduction of diacetate 159 gave 81b in low yield, which

indicated that no acyloxy-ketone exchange had occurred.[94] Rosenfield




81b, R = OAc

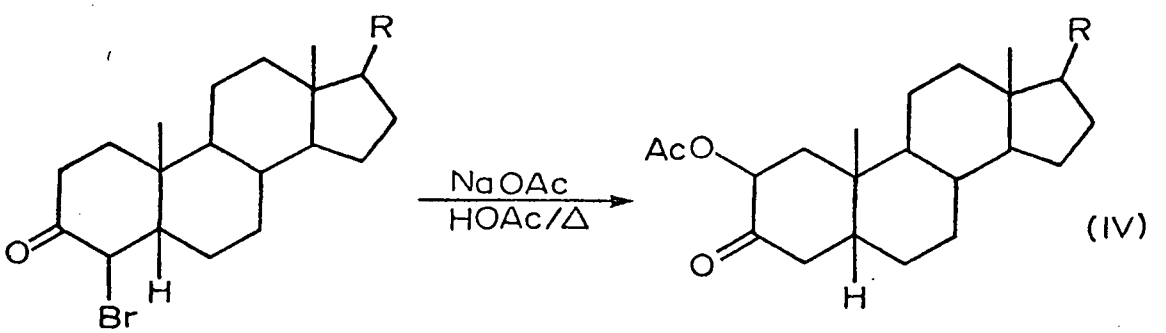
has suggested that the configuration of the acetoxy group is important in these Zn-acetic acid reductions, and elimination occurs in good yield only if the group is axial. Furthermore, bromination of 159 with bromine in acetic acid gave a compound whose n.m.r. spectrum was consistent only with structure 173. The salient features in the n.m.r.




173

spectrum of 173 were a doublet at τ5.02 due to the 4α- hydrogen and a double doublet (J = 5 and 13 Hz) at τ4.79 due to the 2α- hydrogen. In addition, the spectrum was determined at both 60 Mc and 100 Mc. No change in the ABX pattern afforded by the 2α- proton was observed.[93] Therefore, it appears likely that the splittings are good approximations to the coupling constants.

Thus, a practical method had been developed for the introduction of an acetate functionality at carbon 2 in 17β-acetoxy-5β-androstan-3-one (81b). In view of the present aims and the ready synthetic availability of diacetate 159 it was decided to examine the chemical behaviour of 159. Before embarking on these explorations it is in order to consider the mechanistic aspects of transformation IV.



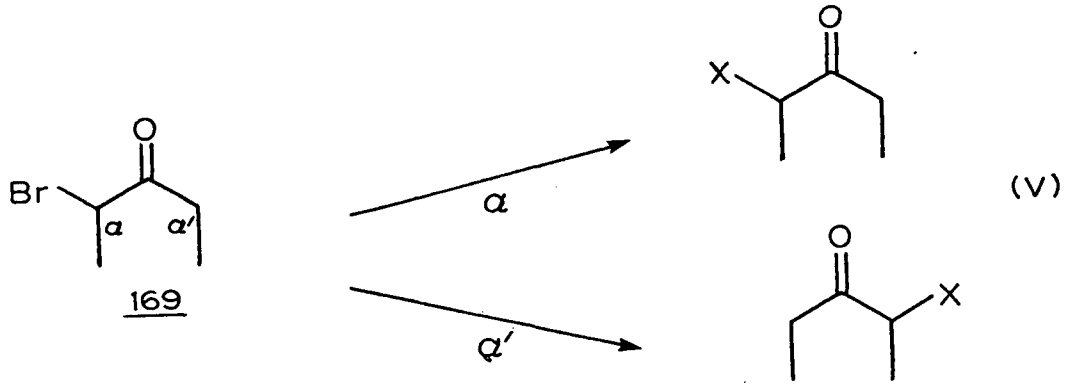

158, R = OAc

159, R = OAc

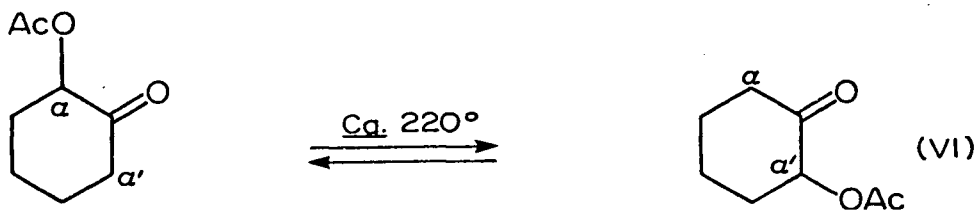
(IV)

Interestingly, at the beginning of this thesis it was mentioned that synthetic studies in the field of natural product chemistry have played a prominent role in the development of reaction mechanisims. There are several examples of cine substitutions in steroidal chemistry[1b,1c] but the above reaction is notable for the good yield and purity of product. This general type of transformation, equation IV, has gained

the attention of several researchers. Firstly, Fieser[90] and Cox[96] have demonstrated that α-bromoketones can undergo substitution at α- or α'-position, equation V. Thus, this led us to consider the intermediacy

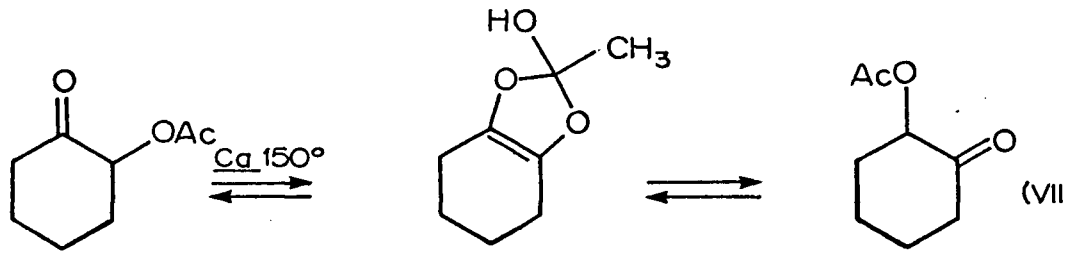



(V)




(VI)

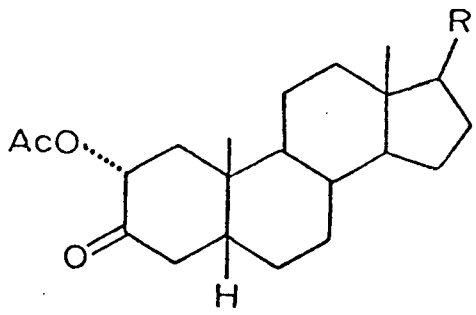
of the 4α- or 4β- acetoxy compound in transformation IV. Secondly, Warnhoff et al.,[94] have found that α-acetoxycyclohexanone transfers the acetate group to the α'- carbon above 220°, equation VI, and similar rearrangements have been found to occur at lower temperatures,[94,98,99]



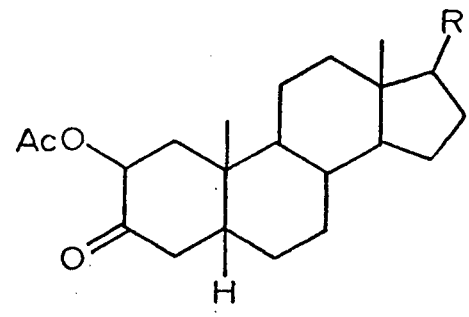

(VII)

equation VII. This further enhances the possibility that the 4-acetoxy isomer may be an intermediate in reaction IV. Finally, Satoh and Takahashi[97] treated bromoketone 157 with (a) potassium acetate-acetic acid, (b) potassium acetate-dioxan, (c) triethylamine-acetic acid at

90-95°, (d) potassium pivalate-dioxan at 70°, and (e) $ACO^{\ominus}N^{\oplus}Me_4$-dioxan at room temperature. Samples were taken from each reaction mixture at



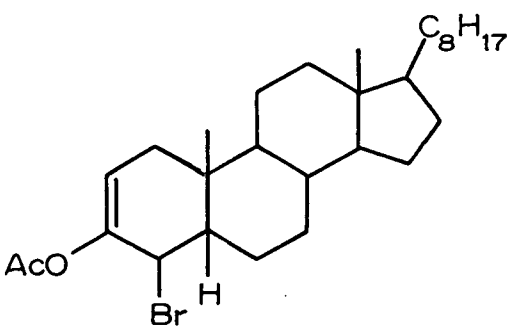

174, R = $C_8H_{17}$




157, R = $C_8H_{17}$

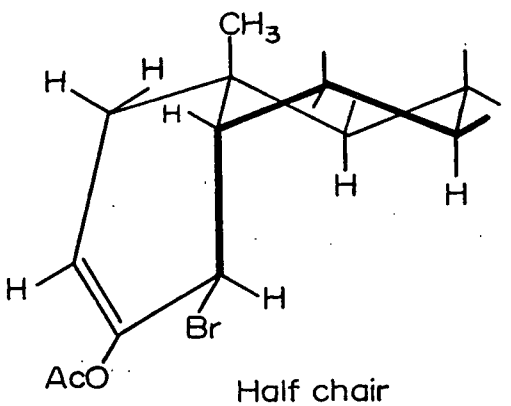
intervals and the progress of the reaction was followed by t.l.c. and by using a Varian HR-220 n.m.r. spectrometer to observe the change in the signals due to the methyl protons of the acetoxy groups. It was suggested that 2α-acetoxy-5β-cholestan-3-one (174) was formed first in each of the above cases. Since the isomerization of the 2α-acetoxy to the 2β-acetoxy derivative is relatively fast for the cases (a) and (c), it was impossible to isolate the initial product, 2α-acetoxy-5β-cholestan-3-one (174). In cases (b), (d), and (e), however, this product was easily obtained. It was reported that the 2α-acetoxy derivative 174 was produced almost stereospecifically in 2.5 hours for method (d) and in five days for method (e), and was gradually isomerized to the 2β-acetoxy derivative 157 when the reaction was continued for longer periods of time. In order to rationalize the initial formation of the 2α-acetoxy derivative 174, Satoh and Takahashi[97] invoked that the reaction proceeds in a trans-$S_N2'$ manner in which the leaving group is trans to the entering group, unlike the ordinary $S_N2'$ reaction, where a cis relationship obtains. Since the α- side of the ring A of a 5β-steroid

is less favoured than the β- side for nucleophilic attack, they considered that the conformation of the intermediate must be responsible for the unexpected attack at the α- face. Fieser[90] and Clarke[100] reported that enolization took place during the acetolysis of 2α-bromo and 6β-bromo derivatives. If 156 undergoes enolization, it is possible that a conformation will result in which ring A is relatively flat with respect to ring B, and hence nucleophiles may attack at the α- face. In order to test this possibility Satoh and Takahashi[97] prepared 4β-bromo-5β-cholest-2-en-3-ol acetate (176) by enol acetylation of the 4β-bromo-3 ketone 156 since the enol derivative was not stable enough to isolate.



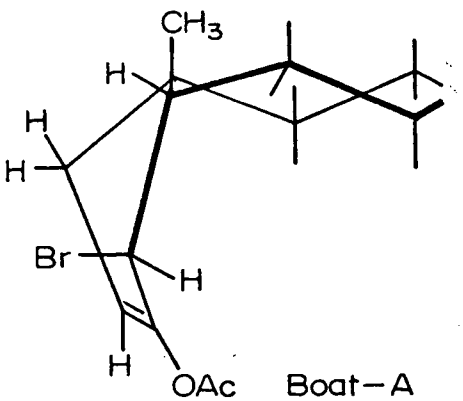

176

Three possible conformers 176a, 176b and 176c were considered for compound 176 (see Page 104 ). After examining the n.m.r. spectrum of 176 Satoh and Takahashi[97] assumed that enol acetate 176 had the boat-B conformation. This conformation provides a favourable environment for the nucleophile to attack at carbon-2. Furthermore, α- attack occurs more readily than β- attack at this position because of the steric effect of the 10-methyl group. In summary, Satoh and Takahashi[97]



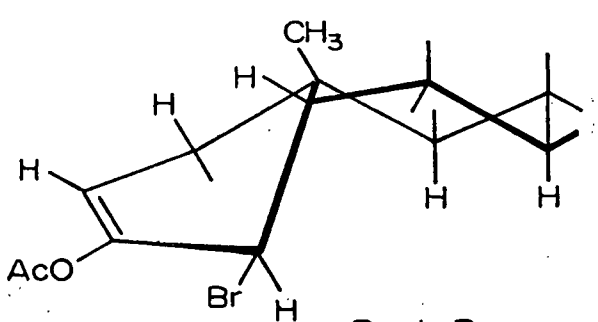

Half chair

176a




Boat–A

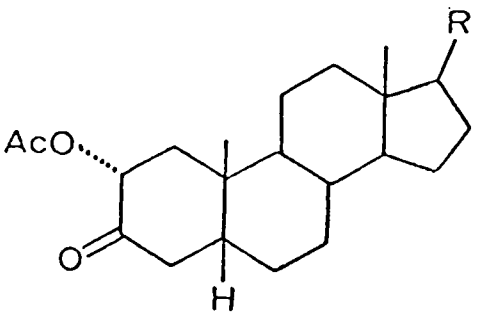
176b



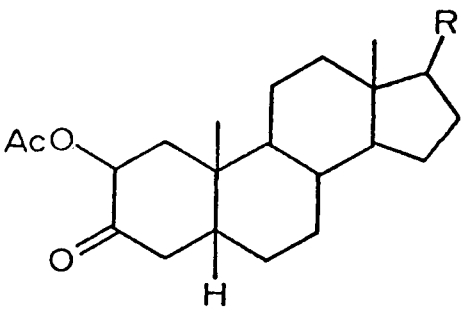

Boat–B

176c

concluded that the 2α-acetoxy derivative 174 was formed as the product of a trans-$S_N2'$ reaction and then isomerized to the more stable 2β-isomer.

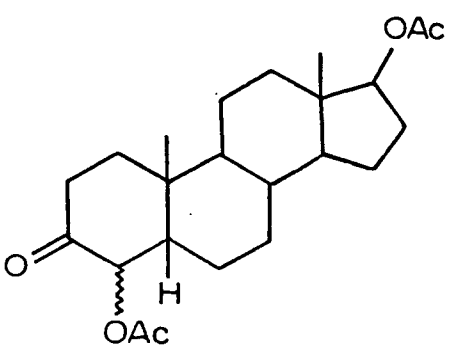



174, R = $C_8H_{17}$




157, R = $C_8H_{17}$

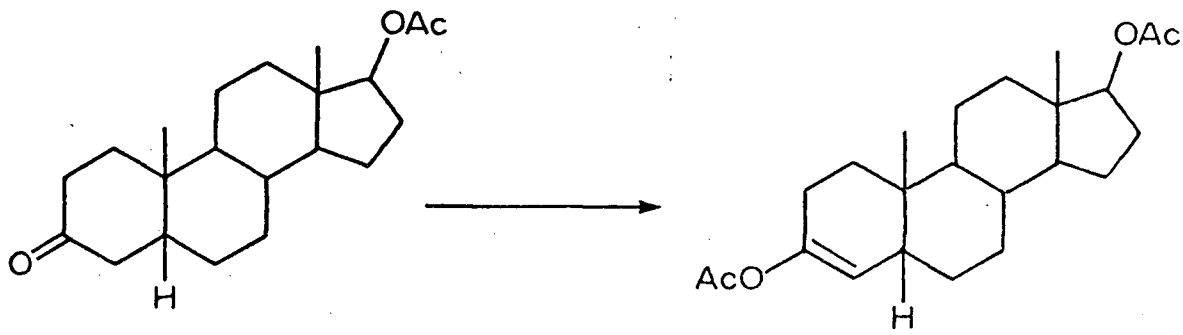
It was, therefore, planned to determine if the 4β- or 4α-acetoxy compounds 175b and 175a, were intermediates in transformation IV and to determine if either 175b or 175a was related to the intermediate isolated by Satoh and Takahashi.[97] Since these workers started with




175a, 4α—OAc
175b, 4β—OAc

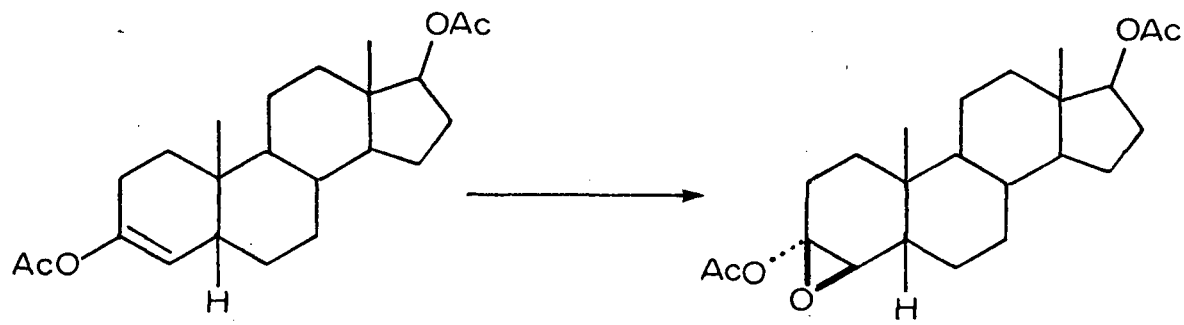
5β-cholestan-3-one, and 17β-acetoxy-5β-androstan-3-one was chosen as starting material direct comparisons could not be made.

Enol acetylation of compound 81b, by employing conditions analogous to those used by Liston gave enol acetate 146 in excellent yield.[42] Epoxidation of the enol acetate 146 with m-chloro




81b 146

acid - sodium bicarbonate gave the β-epoxide 177.[101] Assignment of

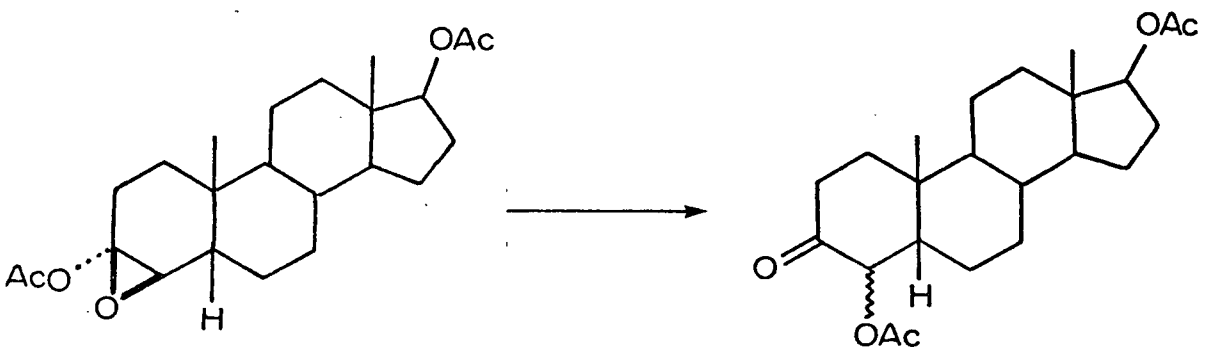



146 177

the β-configuration to the epoxidation product was made on the following bases. The β-face appears to be the sterically more accessible direction for peracid attack.[102] The n.m.r. spectrum of 177 had a singlet at τ6.93 due to the proton on carbon-4. An examination of the Dreiding model of 177 indicated that the dihedral angle between the hydrogens on carbon-4 and carbon-5 is ca. 100°. The dihedral angle between the hydrogens on carbon-4 and carbon-5 in the isomeric α-epoxide was estimated to be 50°. In an extensive study of steroidal epoxides and episulphides it was found

that the coupling constant could approach zero only for dihedral angles of 70-100° while a dihedral angle of 50° was expected to yield a coupling constant of at least 2 Hz.[103] Also, the chemical shift of the carbon-19 methyl protons in 177, τ9.13, agreed closely with that of the carbon-19 methyl protons of 3β, 4β-oxido-5β-cholestane, τ9.14.[104]

Pyrolysis of 177 at 160° for 5 minutes gave 4α, 17β-diacetoxy-5β-androstan-3-one (175a) in ca. 80% yield. The salient feature of the

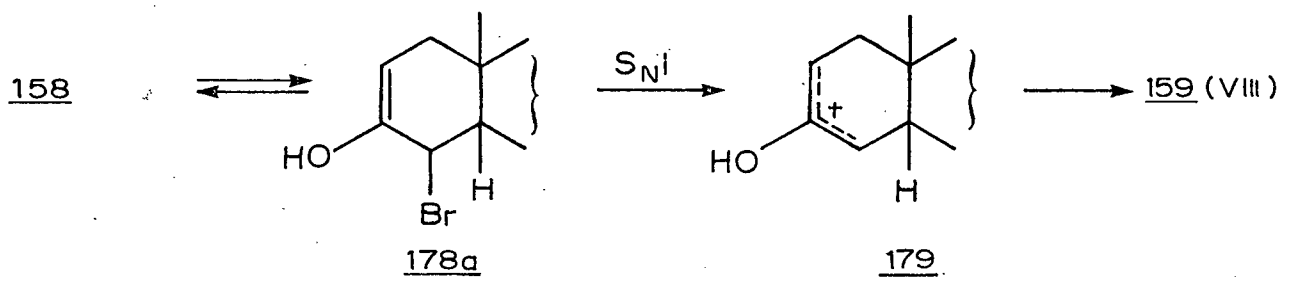



177 175a, 4α—OAc

n.m.r. spectrum of 175a, which suggested its structure, was a one-proton doublet (J = 8 Hz) at τ4.59. This was assigned to the 4β- hydrogen of 175a which probably is in a boat conformation due to the severe interaction of the 4α- acetoxy group with carbon-7 and carbon-9 in the chair conformation. On refluxing in acetic acid - sodium acetate, which were conditions for reaction IV, 175a was converted cleanly to the 4β- acetoxy isomer 175b. The 4β- isomer was also obtained by treatment of 177 with HCl in ether. The 4β- acetoxy compound 175b had in its n.m.r. spectrum a one-proton doublet (J = 12 Hz) at τ4.48 which was assigned to the 4α-hydrogen. These epoxide rearrangements parallel those of the 2α, 3α-oxido-3β-acetoxycholestane.[105] When 175b was subjected to the conditions for reaction IV it was recovered unchanged.

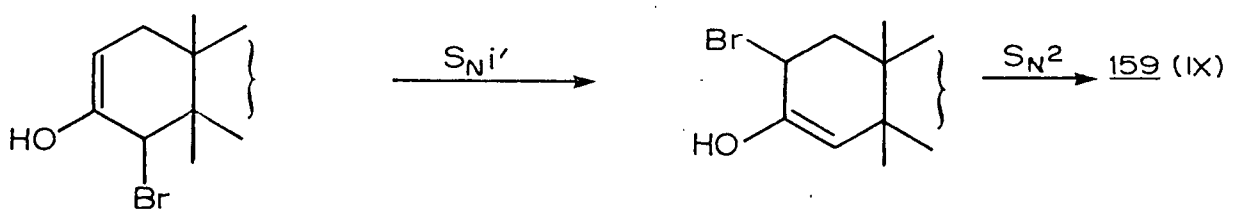
These experiments would indicate that neither 175a nor 175b can be an intermediate in reaction IV. In fact, 175a and 175b did not rearrange to either 2- acetoxy isomer on thermolysis at 160°. Hence, the intermediate isolated by Satoh and Takahashi[97] must be the 2α- acetoxy compound and it does not arise via the 4α- or 4β- acetoxy isomer.

Bordwell[106a] has catalogued some of the possible pathways by which a cine substitution such as reaction IV can occur. The first possibility, a $S_N2$ substitution at carbon-4 followed by a $S_Ni'$ rearrangement via the enol was discarded by the above results. An $S_N1$ pathway, equation VIII, is a possibility. A $S_Ni'$ rearrangement of the bromo enol



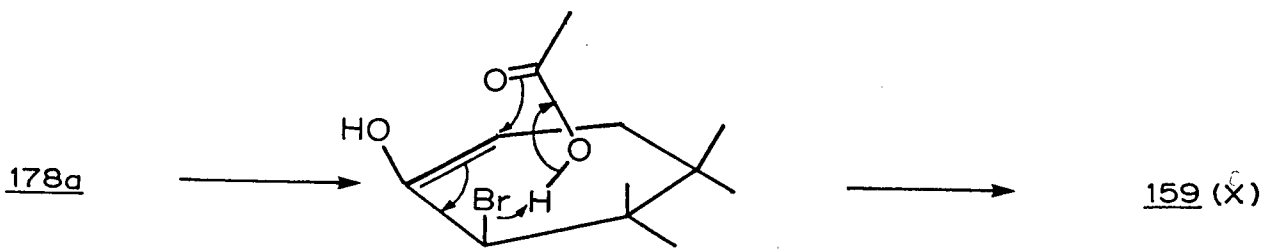

178a 179

178a to 178b followed by a $S_N2$ reaction is also a possibility, equation IX.

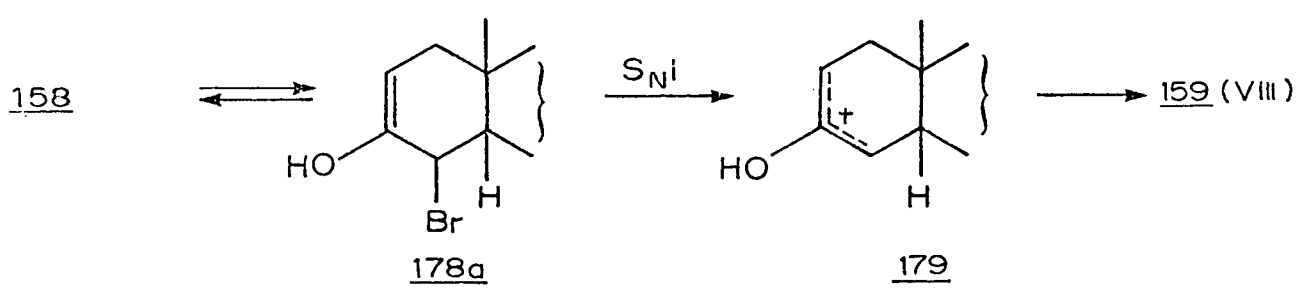



178a 178b

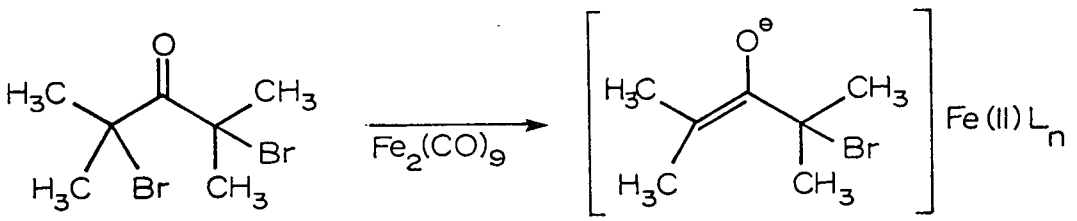
However, Liston[42] has found that the bromoketone 158 and 17β-acetoxy-2β-bromo-5β-androstan-3-one (160a) were not interchanged or equilibrated even in HBr-HOAC. This would suggest that the rearrangement of 178a to 178b does not occur under our conditions. A second type of $S_Ni'$ reaction is shown in equation X; but, this does not require the intermediacy of the 2α- isomer. A final possibility is a $S_N2'$ reaction of



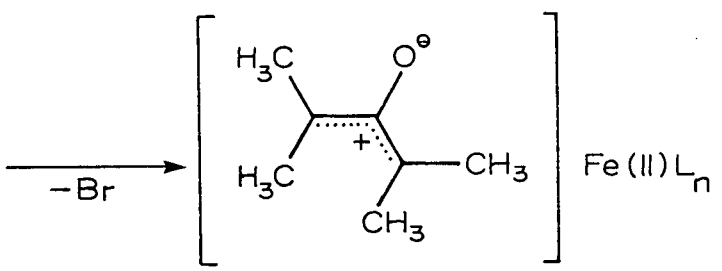

178a. After synthesizing 17β-acetoxy-2β-bromo-5β-androstan-3-one (160a) it was cleanly converted to 159 in refluxing acetic acid - sodium acetate at a rate comparable to reaction IV. This suggested that the mechanism



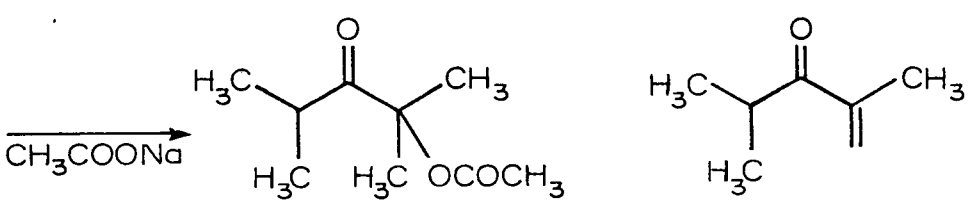

depicted in equation VIII was operating; namely, both bromoketones gave the same intermediate 179. However, more data is required to substantiate this. Mechanistic aspects of the reaction of α,α'-dibromoketones and




180a 180b




180c




180d 180e

iron carbonyl have recently been reported by Noyori et al.[106b] They suggested that initial reduction of the dibromide 180a with $Fe_2(CO)_9$ produces the iron enolate 180b which eliminates bromide ion to form the key oxyallyl - Fe(II) intermediate 180c (see Page 110). Evidence for the intermediacy of 180c during the reduction of dibromoketones was obtained by trapping with nucleophiles. The reduction of 180a in the presence of sodium acetate gave the acetoxy ketone 180d (60%) along with the unsaturated ketone 180e (20%).

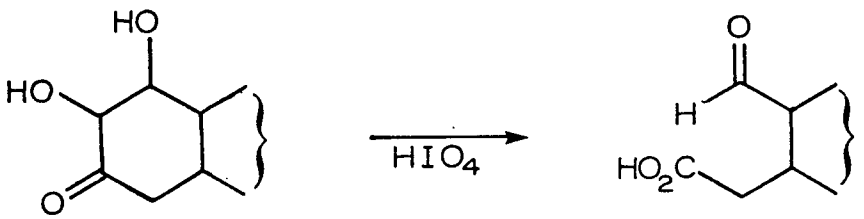
The above mechanistic considerations of α,α'-dibromoketones tend to suggest that bromoenols may undergo an $S_N1$ reaction as proposed in equation VIII.

d. Unsymmetric Ring Cleavage Between Carbons 2 and 3

Having realized the functionalization of carbon-2, experiments were carried out to effect an unsymmetric ring cleavage between carbons 2 and 3. King,[107] Clutterbuck et al.,[108] and others[109] have demonstrated that α-hydroxyketones are oxidized smoothly even in the cold by periodic acid, equation XI. In addition, treatment of diol 181 with periodic

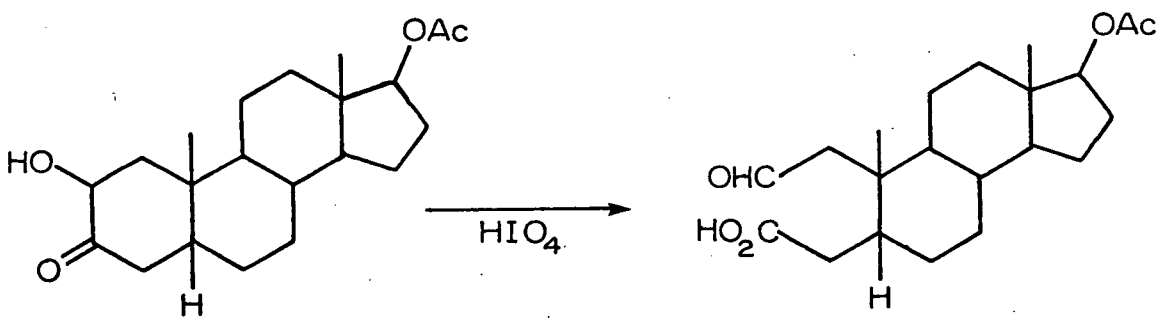
$$R-COCHOH-R' \xrightarrow[HIO_4]{} RCOOH + R'CHO \qquad (XI)$$

acid gives aldehyde 182.[110] In light of these results it appeared highly



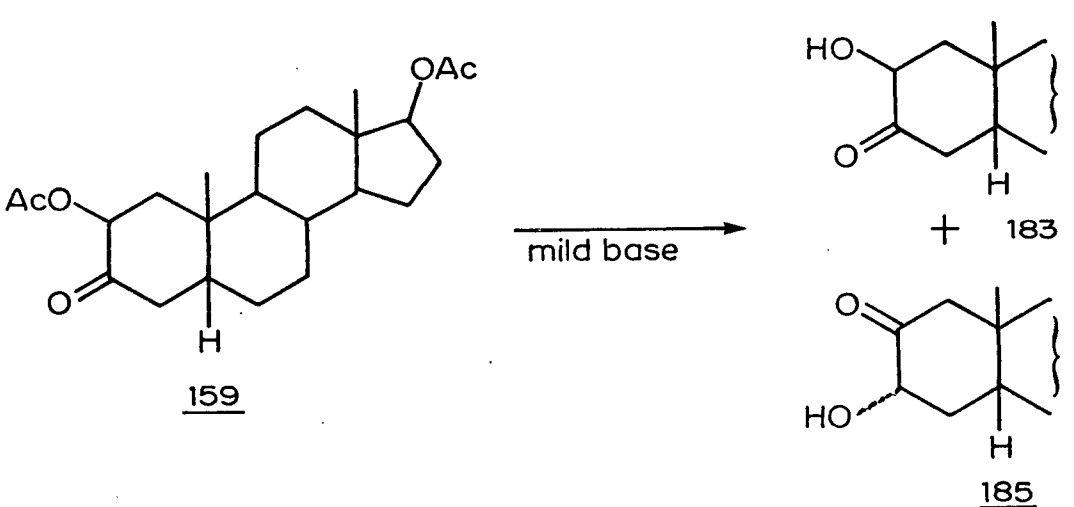

181 182

probable that exposure of hydroxyketone 183 to periodic acid would afford compound 184. However, the action of mild base on diacetate



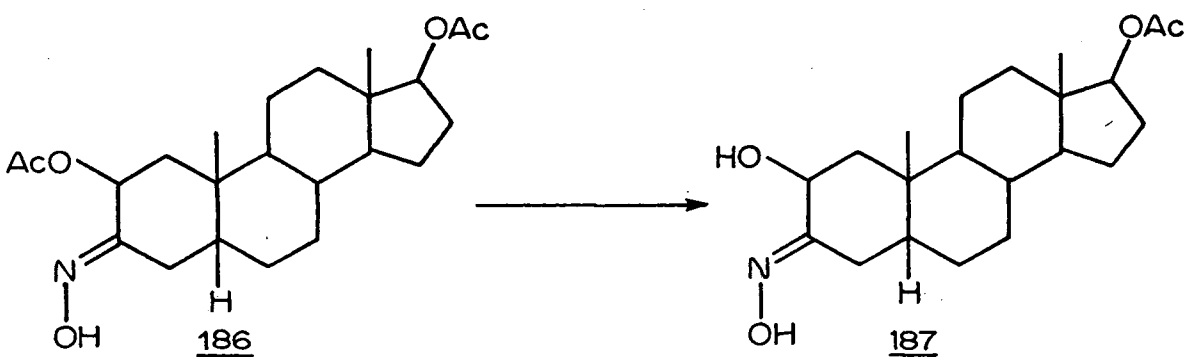

183 184

159 produced two isomeric hydroxyketones 183 and 185 in ca. a 1:1 ratio.




159 185

This was revealed by the t.l.c. and the n.m.r. spectrum of the crude reaction product. The n.m.r. spectrum displayed two sharp singlets (totalling three protons) at $\tau$9.25 and $\tau$9.20 due to the carbon-18 tertiary methyl groups while the appearance of absorptions at $\tau$8.97 and $\tau$8.90 as two singlets (totalling three protons) could be attributed to the carbon-19 tertiary methyl groups. All attempts to prevent this unfavourable reaction--the Lobry de Bruyn-Alberda Ekenstein transformation[111]--by employing very mild hydrolysis conditions proved unfruitful. For example, treatment of diacetate 159 with dilute aqueous methanolic sodium bicarbonate gave hydroxyketones 183 and 185. On the other hand, the hydrolysis of acetoxyoxime 186 would furnish hydroxyoxime 187.

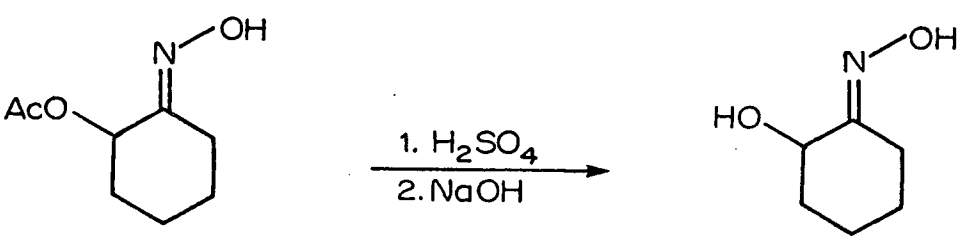



186 187

Thus, exposure of diacetate 159 to hydroxylamine hydrochloride in methanol-sodium acetate under refluxing conditions for three hours afforded two major compounds as indicated by t.l.c. on silica gel. The n.m.r. and infrared spectra of this material suggested that partial hydrolysis of the 2-acetoxy group had occurred to give a mixture of 186 and 187. As a result, the reaction was continued until the 2-acetoxy group had been completely hydrolysed. The course of the hydrolysis was followed by t.l.c. and n.m.r. spectroscopy. The crude hydroxyoxime was obtained as

a white crystalline solid, m.p. 176-182°, in 75-85% yield. This crude material was suitable for preparative work in the subsequent steps. A small sample was recrystallized from methanol for analysis, m.p. 213-215°. The pertinent spectral features in the n.m.r. of 187 were as follows. A double doublet at τ7.21 (J = 4 and 14 Hz) was assigned to the 4β- hydrogen which suggested that the oxime had the stereochemistry shown in 187. As noted previously, the n.m.r. spectrum of syn oxime 87 had a pair of doublets (J = 5 and 15 Hz) at ca. τ7 due to the 4β-hydrogen. A second double doublet at τ5.80 (J = 5 and 13 Hz) could be attributed to the 2α- hydrogen. The n.m.r. spectrum of 187 was determined at both 60 Mc and 100 Mc. No change in the patterns afforded by the 2α- and 4β- hydrogens were observed. It, therefore, appears likely that the splittings are good approximations to the coupling constants. Hence, the ring A acetate had been hydrolysed and the hydroxy group was still at carbon-2. Structure 187 was further corroborated by the mass spectrum which indicated a molecular ion peak at $\frac{m}{e}$ 363.

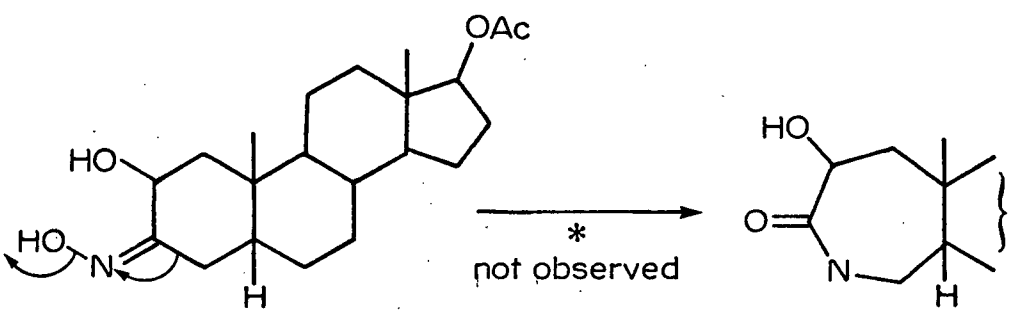
Concurrently, the hydrolysis of diacetoxyoxime 186 was attempted by two other methods. Firstly, treatment of diacetoxyoxime 186 with various bases afforded several products. For example, hydrolysis of the oxime group and the 17β-acetoxy group had also occurred. Kataoka[112] demonstrated that treatment of acetoxyoxime 188 with concentrated sulphuric acid followed by neutralization gave hydroxyoxime 189. Hence,




188 189

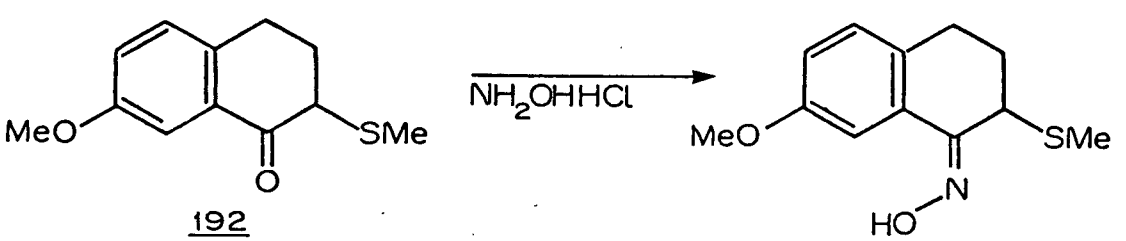
experiments were carried out to effect the hydrolysis of diacetoxyoxime 186 under similar conditions. However, the resulting crude product consisted of numerous compounds as evidenced by t.l.c. Since a suitable method had been developed for obtaining hydroxyoxime 187 this did not necessitate further investigating the above hydrolysis.

It is possible that the isomeric hydroxyoxime 190 could have been formed. Autrey et al.,[40b] found that oximation of the methoxy ketone



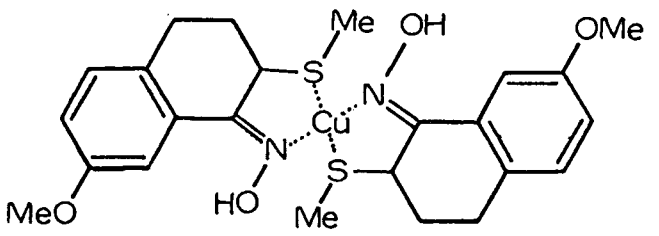

190 191

192 afforded only the anti oxime 193. The convincing criterion for



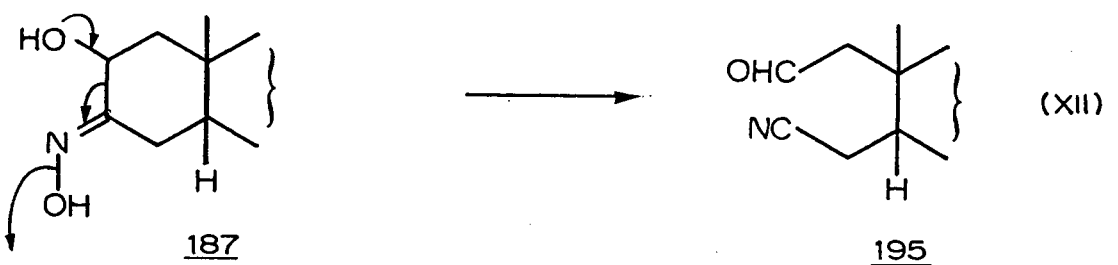

192 193

stereochemistry was the observation of the formation of a chelate, presumed to be 194, on the addition of dilute ethanolic cupric nitrate to an ethanol solution of the oxime.[40b] In light of this work and our




194

n.m.r. data it appeared likely that only hydroxyoxime 187 had been formed. With hydroxyoxime 187 in hand, it was felt that the opportunity existed for a Beckmann fragmentation reaction, equation XI.[40b,113]

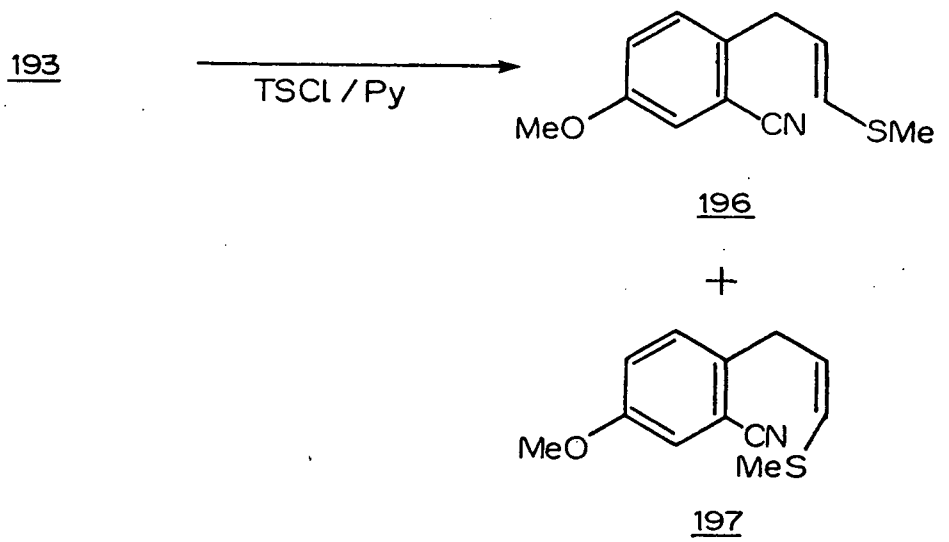



187 195 (XII)

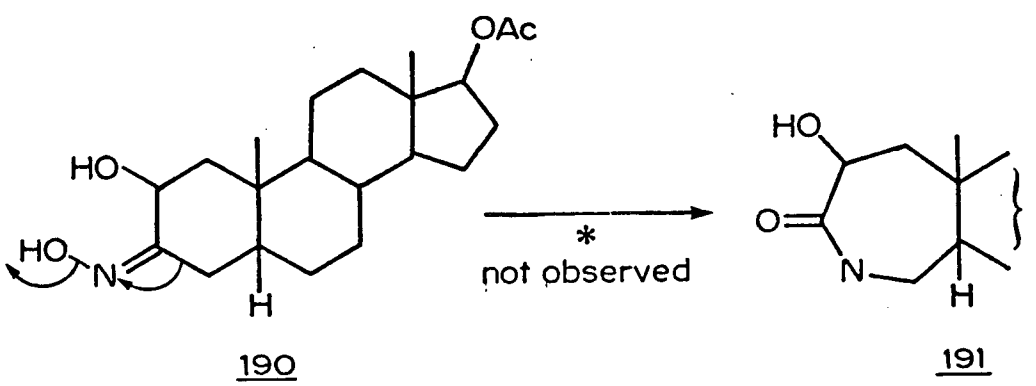
This would give rise to a desired unsymmetric cleavage of ring A in which the termini of the cleaved bond would be left in different oxidation states and, therefore, could be separately modified.

The literature suggested several methods to accomplish the Beckmann fragmentation.[113] Of particular relevance was the work of

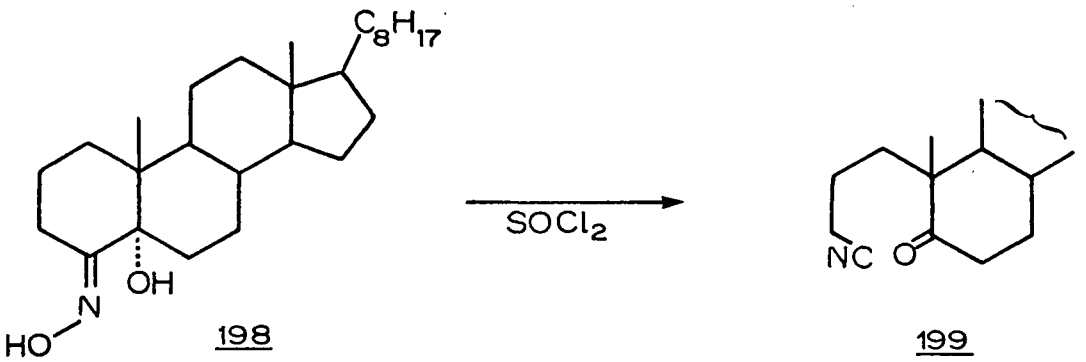
Autrey et al.,[40b] which described the Beckmann fragmentation of anti oxime 193 to the olefins 196 and 197 in ca. a 1:1 ratio. The fragmenta-




tion of hydroxyoxime 187 to cyanoaldehyde 195 was studied under a variety of conditions. Firstly, the traditional use of tosyl chloride in pyridine was examined. Thus, treatment of crude hydroxyoxime 187 with tosyl chloride in refluxing pyridine for five hours afforded cyanoaldehyde 195 as a clear oil in 20% purified yield. Although the yields were low the reaction had evidently taken the desired reaction course. Of additional significance was the fact that hydroxy lactam 191 was not detected.

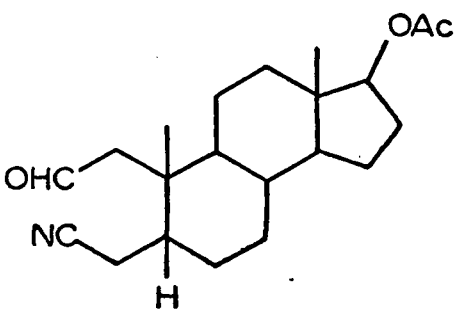


However, according to Grob et al.,[114] the Beckmann fragmentation is not stereospecific and thus this observation of fragmentation could not be used to assign structure to the hydroxyoxime 187. Several attempts were made to improve the yields of the above Beckmann fragmentation reaction by monitoring the reaction, by t.l.c., at regular time intervals. After considerable experimental effort, however, the purified yields of cyanoaldehyde 195 were still ca. 20%. In addition, the isolation of fairly pure cyanoaldehyde 195 from the dark crude product posed a difficult problem. Preparative t.l.c. on silica gel with $CHCl_3$/EtoAC (5/1) as the solvent system was found to be the most practical method to isolate fairly pure cyanoaldehyde. In general, the above procedure gave a very sluggish Beckmann fragmentation reaction, equation XII (see Page 116). Similarly, Autrey et al.,[40b] reported low yields and isolation difficulties when they employed tosyl chloride and pyridine. The low yield was rationalized on the basis that the resulting cyanoaldehyde 195 was very susceptible to oxidation. Even an analytical sample of cyanoaldehyde was found to undergo rapid autoxidation, even in the presence of nitrogen. In summary, the inefficient Beckmann fragmentation reaction, equation XII, and the unavailability of fairly pure cyanoaldehyde thwarted progress for a considerable time. Shoppee et al.,[113c] demonstrated that treatment of 5-hydroxy-5α-cholestan-6-on oxime (198) with thionyl chloride gave excellent yields of cyanoketone 199. Thus, after several trial experiments, brief exposure of hydroxyoxime 187 to thionyl chloride at -20° followed by treatment with 3N potassium hydroxide with subsequent




198 199

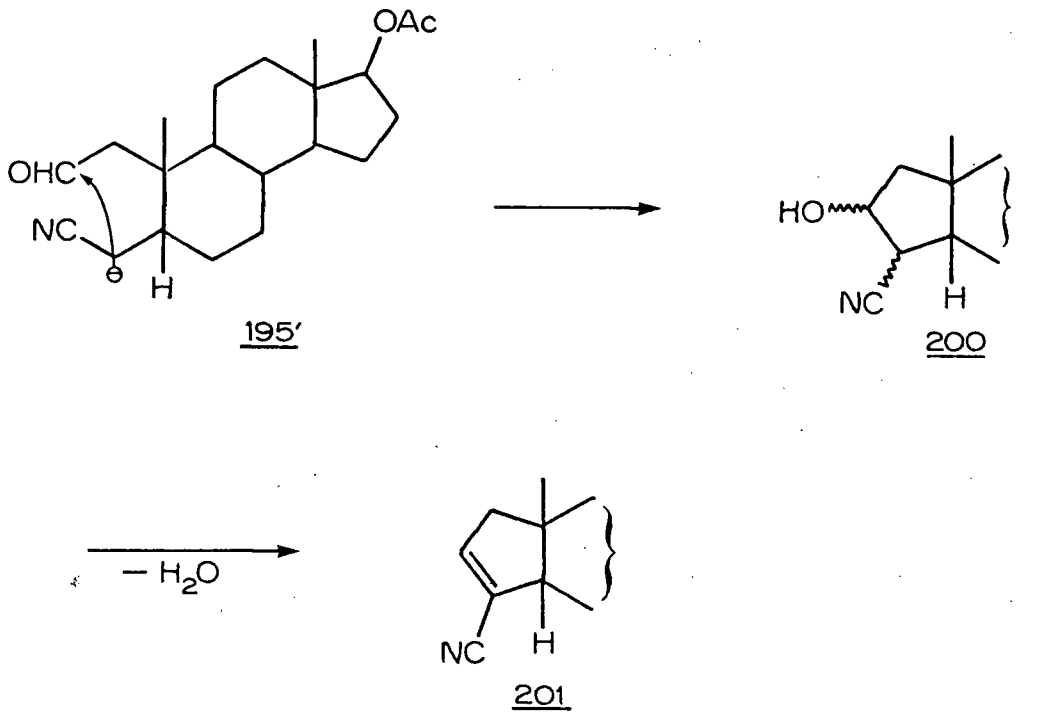
ether extraction afforded cyanoaldehyde 195 in over 80% isolated yield after chromatography, as a white crystalline solid, m.p. 110-112°C.




195

The t.l.c. of the crude reaction product showed the presence of predominantly one product with polar baseline contaminants. Furthermore, the n.m.r. spectrum of the crude material suggested high product purity. However, the purification of cyanoaldehyde 195 was found to be a very temperamental process. The isolated yields by chromatographic methods varied from 25-60%. Fortunately, subsequent synthetic studies obviated this difficulty. After careful chromatography on silica gel hydroxynitrile 200 and olefinic nitrile 201 were isolated as minor components of the crude reaction product. Under the separation conditions, presumably,

the opportunity existed for anion formation to give 195 which could undergo an internal aldol-type cyclization to afford hydroxynitrile 200 and subsequent dehydration would furnish the olefinic nitrile 201. As




195' 200 201

a result, the chromatographic separation of crude cyanoaldehyde was tested on a very inert support, namely, florisil. In this manner, cyanoaldehyde 195 was isolated in greater than 80% yield and neither hydroxynitrile 200 or olefinic nitrile 201 were detected. The isolated cyanoaldehyde 195 crystallized almost immediately to afford beautiful cubes, m.p. 110-112°C. The spectroscopic data of this material were in complete accord with the assigned structure. Thus, the infrared spectrum of 195 exhibited weak absorptions at 2250 $cm^{-1}$ due to the nitrile functionality and at 2740 $cm^{-1}$ due to the aldehydic C-H stretching vibration. In the n.m.r. spectrum of 195 a double doublet (J = 1 and 3 Hz)

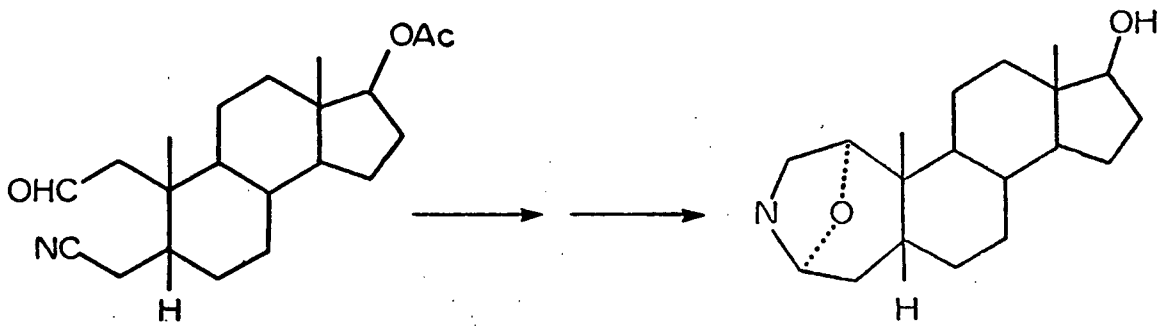
appeared at τ.20 due to the aldehyde proton which is coupled to the two adjacent diastereotopic protons.[115] The n.m.r. spectrum of 195 was determined at both 60 Mc and 100 Mc. No change in the pattern afforded by the aldehydic proton was observed at different field strengths. It, therefore, seems likely that the splittings are good approximations to the coupling constants. Finally, the mass spectrum of 195 had a molecular ion peak at $\frac{m}{e}$ 345. In summary, a convenient and practical method had been developed to effect an unsymmetric ring cleavage between carbons 2 and 3 in 17β-acetoxy-5β-androstan-3-one.

Of additional value was the fact that it seemed highly probable that the aldehyde or nitrile group could be separately modified as in accordance with the general plan.[116] The first synthetic objective had therefore been realized.

## Part II

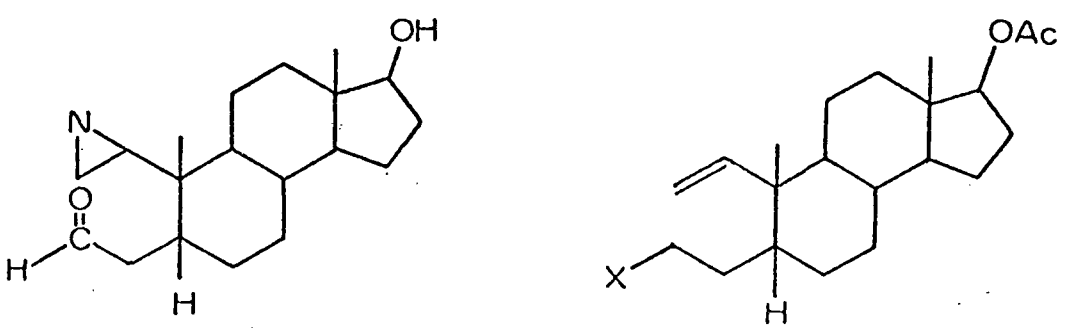
### Attempted formation of the bicycloxazoladine skeleton

Having achieved the desired ring cleavage reaction, the stage was set for entry into the second phase of the program which is the elaboration of cyanoaldehyde 195 to a bicyclooxazolidine. From the




195 47b

outset, it was planned to construct the crucial intermediate 10 from a common olefinic precursor cf. 79 which could arise from the unsymmetric ring cleavage product. Hence, subsequent synthetic studies with cyano-




10 79

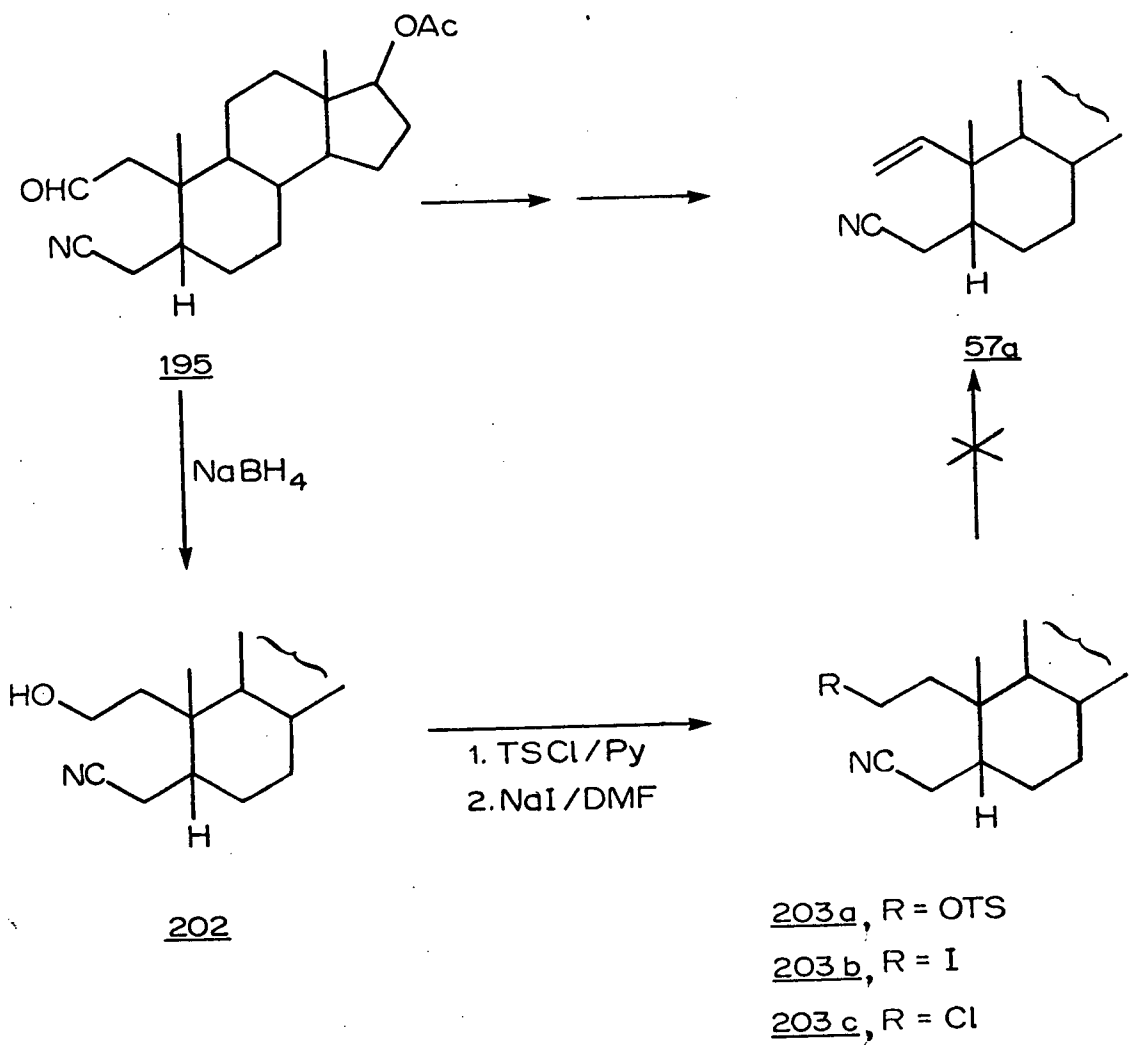
aldehyde 195 would be primarily concerned with the formation of cyanoolefin 57a (CHART XX, Page 124).

Initial investigations with cyanoaldehyde 195 were concerned with the preparation of cyanoiodide 203b via hydroxynitrile 202 since the vinylic side chain could be introduced by effecting the elimination of hydrogen iodide from cyanoiodide 203b as depicted in CHART XX (see Page 124). It could be recalled from previous experiments that treatment of iodo esters 103c and 107c with silver fluoride in pyridine afforded lactones 102a and 106a (CHARTS XIIIa and XIIIb, Pages 57 and 61 ). However, it was hoped that the elimination of hydrogen iodide from cyanoiodide 203b by employing silver fluoride would not be obstructed by nitrile participation.[55,66]

To this end, treatment of cyanoaldehyde 195 with sodium borohydride in ethanol at room temperature for three hours afforded hydroxynitrile 202 (CHART XX, Page 124) in 85% yield as a solid. T.L.C. analysis of this material indicated that it was suitable for use in subsequent steps. The infrared spectrum of this material had a broad band at 3450 $cm^{-1}$ due to the carbon-2 hydroxy group and of note was the absence of the weak band at 2740 $cm^{-1}$ due to the aldehydic C-H stretching vibration. The salient feature in the n.m.r. spectrum of 202 was a triplet (J = 10 Hz) at $\tau$6.30 due to the protons adjacent to the carbon-2 hydroxy group. Finally, the mass spectrum of 202 possessed a molecular ion peak at $\frac{m}{e}$ 347.

In principle, the next step forward involved the dehydration of hydroxynitrile 202 (CHART XX, Page 124). Treatment of hydroxynitrile 202 with tosyl chloride in dry pyridine at room temperature for twenty-four hours afforded cyanotosylate 203a in 81% yield.[64] The t.l.c. of

CHART XX. Synthetic scheme for the formation of cyanoolefin 57a

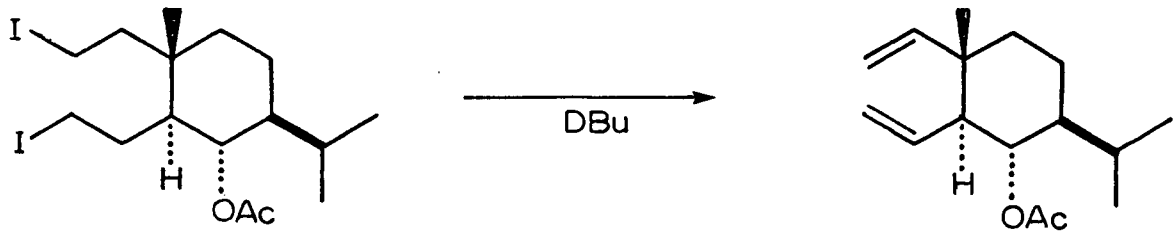


this material indicated predominantly one new compound. Of note was the appearance in the infrared spectrum of a strong doublet at 1190 $cm^{-1}$ due to the tosylate functionality and the disappearance of the broad hydroxy band at 3450 $cm^{-1}$. Treatment of cyanotosylate 203a (CHART XX, Page 124) with sodium iodide in dimethylformamide yielded cyanoiodide 203b in ca. 70% yield.[65] The t.l.c. of this material indicated the formation of a new compound with baseline contaminants. The infrared spectrum of the crude reaction product did not have absorption bands due to the tosylate functionality. In addition, the mass spectrum of 203b had a molecular ion peak at $\frac{m}{e}$ 457 with a prominent peak at $\frac{m}{e}$ 330 due to cleavage of the R-I bond. It appeared that the overall conversion of cyanoaldehyde 195 to cyanoiodide 203b had proceeded in a satisfactory manner.

Unfortunately, treatment of cyanoiodide 203b (CHART XX, Page 124) with silver fluoride in pyridine at room temperature afforded predominantly recovered starting material, with no trace of an olefinic compound. Every precaution was now observed; for instance, activation of silver fluoride,[66] use of dry pyridine, exclusion of oxygen, vigorous stirring and performing the reaction in the dark. In short, all attempts to eliminate hydrogen iodide from cyanoiodide 203b by employing silver fluoride failed even after long reaction times. It should be mentioned that cyanoiodide 203b was very sensitive to light and air. These results with silver fluoride were very annoying since the major factors hindering the conversion of cyanoiodide 203b into cyanoolefin 57a were not clearly apparent.

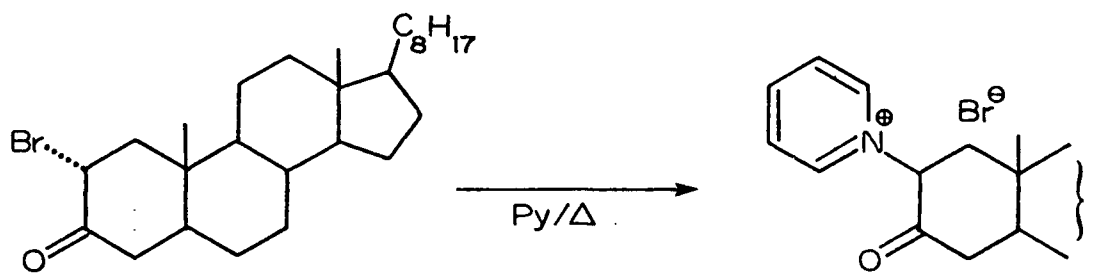
At this stage, a pertinent communication by Kato and Hirata[117] appeared in the literature. In particular, they reported the dehydro-

halogenation of diiodide 204 with 1,5-diazabicyclo[5.4.0]undec-5-ene to afford acetoxy-diene 205 in 39% yield, as a clear oil. 1,5-Diaza-



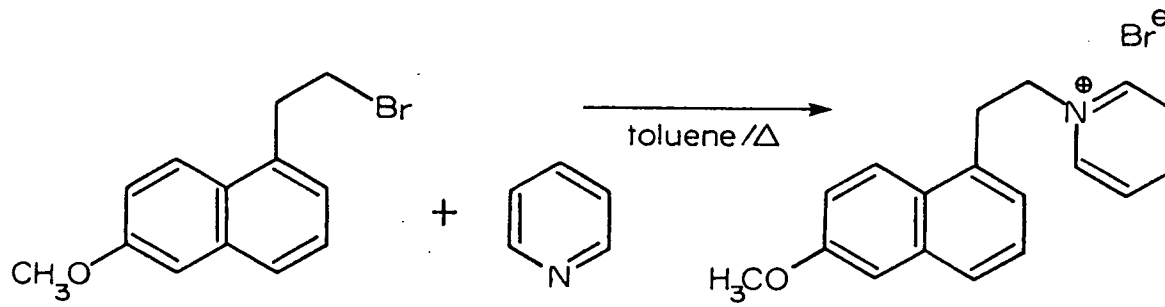

204 205

bicyclo[5.4.0]undec-5-ene (DBU),[118] and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[119] have been shown to be very versatile dehydrohalogenating agents. As both are much more reactive than the amines generally used, much milder conditions can be employed. Accordingly, the reaction of cyanoiodide 203b (CHART XX, Page 124) with DBU and DBN was examined over a wide temperature range. At lower temperatures (below 70° ) impure starting material was recovered. When the reaction was carried out at temperatures above 100° there was a marked tendency for hydroxynitrile 202 to be formed. Taurins et al.,[120] have reported that treatment of α-bromoketone 206 with pyridine under refluxing conditions yields the pyridinium salt 207. Furthermore, the action of pyridine on bromide



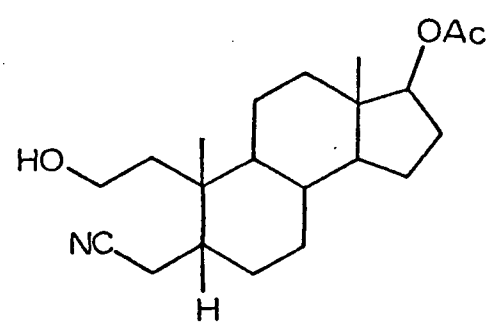

206 207

208 gives pyridinium bromide 209. Nucleophilic attack upon the quaternary




208 209

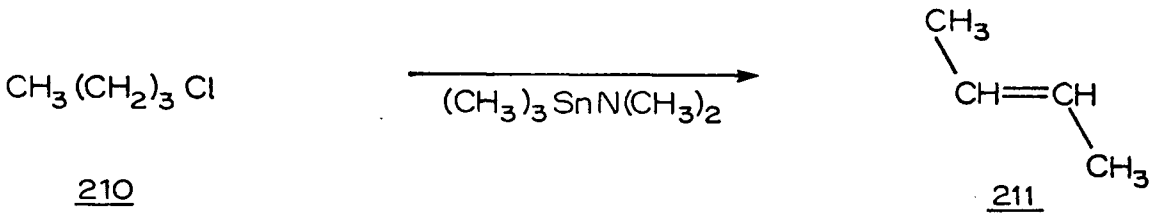
salt may displace the pyridine ring from the quaternizing group.[122] For example, substituted alkylation of primary alcohols has been carried out with alkoxymethyl pyridinium salts.[123] In view of these considerations it appeared reasonable to assume that 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) had displaced the iodide in a $S_N2$ manner to give a quaternary salt which on work up afforded hydroxynitrile 202. As a result, experiments were carried out with




202

dimethylaminotrimethylstannane, a powerful dehydrochlorinating reagent, which is notable for effecting dehydrochlorination under mild conditions.[124] For example, the reaction of n-butyl chloride (210) with dimethylamino-

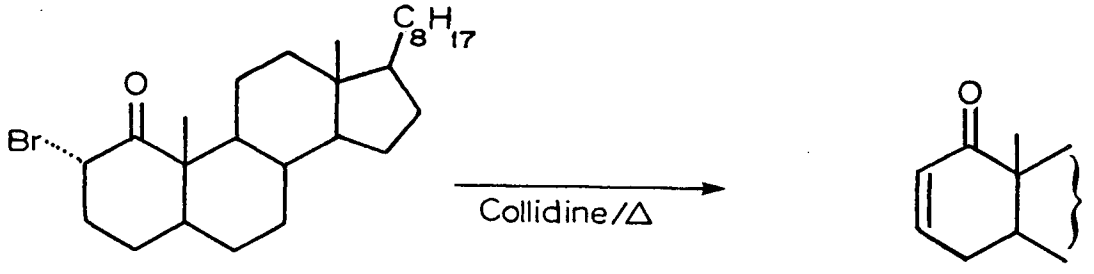
trimethylstannane at 40° gives trans but-2-ene (211) in over 80% yield.[124]




210 211

Treatment of cyanochloride 203c with dimethylaminotrimethylstannane at 40° for four hours afforded several products as evidenced by t.l.c. The infrared spectrum of the crude reaction product, however, did not indicate any olefinic products.

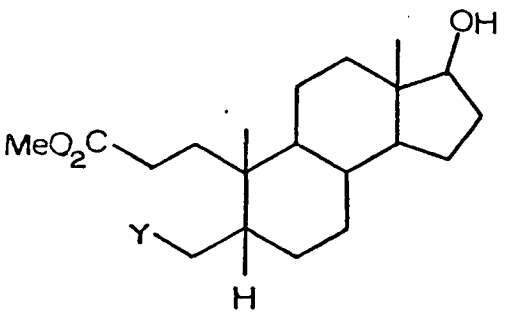
Because of this result and since considerable quantities of cyanochloride 203c (CHART XX, Page 124) had been obtained, experiments were carried out to effect dehydrochlorination by employing collidine.[125] For example, the action of refluxing collidine on bromoketone 212 gives 213 in excellent yield.[125a] In contrast, when cyanochloride 203c was



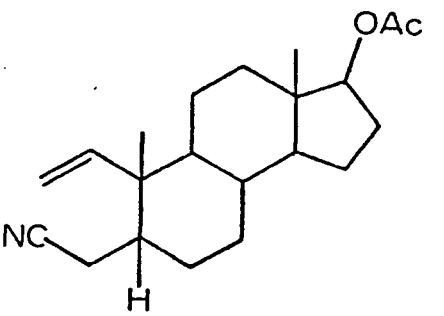

212 213

subjected to refluxing collidine under nitrogen, impure starting material was recovered. It is worthy of mention that ethyldicyclohexylamine has been recommended as a base for the dehydrochlorination of primary chlorides.[126] This base was not employed because of steric factors and the results from previous experiments with collidine.

At this stage, other well documented synthetic procedures for introducing the vinylic side chain were considered.[127] The presence of the cyano functionality, however, severely limited the number of promising methods. Since the dehydrotosylation of compound 107b had been effected by employing collidine, experiments were carried out to prepare cyanoolefin 57a by a similar procedure. All attempts to produce




107b, Y = OTS

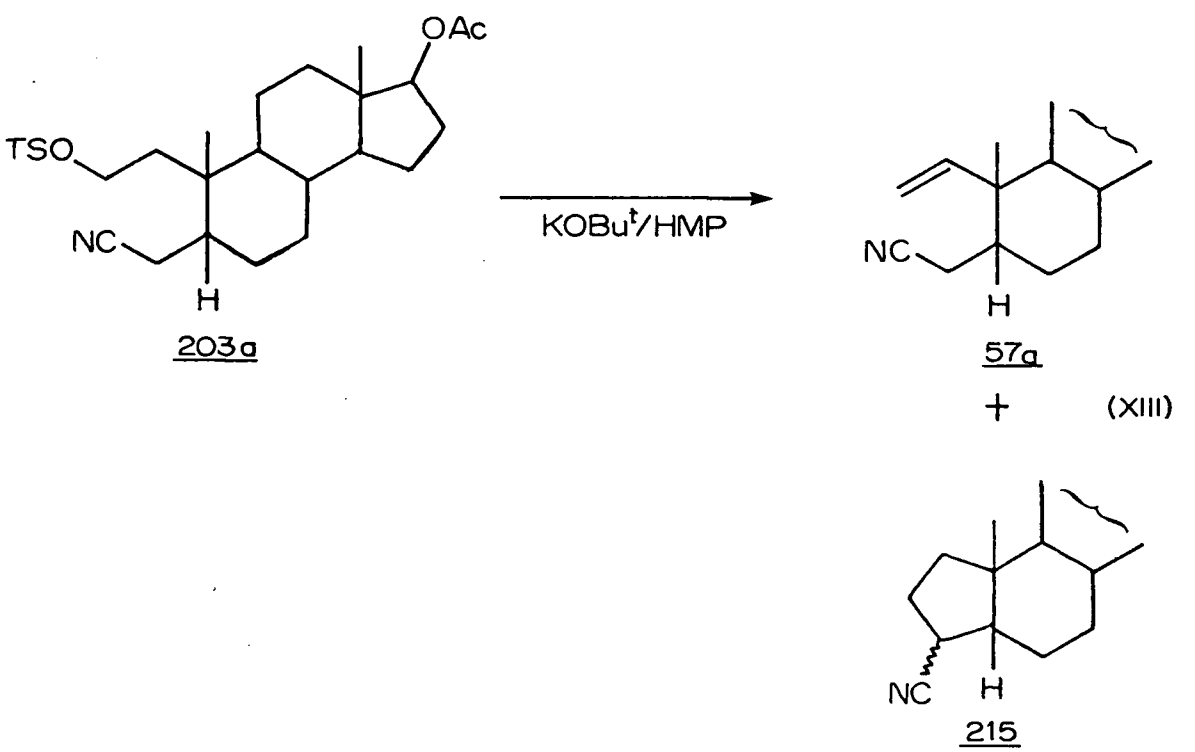



57a

any of cyanoolefin 57a by this method failed.

Synder and Soto[128] have studied the action of potassium t-butoxide in dimethylsulphoxide on sulphonate esters of primary aliphatic alcohols. They reported that the sulfonate esters of primary aliphatic alcohols afforded predominantly t-butyl esters. Nace[129] has demonstrated that hexamethylphosphoramide is an excellent solvent for converting secondary sulphonates to the corresponding olefins. These reports

prompted an examination of the action of potassium t-butoxide on cyanotosylate 203a in dimethylsulphoxide and hexamethylphosphoramide over a wide temperature range. As noted earlier, strong base and high temperatures favours elimination over substitution. No useful results were obtained with dimethylsulphoxide as the reaction medium. On the other hand, treatment of cyanotosylate 203a with potassium t-butoxide in hexamethylphosphoramide at 160° under $N_2$ gave two major products as indicated by t.l.c. Of note was the appearance in the infrared of the



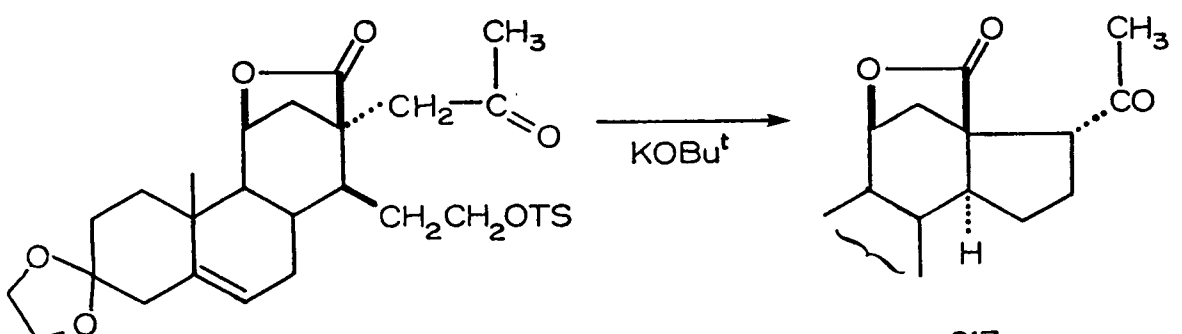

203a

57a + (XIII)

215

crude product of absorption bands at 930 $cm^{-1}$ and 1000 $cm^{-1}$ due to out-of-plane C-H bending vibrations of the vinylic side chain. A weak absorption band was evident at 1630 $cm^{-1}$ which could be attributed to the C=C stretching vibration of the vinylic side chain. Absorptions at

2250 $cm^{-1}$ and 1720 $cm^{-1}$ indicated that the nitrile and 17β-acetate groups had remained intact. The pertinent spectral features in the n.m.r. of the crude reaction product were as follows. A broad singlet totalling three protons appeared at τ9.20 due to the carbon-18 tertiary methyl protons of compounds 57a and 215 while two singlets totalling three protons at τ8.83 and τ8.75 could be attributed to the carbon-19 tertiary methyl protons of compounds 57a and 215, respectively. A broad multiplet between τ5.10 and τ4.20 totalling ca. two and half protons was evident for the olefinic protons of 57a and the carbon-17 protons of 57a and 215. In fact, the n.m.r. signals which have been assigned to the above olefinic compound 57a were in accord with the n.m.r. signals of pure cyanoolefin 57a prepared subsequently. The assumption that compound 215 had been formed also was made on mechanistic grounds. Heusler, Wieland, and Wettstein[130] have reported the conversion of ketotosylate 216 to compound 217 by employing potassium t-butoxide. In view of this

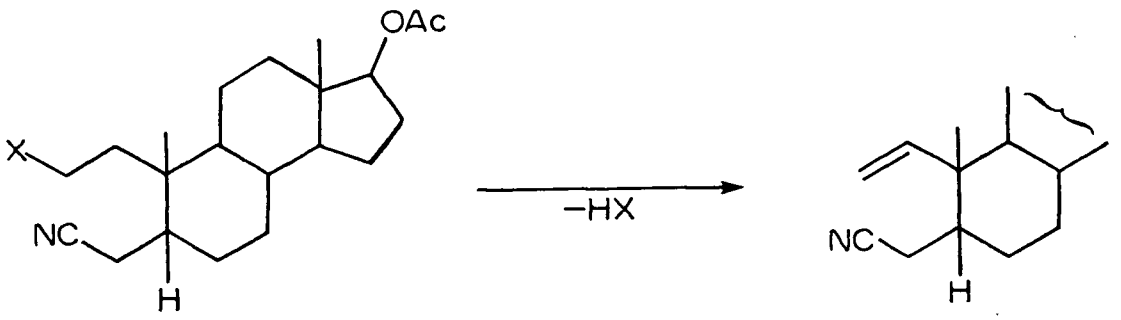



216 217

result it appeared reasonable to assume that the α nitrile anion had displaced the tosylate group in a $S_N2$ type reaction. Even after con-

siderable experimentation the maximum yield of cyanoolefin 57a, prepared from cyanotosylate 203, was always less than 40%.

In general, the incorporation of the double bond by effecting the elimination of HX from a compound of general type 218 had proved rather unpromising. One of the major difficulties was that substitution




218 57a

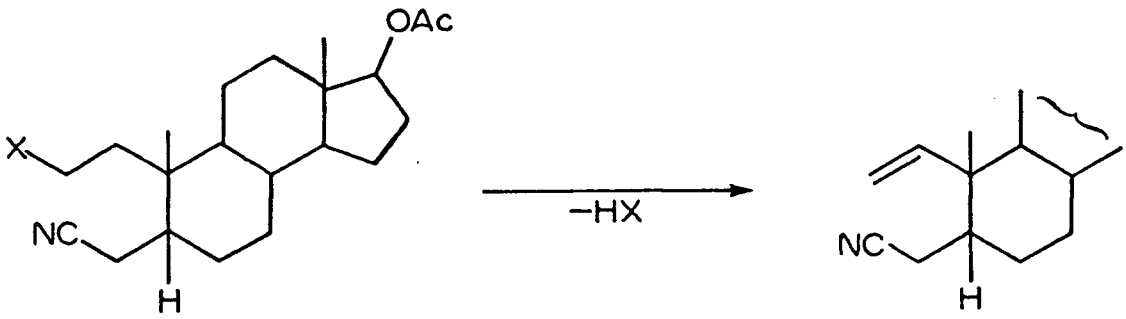
occurred at carbon-2. It is now appropriate to discuss the effects of changes in the substrate on elimination versus substitution.[127] The carbon containing the leaving group is referred to as the α-carbon and the carbon which loses the proton as the β-carbon. Under second-order conditions α branching increases elimination to the point where tertiary substrates undergo few $S_N2$ reactions. For example, Table IV (see Page 133) shows results on some simple alkyl bromides. Two reasons may be presented for this trend. One is statistical: as α branching increases, there are usually more hydrogens for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. β Branching also increases the amount of E2 elimination with respect to $S_N2$ substitution, as shown in Table IV (see Page 133), not because elimination is faster but because the $S_N2$ mechanism is so greatly slowed due to steric factors. These considerations tend to

Table IV

The effect of α and β branching on the rate of E2 elimination and on the amount of olefin formed. The reactions were between the alkyl bromide and $OEt^{\ominus}$. [127]

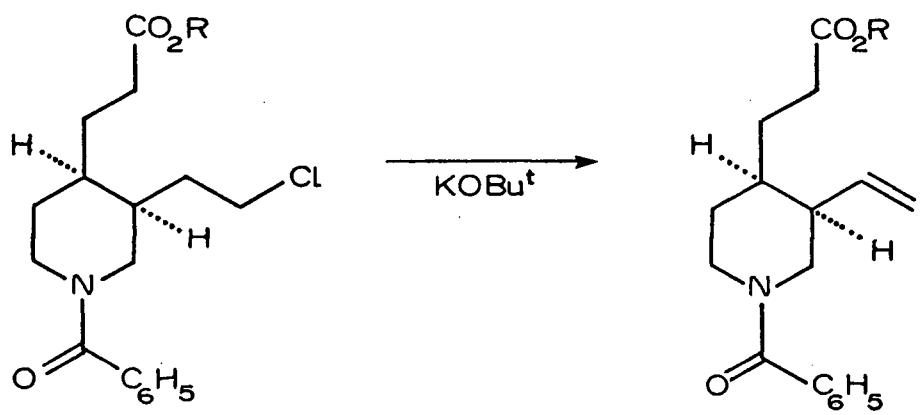
| Substrate | Temperature | Olefin % |
|---|---|---|
| $CH_3CH_2Br$ | 55° | 0.9 |
| $(CH_3)_2CHBr$ | 25° | 80.3 |
| $(CH_3)_3CBr$ | 25° | 97 |
| $CH_3CH_2CH_2Br$ | 55° | 8.9 |
| $CH_3CH(CH_3)CH_2Br$ | 55° | 59.5 |

indicate that the introduction of unsaturation into a compound of general type 218 by a base catalysed elimination of HX is rather unfavourable.




218 57a

However, most recently Uskoković and his colleagues[131] reported the synthesis of 9-epi-quinine and 9-epi-quinidine in which they converted chloride 219a to olefin 220b. The most efficient method to introduce

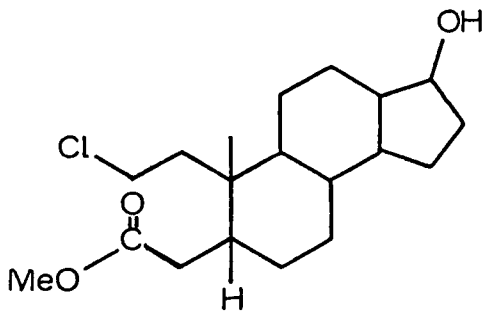



219 a, R = $C_2H_5$
219 b, R = H

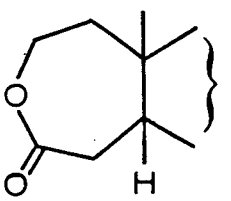
220 a, R = H
220 b, R = $C_2H_5$

the double bond consisted of a reaction sequence involving saponification of 219a, dehydrochlorination of acid 219b with potassium t-butoxide in

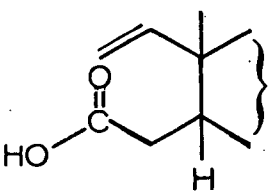
dimethylsulphoxide/benzene, and esterification of the resulting acid 220a to give the desired N-benzoylhomomeroquinene ethyl ester 220b. Hence,




221



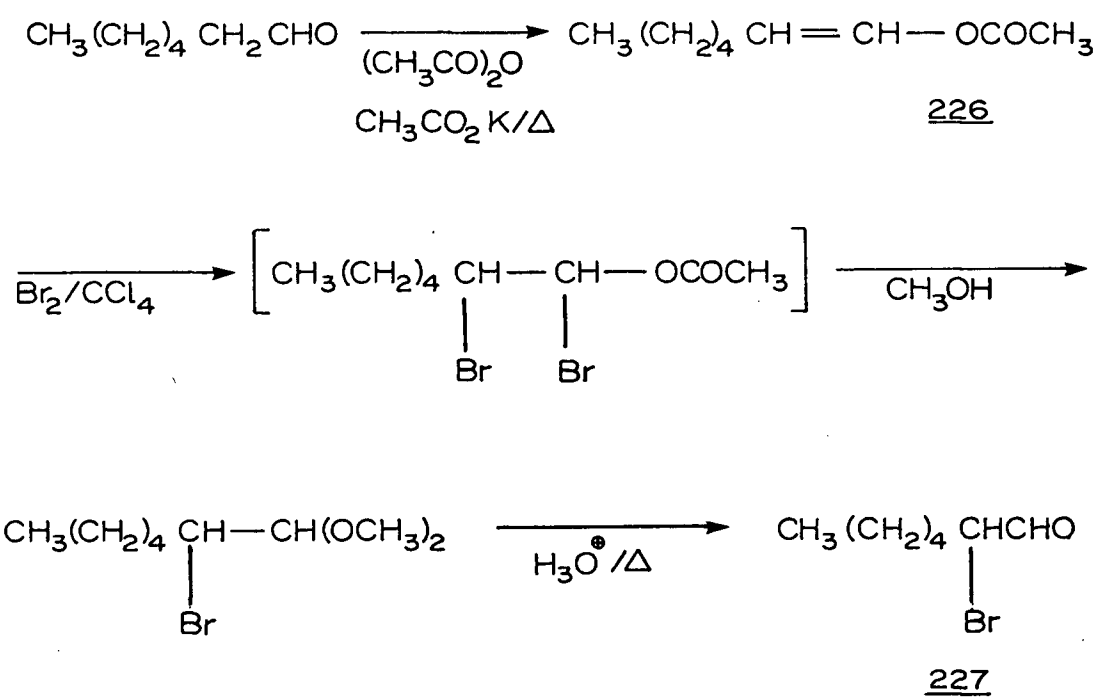

102a




222

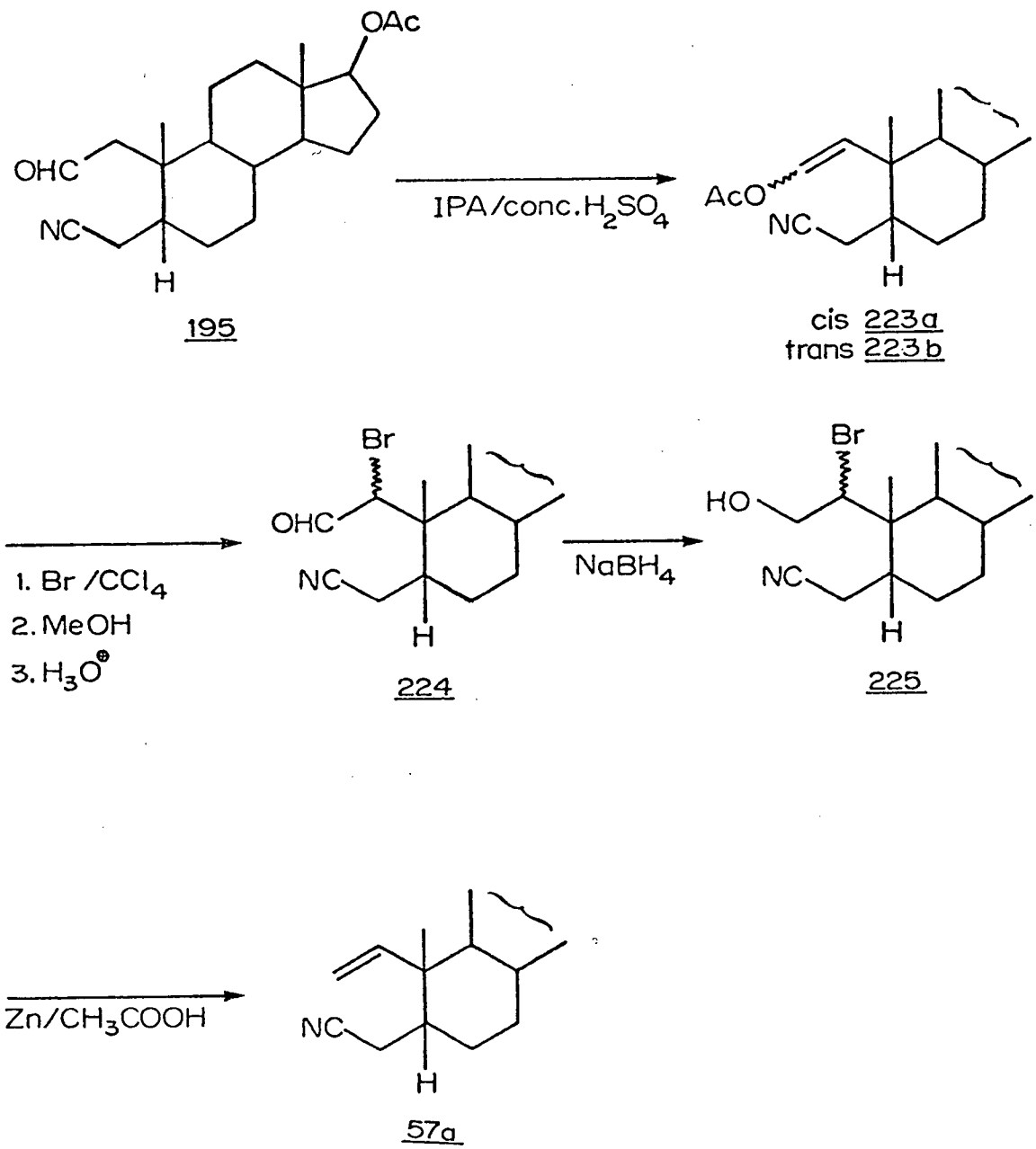
converting the ester functionality to the acid group presumably prevented an intramolecular cyclization reaction similar to reaction XIII from occurring. The possibility would also exist for the formation of a lactone. However, cyclization to an eight-membered ring lactone has low probability. On the other hand, the action of potassium t-butoxide on chloroacid 221 may form the seven-membered ring lactone 102a rather than effect dehydrochlorination to afford compound 222. Dehydrochlorination of acid 219b involves the elimination of hydrogen chloride adjacent to a tertiary centre while in compound 221 dehydrochlorination would occur adjacent to a quaternary centre.

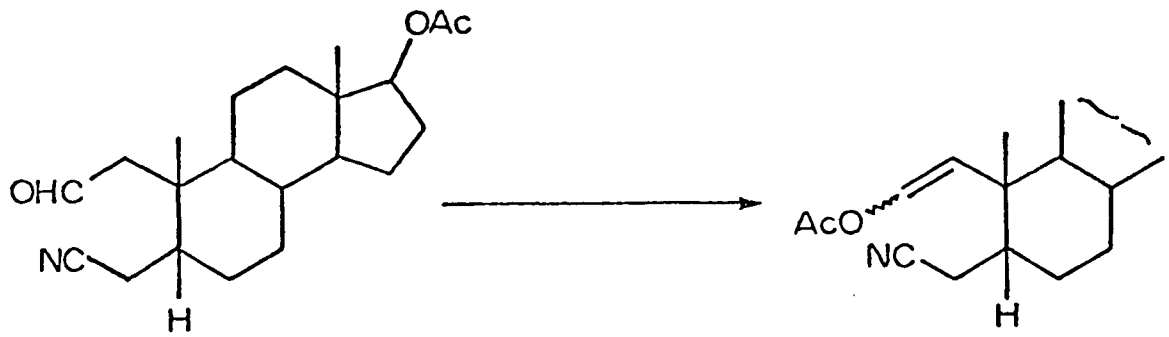
Several methods had been employed to synthesize compound 57a which formally represents an oxidization of carbon-1. It was now con-



templated that the introduction of an appropriate substituent at carbon-1 (oxidation process) could facilitate the introduction of the double bond. For example, halohydrins can be converted into the corresponding olefinic product by zinc dust/acetic acid.[132] Hence, the generation of the double bond might be accomplished by reduction of hydroxybromide 225 (CHART XXI, see Page 137). Examination of the literature revealed that the direct bromination of aldehydes is often complicated by a competing reaction with the aldehyde C-H bond.[133] Bedoukian[134] has reported the formation of the bromoaldehyde 227 by bromination of the enol acetate 226 followed by the action of methanol and subsequent acid treatment. As a result, experiments were carried out to investigate

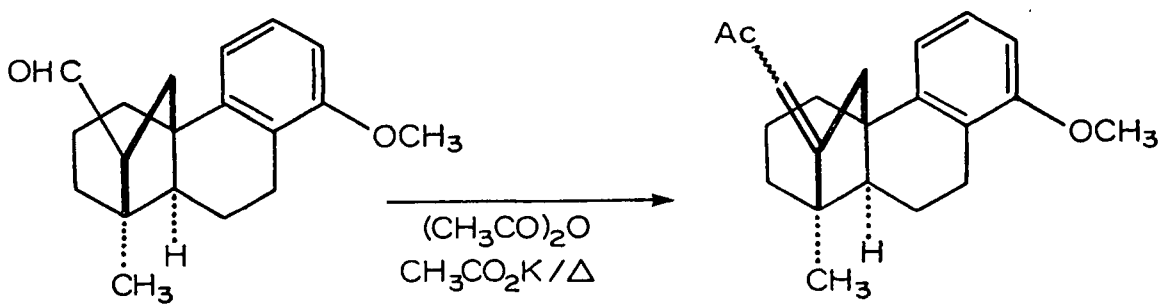
CHART XXI. Second general scheme for the formation of cyanoolefin 57a





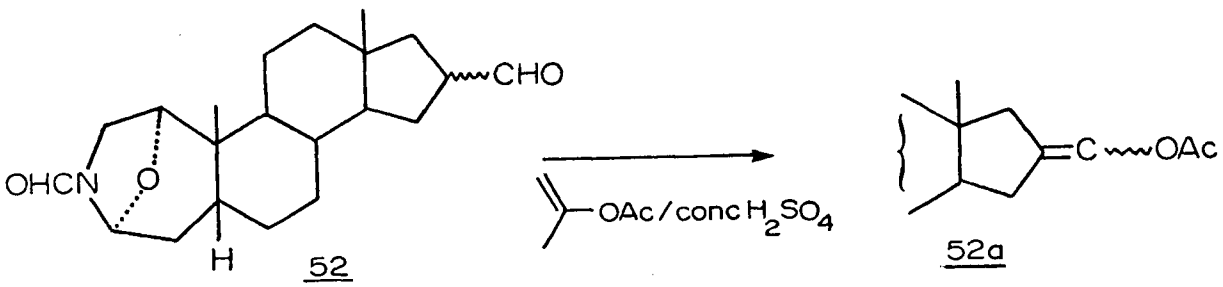

195 cis 223a trans 223b

the enol acetylation of cyanoaldehyde 195. It was rather surprising to



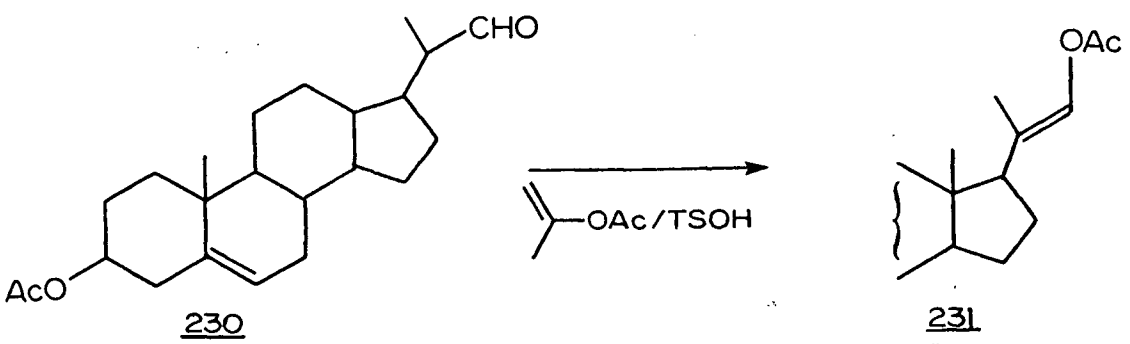

228 229

find that the conversion of an aldehyde into the corresponding enol acetate has been the subject of only limited experimentation. Grafen and his colleagues[135] treated aldehyde 228 with potassium acetate in acetic anhydride at 135° for six hours to afford enol acetate 229. Oka




52 52a

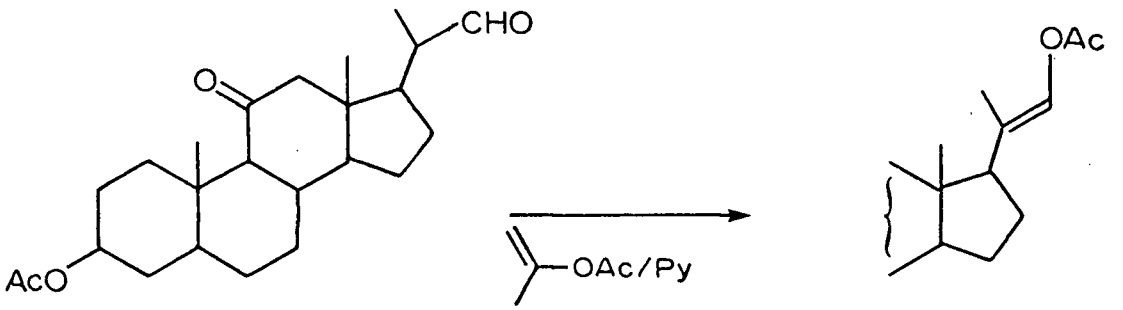
and Hara[4] employed isopropenyl acetate containing sulphuric acid to convert aldehyde 52 to the enol acetate 52a. The action of isopropenyl




230 231

acetate containing p-toluenesulphonic acid on aldehyde 230 gave enol acetate 231 in 35% yield as reported by Moffett et al.[136]. Cameron et

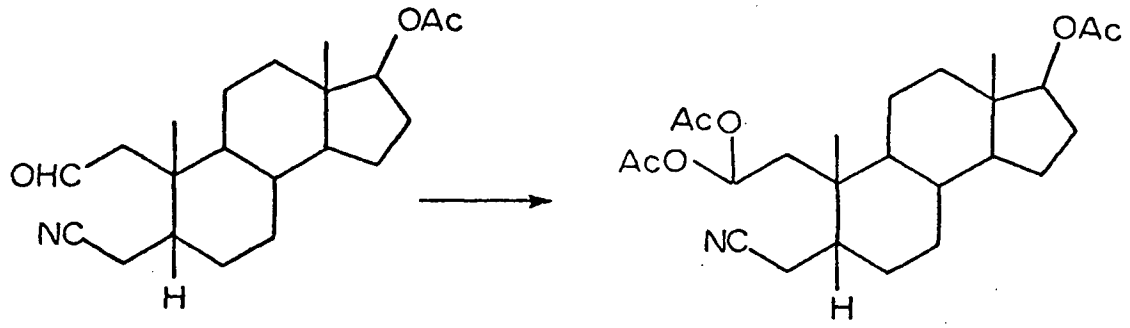
al.,[137] demonstrated that treatment of aldehyde 232 with isopropenyl acetate in the presence of pyridine gave enol acetate 233. At this juncture it




232 233

was considered by us that the chemical behaviour of aldehydes and ketones were comparable. Since Grafen and his colleagues,[135] Bedoukian,[134] and others[138] have employed potassium acetate - refluxing acetic anhydride for enol acetylations with varying degrees of success attempts were made to form the enol acetate of the cyanoaldehyde 195 under similar conditions. The dark reaction product, however, consisted of numerous products accompanied by insoluble material. A number of trial experiments were, therefore, initiated to ascertain the most favourable conditions for this reaction. For example, iospropenyl acetate - concentrated sulphuric acid,[4,139] acetic anhydride - perchloric acid,[140] isopropenyl acetate - p-toluenesulphonic acid,[136,141] Edwards-Rao reagent,[142] and isopropenyl acetate - pyridine were employed.[137] The reactions were carefully monitored by t.l.c. on silica gel. In summary, the reaction of cyanoaldehyde 195 with refluxing isopropenyl acetate - concentrated sulphuric acid was of sufficient interest to warrant further investigatons. It was found that the action of acetic anhydride - perchloric acid in ethyl acetate on cyano-

aldehyde 195 gave compound 234 with several minor components as indicated by t.l.c. analysis. The infrared spectrum of this crude product indicated



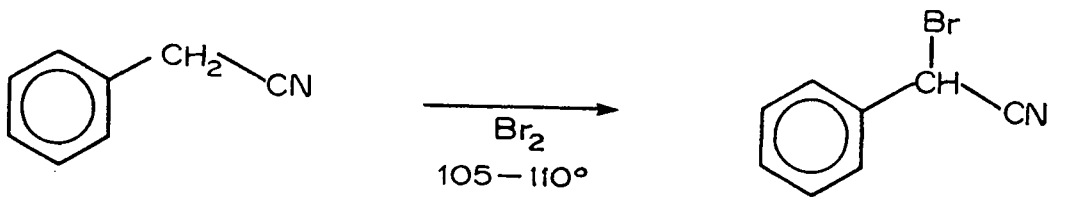

195 234

the absence of the aldehyde C-H stretching vibration at 2750 $cm^{-1}$. Of note was the appearance of a strong carbonyl band at 1750 $cm^{-1}$ which could be attributed to the acetic acylal carbonyls. The n.m.r. spectrum of the crude product had three three-proton singlets at ca. $\tau$8 due to the acetic acylal group and the 17$\beta$-acetoxy functionality. A one-proton triplet (J = 7 Hz) appeared at $\tau$3.14 due to the proton adjacent to the acetic acylal group. Most recently, Andersen et al.,[143] have found that the action of acetic anhydride - perchloric acid in ethyl acetate on an aliphatic aldehyde gave predominantly the corresponding acetic acylal. With the other reaction conditions an overwhelming mixture of compounds were formed and it appeared that extensive oxidation had occurred. Employing isopropenyl acetate - concentrated sulphuric acid conditions attempts were made to improve the yield by varying the reaction parameters. Of overriding importance, however, was the awareness that cyanoaldehyde 195 was very susceptible to oxidation. Under the general reaction conditions it would readily undergo oxidation. Undoubtedly this would lower yields and present purification difficulties. Attempts to obviate these problems

by adding an inhibitor and continuously bubbling nitrogen through the reaction solution proved promising. The addition of hydroquinone, 2,6-di-tert-butyl-phenol, or 2,5-di-tert-butyl-p-benzoquinone to the reaction prevented appreciable oxidation. However, it was most critical to employ more than 100 mg. of inhibitor to 500 mg. of cyanoaldehyde otherwise appreciable amounts of dark intractable material was formed. The utility of the inhibitor was governed by its chromatographic behaviour. 2,5-Di-tert-butyl-p-benzoquinone was found to be the most effective and practical inhibitor in terms of preventing oxidation and chromatographic separation from the reaction product. It is noteworthy that the enol acetylation was very sensitive to reactant concentration, reaction time, and temperature. The isolation of enol acetates 223a and 223b (CHART XXI, Page 137) as a mixture was achieved by column chromatography on silica gel with $CHCl_3$ as the eluent. In summary, the enol acetates could be obtained in 62-68% isolated yield when the reaction was carried out by employing isopropenyl acetate - concentrated sulphuric acid under carefully controlled conditions in the presence of 2,5-di-tert-butyl-p-benzoquinone. T.L.C. analysis of this material indicated the presence of two compounds in ca. a 1:1 ratio. The spectroscopic properties of the mixture of enol acetates 223a and 223b were in accord with the assigned structures. Of note was the appearance in the infrared spectrum of an intense band at 1745 $cm^{-1}$ due to the vinylic acetate carbonyl. A weak band at 1660 $cm^{-1}$ was evident for the carbon-1 carbon-2 double bond. The salient features in the n.m.r. spectrum of the mixture of enol acetates were a broad singlet at $\tau$9.20 due to the carbon-18 tertiary methyl groups of 223a and 223b while two sharp singlets at $\tau$8.80 and $\tau$8.70 (totalling

three protons) could be attributed to the carbon-19 tertiary methyl groups of 223a and 223b. Two AB pair of doublets (totalling two protons) appeared at τ5.42, τ4.74 and τ3.04, τ2.96 (J = 8 and 13 Hz) due to the carbon-1 and carbon-2 olefinic protons of the cis and trans enol acetates. The n.m.r. spectrum of the isolated mixture of enol acetates (small scale) suggested that the cis and trans enol acetates 223a and 223b were present in ca. a 1:1 ratio. However, their separation was unnecessary since in subsequent steps the mixture of enol acetates would afford compound 57a (CHART XXI, Page 137). Finally, the mass spectrum of the mixture of enol acetates had a molecular ion peak at $\frac{m}{e}$ 387.

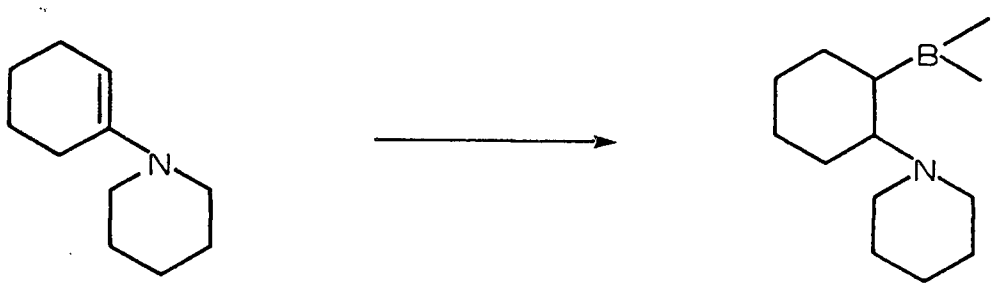
Having achieved the enol acetylation of cyanoaldehyde 195 it was decided to brominate the enol acetates in a manner analogous to that employed by Bedoukian.[134](see Page 136) Preliminary studies directed along these lines, however, proved unfruitful and led only to complex mixtures. It is worthy of note that bromine may be introduced alpha to a nitrile group by direct bromination, which could be a complicating factor in this reaction. For example, Robb and Schultz[144] reported that the action of bromine on nitrile 235 gave bromonitrile 236. One



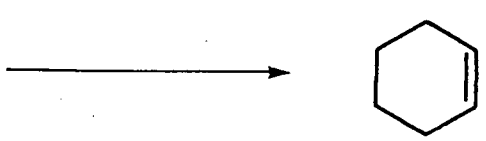

235 236

important aspect of this study was the construction of the mixture of enol acetates 223a and 223b in reasonable quantities.

Hydroboration of the enol acetates followed by treatment with acetic anhydride could give cyanoolefin 57a.[145] However, the directive effect of the acetoxy group is small and both α- and β- boron intermediates would be formed.[146] The situation is also complicated by the greatly enhanced tendency for the intermediate to undergo elimination with subsequent rehydroboration.[146] Lewis and Pearce[147] have reported that when N-cyclohex-1-enylpiperidine (237) was treated with diborane in tetrahydrofuran and the resulting organoborane 238 was subjected to refluxing diglyme in the presence of a carboxylic acid, cyclohexene (239) was formed. This procedure has been applied to a number of enamines of



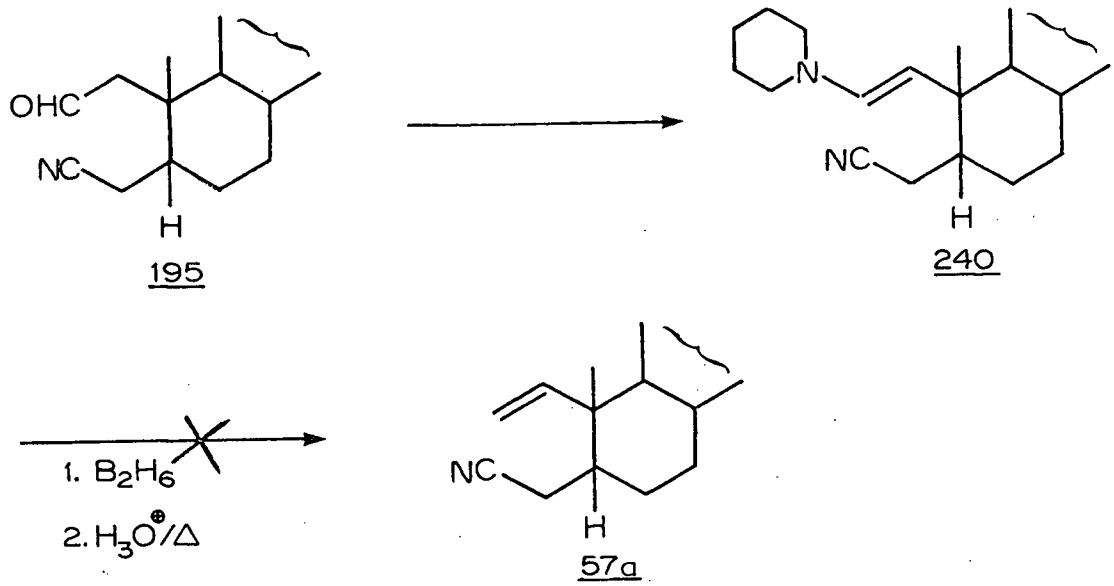

237 238



239

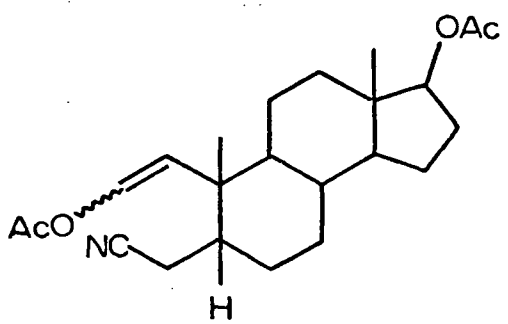
cyclic and acyclic ketones and the alkenes have been obtained in yields of greater than 80%. It is worthy of note that they did not report the formation of alkenes from the corresponding aldehydes via hydroboration

of the enamines Nevertheless, experiments were carried out to prepare cyanoolefin 57a from enamine 240 via hydroboration. Enamine 240 was




prepared by employing conditions analogous to that used by Herr and Heyl.[148] Treatment of cyanoaldehyde 195 with piperidine in benzene under refluxing conditions using a Dean Stark trap gave enamine 240 in good yield. T.L.C. analysis of the crude product indicated one major component. The infrared spectrum of the crude product had a weak band at 1640 $cm^{-1}$ due to the carbon-1 carbon-2 double bond and a weak band at 960 $cm^{-1}$ due to the out-of-plane olefinic C-H bending vibrations. The salient features in the n.m.r. of the crude product were a three-proton singlet at $\tau$8.87 due to the carbon-19 tertiary methyl group of 240 and a two proton AB pair of doublets (J = 15 Hz) at 5.84 and 4.24 due to the carbon-1 and carbon-2 olefinic protons of 240, respectively. Treat-

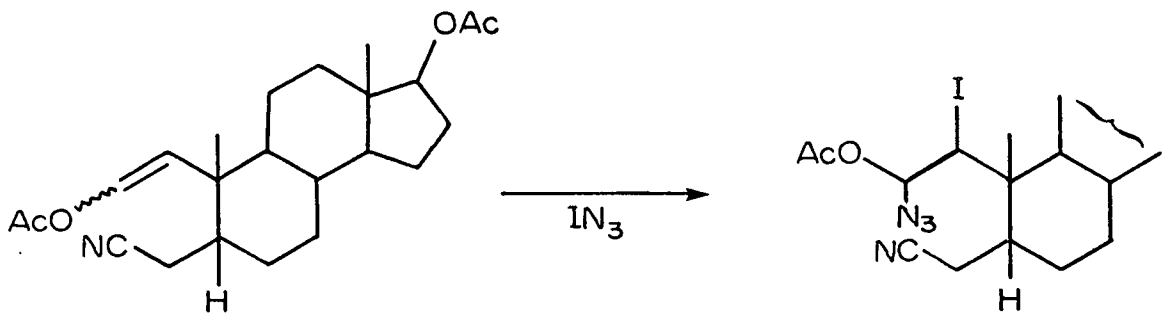
ment of enamine 240 with diborane in tetrahydrofuran with subsequent refluxing in diglyme in the presence of acetic acid did not give cyano-olefin 57a. T.L.C. analysis of the crude product indicated the presence of one major compound with baseline contaminants. However, the infrared spectrum of the major component did not indicate any vinylic side chain characteristics. Of note was the appearance in the infrared spectrum of a very weak nitrile band at 2250 $cm^{-1}$. It is documented that diborane can effect the reduction of nitriles to primary amines. In summary, the hydroboration approach had proved unpromising and, therefore, it was planned to further investigate the utility of the mixture of enol acetates 223a and 223b.



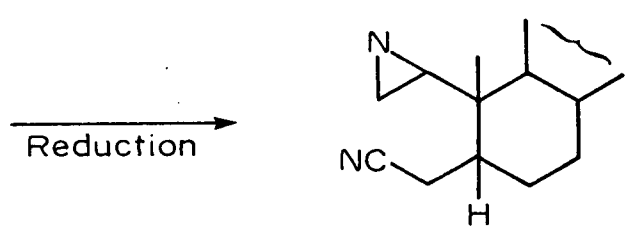

223a, cis
223b, trans

The formation of the enol acetates formally represented the oxidation of carbon-1 with the introduction of the required degree of unsaturation. On this basis two possible pathways became apparent for advancing the general plan. The first approach fully exploited the unsaturated nature of the enol acetates. Hassner et al.,[149] have studied the addition of iodine azide to olefins followed by lithium aluminum hydride reduction to afford aziridines. As a result of this work it was

hoped that iodine azide would add to enol acetates 223a and 223b. The possibility could then exist for the reduction of the iodo azide adduct 241 to give an aziridine of general type 242. The mode of addition



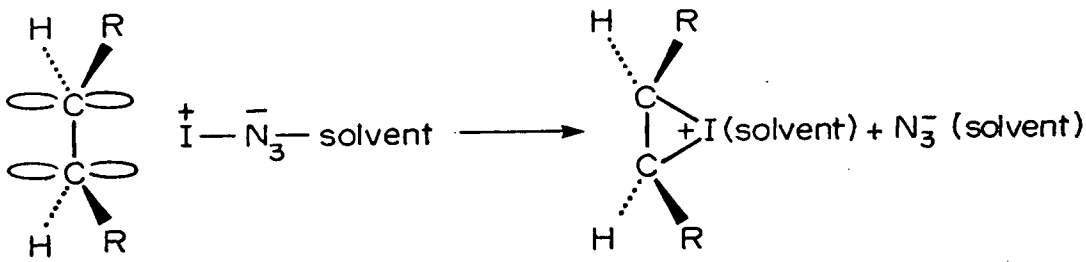

223 241



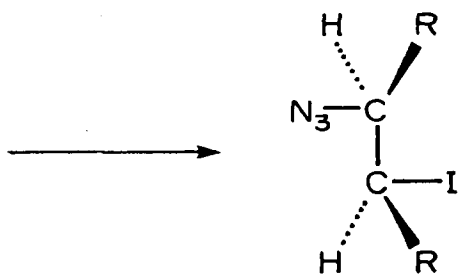

242

would presumably govern the course of the reduction reaction. The stereochemical aspects of this addition reaction are worthy of consideration. Hassner[149c] has suggested that iodine azide addition involves

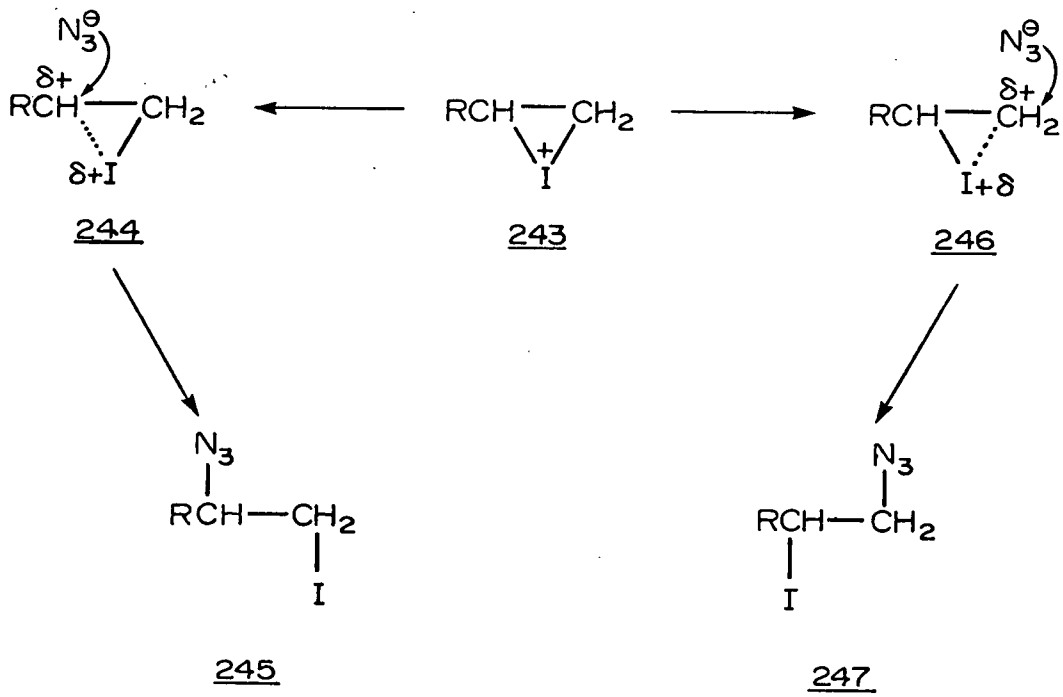
electrophilic attack on the olefin with formation of a three-membered-ring iodonium ion, equation XIV. Once a three-membered-ring is formed,




(XIV)

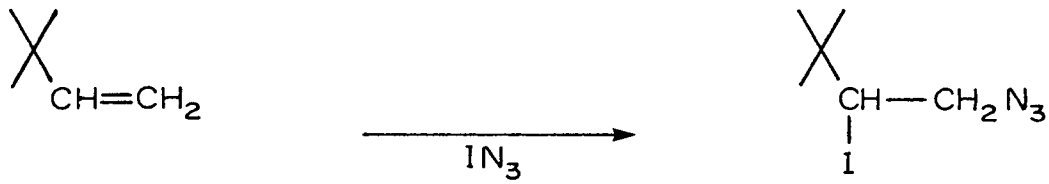



opening will occur from the back side resulting in trans addition of iodine azide. A good probe for the mechanism is often the regiochemistry of a reaction. The addition of iodine azide to terminal olefins gives a three-membered-ring ion itermediate 243 which undergoes opening via the lower energy transition state 244 rather than 246 when R can stabilize an incipient positive charge. If these considerations are valid, then an



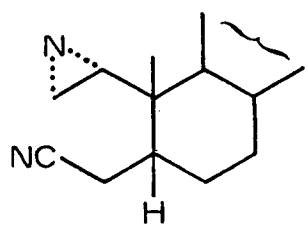
$C_2H_5O_2CCH = CH_2$ 248

electron-withdrawing R group in 243 should destabilize transition state 244 relative to 246. In fact, Hassner demonstrated that ester 248 leads to a 20:30 mixture of 247:245 (R = $CO_2C_2H_5$). In addition to the electronic factors one must consider steric factors. Hassner[149c] found that addition of iodine azide to t-butylethylene (249) gave exclusively 250. Thus the large t-butyl group exerts a strong steric effect in the opening of the three-membered-ring iodonium ion. On the basis of these considerations it was felt that the addition of iodine azide to enol acetates 223a and

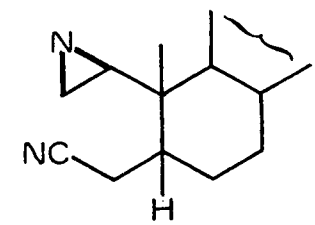



249 250

223b would give predominantly, if not exclusively, an adduct of general type 241. It is interesting to note that since two new asymmetric centres



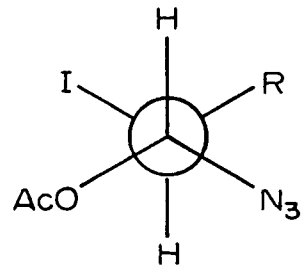

242a



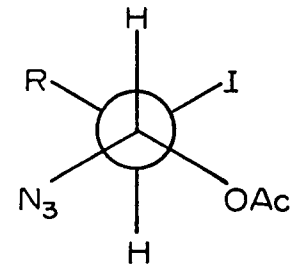

242b

are being created in both the cis and trans enol acetates 223a and 223b there exists the possibility for the formation of eight new compounds (CHART XXII, Page 151). In view of the above discussion it appeared likely that compounds 241-a,b,c, and d would be formed. However, the reduction reaction would give rise to only two aziridines 242a and 242b. Therefore, the stereochemical problem of the addition reaction did not cause concern.

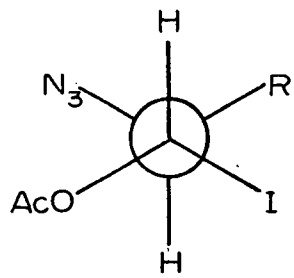
CHART XXII. Possible iodo azide adducts of enol acetates 223a and 223b

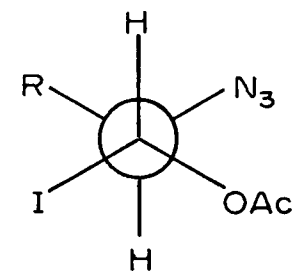


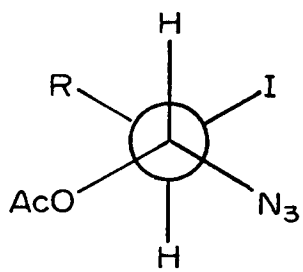

241a



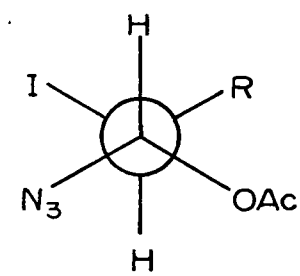

241b



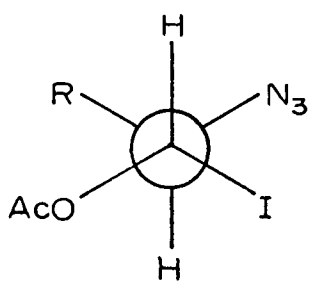



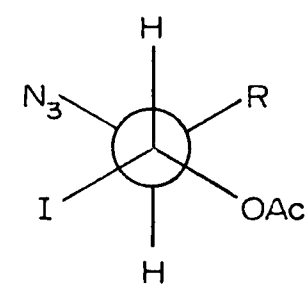



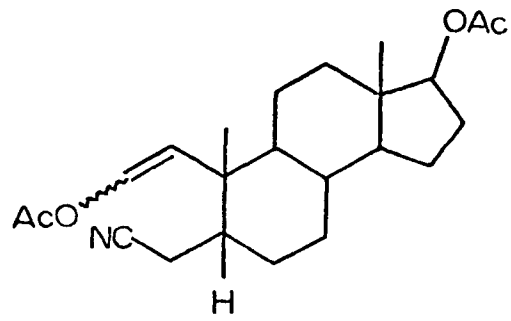

241c




241d

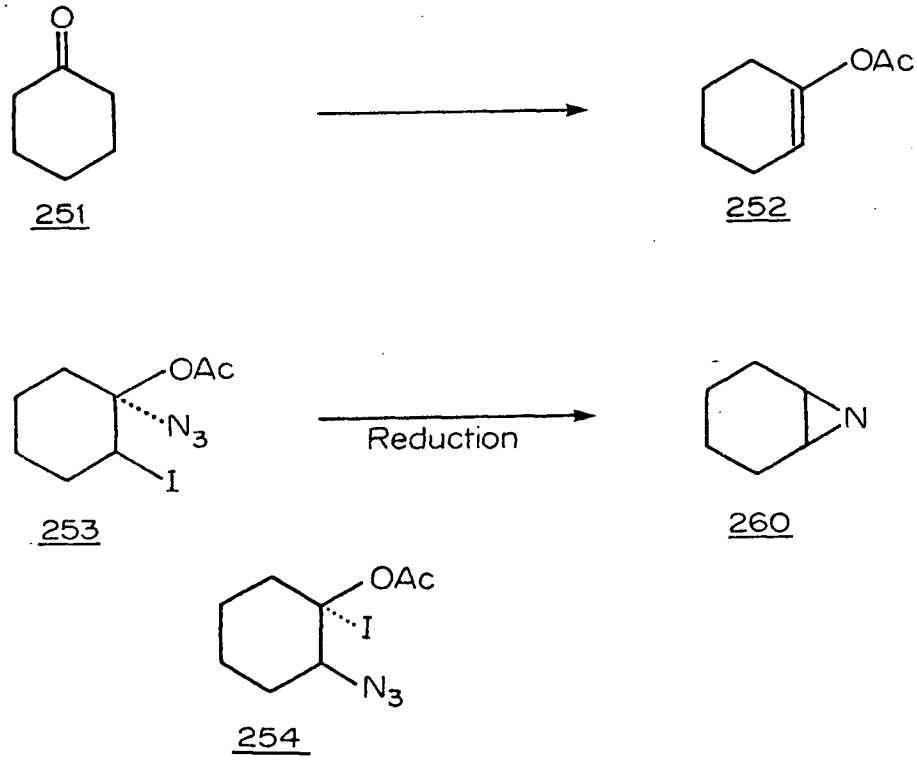





223a, cis
223b, trans

In order to find general reaction conditions which would give the smooth addition of iodine azide to enol acetates 223a and 223b a series of model experiments were initiated. To this end cyclohexanone (251) was converted into enol acetate 252. Treatment of enol acetate

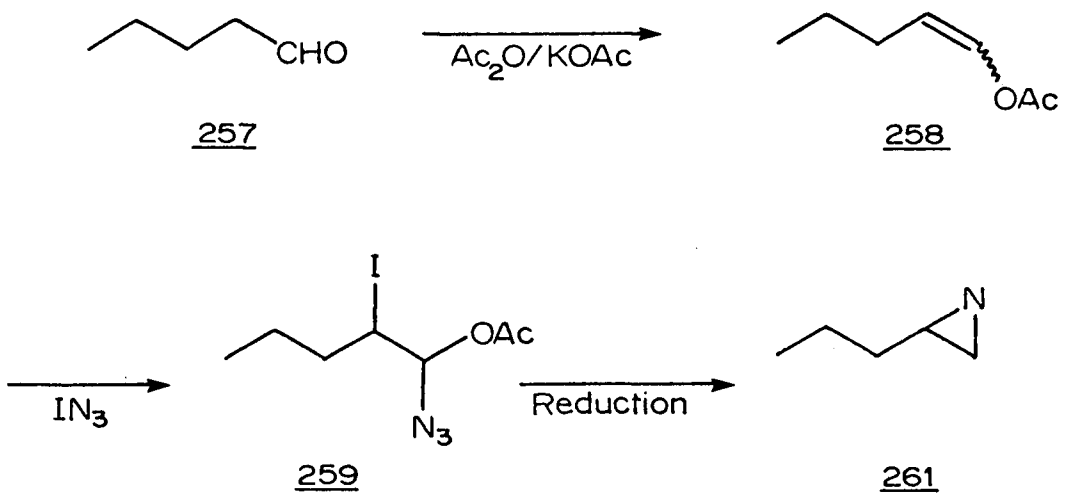



251 252 253 260 254

252 with iodine azide under conditions similar to that employed by Hassner et al.,[149] gave ca. 50% addition as indicated by t.l.c. and infrared spectroscopy. On the other hand, when the concentration of iodine azide (in situ) was doubled complete addition occurred. The t.l.c. of the crude product on silica gel suggested the presence of one major component with polar baseline contaminants. The crude product was chromatographed on silica gel in benzene to afford a pure iodo azide adduct. The spectroscopic properties of this adduct were in accord with structure 253. The infrared spectrum of 253 had a strong band at 2120 $cm^{-1}$ due to the azide group and a carbonyl band at 1740 $cm^{-1}$. The n.m.r. spectrum of 253 had a one-proton triplet (J = 6 Hz) at $\tau$5.37 which could be attributed to the proton adjacent to the iodide group. Although this assignment of structure was ambiguous, in view of electronic considerations it was felt that 253 would be formed rather than 254, since opening of iodonium ion 255 would proceed via transition state 256 where the acetoxy group

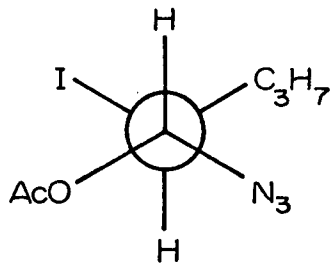

255 256

can stabilize the incipient positive charge. Treatment of aldehyde 257 with potassium acetate in refluxing acetic anhydride gave enol acetate 258 in fair yield. Subjecting enol acetate 258 to 2.3 molar equivalents of

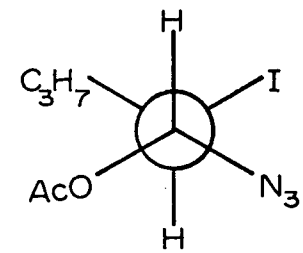



iodine azide (in situ) for two hours gave iodo azide 259. The t.l.c. of the crude product indicated predominantly one compound. The crude product was chromatographed on silica gel in $CHCl_3$ to give an iodo azide in 63% yield. The spectroscopic properties of iodo azide 259 were in agreement with the assigned structure. Thus, the infrared spectrum of 259 had a strong absorption band at 2120 $cm^{-1}$ due to the azide band and a carbonyl band at 1740 $cm^{-1}$. The n.m.r. spectrum of 259 displayed a one proton multiplet at $\tau$5.90 due to the proton adjacent to the iodide group and a pair of doublets (J = 4.5 Hz) appeared at $\tau$4.13 and $\tau$4.0 which could be attributed to the proton adjacent to the azide and acetate functionalities. Since the v.p.c. of the crude enol acetylation product indicated a mixture of cis and trans isomers the addition of iodine azide to the mixture

of enol acetates 258 could give two iodo azide diastereoisomers 259a and 259b which may account for the appearance of a pair of doublets in the n.m.r. spectrum of the iodo azide adduct. It was now hoped that




259a



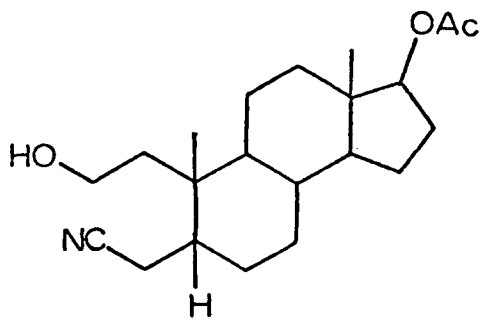

259b

the reduction of iodo azides 253 and 259 would give rise to aziridines 260 and 261, respectively. At this point, it was important to bear in mind that with iodo azide 241 it would be necessary to selectively reduce the azide group in the presence of the nitrile functionality. It is well documented that lithium aluminum hydride can reduce nitriles to primary amines.[150] However, in light of the work of Hassner et al.,[149] it was decided to study the reduction of iodo azides 253 and 259 with lithium aluminum hydride in order to ascertain the validity of this approach. Treatment of iodo azide 253 with lithium aluminum hydride in diethyl ether for twelve hours at room temperature followed by the action of 20% aqueous sodium hydroxide gave predominantly one product as indicated by v.p.c. The infrared spectrum of a v.p.c. sample showed the absence of both azide and carbonyl bands and the product had a strong band at 3400 $cm^{-1}$. Concurrently, the lithium aluminum hydride reduction of iodo azide 259 was carried out. This reduction reaction gave a product which had similar spectral features to the above product. However, the yields of crude product in these reduction reactions were very low. This could possibly be attributed

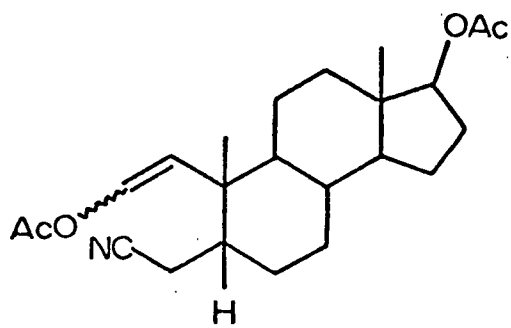
to the volatile nature of the resulting compounds and to their high solubility in water. In general, it was felt that the reduction of the iodo azides should be further investigated with more selective reducing agents. Smith et al.,[151] have reported that sodium borohydride in refluxing isopropanol can reduce azide groups to the corresponding amine. Since nitrile functionalities are not usually reduced with sodium borohydride,[152] it was decided to study the reduction of iodo azides 253 and 259 under these conditions. For example, treatment of iodo azide 253 with an excess of sodium borohydride in refluxing isopropanol for three hours gave a product whose infrared spectrum showed the absence of the azide band at 2120 $cm^{-1}$ and of the carbonyl band at 1740 $cm^{-1}$. However, the yields of crude product again were very low. Similarly, the reduction of iodo azide 259 with sodium borohydride gave low yields of crude product. Attempts to isolate products from other reduction reactions were not fruitful. Very limited studies on the addition of iodine azide to other enol acetates and the subsequent reduction of the adducts did not yield positive results. The addition of iodine azide to the mixture of enol acetates 223a and 223b by employing conditions analogous to that used in the model studies gave predominantly starting material. On the other hand, addition under more drastic conditions led to a complex mixture of products. As a result, this type of approach was abandoned and an alternate pathway was considered.

This second pathway involved the ozonolysis of enol acetates 223a and 223b with subsequent reductive work up[4,135,153] to afford cyanoaldehyde 262. Wittig[154] reaction on cyanoaldehyde 262 could then give rise to cyanoolefin 57a(CHART XXIII Page 158). Although the removal and

reintroduction of carbon-2 did not seem attractive from a logistic viewpoint, this approach, nevertheless, represented a possible pathway which would circumvent the problems associated with the dehydration of hydroxynitrile 202, the bromination of the enol acetates 223a and 223b, and the generation of the double band *via* hydroboration of enamine 240. This



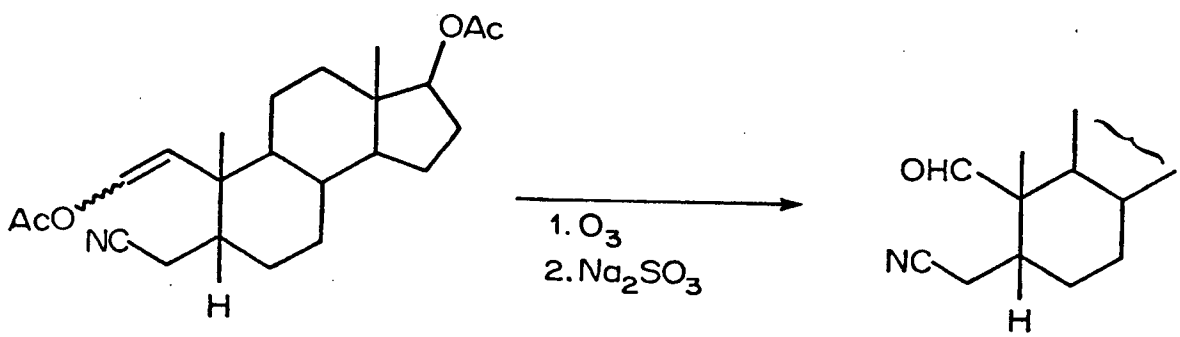

202




223a, cis
223b, trans

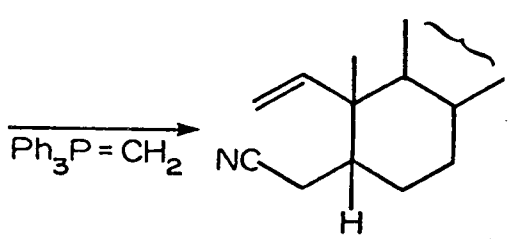
scheme (CHART XXIII, Page 158) was therefore subjected to experimental scrutiny. Ozonolysis of enol acetates 223a and 223b under conditions analagous to that employed by Grafen and his colleagues[135] followed by zinc-acetic acid work up gave cyanoaldehyde 262 accompanied by several contaminants as evidenced by t.l.c. and n.m.r. spectroscopy of the crude product. Several attempts were made to purify cyanoaldehyde 262 by chromatographic methods. Because of the sensitive nature of cyanoaldehyde 262 the isolated yields were very low. The crude cyanoaldehyde 262 appeared to be very susceptible to aerial oxidation. In addition, this material was found to give poor results in the next step of the projected synthesis. The ozonolysis was then carried out in various solvents for different reaction times and several reductive work up procedures were examined; for example, dimethyl sulphide,[155] palladium - hydrogen,[156] and sodium sulphite.[157] In contrast to the earlier experiments, the

CHART XXIII. Formation of cyanoolefin 57a via a Wittig reaction




223a, cis
223b, trans

262

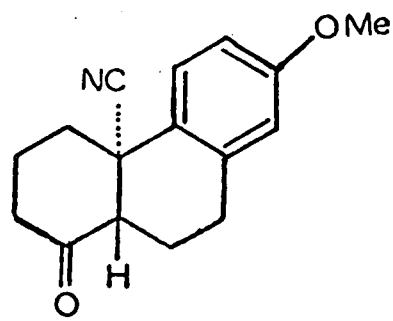



57a

ozonolysis of enol acetates 223a and 223b in ethyl acetate with subsequent standing at dry ice acetone temperatures for thirty-five minutes followed by the action of 5% aqueous sodium sulfite in aqueous methanol for two and one-half hours gave cyanoaldehyde 262 in ca. 86% yield and in a good state of purity. It is worthy of mention that these conditions must be adhered to rigorously otherwise there is a marked tendency for impurities to arise and lower yields. The spectroscopic properties of this material were in complete accord with the assigned structure. Of note was the disappearance in the infrared spectrum of the enol acetate carbonyl band at 1740 $cm^{-1}$ and the appearance of a weak band at 2725 $cm^{-1}$ due to the aldehydic C-H stretching vibration. In the n.m.r. spectrum of 262 a three-proton singlet appeared at $\tau$8.97 due to the carbon-19 tertiary methyl group and a sharp singlet at $\tau$.46 could be attributed to the aldehydic proton. The mass spectrum of 262 had a molecular ion peak at $\frac{m}{e}$ 331. Cleavage of the C-H bond next to the oxygen atom gave a strong peak at $\frac{m}{e}$ 330. Finally, a small sample was converted into its 2.4 D.N.P. derivative, m.p. 186-188°, for analysis.

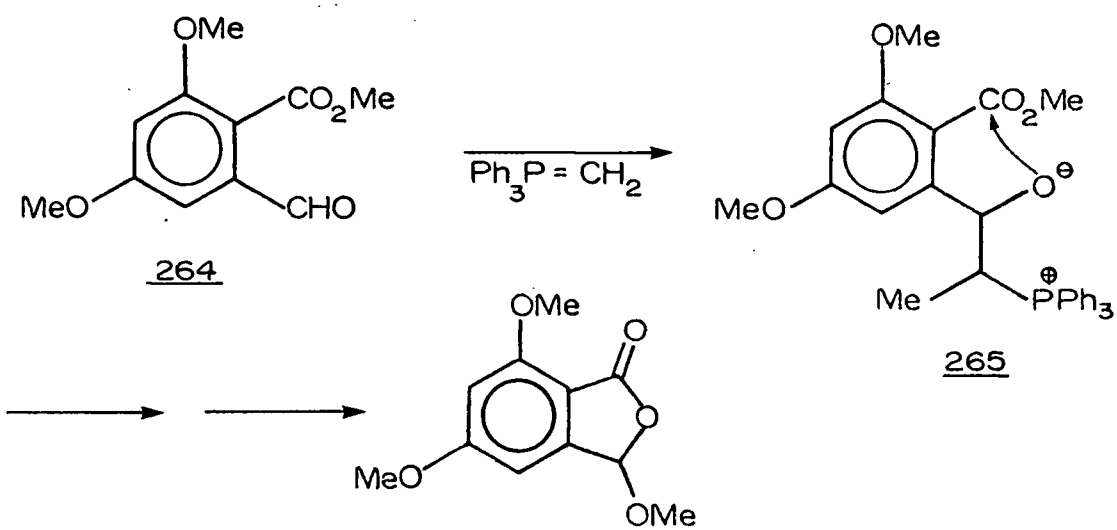
Having obtained considerable quantities of aldehyde 262 it was next planned to investigate the formation of cyanoolefin 57a via a Wittig reaction (CHART XXIII, Page 158). Corey et al.,[158] have reported a Wittig condensation reaction with a tertiary aldehyde using methylsulfinyl carbanion - dimethylsulphoxide.[159] However, the condensation of cyano-aldehyde 262 with methylenetriphenylphosphorane under conditions analogous to that employed by Corey et al.,[158] led to a mixture of compounds. The major component was isolated by preparative t.l.c. in low yield. The infrared spectrum of this material showed the absence of the nitrile band

at 2250 $cm^{-1}$. It is interesting to note that Nagata et al.,[160] had effected a Wittig condensation with cyanoketone 263 although in this case the opportunity may not exist for the ylide to react with the nitrile group. In addition, it has been reported that the resulting




263

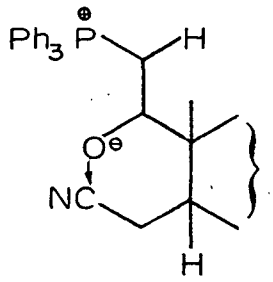
ylide in the Wittig reaction can react with a neighbouring group. For instance, Taub and his colleagues[162] have found that in the Wittig condensation with aldehyde 264 the ylide 265 reacts with the ester group.




264

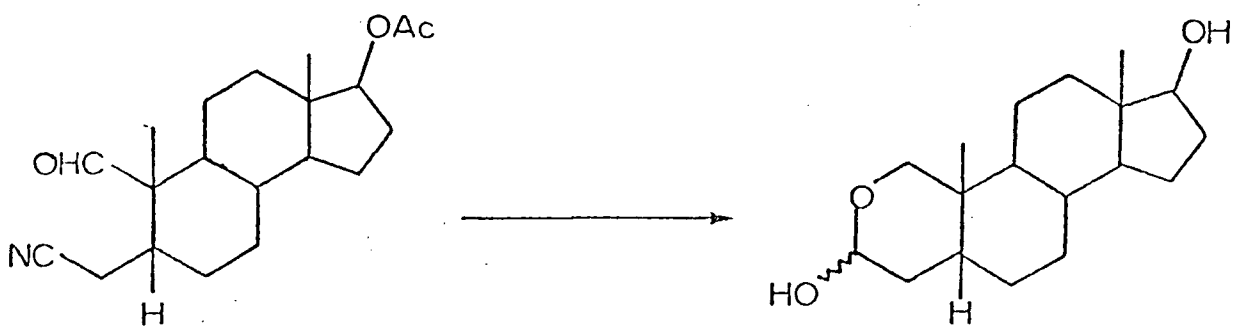
265

The yields of desired olefin were very low. Similarly, the resulting ylide 266 could react with the nitrile group. This type of reaction



266

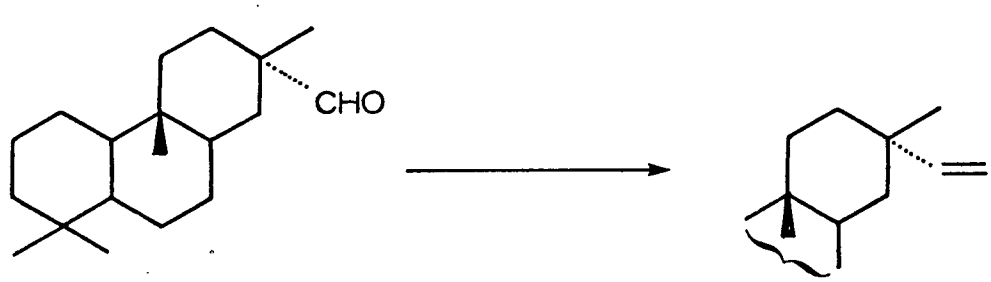
could explain the formation of diverse products not having a nitrile functionality. Furthermore, sodium borohydride reduction of cyanoaldehyde 262 in refluxing isopropanol gave one major component whose infrared spectrum indicated the absence of the nitrile band at 2250 $cm^{-1}$. Mass



262 267

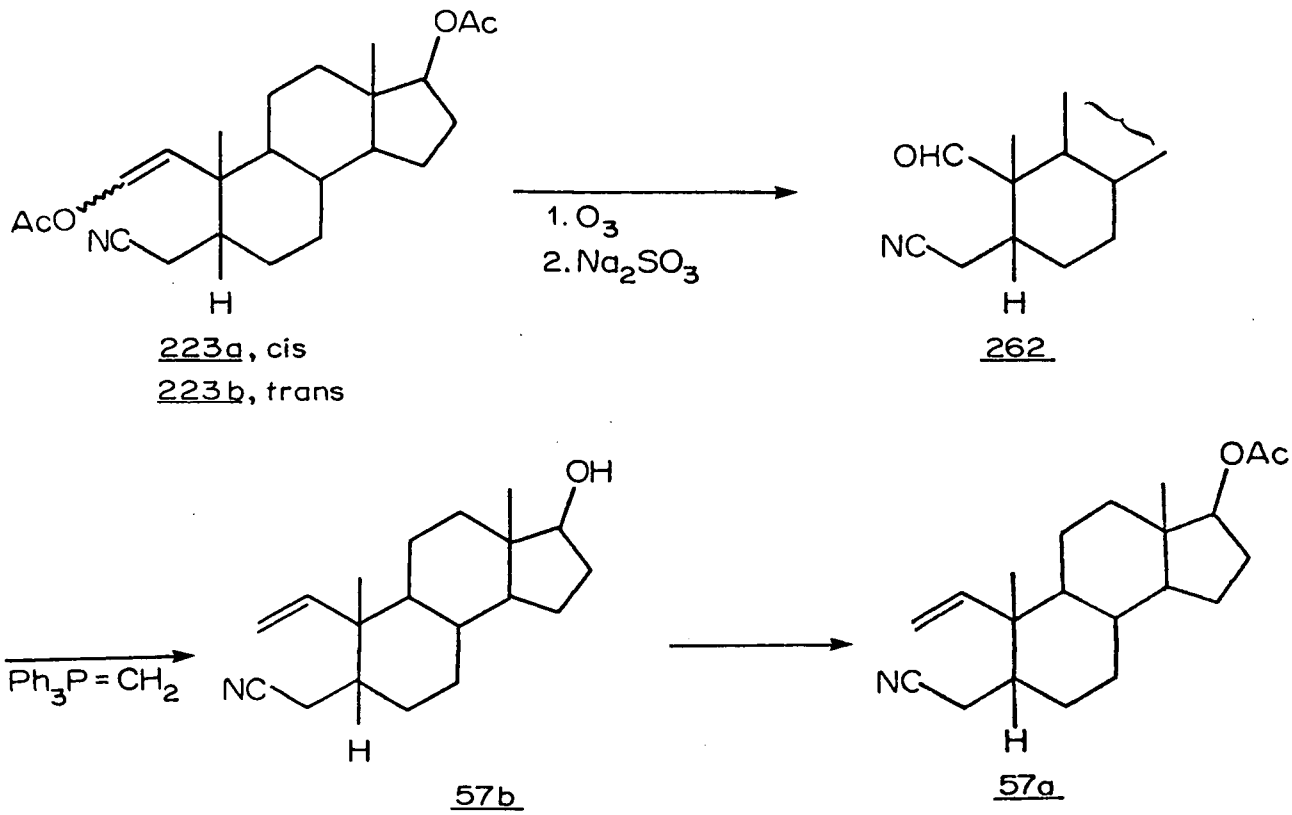
spectral evidence suggested that compound 267 had been formed. The Wittig condensation reaction was studied in various solvents and the phosphorane was generated by employing other well documented procedures. It was hoped that the above interfering reaction could possibly be prevented by carrying out the condensation in a non polar solvent. Generation of the

phosphorane by the action of n-butyl lithium on (methyl)-triphenylphosphonium bromide in benzene followed by the addition of cyanoaldehyde 262 with subsequent stirring at room temperature for two days yielded cyanoolefin 57a in ca. 25% isolated yield. Although the isolated yield was low the reaction had taken the desired reaction course. In order to optimize the yields, the reaction times and reactant concentrations were varied. Fortunately, the progress of the reaction could be followed by t.l.c. on silica gel. After considerable experimental effort in this direction the average yield of purified cyanoolefin was still low. Of particular importance, however, was the fact that several compounds had been isolated which did not bear an acetate group. A survey of the Wittig reaction with various ketosteroids indicated that functional groups, for example, hydroxy and acetoxy, decreased the yield.[162] At this stage, the low yield of cyanoolefin 57a was ascribed to the presence of an additional reactive site, namely, the 17β-acetoxy group and the hindered nature of the carbonyl functionality.[163] Ireland et al.,[164] have reported the condensation of tertiary aldehyde 268 with methylenetriphenylphosphorane to afford compound 269 in ca. 75% yield by employing a large excess of phosphorane reagent. When, in the event, a large excess of methylenetri-




268 269

phenylphosphorane was employed for short reaction times compound 57b was isolated. Subsequent acetylation of compound 57b gave cyanoolefin 57a




223a, cis
223b, trans

262

57b

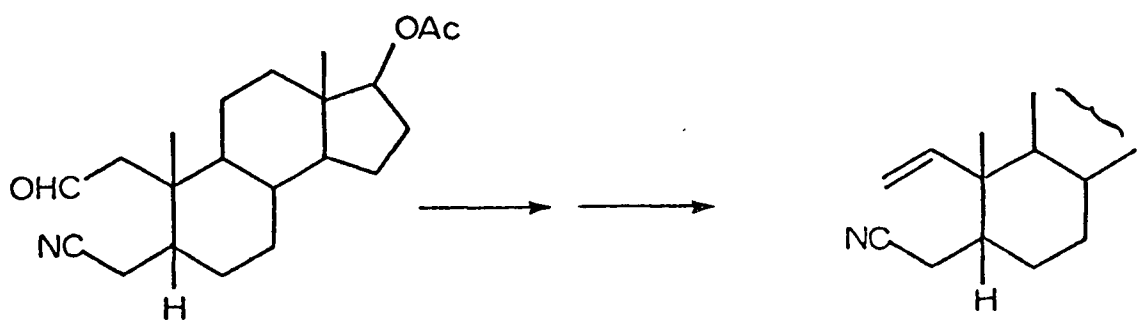
57a

in ca. 50% purified yield as a white crystalline solid, m.p. 132-135°. A small sample was sublimed at 125° (.1mm. pressure) to yield beautiful needles, m.p. 134-135°, for analysis. The spectroscopic properties of 57a were in complete accord with the assigned structure. Thus, the infrared spectrum of 57a had bands at 920 $cm^{-1}$ and 980 $cm^{-1}$ due to out-of-plane olefinic C-H bending vibrations. A weak band appeared at 1630 $cm^{-1}$ due to the carbon-1 carbon-2 double bond stretching vibration and a band at 2250 $cm^{-1}$ indicated that the nitrile group had remained intact. The n.m.r. spectrum of 57a possessed a three-proton multiplet

between τ5.10 and τ4.20 due to the carbon-1 and carbon-2 olefinic protons. Finally, the mass spectrum of 57a had a molecular ion peak at $\frac{m}{e}$ 329 with a prominent peak at $\frac{m}{e}$ 301.

More recently, Corey et al.,[165] have described conditions for effecting a Wittig reaction with a hindered aldehyde in good yield. Employing Corey's reaction conditions with a large excess of methylene-triphenylphosphorane afforded cyanoolefin 57b in ca. 65% purified yield. The spectroscopic data of 57b were also in accord with the assigned structure. Thus, the infrared spectrum of 57b had bands at 920 $cm^{-1}$, 990 $cm^{-1}$, and 1630 $cm^{-1}$ due to the olefinic side chain and a broad band at 3400 $cm^{-1}$ was ascribed to the 17β-hydroxy group. In the n.m.r. spectrum of 57b a three-proton multiplet at τ5.0 - 4.0 could be attributed to the carbon-1 and carbon-2 olefinic protons and a one-proton triplet (J = 9 Hz) at τ6.34 was ascribed to the proton adjacent to the 17β-hydroxy group. Lastly, the mass spectrum of 57b possessed a molecular ion peak at $\frac{m}{e}$ 287 with a prominent peak at $\frac{m}{e}$ 269. Acetylation of compound 57b with acetic anhydride in pyridine afforded 57a in quantitative yield.

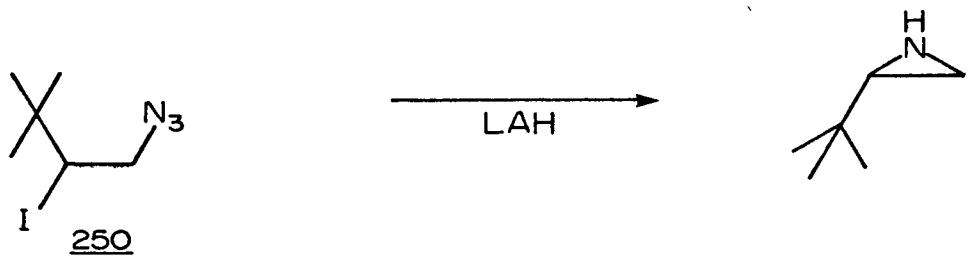
In summary, cyanoolefin 57a had been obtained in ca. 34% overall yield based on cyanoaldehyde 195. At the beginning of this thesis




195 57a

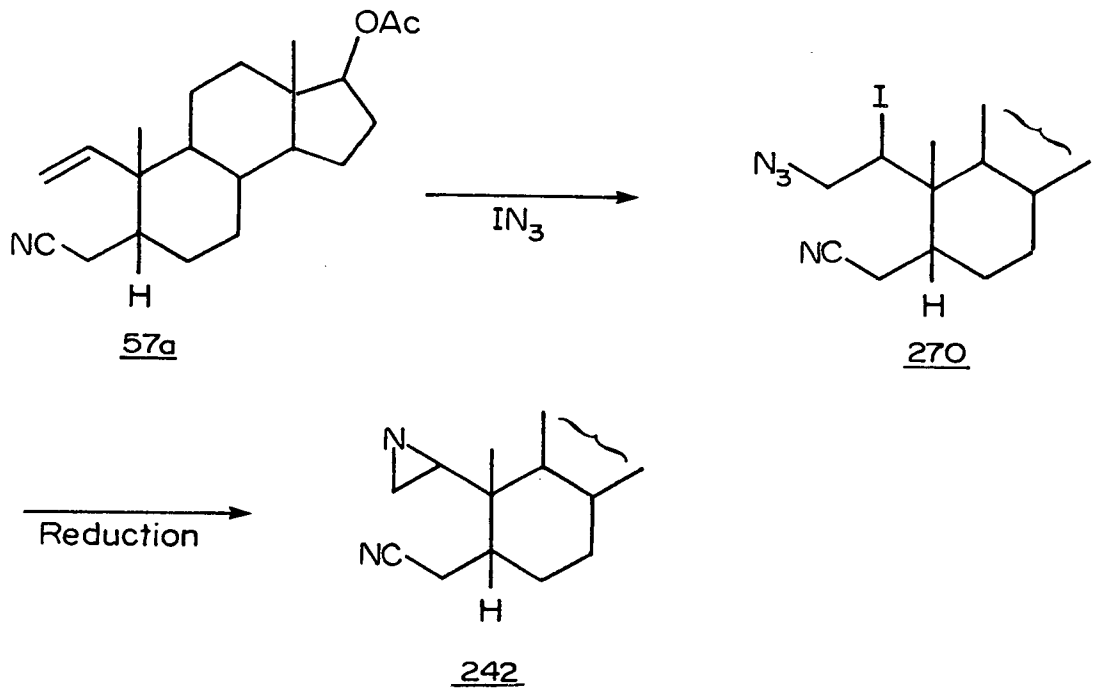
it was mentioned that an olefinic compound could serve as a common precursor. Cyanoolefin 57a represents such a precursor where $-CH_2X$ is a nitrile group (See 79, Page 41). The preceeding synthetic work had therefore proceeded along lines in accordance with the general plan.

It should be recalled that the next phase of the projected synthesis involved the elaboration of the cyanoolefin 57b to an aziridine of general type 75 (CHART IX, Page 40). As noted previously, Hassner et al.,[149] reported that the addition of iodine azide to t-butylethylene (249) gave only compound 250. Subsequently, lithium aluminum hydride reduction of 250 afforded the appropriate aziridine in excellent yield.[149]




250

In light of this work it was proposed that the addition of iodine azide to 57a followed by reduction would afford an aziridine of general type 242. It is important to note that compounds possessing a primary iodo group are susceptible to hydrogenolysis with lithium aluminum hydride.[149] As a result of these considerations two possible pathways became apparent. Firstly, direct addition of iodine azide to cyanoolefin 57a

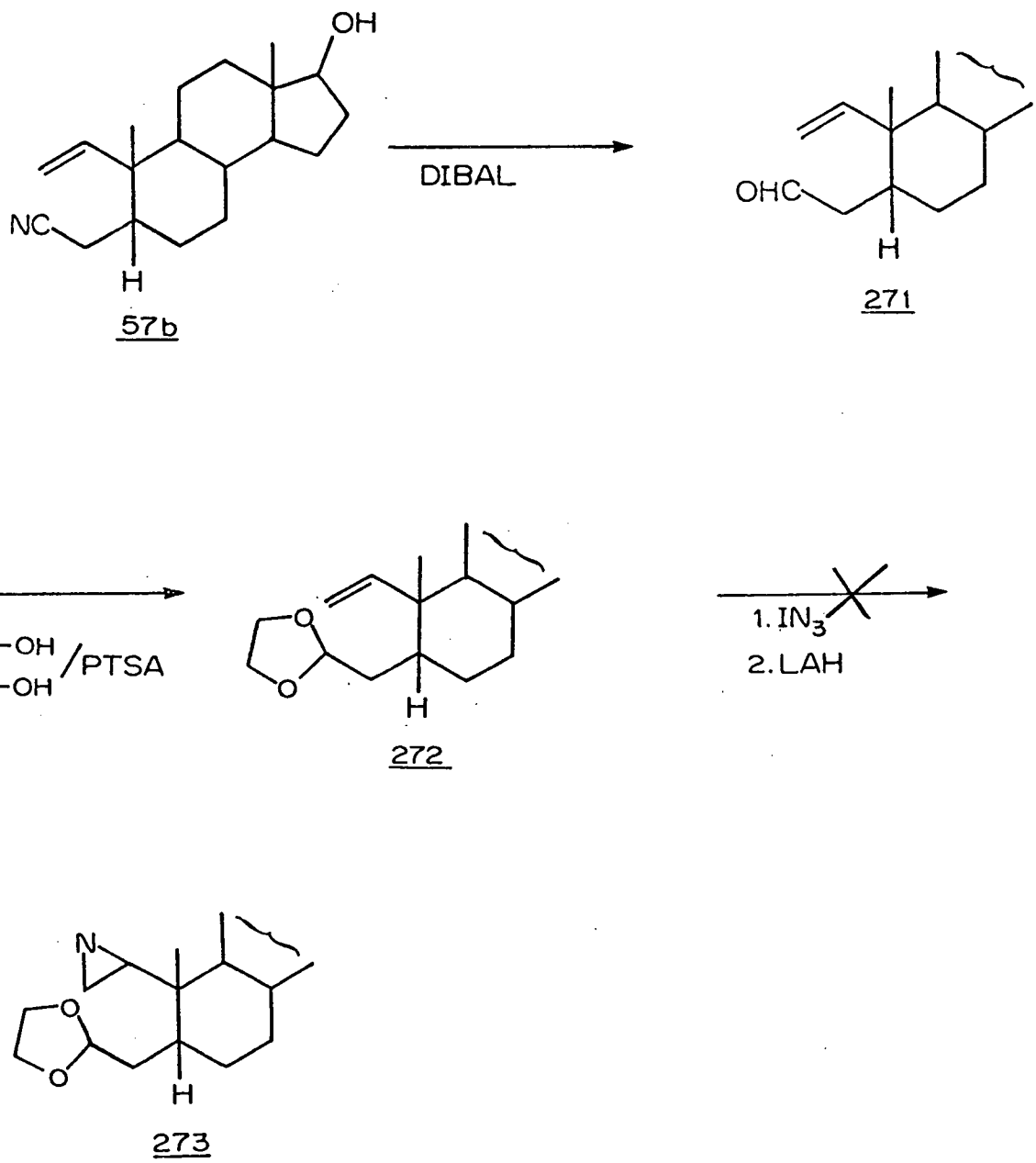



57a 270 242

followed by reduction could give aziridine of general type 242. This approach would necessitate the selective reduction of the azide group in the presence of the nitrile functionality. Undoubtedly, employing lithium aluminum hydride as the reducing agent the reduction of the nitrile group would be a complicating factor. On the other hand, it was hoped that sodium borohydride,[151,152] sodium bis(2-methoxyethoxy)-aluminum hydride,[166] or aluminum/amalgam[167] would selectively reduce the azide functionality.

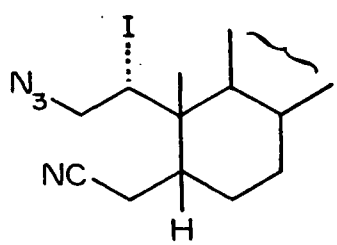
Alternatively, the nitrile group could be converted into an acetal group which would be inert to lithium aluminum hydride. Hence, the addition of iodine azide to compound 272 followed by lithium aluminum hydride reduction would furnish aziridine of general type 273 (CHART XXIV, Page 167).

CHART XXIV. Elaboration of cyanoolefin 57b to aziridine 273

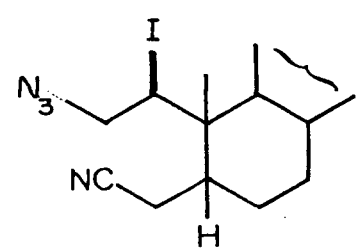



57b 271 272 273

Since the first pathway appeared attractive and potentially efficient the addition of iodine azide to cyanoolefin 57a was examined. In contrast to the behaviour of enol acetates 223a and 223b, treatment of cyanoolefin 57a with 3 molar equivalents of iodine azide in acetonitrile for five hours at room temperature gave an adduct 270 (see Page 166) in ca. 80% crude yield. The progress of the reaction was followed by infrared spectroscopy. T.L.C. analysis of the crude product suggested essentially one compound. Of note was the appearance in the infrared spectrum of a broad band at 2200 $cm^{-1}$ due to the azide. The olefinic bands at 920, 980, and 1630 $cm^{-1}$ were not present. The n.m.r. spectrum of the crude product had a broad singlet (totalling three protons) at $\tau$9.20 due to the carbon-18 tertiary methyl groups of compounds 270a and 270b while the carbon-19 tertiary methyl groups appeared as two sharp singlets of about equal intensity at $\tau$8.74 and $\tau$8.62. The stereochemical factors in this addition reaction are worthy



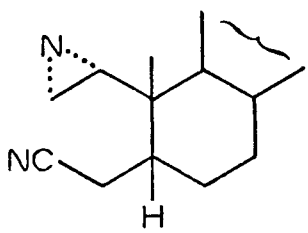

270a



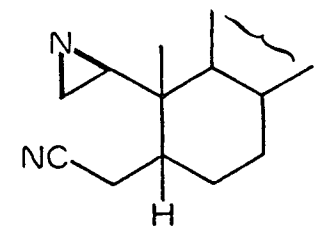

270b

of comment. Since one new asymmetric centre has been created the possibility exists for the formation of two compounds, namely 270a and 270b. Examination of a model of cyanoolefin 57a suggested that both

modes of addition were favourable as indicated by the n.m.r. spectrum of the addition product. If compounds 270a and 270b were formed in ca. a 1:1 ratio, the reduction reaction would presumably give rise to aziridines 242a and 242b. Since the prime objective at this point




242a

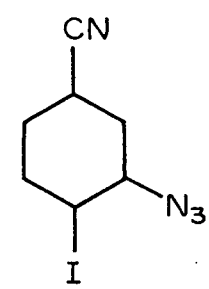



242b

was to test the feasibility of this type of approach the above stereochemical problem did not cause concern.

Before attempting to selectively reduce the azide functionality in compound 270 a model compound was studied; namely, iodo azide 275.


274

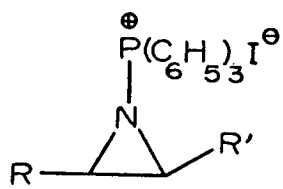



275

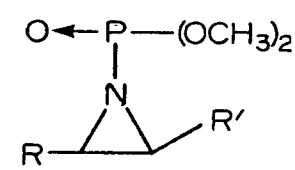
The selectivity of various reducing agents were examined; for example, sodium bis(2-methoxyethoxy)-aluminum hydride,[166] aluminum amalgam,[167] $Pt/H_2$[158] and sodium borohydride.[151,152] In summary, the selective reduction of

the azide group in the presence of the nitrile functionality could not be achieved by employing any of these reagents. Nevertheless, iodo azide 270 was treated with excess sodium borohydride in refluxing isopropanol for three hours. T.L.C. Analysis of the crude product indicated minor quantities of starting material and a major compound. The infrared spectrum of the crude product indicated that the azide and nitrile groups had been partially reduced. Several attempts were now made to selectively reduce the azide group with sodium bis(2-methoxyethoxy)-aluminum hydride. Employing 3 molar equivalents of sodium bis(2-methoxyethoxy)aluminum hydride also caused partial reduction of both azide and nitrile groups as suggested by infrared spectroscopy.

The reaction between phosphorus nucleophiles and azides (Staudinger reaction) gives phosphine imines,[168] and the subsequent reaction of these compounds with alkyl halides gives dialkylaminophosphonium salts.[169] Alkyl or arylphosphines react with alkyl halides readily to produce phosphonium salts.[170] With very few exceptions,[171] no attention has been given to incorporating both the phosphine imine and the halide function into one molecule with the possibility of creating a cyclic compound. Recently, Hassner et al.,[172] found that 2-iodoalkyl azides react with triphenylphosphine or trimethyl phosphite




276

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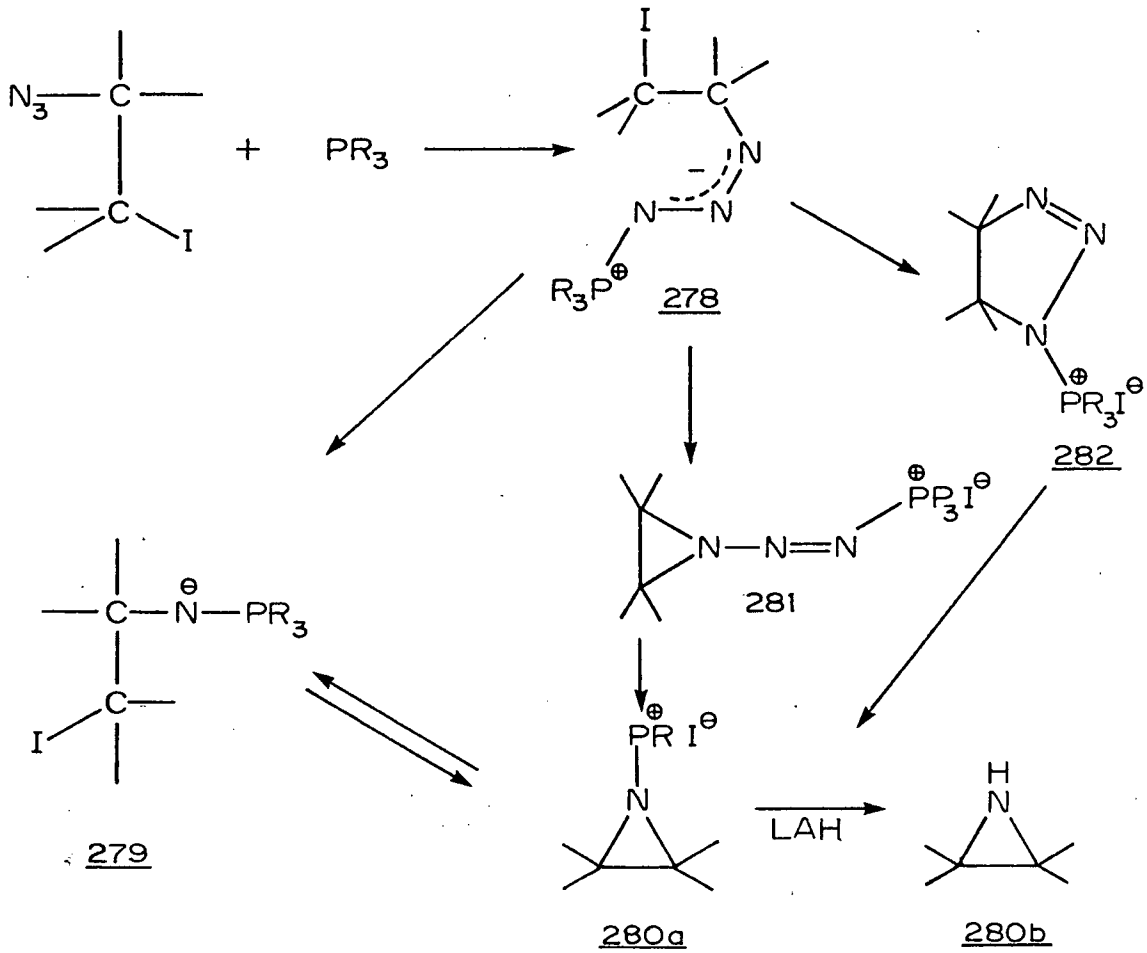
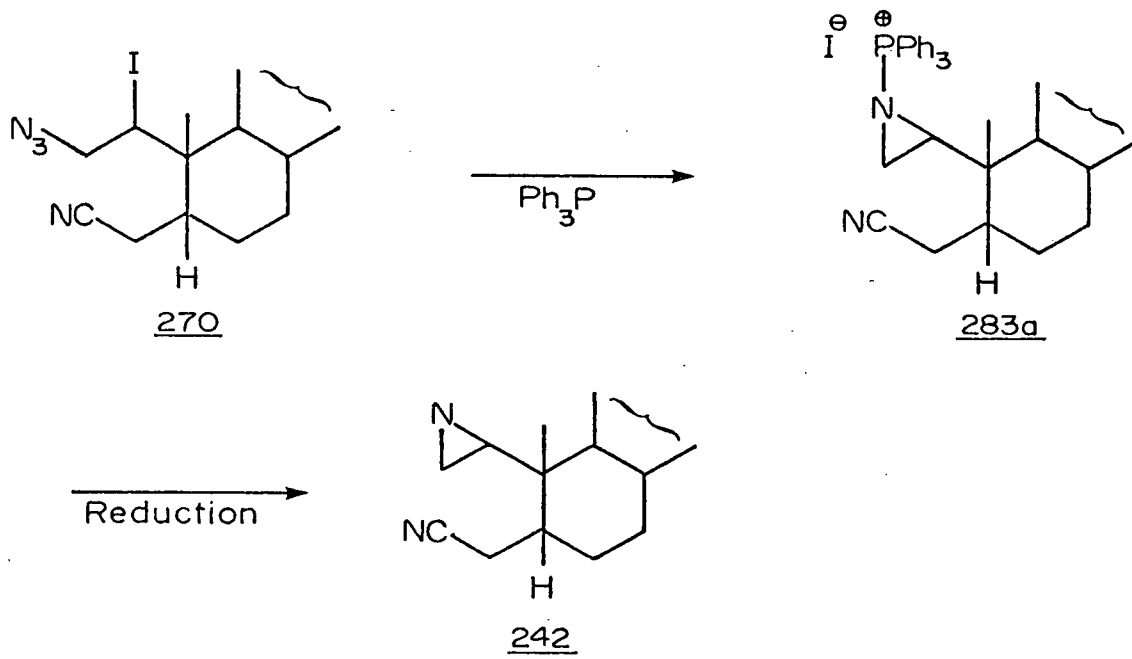


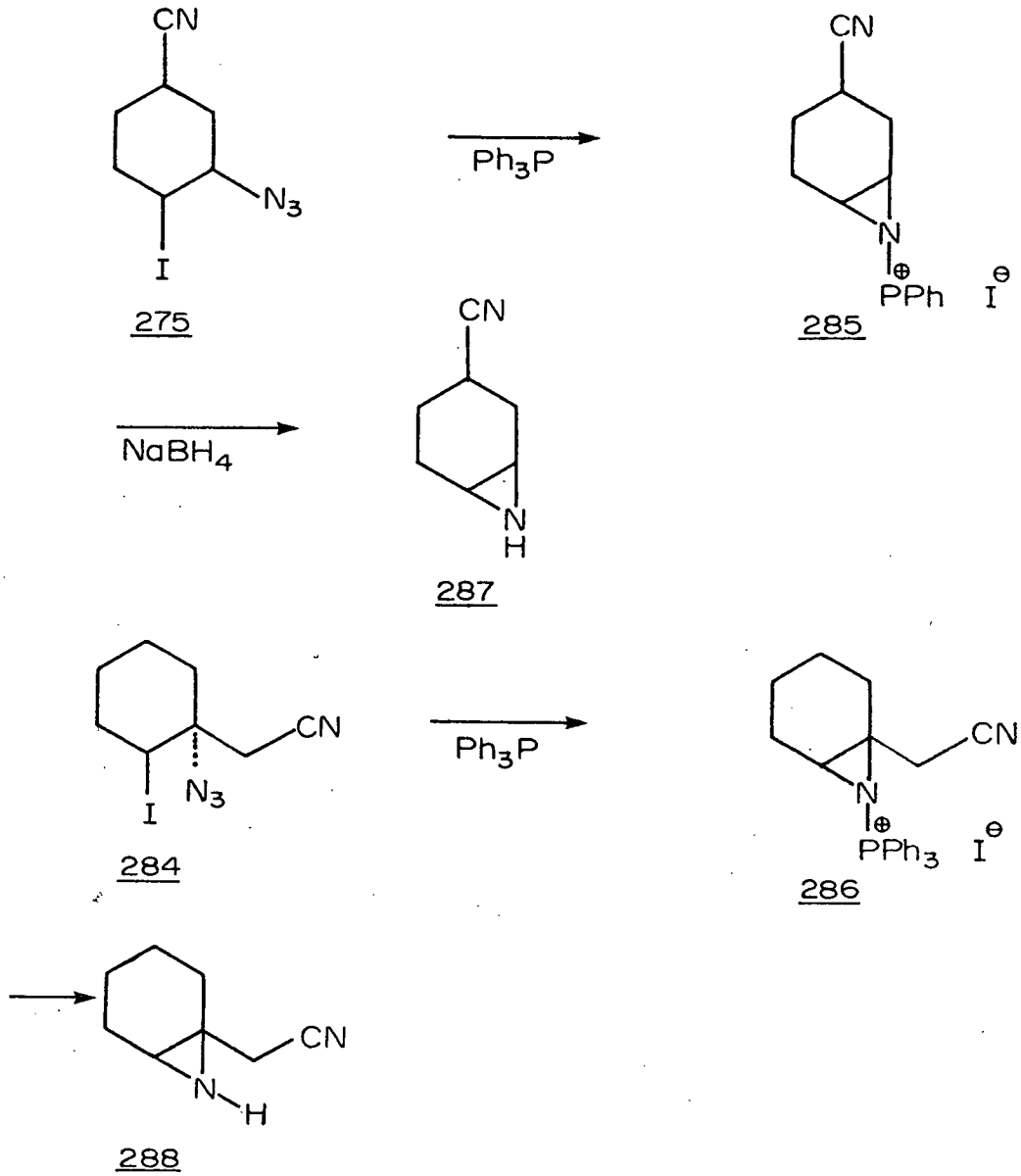

to afford in good yield an aziridine derivative of type 276 and 277, respectively. They showed that 2-iodoalkyl azides react with trivalent phosphorus nucleophiles almost exclusively at the azide function. These reactions are thought to involve initial nucleophilic attack on the terminal azide nitrogen to give an intermediate of type 278. This can then undergo loss of nitrogen to give ylide 279 which cyclizes to 280a with displacement of iodide anion. Alternatively, cyclization to 281 or 282 may precede loss of nitrogen, although the rate of nitrogen loss from azide phosphine adducts of type 278 is believed to be faster than their rate of formation. Lithium aluminum hydride reduction of 280a leads to the formation of the free aziridine 280b. This is in agreement with

the general principle that reduction of phosphonium salts liberates the most electronegative group from the phosphorus. Bailey et al., [173] obtained similar results in the lithium aluminum hydride reduction of tetraalkyl phosphonium salts. As a result, it was contemplated that iodo azide of type 270 could react with triphenylphosphine or trimethylphosphite to give aziridine derivative of general type 283 and subsequent reduction or hydrolysis could lead to aziridine of general type 242. It was hoped that sodium borohydride,




270 283a 242

mild hydrolysis conditions,[174] or dry HCl could liberate the cyanoaziridine 242.[175] Before attempting to prepare aziridine of type 242 the reaction of iodo azides 275 and 284 with phosphines was investigated. Iodo azide 275



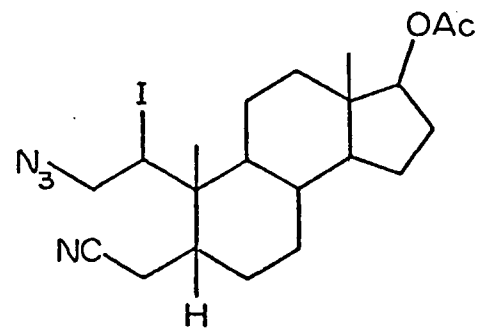

275 285 287 284 286 288

reacted with triphenylphosphine in benzene at room temperature to afford 285 as a white insoluble solid in quantitative yield. The spectroscopic properties of 285 were in accord with the assigned structure. The infrared spectrum of 285 had a band at 2250 $cm^{-1}$ due to the nitrile functionality and of note was the disappearance of the azide band at 2120 $cm^{-1}$. The n.m.r. spectrum of 285 had a two-proton multiplet at $\tau$7.0 which could be attributed to the tertiary aziridinyl CH absorptions. Of significance was the absence of the multiplet at $\tau$6.0 due to the

protons adjacent to the iodide and azide groups. The 15 aromatic protons of 285 appeared as a multiplet at $\tau$2.20. It is noteworthy that the n.m.r. spectra of aziridine protons (C-H) are shielded compared to C-Hs in open chain amines due to the magnetic field generated in three-membered rings.[176] Tertiary aziridinyl CH absorptions usually occur at $\tau$7.6 - 8.10 but these chemical shifts vary from $\tau$7.20 to $\tau$8.50 depending on substituents and their stereochemistry. Hassner et al., demonstrated that $\overset{\oplus}{P}(Ph_3)$ as a N substituent effects ca. 0.8 - 1.2 ppm downfield shift.[172] In addition, iodo azide 284 was treated with triphenylphosphine to afford aziridine derivative 286 as a white solid. The n.m.r. and infrared spectra of 286 were closely similar to that of 285.

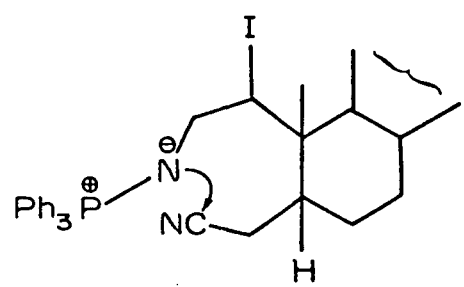
Having achieved the formation of aziridine derivatives 285 and 286 experiments were carried out to liberate aziridines 287 and 288, respectively, by employing mild hydrolysis conditions.[174] However, the action of methanol, methanol/water, or methanol polyphosphoric acid on compound 285 yielded recovered starting material. Exposure of 285 to dry HCl in ether or chloroform gave starting material. On the other hand, reduction of compound 285 with sodium borohydride in 95% ethanol at room temperature appeared to afford aziridine 287 as evidenced by t.l.c. and infrared spectroscopy. However, the isolated yields of 287 were low. The infrared spectrum of 287 indicated the absence of aromatic bands and the appearance of a weak band at 3350 $cm^{-1}$ could be attributed to the N-H stretch of the aziridine group. Attempts to liberate aziridine 288 by hydrolysis methods proved unrewarding. However, the action of sodium borohydride on aziridine derivative 286 gave aziridine 288, in low yield. The infrared spectrum of 288 was very similar to the infrared spectrum of 287.

As a result of these studies, the reaction of iodo azide 270 with triphenylphosphine in benzene at room temperature was investigated.




270

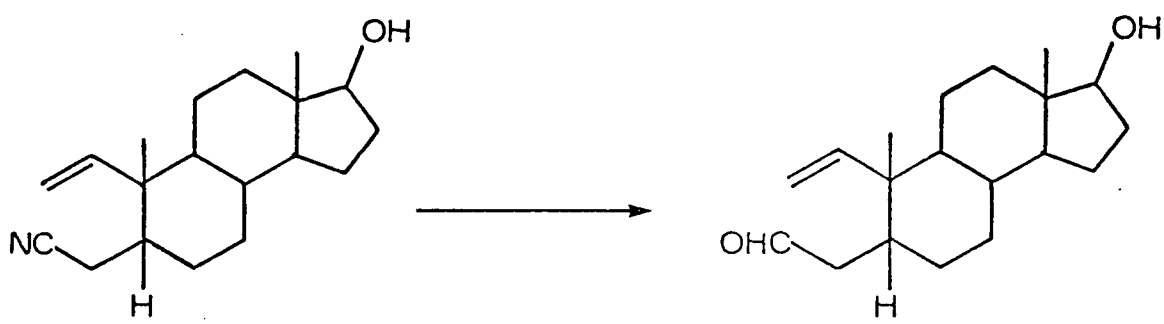
In contrast to iodo azides 275 and 284 no insoluble phosphonium salt was observed to form during the course of this reaction. The progress of the reaction was followed by infrared spectroscopy. The infrared of the crude material indicated the absence of the azide band at 2120 $cm^{-1}$. However, the nitrile band at 2250 $cm^{-1}$ also appeared to have decreased considerably. The t.l.c. of the crude oil showed the presence of several compounds with baseline contaminants and the disappearance of starting material. In order to rationalize these results it was assumed that triphenylphosphine reacted with iodo azide 270 to afford 283b, because of steric interactions between the phosphorus groups and the carbon-19 tertiary group. Presumably, the opportunity would exist for the ylide




283 b

283b to react with the nitrile functionality. Carrying out the reaction at higher temperatures (ca. 45° ) gave an overwhelming mixture of products. It is worthy of comment that azides and nitriles can react under various conditions to afford tetrazoles,[177] which could be a complicating factor in the case of iodo azide 270.

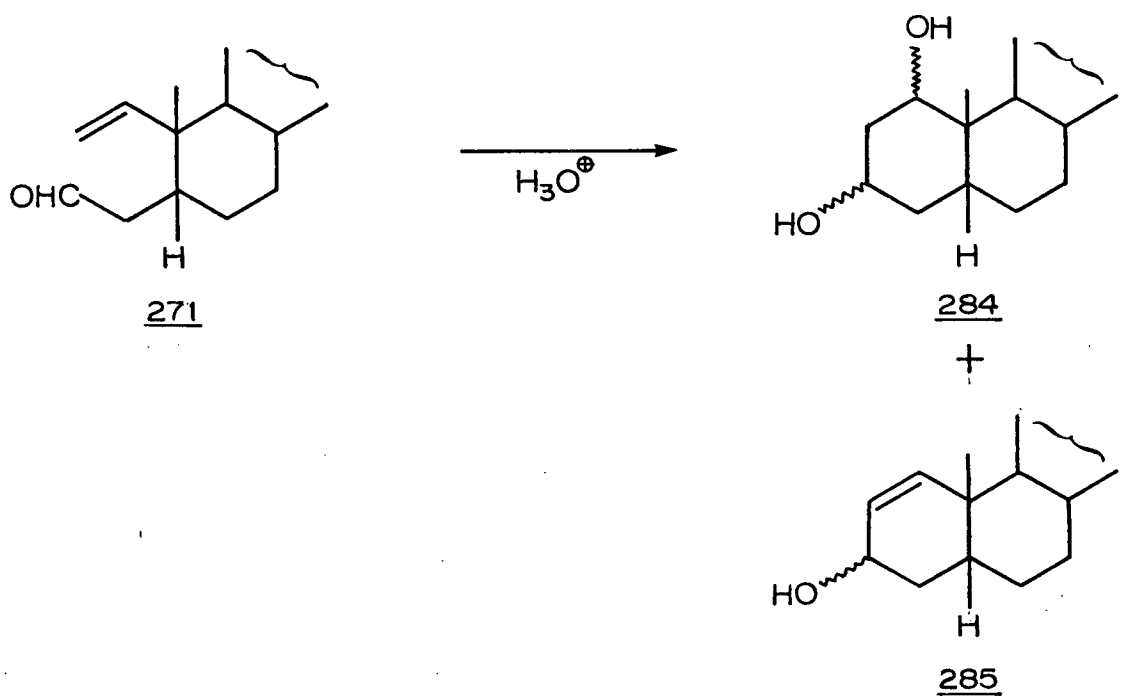
Because of these serious setbacks it was proposed to examine an alternative sequence, to which reference has already been made (CHART XXIV, Page 167). The first step involved the conversion of cyanoolefin 57b into olefinic acetal 272. Toward this end, treatment of cyanoolefin 57b with diisobutylaluminum hydride (2.5 equivalents) in benzene at room temperature for one hour followed by dilute acetic acid yielded olefinic aldehyde 271 as a clear oil in ca. 75% yield.[178] The t.l.c.



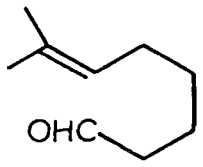

57b 271

of the crude product indicated essentially one compound. The spectroscopic properties of 271 were in accord with the assigned structure. The infrared spectrum of 271 had bands at 910 $cm^{-1}$, 990 $cm^{-1}$ and 1630 $cm^{-1}$ due to the olefinic side chain. Of note was the appearance of a strong carbonyl band at 1720 $cm^{-1}$ and of a weak band at 2750 $cm^{-1}$ due to the CH stretching vibration of the aldehydic group. The salient

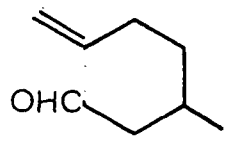
features in the n.m.r. spectrum of 271 were a three-proton multiplet at τ5.4 - 4.0 due to the carbon-1 and carbon-2 olefinic protons and a one-proton triplet (J = 2 Hz) at τ.47 was attributed to the aldehydic proton. Olefinic aldehyde 271 was found to be very sensitive to dilute mineral acid. For instance, dilute hydrochloric acid effected a Prins




reaction[179] to give, presumably, triol 284 and olefinic diol 285. LeBel et al.,[180] reported that olefinic aldehyde 286 appeared to be unstable while olefinic aldehyde 287 seemed to be stable. In addition, it is well documented that certain unsaturated aldehydes like citronellal readily undergo acid-catalyzed cyclizations.[181] Johnson et al.,[181b,182]

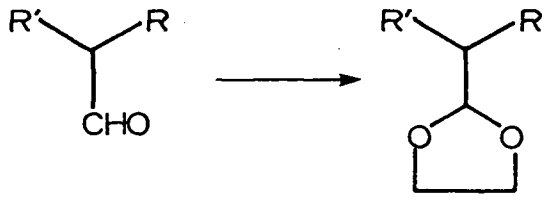



286




287

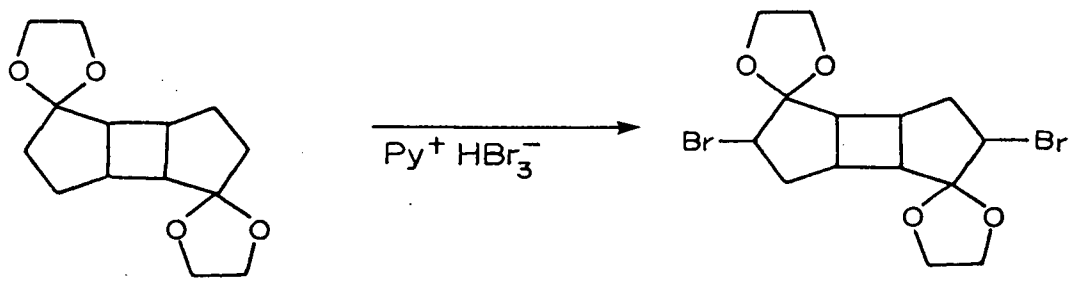
have found that polyolefinic acetals can also undergo acid-cyclizations to form mono and bicyclic products in very good yield. As a result, it was anticipated that olefinic acetal 272 might undergo an acid-catalyzed cyclization as well under too strong conditions. Nagata et al.,[183] have reported the conversion of an aldehyde into the corresponding acetal under very mild conditions at room temperature. For example, the action of a catalytic amount of p-toluenesulphonic acid, ethylene glycol, and dry methylene chloride on an aldehyde of type 288 at room temperature for twenty four hours gave acetal 289 in high yield. Thus, treatment of olefinic aldehyde 271 (CHART XXIV, Page 167) with ethylene glycol-




288 289

methylene chloride in the presence of a trace of p-toluenesulphonic acid, with vigorous shaking, at room temperature for twenty-four hours yielded olefinic acetal 272 in 70% purified yield. The spectroscopic properties of this material were in accord with the assigned structure. Of note was the disappearance in the infrared spectrum of the weak band at 2725 $cm^{-1}$ and of the carbonyl band at 1720 $cm^{-1}$. The olefinic bands were evident at 910 $cm^{-1}$, 990 $cm^{-1}$, and 1630 $cm^{-1}$. In the n.m.r. spectrum of 272 a five-proton multiplet appeared at ca. $\tau$6.3 due to the carbon-17 $\alpha$-proton and the methylene protons of the acetal group. A one-proton triplet (J = 5 Hz) was evident at $\tau$5.32 due to the methine proton of the acetal functionality and the olefinic protons appeared as a three-proton multiplet at ca. $\tau$5.3 - 4.0. Finally, the mass spectrum of 272 had a molecular ion peak at $\frac{m}{e}$ 334.

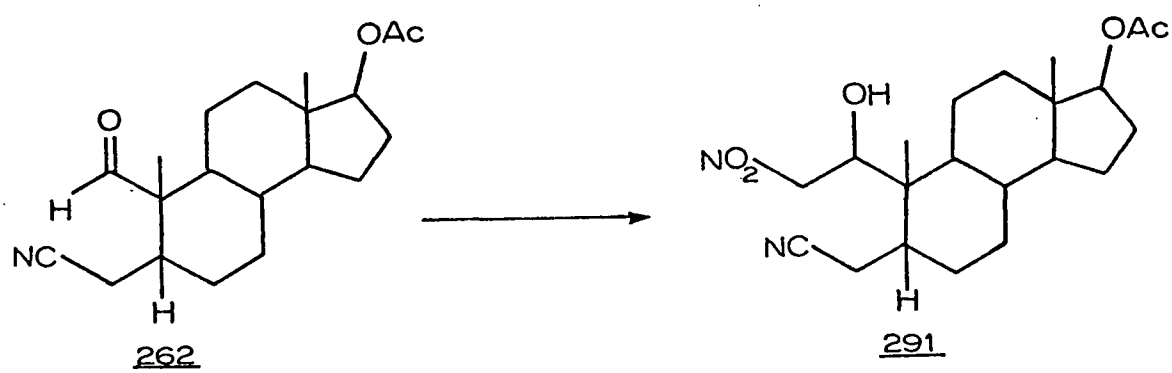
Having constructed olefinic acetal 272 the formation of aziridine of type 273 was now investigated (CHART XXIV, Page 167). The addition of iodine azide to olefinic acetal 272 was found to be a very sluggish reaction. Employing Hassner's standard conditions returned copious amounts of starting material. On the other hand, employing more drastic conditions afforded only trace amounts of starting material and several new compounds as indicated by t.l.c. The infrared spectrum of the crude product indicated a carbonyl band at 1740 $cm^{-1}$ and a broad azide band at 2100 $cm^{-1}$. It appeared that the 17$\beta$-hydroxy group had been oxidized to a carbonyl functionality. This difficulty could, however, have been obviated if the 17$\beta$-hydroxy group had been masked as an acetate functionality. Eaton[184] has reported that the action of pyridinium bromide perbromide on ketal 290 afforded dibromide 290a. Furthermore, acetals




290 290a

are sometimes brominated directly.[185] In view of these considerations the iodination of the acetal group could be a complicating factor in the addition of iodine azide to olefinic acetal 272. Also, the acetal group may be participating in this reaction.[186]

At this stage, the capacity of the carbonyl functionality of compound 262 to undergo addition reactions was investigated.[187] Thus,

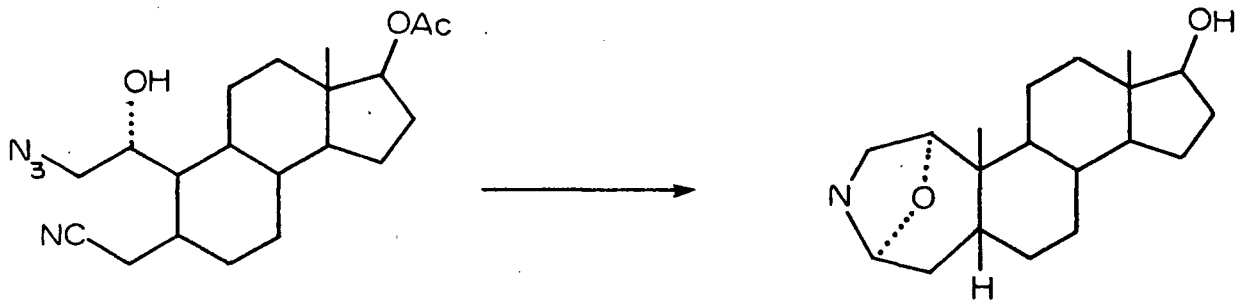



262 291

the action of nitromethane on cyanoaldehyde 262 was studied.[188] It was hoped that a hydroxy nitro compound of general type 291 would be obtained.

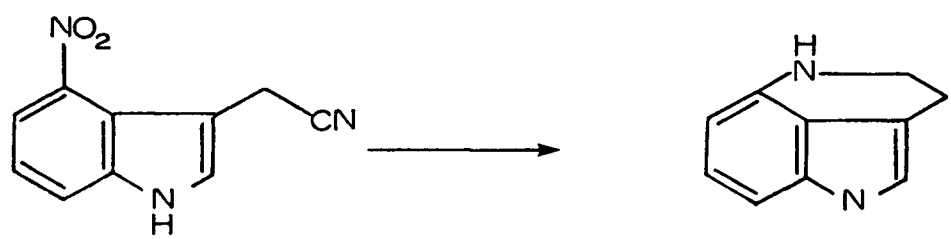
As previously mentioned, Shimizu[39] converted hydroxy azide 58

to the bicyclooxazolidine skeleton 47b by employing sodium borohydride




58 47b

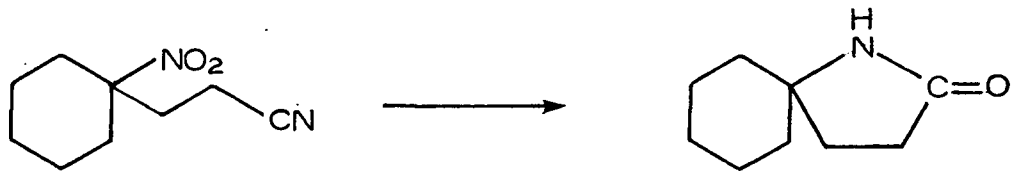
in refluxing isopropanol. Furthermore, the reductive cyclization of cyano nitro compounds have been reported by several workers.[189] Hester[190] has reported that hydrogenation of compound 292 over 10% palladium-on-carbon in ethyl acetate gave compound 293. Buckely and




292 293

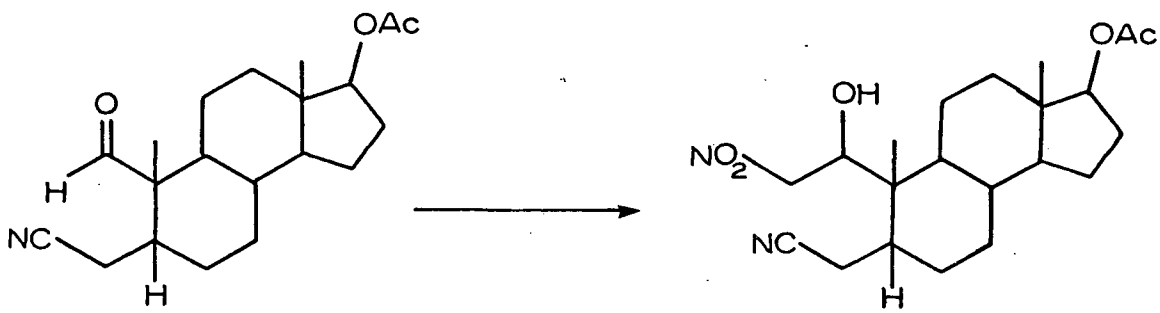
Elliot[191] have found that hydrogenation of cyano nitro 294 over Raney-

Nickel in methanol afforded lactam 295. Hence, it appeared likely




294 295

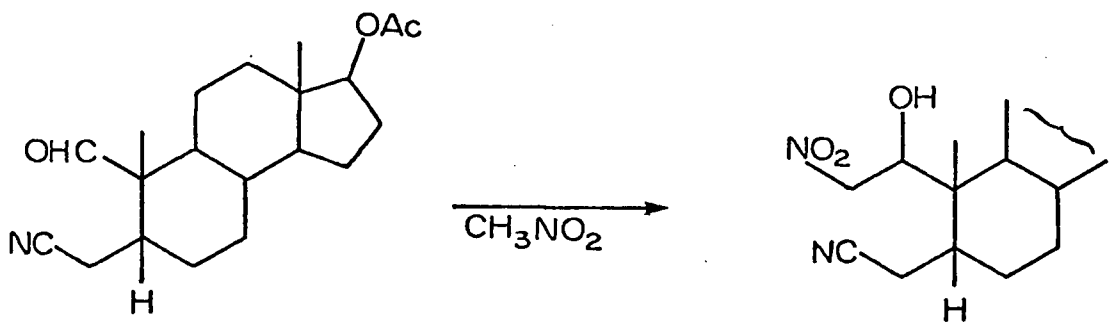
that the reductive cyclization of hydroxy nitro compound 291 to compound 47b could be effected by employing sodium borohydride or by catalytic hydrogenation.




262 291

Fieser et al.,[192] have effected the condensation of nitrobenzaldehyde with nitromethane in the presence of a trace of triethylamine. However, treatment of cyanoaldehyde 262 with nitromethane in the presence of a trace of triethylamine at room temperature for twenty four hours returned starting material. On the other hand, performing the reaction in the presence of excess triethylamine for five days at

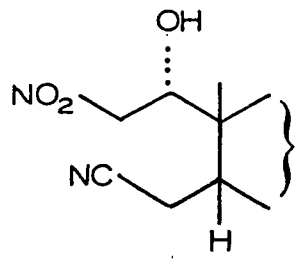
room temperature, in the dark under an atmosphere of nitrogen, yielded hydroxy nitro compound of general type 291 in ca. 70% purified yield, m.p. 186-188°. The spectroscopic properties of 291 were in accord with



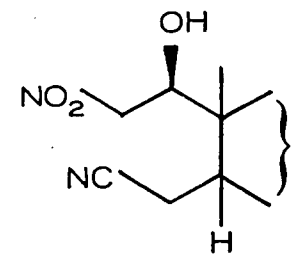

262 291

the assigned structure. The infrared spectrum of 291 had a broad band at 3400 $cm^{-1}$ due to the carbon-1 hydroxy group, and intense bands appeared at 1560 $cm^{-1}$ and 1380 $cm^{-1}$ due to the symmetrical and asymmetrical stretching vibrations of the nitro functionality, respectively. The n.m.r. of 291 had two three-proton singlets at $\tau$9.21 and $\tau$8.95 due to the carbon-18 and carbon-19 tertiary methyl groups, and a one-proton doublet (J = 3Hz) appeared at $\tau$6.36 due to the proton adjacent to the carbon-1 hydroxy group. A three-proton multiplet was evident at $\tau$4.60 due to the protons adjacent to the 17$\beta$-acetoxy and nitro groups. Finally, the mass spectrum of 291 had a weak molecular ion peak at $\frac{m}{e}$ 392. The stereochemical aspects of the above reaction are worthy of consideration. Since one new asymmetric centre has been created there is the possibility

for the formation of two compounds; namely, 291a and 291b. It was anti-




291a

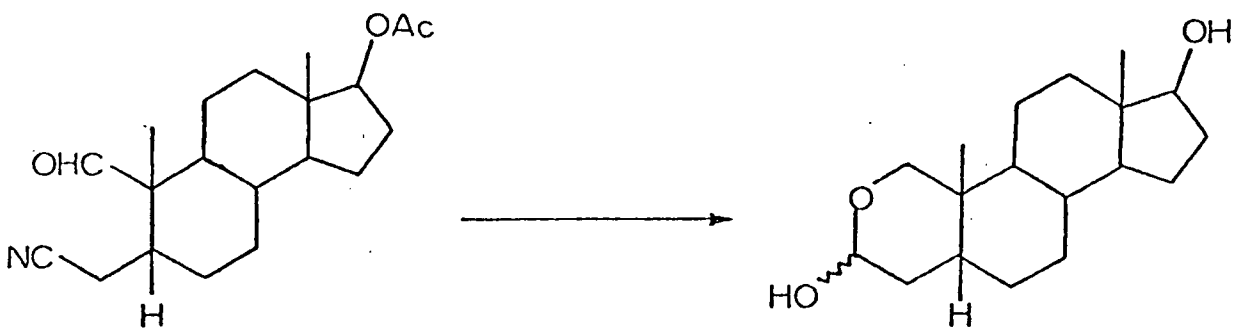



291b

cipated that the thermodynamically more stable compound would be formed since the reaction was performed under equilibrating conditions. Examination of molecular models of 291a and 291b suggested that the formation of 291a and 291b was equally favourable. However, the t.l.c. and m.p. of the isolated product tended to indicate the presence of one compound. In addition, the appearance of a sharp three-proton singlet at $\tau$8.95 due to the carbon-19 tertiary methyl group tended to suggest the presence of one compound. In light of the work of Hara and Oka[43] (see CHART V, Page 27 ), and Shimizu[39] (see CHART VI, Page 29 ), it was felt that the reductive cyclization of compound 291a would afford 47b and compound 291b would give an uncyclized product which could subsequently be converted into 47b.

Treatment of hydroxy nitro compound 291 with sodium borohydride in refluxing isopropanol for twenty six hours afforded predom-

inantly compound 267. T.L.C. analysis of the crude product on silica

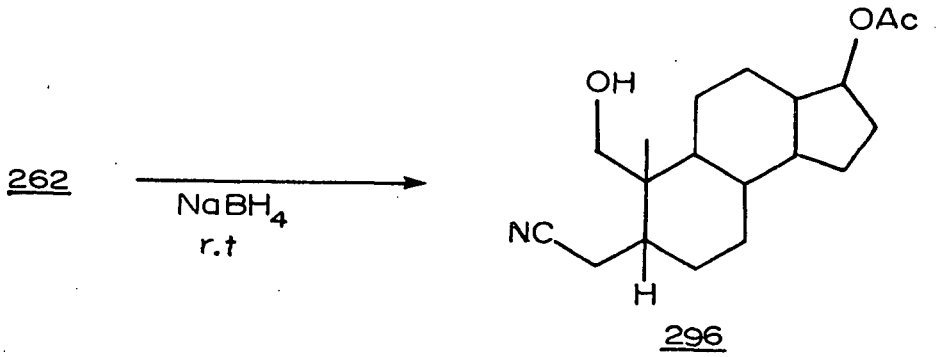



262 267

gel with ethyl acetate as eluent indicated one major compound, $R_f$ 0.75. V.P.C. analysis (column D, 250°, 45 ml/min) indicated one compound (Retention time, 2.8 min). Preparative t.l.c. of the crude product gave 267 in ca. 50% yield as a crystalline solid, m.p. 136-140°. Of note was the disappearance of the nitro, nitrile and acetate bands in the infrared spectrum of 267. The mass spectrum of 267 had a molecular ion peak at $\frac{m}{e}$ 294 with a prominent peak at $\frac{m}{e}$ 276 due to loss of water. Evidently, sodium borohydride had effected a retro-aldol reaction to give cyanoaldehyde 262 which subsequently was reduced to afford compound 267 after work up. It was found that sodium borohydride reduction of cyanoaldehyde 262 in refluxing isopropanol yielded compound 267 (t.l.c., v.p.c., i.r. and mass spectral studies). Attempts were made to prevent the retro-aldol reaction from occurring by performing the reduction in the presence of acetic acid. However, this led to a complex mixture of

products as indicated by t.l.c. analysis.

Catalytic hydrogenation of compound 291 over 10% palladium-on-charcoal in methanol for five hours yielded cyanoaldehyde 262 and hydroxy nitrile 296. T.L.C. analysis of the crude product on silica gel with

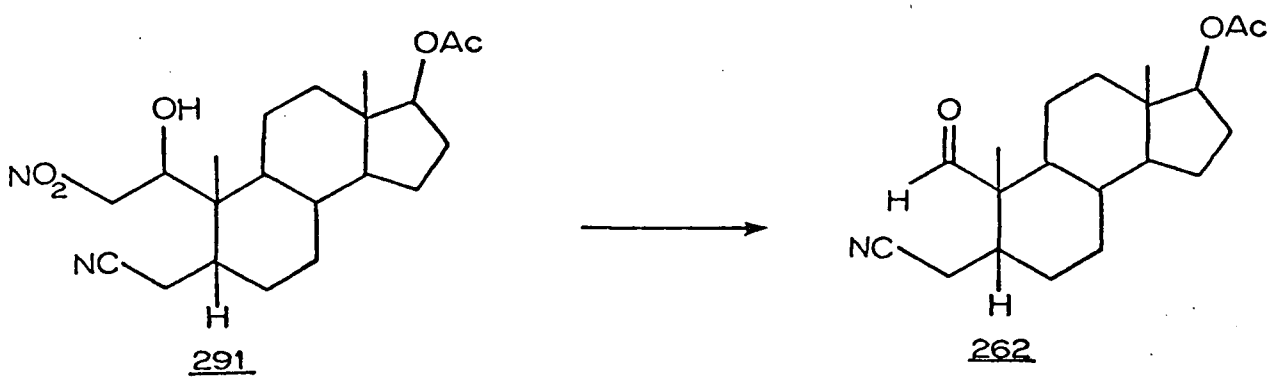



296

a mixture of chloroform and ethyl acetate (5:1, v/v) as the eluent indicated two major compounds and several minor components. Acid extraction of the crude product, followed by neutralization and subsequent diethyl ether extraction was performed. T.L.C. examination of the diethyl ether solution suggested the absence of basic compounds in the crude product. V.P.C. analysis (column D, 250°, 45 ml/min) of the crude product indicated two compounds (Retention times 9 and 18 min). The infrared spectrum of the crude product had a nitrile band at 2250 $cm^{-1}$ and of note was the absence of the nitro bands at 1560 $cm^{-1}$ and 1380 $cm^{-1}$. Sodium borohydride reduction of 262 at room temperature for twenty four hours gave compound 296. The t.l.c. and v.p.c. of 296 was identical with the t.l.c. and v.p.c. of one of the products derived from the catalytic hydrogenation of hydroxy nitro 291. The infrared spectrum of 296 had bands at 3450 $cm^{-1}$, 2250 $cm^{-1}$ and 1720 $cm^{-1}$ due to the hydroxy,

nitrile and acetate functionalities, respectively. The salient feature in the n.m.r. spectrum of 296 was a two-proton double doublet (J = 11 Hz) at τ6.53, 6.49 due to the protons adjacent to the carbon-1 hydroxy group. Finally, the mass spectrum of 296 had a molecular ion peak at $\frac{m}{e}$ 333.

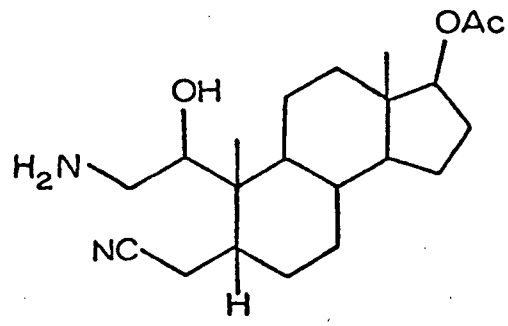
Performing the catalytic hydrogenation of 291 in the presence of oxalic[193] or acetic acid[194] with various catalysts appeared to effect a retro-aldol type reaction as indicated by t.l.c., v.p.c. and infrared studies. It is documented that hydrogenation of hydroxy nitro compounds




291 262

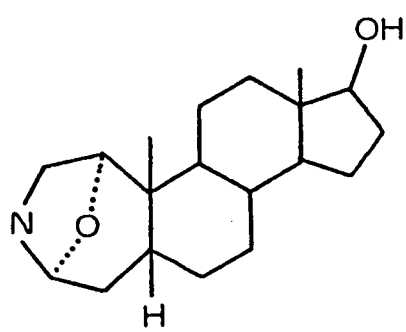
can be complicated by a reversal reaction.[189b] Corey et al.,[195] have employed aluminum amalgam to reduce a nitro group to an amine. Accordingly, treatment of hydroxy nitro compound 291 in diethyl ether-methanol at 0° with aluminum amalgam did not yield compound 297 but afforded

cyanoaldehyde 262 as indicated by t.l.c., v.p.c., and infrared studies.



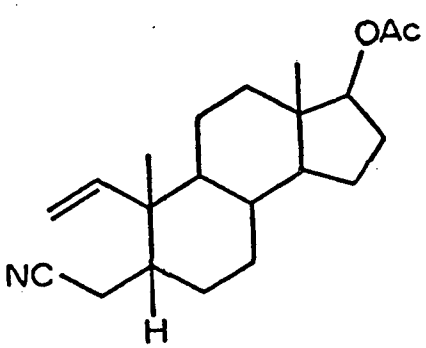

297

A further extension of this work would be to protect the carbon-1 hydroxy group of compound 291 as an acetate functionality,[196] followed by reduction and subsequent cyclization to afford the bicyclooxazolidine 47b.

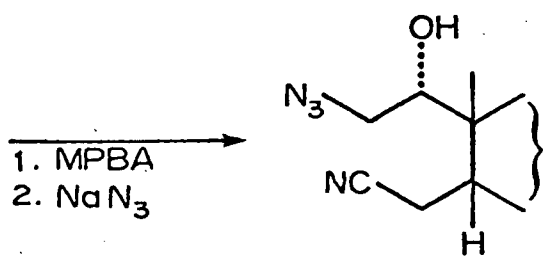



47b

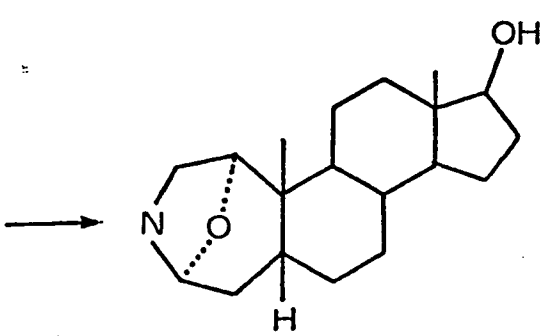
In summary, the original goal to develop an efficient method of synthesizing compound 47b had not been fully realized. However, our synthetic investigations led to the preparation of 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a) which Shimizu[39] has recently converted to the 17β-hydroxy isomer of samandarine 47b.




57a




58




47b

## EXPERIMENTAL

Melting points, which were determined on a Kofler hot stage, and boilings are uncorrected. Optical rotations were recorded at the sodium D line using a Perkin-Elmer Model 141 Automatic Polarimeter. Ultraviolet spectra were measured in methanol solution on a model SP800 spectrophotometer. The infrared spectra were recorded on a Perkin-Elmer model 700 and were calibrated using the 1601 $cm^{-1}$ band of polystyrene. The 'H n.m.r. spectra were recorded in deuterochloroform solution on either a Varian T-60 or Varian HA-100. Line positions are given in the Tiers $\tau$ scale, with tetramethylsilane as internal standard; the multiplicity, integrated peak areas and proton assignments are indicated in parentheses. The mass spectra were obtained using an Atlas CH-4 mass spectrometer and high resolution determinations were performed on an AEI MS-9 mass spectrometer. Microanalyses were performed by Mr. Peter Borda, University of British Columbia. The vapour phase chromatography (v.p.c.) analyses were performed with a Varian Aerograph 90-P-3 using column A, 8 ft. x ¼ in. column of 5% Fluoro Silicone (QF-1) on 60-80 mesh Diaport "S", column B, 5 ft. x ¼ in. column of 3% SE 30 on Chromosorb W, and column C, 5 ft. x ¼ in. column of 10% carbowax on 60-80 mesh Chromosorb W, or with a Perkin-Elmer Model 900 using

column D, 6 ft. x $\frac{1}{8}$ in. column of 8% SE 30 on 80-100 mesh Chromosorb W. The specific column used, along with the column temperature and carrier gas (helium) flow-rate (in ml/min) are indicated in parentheses. Silica Gel GF-254 and a Woelm neutral alumina were used for thin layer chromatography (t.l.c.). Silica Gel PF-254 and Aluminum Oxide F-254 were used for preparative layer chromatography. Silica Gel, Woelm alumina, and Fluorisil (100-200 mesh) were used for column chromatography.

Preparation of 17β-hydroxy-5β-androstan-3-one (81a)[42]

A solution of testosterone (93, 5.0 g, 0.017 moles) in 95% ethanol (100 ml) containing 3N hydrochloric acid (8 ml) and 10% palladium-on-charcoal catalyst (250 mg) was hydrogenated at ambient pressure and temperature by stirring in an atmosphere of hydrogen. After the uptake of hydrogen had ceased (400 ml, 30 min) the catalyst was removed by filtration and washed with acetone. The combined washings and ethanolic solution were concentrated to 20 ml under reduced pressure. The suspension was extracted with ether (2 x 75 ml), the organic layer was washed with dilute aqueous sodium bicarbonate (2 x 20 ml) and saturated sodium chloride (2 x 20 ml) solutions, dried over sodium sulphate, and filtered. The solvent was removed under reduced pressure to afford 4.98 g of a crystalline residue, m.p. 123-128°. Recrystallization of the residue from methanol afforded 1.43 g (21%) of 81a as a crystalline solid, m.p. 138-140°, $[\alpha]_D^{20}$+34° (c=1, EtOH) (lit.[54] m.p. 139-140°, $[\alpha]_D$+32.7°).

Infrared ($CHCl_3$), 3450, 1705 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $C\underline{H}_3$), 8.95 (singlet, 3H, C-19 $C\underline{H}_3$), 6.35 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 9 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 290(100),275(10),273(10),248(32), 323(33),221(35).

Preparation of 17β-acetoxy-5β-androstan-3-one (81b)[42]

The hydrogenation of testosterone (93, 5.0 g, 0.017 moles) was carried out by employing the procedure of Liston[42] to yield 4.98 g of a crystalline residue, m.p. 123-127°. To a solution of this material (4.98 g) in dry pyridine (20 ml) was added acetic anhydride (5 ml). The solution was stirred at room temperature for 16 hr, then diluted with water (200 ml), and shaken for 15 min. The precipitate was collected, washed with 1N hydrochloric acid (100 ml) and with water (100 ml), and air dried. Recrystallization from ether afforded 2.19 g (38%) of 17β-acetoxy-5β-androstan-3-one (81b), m.p. 142-144°, $[\alpha]_D^{25}$+43° (c=1, MeOH) (lit.[42] m.p. 140-142°, $[\alpha]_D^{25}$+45.2°). V.P.C. analysis (column A, 225°, 60 ml/min) of the crude product indicated 75% of 17β-acetoxy-5β-androstan-3-one (81b) and 25% of 17β-acetoxy-5β-androstan-3-one (Retention times 7.5 and 8.6 min, respectively).

Infrared ($CHCl_3$), 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $C\underline{H}_3$), 8.97 (singlet, 3H, C-19 $C\underline{H}_3$), 7.97 (singlet, 3H, acetate), 5.37 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 9 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 332(49),272(85),257(32),230(16), 214(12),160(20),148(35),42(100).

Anal. Calcd for: $C_{21}H_{32}O_3$ : C, 75.86; H, 9.70. Found: C, 75.86; H, 9.52.

Preparation of a mixture of syn and anti 17β-hydroxy-5β-androstan-3-one oximes (87) and (88), respectively

A solution of 17β-hydroxy-5β-androstan-3-one (81b, 801 mg, 2.76 mmoles), hydroxylamine hydrochloride (3.095 g, 0.044 moles) and sodium acetate trihydrate (4.0 g, 0.048 moles) in 90% methanol (60 ml) was refluxed for 2.5 hr and then allowed to cool. The precipitate was collected, washed with water (75 ml), dried, and recrystallized from methanol to afford 0.50 g (60%) of syn and anti oximes 87 and 88, respectively, m.p. 210-214° (lit. [53a] m.p. 211-213°).

Infrared ($CHCl_3$), 1650, 3350 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.27 (broad singlet, 3H, C-18 $CH_3$), 9.03 (broad singlet, 3H, C-19 $CH_3$), ca. 7 (unresolved multiplet, 1H, C-4 $H_{eq}$ 87 and C-2 $H_{eq}$ 88), 6.35 (triplet, 1H, C-17, $H_\alpha$, J = 9 Hz).

mass spectrum $\frac{m}{e}$ (relative intensity), 305(13),298(10),278(22),275(100), 257(70),216(75).

Attempted separation of the mixture of *syn* and *anti* oximes 87 and 88

A mixture of *syn* and *anti* oximes 87 and 88 (100 mg, 0.32 mmoles) was chromatographed on a 20 x 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of benzene and ethyl acetate (4:1, v/v) as eluent. After elution, the band lying in the region $R_f$ 0.60 - 0.68 was removed and extracted with ethyl acetate (40 ml). The solvent was removed by evaporation under reduced pressure to give 23.2 mg (23%) of *anti* oxime 88, m.p. 211-213° (lit. [50a,53a] m.p. 211-212°).

Infrared ($CHCl_3$), 1650, 3350 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.28 (singlet, 3H, C-18 $CH_3$), 9.03 (singlet, 3H, C-19 $CH_3$), *ca.* 7 (unresolved multiplet, 1H), 6.35 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz).

The band lying in the region $R_f$ 0.52 - 0.59 was removed and extracted with ethyl acetate (40 ml). The solvent was removed by evaporation under reduced pressure to afford 21.2 mg (21%) of *syn* oxime 87, m.p. 211-213° (lit. [50a,53a] m.p. 211-213°);

Infrared ($CHCl_3$), 1650, 3350 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.27 (singlet, 3H, C-18 $CH_3$), 9.05 (singlet, 3H, C-19 $CH_3$), *ca.* 7 (unresolved multiplet, 1H), 6.36 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz).

Attempted separation of the mixture of syn and anti oximes 87 and 88

A mixture of syn and anti oximes 87 and 88 (100 mg, 0.32 mmoles) was dissolved in ethyl acetate (3 ml) and chromatographed on a column of silica gel (100 g). Elution with a mixture of benzene and ethyl acetate (4:1, v/v) afforded 40.0 mg (40%) of the anti oxime 88, m.p. 211-213° (lit. [50a,53a] m.p. 211-212°), as the first fraction and then 41.0 mg (41%) of the syn oxime 87, m.p. 210-213° (lit.[50a,53a] m.p. 211-213°).

First Fraction:

Infrared ($CHCl_3$), 1650 $cm^{-1}$, 3350 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.28 (singlet, 3H, C-18 $CH_3$), 9.05 (singlet, 3H, C-19 $CH_3$), ca. 7 (unresolved multiplet, 1H), 6.40 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz).

Second Fraction:

Infrared ($CHCl_3$), 1650, 3350 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.27 (singlet, 3H, C-18 $CH_3$), 9.05 (singlet, 3H, C-19 $CH_3$), ca. 7 (unresolved multiplet, 1H), 6.40 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz).

Beckmann Rearrangement of syn 17β-hydroxy-5β-androstan-3-one oxime (87)

To a solution of syn oxime 87 (15.1 mg, 0.049 mmoles) in pyridine (.8 ml, 9.8 mmoles) was added p-toluenesulphonyl chloride (27.6 mg, 0.148 mmoles). The solution was stirred at room temperature for 2 days; then ethyl acetate (3 ml) was added, followed by 5% aqueous sodium

bicarbonate (3 ml). The mixture was stirred for 5 min, then diluted with 5% sodium bicarbonate solution (5 ml) and ethyl acetate (5 ml). The aqueous layer was separated and extracted with ether (2 x 5 ml) and the combined organic layers were dried over sodium sulphate. The solvent was removed under reduced pressure to afford 18.2 mg of a colourless foamy residue. Crystallization of the residue from methanol afforded 9.8 mg (65%) of 17β-hydroxy-3-aza-A-homo-5β-androstan-4-one (82a), m.p. 241-242° (lit.[53b] m.p. 242-244°). T.L.C. analysis of this material (silica gel or alumina) in various solvent systems indicated the presence of one compound.

Infrared ($CHCl_3$), 3440, 1660 $cm^{-1}$.

Attempted preparation of pure 17β-hydroxy-3-aza-A-homo-5β-androstan-4-one (87a)

To a solution of the syn and anti oximes 87 and 88 (200 mg, 0.65 mmoles) in pyridine (13.5 ml) was added p-toluenesulphonyl chloride (500 mg, 2.63 mmoles). The reaction mixture was stirred at room temperature for ca. 2 days. The pyridine was removed under reduced pressure (below 70°) and the crude dark red oil was dissolved in chloroform. The chloroform solution was washed with 1N hydrochloric acid (5 x 2 ml), 1N sodium hydroxide (2 x 2 ml) solution and saturated sodium chloride (5 x 2 ml) solution. The organic layer was dried over sodium sulphate, filtered, and the solvent removed by evaporation under reduced pressure. The resulting crude oil was dried under vacuum to yield 210 mg of a mixture of crude lactams 82a and 83a as an off-red solid. T.L.C. analysis

on alumina, with benzene and n-pentanol (9:1, v/v) as the solvent system, indicated partial separation of the lactams 82a and 83a. The crude material (200 mg) was chromatographed on a 20 x 20 cm alumina coated plate, adsorbant thickness 0.9 mm, using a mixture of benzene and n-pentanol (9:1, v/v) as eluent. After elution, the bands lying in the region $R_f$ 0.81-0.65 and $R_f$ 0.55-0.62 were removed and extracted with chloroform. The solvent was removed by evaporation under reduced pressure to afford 40.0 mg (20%, $R_f$ 0.81-0.65) of an oil and 100.3 mg (50%, $R_f$ 0.55-0.62) of a semi-solid. T.L.C. examination of these products indicated that the first fraction ($R_f$ 0.81-0.65) consisted of one major compound with a minor component while the second fraction ($R_f$ 0.55-0.62) consisted of a mixture of compounds.

## Attempted preparation of methyl 17β-hydroxy-2,3-seco-5β-androst-1-en-3-oate (104a) from a mixture of syn and anti 17β-hydroxy-5β-androstan-3-one oximes 87 and 88

### Attempted preparation of a mixture of 17β-hydroxy-3-aza-A-homo-5β-androstan-4-one (82a) and 17β-hydroxy-4-aza-A-homo-5β-androstan-3-one (83a)

To a solution of a mixture of syn and anti oximes 87 and 88 (800 mg, 2.62 mmoles) in pyridine (16 ml) was added p-toluene-sulphonyl chloride (1.5 g, 0.007 moles). The reaction mixture

was stirred at room temperature for 3 days. The pyridine was removed by evaporation under reduced pressure (below 70°) and the crude oil was dissolved in diethyl ether (100 ml). The diethyl ether solution was washed with 1N hydrochloric acid (3 x 20 ml), 1N sodium hydroxide (2 x 20 ml) and saturated sodium chloride solution (3 x 20 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 1.10 g of a crystalline solid. Recrystallization of this material yielded 789 mg (65%) of a mixture of 17β-tosyloxy-3-aza-A-homo-5β-androstan-4-one (82b) and 17β-tosyloxy-4-aza-A-homo-5β-androstan-3-one (83b), m.p. 200-202°, $\lambda_{max}$ 225 mμ.

Infrared ($CHCl_3$), 3400, 1660, 1190 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.20 (singlet, 3H, C-18 $C\underline{H}_3$), 9.0 (singlet, 3H, C-19 $C\underline{H}_3$), 7.53 (singlet, 3H, tosylate group), 5.70 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 10 Hz), 3.50 (broad singlet, 1H, exchangeable proton), 2.64, 2.17 (double doublet, 4H, tosylate group, J = 8 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 459(26),287(72),272(15),91(100);

Anal. Calcd. for: $C_{26}H_{37}NO_4S$: C, 67.94; H, 8.11; N, 3.04. Found C, 67.92; H, 8.21.

Preparation of a mixture of N-nitroso-17β-tosyloxy-3-aza-A-homo-5β-androstan-4-one (101b) and N-nitroso-17β-tosyloxy-4-aza-A-homo-5β-androstan-3-one (105b)

Sodium acetate (500 mg) was added to carbon tetrachloride (20 ml) saturated with nitrogen dioxide. This mixture was cooled to -60° and then a mixture of lactams 82b and 83b (50 mg, 0.108 mmoles) was added. After 5 min the reaction mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure to afford 54.1 mg (101%) of a mixture of compounds 101b and 105b as an unstable yellow powder. The t.l.c. of this material on silica gel with ethyl acetate as the eluent showed one broad spot ($R_f$ 0.82).

Infrared ($CHCl_3$), 1720, 1415, 1385, 1360 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.2 (singlet, 3H, C-18 $C\underline{H}_3$), 9.0 (singlet, 3H, C-19 $C\underline{H}_3$), 7.54 (singlet, 3H, tosylate group), 5.7 (triplet, 1H, C-17 $\underline{H}_\alpha$), 2.67, 2.24 (double doublet, 4H, tosylate group).

Pyrolysis of a mixture of N-nitroso-17β-tosyloxy-3-aza-A-homo-5β-androstan-4-one (101b) and N-nitroso-17β-tosyloxy-4-aza-A-homo-5β-androstan-3-one (105b)

A mixture of compounds 101b and 105b (50 mg, 0.102 mmoles) was heated at 125° under an atmosphere of nitrogen for 2 min to afford 48 mg (crude, 101%) of a mixture of 17β-tosyloxy-3-oxa-A-homo-5β-androstan-4-one (102b) and 17β-tosyloxy-4-oxa-A-homo-5β-androstan-3-one (106b). T.L.C. analysis of this product on silica gel with ethyl acetate as the eluent indicated the presence of two compounds, $R_f$ 0.40 and $R_f$ 0.35.

Infrared ($CHCl_3$), 1720, 1600, 1190 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.2 (broad singlet, 3H, C-18 $C\underline{H}_3$), 9.04 (broad singlet, 3H, C-19 $C\underline{H}_3$), 7.27 (singlet, 3H, tosylate group), 5.80 (triplet, 1H, C-17 $\underline{H}_\alpha$), 2.70, 2.24 (double doublet, 4H, tosylate group);

mass spectrum $\frac{m}{e}$ (relative intensity), 460(1),289(1),288(3), 287(1),172(1),107(6),105(3),91(15),44(100);

Mol. Wt. Calcd. for $C_{26}H_{36}O_5S$: 460.2283. Found: (high resolution mass spectrometry): 460.2261.

Pyrolysis of a mixture of 17β-acetoxy-N-nitroso-3-aza-A-homo-5β-androstan-4-one (101c) and 17β-acetoxy-N-nitroso-4-aza-A-homo-5β-androstan-3-one (105c)

A mixture of compounds 101c and 105c (50 mg, 0.13 mmoles) was added to boiling toluene (10 ml) under an atmosphere of nitrogen. After 5 min the reaction mixture was cooled and the solvent removed under reduced pressure to afford 47 mg (100%) of a mixture of 17β-

acetoxy-3-oxa-A-homo-5β-androstan-4-one (102c) and 17β-acetoxy-4-oxa-A-homo-5β-androstan-3-one (106c). This crude product was identical (t.l.c., v.p.c., i.r., and n.m.r.) with the products derived from the Baeyer-Villiger oxidation of 17β-acetoxy-5β-androstan-3-one (81b). T.L.C. analysis of the crude product on silica gel with ethyl acetate as the eluent indicated the presence of two compounds, $R_f$ 0.55 and $R_f$ 0.60. V.P.C. analysis (column B, 300°, 45 ml/min) of the crude product indicated the presence of two compounds (Retention times, 18 and 31 min) in ca. a 3:2 ratio.

Infrared ($CHCl_3$), 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.20 (singlet, 3H, C-18 $CH_3$), 8.97 (singlet, 3H, C-19 $CH_3$), 8.0 (singlet, 3H, acetate), 6.20 - 5.20 (multiplet, 3H, C-17 $H_\alpha$ and C-2 $H_2$, 102c, C-4a $H_2$, 106c);

mass spectrum $\frac{m}{e}$ (relative intensity), 348(6),288(16),260(8),187(16), 147(16),133(23),94(100).

Preparation of a mixture of 17β-acetoxy-3-oxa-A-homo-5β-androstan-4-one (102c) and 17β-acetoxy-4-oxa-A-homo-5β-androstan-3-one (106c)

To a solution of 17β-acetoxy-5β-androstan-3-one (81b, 200 mg, 0.60 mmoles) in chloroform (15 ml) was added meta-chloroperbenzoic acid (155 mg, 0.90 mmoles). The reaction mixture was stirred in the dark at room temperature for 2 days. The solution was then poured into saturated sodium bicarbonate solution (30 ml) and then extracted with chloroform (50 ml). The chloroform solution was washed with

water ( 2 x 10 ml) and saturated sodium chloride solution (2 x 10 ml), dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to afford 180 mg (85%) of a mixture of compounds 102c and 106c as a crystalline solid, m.p. 118-125°. T.L.C. analysis of this product on silica gel with ethyl acetate as the eluent indicated the presence of two compounds, $R_f$ 0.58 and $R_f$ 0.61. V.P.C. analysis (column B, 300°, 60 ml/min) of the crude product showed two peaks (Retention times 18 and 31 min) in ca. a 1:4 ratio. An analytical specimen was obtained by three recrystallizations from methanol, m.p. 207-208°.

Infrared ($CHCl_3$), 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.20 (singlet, 3H, C-18 $CH_3$), 8.97 (singlet, 3H, C-19 $CH_3$), 8.0 (singlet, 3H, acetate), 6.20 - 5.20 (multiplet, 3H, C-17 $H_\alpha$ and C-2 $H_2$ 102c, C-4a $H_2$ 106c);

mass spectrum $\frac{m}{e}$ (relative intensity), 348(15),288(25),260(9),94(100);

Anal. Calcd. for $C_{21}H_{32}O_4$ : C, 72.30; H, 9.25. Found: C, 72.02; H, 9.48.

Attempted preparation of methyl 17β-hydroxy-2,3-seco-5β-androst-1-en-3-oate (104a) from a mixture of 17β-acetoxy-3-oxa-A-homo-5β-androstan-4-one (102c) and 17β-acetoxy-4-oxa-A-homo-5β-androstan-3-one (106c)

Preparation of a mixture of methyl 2,17β-dihydroxy-2,3-seco-5β-androstan-3-oate (103a) and methyl 4,17β-dihydroxy-3,4-seco-5β-androstan-3-oate (107a)

A solution of compounds 102c and 106c (100 mg, 0.258 mmoles) in 5% methanolic sodium hydroxide (30 ml) was heated to reflux. After 2 hr of refluxing, the reaction mixture was cooled and the solvent removed under reduced pressure. The residue was dissolved in water (30 ml) and the solution was carefully acidified with dilute acetic acid, extracted with chloroform (2 x 30 ml). The combined chloroform extracts were washed with saturated sodium chloride (2 x 10 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to yield 100 mg of a crystalline solid, m.p. 185-189°. To a solution of this material (100 mg, 0.30 mmoles) in methanol (30 ml) was added a solution of diazomethane in ether (0.35 mmoles). After stirring the reaction mixture at room temperature for 5 min the solvent was removed under reduced pressure to yield 66 mg (75%) of a mixture of hydroxy methyl esters 103a and 107a as an oil. Attempts to induce crystallization failed. The t.l.c. of this material on silica gel with ethyl acetate as the solvent system showed one broad spot, $R_f$ 0.80.

Infrared ($CHCl_3$), 3600, 3450, 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.27 (singlet, 3H, C-18 $C\underline{H}_3$), 9.02, 8.93 (singlets, 3H, C-19 $C\underline{H}_3$), ca. 6.35 (multiplet, 3H, C-2 $\underline{H}_2$ and C-17 $\underline{H}_\alpha$), 6.32 (singlet, 3H, methyl ester group);

mass spectrum $\frac{m}{e}$ (relative intensity), 338(8), 320(11),306(76), 274(100),263(65),233(84).

Mol. Wt. Calcd. for $C_{20}H_{34}O_4$ : 338.2456 Found (high resolution mass spectrometry): 338.2442

Preparation of a mixture of methyl 17β-hydroxy-2-tosyloxy-2,3-seco-5β-androstan-3-oate (103b) and methyl 17β-hydroxy-2-tosyloxy-2,3-seco-5β-androstan-3-oate (107b)

To a solution of compounds 103a and 107a (30 mg, 0.088 mmoles) was added p-toluenesulphonyl chloride (17.1 mg, 0.089 mmoles). The reaction mixture was allowed to stand at 20° for 2 days. The pyridine was removed under reduced pressure and the resulting residue dissolved in diethyl ether (40 ml). The diethyl ether solution was washed with 1N hydrochloric acid (4 x 10 ml), 1N sodium hydroxide (4 x 10 ml), and saturated sodium chloride solution (2 x 10 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to yield 39.3 mg (88%) of a mixture of the tosyloxy methyl esters 103b and 107b as a clear oil. Attempts to induce crystallization failed. The t.l.c. of this material on silica gel with various solvent systems showed one broad spot.

Infrared ($CHCl_3$), 3600, 3400, 1720, 1600, 1190 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.29, 9.27 (singlets, 3H, C-18 $CH_3$), 9.07, 9.03 (singlets, 3H, C-19 $CH_3$), 7.55 (singlet, 3H, tosylate group),

6.67 (singlet, 3H, methyl ester group), ca. 6.4 (multiplet, 1H, C-17 $H_\alpha$), 5.90 (multiplet, 2H, C-2 $H_2$ 103b and C-4 $H_2$ 107b), 2.68, 2.20 (double doublet, 4H, tosylate group, J = 9 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity),492(1),474(1),460(1),305(3), 304(4),288(3),287(4),234(12),233(30),215(30),187(20),91(100).

Attempted preparation of methyl 17β-hydroxy-2,3-seco-5β-androst-1-en-3-oate (104a)

A mixture of compounds 103b and 107b (160 mg, 0.32 mmoles) was added to collidine (10 ml). The reaction mixture was refluxed for 4 hr under an atmosphere of nitrogen. The solvent was removed by evaporation under reduced pressure to afford a brown oil which was dissolved in diethyl ether (35 ml). The diethyl ether solution was washed with saturated sodium bicarbonate (2 x 10 ml) and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to yield 753 mg of a brown oil which was chromatographed on a 20 x 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of benzene and ethyl acetate (1:1, v/v) as the eluent. After elution, the band lying in the region $R_f$ 0.55 - 0.60 was removed and extracted with ethyl acetate (50 ml). The solvent was removed under reduced pressure to afford 35.5 mg (extrapolated yield, 32%) of methyl 17β-hydroxy-3,4-seco-5β-androst-4-en-3-oate (108a) as a clear oil. Attempts to induce crystallization failed.

Infrared ($CHCl_3$), 3600, 3450, 1720, 1630, 900 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.27 (singlet, 3H, C-18 $\underline{CH_3}$), 8.97 (singlet, 3H, C-19 $\underline{CH_3}$), ca. 6.5 (multiplet, 1H, C-17 $\underline{H_\alpha}$), 6.37 (singlet, 3H, ester group), 5.35 (doublet, 2H, C-4 $\underline{H_2}$, J = 4 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity),320(5),234(6),233(25),215(12), 205(6),187(9),160(10),62(100);

Mol. Wt. Calcd. for $C_{20}H_{32}O_3$ : 320.2351. Found (high resolution mass spectrometry): 320.2327.

## Attempted preparation of 3,17β-diacetoxy-5β-androst-2-ene (85b)

To a solution of triphenylmethane (133 mg, 0.56 mmoles) in dimethoxyethane under nitrogen was added potassium (22 mg, 0.55 mmoles). The resulting red solution was stirred for 10 min at room temperature and then 17β-acetoxy-5β-androstan-3-one (81b, 166 mg, 0.50 mmoles) was added. The reaction mixture was stirred for 1 hr at room temperature, then acetyl chloride (61.2 mg, 0.60 mmoles) was added, and the solution was diluted with diethyl ether (30 ml). The diethyl ether solution was washed with saturated sodium bicarbonate (3 x 20 ml) and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to afford 142 mg (75%, crude) of a clear oil. This material was identical with 3,17β-diacetoxy-5β-androst-3-ene (146) by infrared and n.m.r. spectroscopy.

Infrared ($CHCl_3$), 1750, 1725, 1685, 1660 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $\underline{CH_3}$), 9.02 (singlet, 3H, C-19 $\underline{CH_3}$), 7.97 (singlet, 3H, acetate), 7.89 (singlet, 3H, vinyl acetate), 5.36 (triplet, 1H, C-17 $\underline{H_\alpha}$, J = 9 Hz), 4.95 (broad singlet, 1H, C-4 $\underline{H_2}$).

## Attempted preparation of 17β-hydroxy-5β-androst-1-en-3-one (155) from 17β-hydroxy-5β-androstan-3-one (81a)[86]

### Preparation of 2-Hydroxymethylene-5β-androstan-17β-ol-3-one (153)[80e]

To a suspension of sodium hydride (31.2 mg, 1.3 mmoles) in dry benzene (5 ml), under nitrogen, was added absolute methanol (40 ml). The mixture was stirred and heated briefly to boiling. After the mixture was cooled to room temperature, 17β-hydroxy-5β-androstan-3-one (81a, 200 mg, 0.68 mmoles) and ethyl formate (50.3 mg, 0.68 mmoles) were added. The mixture was stirred at room temperature under nitrogen for 30 hr. After the careful addition of water (10 ml) to destroy the excess sodium hydride, the mixture was diluted with water (5 ml) and diethyl ether (25 ml). The ether-benzene layer was separated and re-extracted with water (10 ml). The combined aqueous layers were washed once with diethyl ether (10 ml) and then neutralized with carbon dioxide to pH 7. The mixture was filtered and the collected solid washed thoroughly

with water (3 x 20 ml). Recrystallization of this material from acetonitrile gave 131 mg (60%) of the hydroxymethylene derivative 53 as a crystalline solid, m.p. 153-159° (evacuated sealed tube), $[\alpha]_D^{25}$+30.2° (c=1, MeOH), $\lambda_{max}$ 290 mμ (ε = 8000), (lit.[80e] m.p. 157-163°, $[\alpha]_D$+26.9°, $\lambda_{max}$ 284 mμ (ε = 7900)).

Preparation of 2-formyl-17β-hydroxy-5β-androst-1-en-3-one (154)[86]

To a solution of hydroxymethylene derivative 153 (100 mg, 0.31 mmoles) in dry benzene (22 ml) was added dichlorodicyanoquinone (70.4 mg, 0.31 mmoles). The mixture was refluxed under an atmosphere of nitrogen for 30 hr. The solvent was removed by evaporation under reduced pressure to afford 170 mg of a yellow oil which was chromatographed on silica gel (5 g). Elution with ethyl acetate gave 30.6 mg (31%) of 2-formyl-17β-hydroxy-5β-androst-1-en-3-one (154) as a clear oil, $\lambda_{max}^{EtOH}$ 245 mμ (ε = 5760),, $\lambda_{max}^{EtOH-NaOH}$ 306 mμ (ε = 10850), (lit.[86] $\lambda_{max}^{EtOH}$ 249 mμ, ε = 5700; $\lambda_{max}^{EtOH-NaOH}$ 306 mμ, ε = 10800):

Infrared ($CHCl_3$), 3450, 2750, 1720, 1670, 1600 $cm^{-1}$.

Preparation of 17β-hydroxy-5β-androst-1-en-3-one (155)[86]

To a solution of compound 154 (15.4 mg, 0.047 mmoles) in dry benzene (20 ml) was added chlorotris(triphenylphosphine)rhodium

(46.2 mg, 0.141 mmoles). The mixture was refluxed for 3 hr under nitrogen. The solid yellow chlorocarbonylbis-(triphenylphosphine)-rhodium (m.p. 199-207°) was collected. The solvent was removed by evaporation under reduced pressure to afford 34.1 mg of a yellow oil which was chromatographed in a 5 x 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (4:1, v/v) as eluent. After elution, the band lying in the region $R_f$ 0.70 - 0.75 was removed and extracted with ethyl acetate (50 ml). The ethyl acetate was removed by evaporation under reduced pressure to afford 10.2 mg of 17β-hydroxy-5β-androst-1-en-3-one (155) contaminated with triphenylphosphine oxide.

Infrared ($CHCl_3$), 3350, 1660, 840 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.24 (singlet, 3H, C-18 $C\underline{H}_3$), 8.80 (singlet, 3H, C-19 $C\underline{H}_3$), 6.34 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 9 Hz), 4.14, 3.15 (double doublet, 2H, vinyl protons, J = 10 Hz).

## Preparation of 17β-acetoxy-4β-bromo-5β-androstan-3-one (158)[90]

To a solution of 17β-acetoxy-5β-androstan-3-one (81b, 9.197 g, 0.027 moles) in glacial acetic acid (50 ml) was added a solution of bromine (1.53 ml, 28.5 mmoles) in acetic acid (40 ml) over a period of 20 min with vigorous stirring at 10°. Absorption of bromine was rapid, and 30 min later water (300 ml) was added and the mixture was allowed to stand for 1 hr at 10°. The precipitated product was

collected, washed with water (3 x 100 ml) and dissolved in diethyl ether (300 ml). The organic layer was washed with saturated sodium chloride (2 x 20 ml) solution, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to give 10.44 g (92%) of a crystalline solid, m.p. 135-151°. V.P.C. analysis (column D, 250°, 45 ml/min) of this product indicated the presence of two compounds (Retention times 9.0 and 8.9 min) in ca. a 4:1 ratio. Two recrystallizations from diethy ether gave compound 158 as a crystalline solid, m.p. 174-175°, $[\alpha]_D$+43.0° (c=1, MeOH) (lit.[90] m.p. 174-175°, $[\alpha]_D$+44.7° ± 2° $CHCl_3$).

Infrared ($CHCl_3$), 1730 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.18 (singlet, 3H, C-18 $CH_3$), 8.90 (singlet, 3H, C-19 $CH_3$), 7.97 (singlet, 3H, acetate), 5.37 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz), 5.0 (doublet, 1H, C-4 $H_{ax}$, J = 12 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity),412(30),410(30),353(70),351(70), 333(100),332(70),273(100),258(80),245(70),273(100).

Preparation of 2β,17β-diacetoxy-5β-androstan-3-one (159)

A solution of crude 17β-acetoxy-4β-bromo-5β-androstan-3-one (158, 10.3 g, 0.025 moles) and anhydrous sodium acetate (50.2 g, 0.612 moles) in glacial acetic acid (730 ml) was refluxed for 2.5 hr. After cooling the solution was poured into water (500 ml) and extracted with diethyl ether (2 x 200 ml). The combined

ethereal extracts were washed with saturated sodium bicarbonate (4 x 50 ml) and saturated sodium chloride (2 x 50 ml) solutions, dried over sodium sulphate, and filtered. The solvent was removed under reduced pressure to afford a crystalline residue. Recrystallization of the residue from methanol gave 6.80 g (70%) of diacetate 159, m.p. 170-173°. V.P.C. analysis (column D, 250°, 45 ml/min) indicated the presence of one compound (Retention time 16.8 min). The analytical specimen was obtained by two recrystallizations from methanol, m.p. 161-162°.

Infrared ($CHCl_3$), 1720 $cm^{-1}$ (see Figure I, Page 250);

n.m.r. ($CDCl_3$), τ9.20 (singlet, 3H, C-18 $\underline{CH_3}$), 8.95 (singlet, 3H, C-19 $\underline{CH_3}$), 8.00 (singlet, 3H, acetate), 7.90 (singlet, 3H, acetate), ca. 7.8 (double doublet, 1H, C-4 $\underline{H_\alpha}$, J = 5 and 13 Hz), 7.19 (broad triplet, 1H, C-4 $\underline{H_\alpha}$, J = 9 Hz), 5.43 (triplet, 1H, C-17 $\underline{H_\alpha}$, J = 9 Hz), 4.85 (double doublet, 1H, C-2 $\underline{H_\alpha}$, J = 6 and 14 Hz) (see Figure X, Page 253 );

mass spectrum $\frac{m}{e}$ (relative intensity), 390(4), 348(15), 346(9), 331(7), 330(30), 304(10), 288(14), 270(12), 55(100); (see Figure XIX , Page 256 );

Anal. Calcd. for $C_{23}H_{34}O_5$ : C, 70.74; H, 8.77. Found: C, 70.70; H, 8.82.

Zinc-acetic acid reduction of 2β,17β-diacetoxy-5β-androstan-3-one (159)

To a solution of diacetate 159 (100 mg, 0.25 mmoles) in glacial acetic acid (30 ml) was added dry zinc dust (500 mg). The reaction mixture was refluxed for 30 hr, then cooled and poured into water (50 ml). The aqueous solution was extracted with diethyl ether (3 x 30 ml). The combined ethereal extracts were washed with water (3 x 10 ml), saturated sodium bicarbonate (3 x 10 ml) and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 72.5 mg of a yellow oil which was chromatographed on a 5 x 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (5:1, v/v) as the eluent. After elution, the band lying in the region $R_f$ 0.52 - 0.59 was removed and extracted with ethyl acetate (50 ml). The solvent was removed by evaporation under reduced pressure to yield 25.7 mg (extrapolated yield, 31%) of a clear oil. This material was identical (t.l.c., infrared, n.m.r., and mass spectrum) with 17β-acetoxy-5β-androstan-3-one (81b).

Preparation of 3,17β-diacetoxy-5β-androst-3-ene (146)[42]

To a solution of 17β-acetoxy-5β-androstan-3-one (81b, 250 mg, 0.75 mmoles) in isopropenyl acetate (5 ml) was added hydroquinone (30 mg) and concentrated sulphuric acid (10 μl) under an atmosphere

of nitrogen. The reaction mixture was heated to a gentle reflux and acetone formed during the reaction was collected. Isopropenyl acetate was periodically added to maintain a solvent volume of ca. 5 ml. After refluxing under nitrogen for 2 hr, the reaction mixture was cooled to 0° and diluted with diethyl ether (30 ml). This organic mixture was washed with saturated sodium bicarbonate (3 x 25 ml) and sodium chloride (15 ml) solutions, dried over sodium sulphate and filtered. The solvent was distilled to afford 361 mg of a light yellow oil. V.P.C. analysis (column A, 225°, 60 ml/min) of the crude product indicated the presence of 59% 3,17β-diacetoxy-5β-androst-3-ene (146) and 23% 3,17β-diacetoxy-5β-androst-2-ene (85b). (Retention times 12 and 14 min, respectively).

Infrared ($CHCl_3$), 1750, 1725, 1685 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $CH_3$), 9.01 (singlet, 3H, C-19 $CH_3$), 7.98, 7.90 (singlets, 6H, vinyl acetates), 5.36 (triplet, 2H, C-17 $H_\alpha$, J = 9 Hz), 4.95 (singlet, 1H, C-4 H ), 4.80 (multiplet, 1H, C-2 H ).

## Equilibration of enol acetates 146 and 85b[42]

The crude enol acetates were not purified but were equilibrated immediately. The enol acetate mixture (150 mg) was dissolved in benzene (12 ml), carbon tetrachloride (6 ml) and acetic anhydride (2.4 ml). To this solution was added 70% perchloric acid (30 μl)

under an atmosphere of nitrogen. The reaction mixture was stirred under nitrogen at room temperature for 22 hr. Then the reaction mixture was poured into diethyl ether (50 ml) and washed with water (25 ml), saturated sodium bicarbonate (4 x 20 ml) and sodium chloride (20 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to yield 121 mg of a light yellow oil. V.P.C. analysis (column A, 225°, 60 ml/min) of this product indicated 88% of 2,17β-diacetoxy-5β-androst-3-ene (146, Retention time 12 min) and 2% of 2,17β-diacetoxy-5β-androst-2-ene (85b, Retention time 14 min).

Infrared ($CHCl_3$), 1750, 1725, 1685, 1660 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $CH_3$), 9.02 (singlet, 3H, C-19 $CH_3$), 7.97 (singlet, 3H, acetate), 7.89 (singlet, 3H, vinyl acetate), 5.36 (triplet, 1H, C-17 $H_\alpha$, J= 9 Hz), 4.95 (singlet, 1H, C-4 H ).

Preparation of 3α,17β-diacetoxy-3β,4β-oxido-5β-androstane (177)[197]

The equilibrated enol acetate mixture containing predominantly compound 146 (53 mg, 0.14 mmoles) was dissolved in chloroform (5 ml). To this solution was added m-chloroperoxybenzoic acid (70 mg, 0.40 mmoles) and sodium bicarbonate (50 mg). The reaction mixture was stirred at 0° for 4 hr and then the reaction was allowed to stand at -5° for 40 hr. The reaction mixture was

poured into cold saturated sodium bicarbonate solution (10 ml) and extracted with diethyl ether (3 x 10 ml). The organic layer was separated and washed with 20% sodium carbonate (3 x 15 ml) and saturated sodium chloride (10 ml) solutions, dried over sodium sulphate and filtered. Removal of the solvent under reduced pressure afforded 46 mg (84%) of β-epoxide 177 as a light yellow oil, with no trace of the starting enol acetate 146 by v.p.c.

Infrared ($CHCl_3$), 1720-1745, 860 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.20 (singlet, 3H, C-18 $CH_3$), 9.13 (singlet, 3H, C-19 $CH_3$), 7.97 (singlet, 3H, acetate), 7.93 (singlet, 3H, acetate), 6.93 (singlet, 1H, C-4 H ), 5.36 (triplet, 1H, C-17 $H_\alpha$).

Preparation of 4α,17β-diacetoxy-5β-androstan-3-one (175a)[197]

3α,17β-diacetoxy-3β,4β-oxido-5β-androstan-3-one (177, 25 mg, 0.064 mmoles) was pyrolyzed at 160° for 5 min under an atmosphere of nitrogen to afford 20.0 mg (80%) of compound 175a. V.P.C. analysis (column A, 225°, 60 ml/min) of this product indicated one compound (Retention time 24 min).

Infrared ($CHCl_3$), 1740, 1725 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.21 (singlet, 3H, C-18 $CH_3$), 8.90 (singlet, 3H, C-19 $CH_3$), 7.97 (singlet, 3H, acetate), 7.85 (singlet, 3H, acetate), 5.38 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz), 4.59 (doublet, 1H, C-4 $H_\beta$, J = 8 Hz).

Preparation of 4β,17β-diacetoxy-5β-androstan-3-one (175b)[197]

Hydrogen chloride was bubbled through a stirred solution of 3α,17β-diacetoxy-3β,4β-oxide-5β-androstane (177, 25 mg, 0.064 mmoles) in diethyl ether at 12° for 5 min. The solution was stirred for 30 min, then allowed to stand at -5° for 20 hr. The reaction mixture was diluted with diethyl ether (30 ml), washed with saturated sodium bicarbonate (3 x 20 ml) and sodium chloride (20 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to afford 20.0 mg (80%) of crude compound 175b. V.P.C. analysis (column A, 225°, 60 ml/min) of the crude product indicated the presence of one compound (Retention time 24 min).

Infrared ($CHCl_3$), 1740, 1725 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.21 (singlet, 3H, C-18 $C\underline{H}_3$), 8.93 (singlet, 3H, C-19 $C\underline{H}_3$), 7.98 (singlet, 3H, acetate), 7.85 (singlet, 3H, C-4 acetate), 5.39 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 9 Hz), 4.48 (doublet, 1H, C-4 $\underline{H}$ , J = 12 Hz).

Preparation of 4β,17β-diacetoxy-5β-androstan-3-one (175b)[197]

To a solution of 4α,17β-diacetoxy-5β-androstan-3-one (175a, 19 mg, 0.048 mmoles) in hexamethylphosphoramide (1.5 ml) was added a crystal of p-toluenesulphonic acid and the reaction mixture was heated under nitrogen at 160° for 15 min. The reaction mixture was

then cooled to room temperature and diluted with diethyl ether (25 ml). This organic layer was washed with water (3 x 20 ml), saturated sodium bicarbonate (2 x 15 ml) and sodium chloride (15 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 12 mg of compound 175b with no trace of compound 175a detectable by n.m.r. spectroscopy.

Formation of 4β,17β-diacetoxy-5β-androstan-3-one (175b)[197]

To a solution of 4α,17β-diacetoxy-5β-androstan-3-one (175a, 30 mg, 0.076 mmoles) in glacial acetic acid (4.5 ml) was added sodium acetate (300 mg, 3.65 mmoles). The reaction mixture was refluxed under an atmosphere of nitrogen for 2 hr. The reaction mixture was then cooled to 0°, diluted with cold water (25 ml) and extracted with diethyl ether (3 x 25 ml). The diethyl ether was washed with saturated sodium bicarbonate (3 x 20 ml) and sodium chloride (20 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 19 mg (63%) of 4β,17β-diacetoxy-5β-androstan-3-one (175b).

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $CH_3$), 9.02 (singlet, 3H, C-19 $CH_3$), 9.79 (singlet, 3H, C-17 acetate), 7.89 (singlet, 3H, C-19 $H_3$), 5.36 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz), 4.95 (singlet, 1H, C-4 H ).

Attempted preparation of 17β-acetoxy-2β-hydroxy-5β-androstan-3-one (183)

To a solution of 2β,17β-diacetoxy-5β-androstan-3-one (159, 100 mg, 0.255 mmoles) in methanol (4 ml) and water (1 ml) was added sodium bicarbonate (100 mg). The reaction mixture was heated at 50° for 30 min and then stirred for ca. 1 hr at room temperature. The solvent was removed under reduced pressure and the resulting residue was dissolved in water (10 ml) and extracted with diethyl ether (2 x 10 ml). The combined ethereal extracts were washed with saturated sodium chloride (2 x 5 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 75 mg (84%, crude) of a mixture of 17β-acetoxy-2β-hydroxy-5β-androstan-3-one (183) and 17β-acetoxy-3α-hydroxy-5β-androstan-2-one (185). T.L.C. analysis of the crude product on silica gel with a mixture of chloroform and ethyl acetate (5:1, v/v) as the eluent indicated the presence of two compounds, $R_f$ 0.75 and $R_f$ 0.78.

Infrared ($CHCl_3$), 3350, 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.25, 9.20 (singlets, 3H, C-18 $CH_3$), 8.97, 8.90 (singlets, 3H, C-19 $CH_3$), 6.60-5.80 (multiplet, 1H, C-2 $H_\alpha$, 183 and C-3 $H_\beta$, 185), 5.40 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz).

Preparation of anti 17β-acetoxy-2β-hydroxy-5β-androstan-3-one oxime (187)

A solution of 2β,17β-diacetoxy-5β-androstan-3-one (159, 5.10 g, 0.013 moles) hydroxylamine hydrochloride (21.0 g, 0.302 moles), and sodium

acetate trihydrate (27.5 g, 0.202 moles) in 90% methanol (400 ml) was refluxed for 48 hr and then the methanolic solution was concentrated to 20 ml under reduced pressure. Water (100 ml) was added to the solution and the resulting suspension was extracted with diethyl ether (2 x 200 ml). The combined ethereal extracts were washed with aqueous sodium bicarbonate (2 x 30 ml), and saturated sodium chloride (2 x 20 ml) solutions, dried over $Na_2SO_4$ and filtered. The solvent was removed under reduced pressure to afford 4.01 g (85%) of hydroxyoxime 187, m.p. 176-182°. T.L.C. analysis of this material on silica gel using a mixture of ethyl acetate and benzene (5:1, v/v) as eluent indicated one major compound, $R_f$ 0.78. The analytical specimen was obtained by three recrystallizations from methanol, m.p. 214-215°, $[\alpha]_D^{25}$+21.42°(c=.7, MeOH).

Infrared ($CHCl_3$), 3550, 3350, 1660 $cm^{-1}$ (see Figure II , Page 250 );

n.m.r. ($CDCl_3$), τ9.25 (singlet, 3H, C-18 $\underline{CH_3}$), 9.03 (singlet, 3H, C-19 $\underline{CH_3}$), 7.21 (double doublet, 1H, C-4 $\underline{H_\beta}$, J = 4 and 14 Hz), 5.80 (doublet doublet, 1H, C-2 $\underline{H_\alpha}$, J = 5 and 13 Hz), 5.40 (triplet, 1H, C-17 $\underline{H_\alpha}$), (see Figure XI , Page 253);

mass spectrum $\frac{m}{e}$ (relative intensity),363(1),362(6),347(3),345(4),344(5), 334(17),333(78),316(6),303(3),271(3),43(100); (see Figure XX , Page 256);

Anal. Calcd. for $C_{21}H_{33}NO_4$ : C, 69.39; H, 9.15; N, 3.85. Found: C, 69.62; H, 9.37; N, 4.02.

Preparation of 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195)

To a solution of anti 17β-acetoxy-2β-hydroxy-5β-androstan-3-one oxime (187, 1.0 g, 2.75 mmoles) in pyridine (45 ml) was added p-toluenesulphonyl chloride (500 mg, 2.62 mmoles). The reaction mixture was refluxed under an atmosphere of nitrogen for 5 hr. The solution was cooled, poured into dilute sodium bicarbonate solution (50 ml) and extracted with diethyl ether. The organic layer was separated and washed with water (4 x 20 ml), saturated sodium bicarbonate (2 x 15 ml), and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to yield 985 mg of a brown oil. This material was chromatographed on a 20 x 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (5:1, v/v). After elution, the band lying in the region $R_f$ 0.62 - 0.68 was removed and extracted with ethyl acetate (100 ml). The solvent was removed by evaporation under reduced pressure to afford 190 mg (20%) of cyanoaldehyde 195 as a clear oil.

Infrared ($CHCl_3$), 2750, 2250, 1720 $cm^{-1}$ (see Figure III , Page 250 ).

n.m.r. ($CDCl_3$), τ9.21 (singlet, 3H, C-18 $\underline{CH_3}$), 8.68 (singlet, 3H, C-19 $\underline{CH_3}$), 5.40 (triplet, 1H, C-17 $\underline{H_\alpha}$), 0.20 (double doublet, 1H, $\underline{CH}O$, J = 1 and 3 Hz) (see Figure XII, Page 253 ).

mass spectrum $\frac{m}{e}$ (relative intensity),345(2),318(5),302(6),301(11), 290(4),258(7),242(8),241(16),43(100) (see Figure XXI , Page 256 );

Anal. Calcd. for $C_{21}H_{31}NO_3$ : C, 73.01; H, 9.04; N, 4.06. Found: C, 72.82; H, 9.16; N, 3.88.

Preparation of 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195)

Anti 17β-acetoxy-2β-hydroxy-5β-androstan-3-one oxime (187, 1.0 g, 2.75 mmoles) was treated with distilled thionyl chloride (10 ml) at -20° (methanol-ice). After 1.5 min the resulting colourless solution was at once slowly poured into a mixture of 3N potassium hydroxide (300 ml) and diethyl ether (100 ml) at 0°. The organic phase was separated and the aqueous solution was extracted with diethyl ether (2 x 50 ml). The combined ethereal extracts were washed with saturated sodium chloride (2 x 50 ml) solution, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 1.10 g of an oily residue which was chromatographed on fluorisil (50 g). Elution with a mixture of chloroform and benzene (1:2, v/v) afforded 805 mg (85%) of cyanoaldehyde 195 as a clear oil which crystallized on standing, m.p. 110-112°, $[\alpha]_D^{20}$+23.3° (c=1, MeOH). Cyanoaldehyde 195 was converted into its 2,4-DNP derivative, m.p. 238-240°, for analysis.

Infrared ($CHCl_3$), 2750, 2250, 1720 $cm^{-1}$ (see Figure III , Page 250 ).

n.m.r. ($CDCl_3$), τ9.21 (singlet, 3H, C-18 $CH_3$), 8.68 (singlet, 3H, C-19 $CH_3$), 5.40 (triplet, 1H, C-17 $H_\alpha$), 0.20 (double doublet, 1H, CHO, J = 1 and 3 Hz) (see Figure XII , Page 253 );

mass spectrum $\frac{m}{e}$ (relative intensity),345(2),318(5),302(6),301(11), 290(4),258(7),242(8),241(16),43(100) (see Figure XXI , Page 256 );

Anal. Calcd. for $C_{27}H_{35}N_5O_6$ : C, 61.70; H, 6.71; N, 13.32. Found: C, 61.90; H, 6.84; N, 13.13.

Attempted preparation of 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a) from 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195)

Preparation of 17β-acetoxy-2-hydroxy-2,3-seco-5β-androstane-3-nitrile (202)

To a solution of 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195, 80 mg, 0.23 mmoles) in ethanol (10 ml) was added sodium borohydride (4.4 mg, 0.46 mmoles). The reaction mixture was stirred for 3 hr at room temperature under an atmosphere of nitrogen. The solvent was removed by evaporation under reduced pressure, water (20 ml) and diethyl ether (40 ml) were added to the residue. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 ml). The combined ethereal extracts were washed with 1N hydrochloric acid (2 x 20 ml), saturated sodium bicarbonate (3 x 10 ml) and sodium chloride (10 ml) solutions, dried over sulphate and filtered. The solvent was removed by evaporation under reduced pressure to yield 80.2 mg of a crystalline solid. Recrystallization of this material from methanol yielded 68.1 mg (85%) of compound 202, m.p. 139-144°. An analytical specimen was obtained by two recrystallizations from methanol, m.p. 138-140°, $[\alpha]_D^{20}$+34° (c=5, MeOH).

Infrared ($CHCl_3$), 3450, 2250, 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.25 (singlet, 3H, C-18 $CH_3$), 8.97 (singlet, 3H, C-19 $CH_3$), 8.0 (singlet, 3H, acetate),5.47 (triplet, 1H, C-17 $H_\alpha$,

J = 9 Hz), 6.30 (triplet, 1H, C-2 $\underline{H_2}$, J = 10 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 348(6),347(23),329(6), 332(5),303(10),302(39),288(9),287(24),270(31),260(14),43(100);

Anal. Calcd. for $C_{21}H_{33}NO_3$ : C, 72.58; H, 9.57; N, 4.03. Found: C, 72.43; H, 9.56; N, 3.88.

Preparation of 17β-acetoxy-2-tosyloxy-2,3-seco-5β-androstane-3-nitrile (203a)

To a solution of 17β-acetoxy-2-hydroxy-2,3-seco-5β-androstane-3-nitrile (202, 200 mg, 0.57 mmoles) in pyridine (15 ml) was added p-toluenesulphonyl chloride (180.0 mg, 0.94 mmoles). The reaction mixture was stirred at room temperature for 24 hr and then cold saturated sodium bicarbonate (20 ml) solution and diethyl ether (40 ml) were added. The organic layer was separated and washed with .1N hydrochloric acid (3 x 10 ml), saturated sodium bicarbonate (2 x 15 ml) and sodium chloride (10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to afford 310.3 mg of a crystalline solid. This material was recrystallized from diethyl ether to give 232 mg (81%) of compound 203a, m.p. 128-129°. An analytical specimen was obtained by three recrystallizations from diethyl ether, m.p. 129-130 $[\alpha]_D^{20}$+37° (c=1, MeOH).

Infrared ($CHCl_3$), 2250, 1720, 1600, 1190 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.24 (singlet, 3H, C-18 $C\underline{H}_3$), 8.99 (singlet, 3H, C-19 $C\underline{H}_3$), 8.0 (singlet, 3H, acetate), 7.52 (singlet, 3H, tosylate group), 5.92 (triplet, 2H, C-2 $\underline{H}_2$, J = 9 Hz), 5.40 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 9 Hz), 2.60, 2.15 (double doublet, 4H, tosylate group, J = 10 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 501(10),440(16),346(15), 301(15),269(35),268(45),241(29),43(100);

Anal. Calcd. for $C_{28}H_{39}NO_5S$ : C, 67.03; H, 7.83; N, 2.79; S, 6.39. Found: C, 67.02; H, 7.96; N, 2.89; S, 6.18.

Attempted preparation of 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a)

To a solution of 17β-acetoxy-2-tosyloxy-2,3-seco-5β-androstane-3-nitrile (203a, 70 mg, 0.139 mmoles) in hexamethylphosphoramide (20 ml) was added dry potassium t-butoxide (15.0 mg, 0.13 mmoles) under an atmosphere of nitrogen. The reaction mixture was heated at 160° for 2 hr under an atmosphere of nitrogen and then cooled. The solution was poured into cold water (100 ml) and extracted with diethyl ether (2 x 50 ml). The diethyl ether solution was washed with water (6 x 20 ml) and saturated sodium chloride solution (2 x 10 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to yield 78 mg of a brown oil. T.L.C. analysis of this material on silica gel with chloroform and ethyl acetate (5:1, v/v) as the eluent

indicated the presence of two major compounds, $R_f$ 0.82 and $R_f$ 0.68, and polar baseline contaminants.

Infrared ($CHCl_3$), 2250, 1720, 1630, 1000, 930 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.20 (broad singlet, 3H, C-19 $C\underline{H}_3$), 8.83, 8.75 (singlets, 3H, C-19 $C\underline{H}_3$), 5.10-4.20 (multiplet, 2½H, vinylic protons and C-17 $\underline{H}_\alpha$).

Attempted preparation of cis and trans 2,17β-diacetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (223a) and (223b)

Preparation of Reagent B ($10^{-2}MHClO_4$).[142] To absolute ethyl acetate (40 ml) was added 72% perchloric acid (0.05 ml, 0.58 mmoles) and acetic anhydride (4.8 ml, 5.1 mmoles), and the solution was made up to 50 ml with ethyl acetate. 17β-Acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195, 60 mg, 0.17 mmoles) was dissolved in 6 ml of reagent B and the reaction mixture allowed to stand for 5 min at room temperature. The solution was then washed with saturated sodium bicarbonate (2 x 10 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 65 mg (85%) of a clear oil. T.L.C. analysis of this material on silica gel with chloroform and ethyl acetate (5:1, v/v) as the eluent indicated the presence of one major compound, $R_f$ 0.75.

Infrared ($CHCl_3$), 2250, 1750, 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.25 (singlet, 3H, C-18 $\underline{CH_3}$), 8.86 (singlet, 3H, C-19 $\underline{CH_3}$), ca. τ8 (three singlets, 9H, acetates), 5.42 (triplet, 1H, C-17 $\underline{H}_\alpha$, J = 9 Hz), 3.14 (triplet, 1H, C-2 $\underline{H}$, J = 7 Hz).

Preparation of cis and trans 2,17β-diacetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (223a) and (223b)

To a solution of 17β-acetoxy-2-oxo-2,3-seco-5β-androstane-3-nitrile (195, 612 mg, 1.774 mmoles) in isopropenyl acetate (15 ml) was added 2,5-di-tert-butyl-p-benzoquinone (60 mg) and 15 μl of concentrated sulphuric acid, and the mixture was heated to reflux. During addition and reflux a stream of nitrogen was passed through the solution. After 36 hr of refluxing the mixture was cooled to room temperature, poured into dilute aqueous sodium bicarbonate (15 ml) and extracted with diethyl ether (2 x 100 ml). The combined ethereal extracts were washed with saturated sodium chloride (2 x 20 ml) solution, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 930 mg of a brown oil which was chromatographed on silica gel (45 g). Elution with chloroform gave 472 mg (68%) of a mixture of cis and trans enol acetates 223a and 223b as a colourless oil. T.L.C. analysis of this material on a 20 x 5 cm silica coates plate, adsorbant thickness 0.1 mm, using chloroform as eluent indicated the presence of two compounds, $R_f$ 0.81 and $R_f$ 0.72, in a ca. a 1:1 ratio.

Infrared ($CHCl_3$), 1745, 1725, 1660 $cm^{-1}$ (see Figure IV , Page 251 );

n.m.r. ($CDCl_3$), τ9.20 (broad singlet, 3H, C-18 $C\underline{H}_3$), 8.80, 8.70 (singlets, 3H, C-19 $C\underline{H}_3$), 8.02 (singlet, 3H, acetate), 7.93, 7.86 (singlets, 3H, vinyl acetate), 5.42, 4.74 (two doublets, 1H, $C_1\underline{H}$, J = 8 and 13 Hz, respectively), 3.04, 2.96 (two doublets, 1H, $C_2\underline{H}$, J = 8 and 13 Hz, respectively) (see Figure XIII, Page 254 );

mass spectrum $\frac{m}{e}$ (relative intensity), 387(25),360(9),359(35),345(52), 344(45),327(34),318(22),311(46),303(36),302(54),301(23),285(45),49(100) (see Figure XXII, Page 257 );

Mol. Wt. Calcd. for $C_{23}H_{33}NO_4$ : 387.2409. Found (high resolution mass spectrometry): 387.2389.

Preparation of cyclohexenyl acetate (252)[198]

To cyclohexanone (9.3 g, 0.094 moles) was added acetic anhydride (20.4 g, 0.20 mole) and p-toluenesulphonic acid (0.1 g). The reaction mixture was refluxed for 4 hr. During the heating period, acetic acid along with some acetic anhydride was allowed to distill off, care being taken to keep the distillation temperature below 125° in order to avoid excessive losses of acetic anhydride. The crude black oil was distilled through a 10 cm Vigreux column to yield 4.2 g (32%) of enol acetate 252 b.p. 76-78°/20 mm (lit.[199] b.p. 74-76°/17 mm). The V.P.C. analysis (column C, 100°, 60 ml/min) of this material, indicated the presence of one compound (Retention time 4.8 min).

Preparation of 1-azido-2-iodocyclohexyl acetate (253)[198]

Sodium azide (300 mg, 4.6 mmoles) in acetonitrile (4 ml) was cooled in ice-methanol and treated with a solution of iodine monochloride (382 mg, 2.3 mmoles) in acetonitrile (2 ml). The mixture was stirred for 5 - 10 min then treated with a solution of the enol acetate 252 (140 mg, 1.0 mmoles) in acetonitrile (2 ml). After stirring the reaction mixture at room temperature for 2 hr all the enol acetate appeared to be used (by v.p.c.). The reaction mixture was then treated with water (5 ml) and extracted with diethyl ether (4 x 5 ml). The combined ethereal extracts were washed with dilute sodium thiosulphate until colourless, then water (2 x 5 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 212 mg of a light yellow oil which was chromatographed on silica gel (5 g). Elution with benzene afforded 200 mg (60%) of 1-azido-2-iodocyclohexyl acetate (253). T.L.C. analysis of this material on silica gel with benzene as the eluent indicated one compound, $R_f$ 0.85.

Infrared ($CHCl_3$), 2120, 1740 $cm^{-1}$;

n.m.r. ($CDCl_3$), $\tau$8.89 (singlet, 3H, acetate), 5.37 (triplet, 1H, J = 6 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 309(19.6),267(28.7),225(48.1), 224(10.3),222(7.9),180(11.5),140(45.7),128(46.9),127(50.3),112(48.8), 98(55.6),85(17.8),84(45.9),43(100).

Anal. Calcd. for $C_8H_{12}IN_3O_2$ : C, 31.09; H, 3.91; N, 13.59; I, 41.05. Found: C, 30.95; H, 3.95; N, 13.73; I, 41.20.

Preparation of pentenyl acetate (258) [198]

To pentanal (6.0 g, 0.069 moles) was added potassium acetate (1.0 g, 0.01 moles) and acetic anhydride (15.0 g, 0.147 moles). The reaction mixture was refluxed for 10 hr and then poured into diethyl ether (100 ml). The diethyl ether solution was washed with water (4 x 20 ml) and saturated sodium bicarbonate solution, dried over sodium sulphate and filtered. The filtrate was removed under reduced pressure to afford a dark brown oil. Distillation of this material gave 3.37 g (38%) of the enol acetate 258 , b.p. 148-150° (lit.[200] b.p. 148-149°).

Infrared ($CHCl_3$), 1740, 1600 $cm^{-1}$.

Preparation of 1-azido-2-iodopentyl acetate (259) [198]

Sodium azide (1.20 g, 18 moles) in acetonitrile (16 ml) was cooled in ice-methanol and treated with a solution of iodine monochloride (1.53 g, 8.4 mmoles) in acetonitrile (9 ml). The mixture was stirred for 5 - 10 min, then treated with a solution of the enol acetate 258 (470 mg, 3.6 mmoles) in acetonitrile (8 ml). The reaction mixture was stirred at room temperature for 2 hr, then treated with water (20 ml) and extracted with diethyl ether (4 x 20 ml). The combined ethereal extracts were washed with dilute sodium thiosulphate until colourless, then water (2 x 20 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 700 mg of a yellow liquid which was chromatographed on silica gel (10 g).

Elution with chloroform yielded 730 mg (63%) of compound 259 as a clear oil.

Infrared ($CHCl_3$), 2120, 1740 $cm^{-1}$;

n.m.r. ($CDCl_3$), $\tau$7.80 (singlet, 3H, acetate), 5.90 (multiplet, 1H, C-2 H), 4.13, 4.0 (double doublet, 1H, C-1 H, J = 4.5 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 297(.4),255(1.9),209(1.6),183(1.0), 170(1.5),154(2.3),128(22.1),127(16.3),43(100).

Anal. Calcd. for $C_7H_{12}IN_3O_2$ : C, 28.30; H, 4.07; N, 14.14; I, 42.71. Found: C, 28.25; H, 4.15; N, 14.20; I, 42.52.

## Attempted preparation of 2,17β-diacetoxy-2-azido-1-iodo-2,3-seco-5β-androstane-3-nitrile (241)

Sodium azide (29.4 mg, 0.45 mmoles) in acetonitrile (2 ml) was cooled in ice-methanol and then treated with a solution of iodine monochloride (33.7 mg, 0.208 mmoles) in acetonitrile (3 ml). The mixture was stirred for 5 - 10 min then treated with a solution of the enol acetates 223a and 223b (35 mg, 0.09 mmoles) in acetonitrile (2 ml). The reaction mixture was stirred at room temperature for 2 hr, then treated with water (6 ml) and extracted with diethyl ether (2 x 5 ml). The combined ethereal extracts were washed with dilute sodium thiosulphate until colourless, then water (2 x 5 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure

to afford 32 mg of a brown oil. The infrared spectrum and t.l.c. analysis of this product indicated predominantly starting material.

Preparation of 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262)

A solution of cis and trans 2,17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (223a and 223b, 510 mg, 1.318 mmoles) in ethyl acetate (20 ml) at dry ice-acetone temperature was treated with ozone (50 ml/min) for 20 min. The resulting dark blue solution was allowed to stand at dry ice-acetone temperature for 35 min and then the excess ozone was removed with a stream of nitrogen. The solvent was removed under reduced pressure to give an oily residue. Methanol (30 ml) and aqueous sodium sulphite (5%, 70 ml) was added to the residue. The mixture was allowed to stand at room temperature for 2.5 hr and then concentrated (70 ml). The aqueous solution was then extracted with diethyl ether (3 x 50 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate (2 x 50 ml) and saturated sodium chloride (2 x 50 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 378 mg (86%) of compound 262 as a clear oil. T.L.C. analysis of this material on silica gel with a mixture of chloroform and ethyl acetate as the eluent indicated one compound, $R_f$ 0.73. V.P.C. analysis (column D, 250°, 45 ml/min) indicated one compound (Retention time, 9 min). Compound 262 was converted into its 2,4-DNP derivative, m.p. 186-188°, for analysis.

Infrared ($CHCl_3$), 2725, 1720 $cm^{-1}$ (see Figure V , Page 251);

n.m.r. ($CDCl_3$), τ9.24 (singlet, 3H, C-18 $C\underline{H}_3$), 8.97 (singlet, 3H, C-19 $C\underline{H}_3$), 8.01 (singlet, 3H, acetate), 5.41 (triplet, 1H, C-17 $\underline{H}_\alpha$), τ.46 (singlet, 1H, C$\underline{H}$O) (see Figure XIV, Page 254 );

mass spectrum $\frac{m}{e}$ (relative intensity), 331(15),330(8),303(15),302(20),301(15), 270(12),243(36),242(70),241(20),202(15),201(24),200(15),43(100) (see Figure XXIII, Page 257 );

Anal. Calcd. for $C_{26}H_{33}N_5O_6$ : C, 61.04; H, 6.50; N, 13.68. Found: C, 60.90; H, 6.70; N, 13.48.

## Preparation of methylenetriphenylphosphorane[158]

Sodium hydride (25 mmoles as a 50% dispersion in mineral oil) in a 50 ml three-necked flask was washed with several portions of n-pentane to remove the mineral oil. The flask then was equipped with rubber stopples, a reflux condenser fitted with a three-way stopcock, and a magnetic stirrer. The system was alternatively evacuated and filled with nitrogen; dimethyl sulphoxide (28 ml) was introduced via syringe, and the mixture was heated at 75-80° for ca. 45 min. The resulting solution of methylsulfinyl carbonion was cooled in an ice-water bath, and (methyl)-triphenylphosphonium bromide (8.9 g, 0.025 moles) in warm dimethyl sulphoxide (25 ml) was added. The resulting solution of the ylide was stirred at room temperature for 10 min before use.

Attempted preparation of 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a)

To a solution of 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262, 30 mg, 0.090 mmoles) in dimethyl sulphoxide (5 ml) was added methylenetriphenylphosphorane (100 µl, 0.10 mmoles). The reaction mixture was heated at 50° for 6 hr. The solution was cooled and then poured into water (20 ml). The aqueous phase was extracted with pentane (4 x 25 ml). The combined fractions were washed with water (3 x 25 ml) and saturated sodium chloride solution (2 x 25 ml), dried over sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure to afford 15 mg of a brown oil. Preparative layer chromatography of this product on a 20 x 5 cm silica gel coated plate, adsorbant thickness 0.9 mm, using chloroform as eluent, did not yield any olefinic compounds by infrared studies.

Preparation of 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a)

n-Butyllithium (2.1M, 1.3 ml, 2.7 mmoles) was added to (methyl)-triphenylphosphonium bromide (1.00 g, 2.8 mmoles) in dry benzene (50 ml) under an atmosphere of nitrogen. After 1.5 hr, 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262, 160 mg, 0.48 mmoles) was added and the solution was stirred for 6 hr at room temperature. Water (50 ml) was then added, and the organic layer separated. The aqueous phase was extracted with benzene (3 x 30 ml). The combined

benzene extracts were washed with saturated sodium chloride (2 x 20 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford a brown oil (630 mg) which was chromatographed on silica gel (36 g). Elution with a mixture of chloroform ethyl acetate (3:1, v/v) afforded a clear oil which was dissolved in acetic anhydride (3 ml) and pyridine (0.4 ml). The solution was stirred at room temperature for 15 hr, and then the solvent was removed under reduced pressure to give an oily residue which was taken up in diethyl ether (40 ml). The diethyl ether solution was washed with 1N hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate (2 x 20 ml) and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to give 81.2 mg (51%) of compound 57a as a crystalline solid, m.p. 132 - 135°. Compound 57a was sublimed at 125°, 0.1 mm pressure, to afford needles, m.p. 134-135°, $[\alpha]_D^{25}$+31.2° (c=.8, MeOH).

Infrared ($CHCl_3$), 2250, 1720, 1630, 980, 920 $cm^{-1}$ (see Figure VI Page 251 );

n.m.r. ($CDCl_3$), τ9.20 (singlet, 3H, C-18 $C\underline{H}_3$), 8.83 (singlet, 3H, C-19 $C\underline{H}_3$), 5.41 (triplet, 1H, C-17 $\underline{H}_\alpha$), 5.10-4.20 (multiplet, 3H, vinylic protons) (see Figure XV , Page 254 );

mass spectrum $\frac{m}{e}$ (relative intensity), 329(15),303(10),302(7),301(20), 288(6),287(11),286(6),254(10),243(20),242(16),241(23),43(100) (see Figure XXIV , Page 257 );

Anal. Calcd. for $C_{21}H_{31}NO_2$ : C, 76.55; H, 9.48; N, 4.25. Found: C, 76.49; H, 9.54; N, 4.19.

Preparation of 17β-hydroxy-2,3-seco-5β-androst-1-ene-3-nitrile (57b)

n-Butyllithium (2.5M, 2 ml, 5.0 mmoles) was added to (methyl)-triphenylphosphonium bromide (1.80 g, 5.04 mmoles) in dry tetrahydrofuran (20 ml) at 0° under an atmosphere of nitrogen. After 1.5 hr the mixture was cooled to -78°, 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262, 360 mg, 1.08 mmoles) in dry tetrahydrofuran (10 ml) was added, and the solution was stirred for 6.5 hr at room temperature. Water (4 ml) was then added, the tetrahydrofuran was evaporated, and the residue was dissolved in diethyl ether (100 ml). The diethyl ether solution was washed with saturated sodium chloride (5 x 60 ml), dried over sodium sulphate and filtered. Removal of the solvent under reduced pressure afforded 1.04 g of a brown oil which was chromatographed on silica gel (36 g). Elution with a mixture of chloroform ethyl acetate (3:1, v/v) gave 205 mg (65%) of compound 57b as a solid. Compound 57b was sublimed at 125°, 0.1 mm pressure, to yield a crystalline solid, m.p. 129-131°.

Infrared ($CHCl_3$), 3400, 2250, 1630, 920, 990 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.23 (singlet, 3H, C-18 $CH_3$), 8.80 (singlet, 3H, C-19 $CH_3$), 6.34 (triplet, 1H, C-17 $H_\alpha$, J = 9 Hz), 5.0 - 4.0 (multiplet, 3H, vinylic protons);

mass spectrum $\frac{m}{e}$ (relative intensity), 288(32),287(100),272(20),269(15), 260(20),245(25),228(34);

M. W. Calcd. for $C_{19}H_{29}NO$ : 287.2248. Found (high resolution mass spectrometry): 287.2254.

Preparation of 3-azido-4-iodocyclohexyl carbonitrile (275)

Sodium azide (2.38 g, 0.035 moles) in acetonitrile (20 ml) was cooled in ice-methanol and then treated with a solution of iodine monochlorides (2.67 g, 0.016 moles) in acetonitrile (10 ml). The mixture was stirred for 5 - 10 min then treated with a solution of cyclohex-3-enyl carbonitrile (274, 1.57 g, 0.014 moles) in acetonitrile (10 ml). The reaction mixture was stirred at room temperature for 24 hr, then poured into water (40 ml), and extracted with diethyl ether (3 x 50 ml). The combined ethereal extracts were washed with dilute sodium thiosulphate until colourless, then with water (2 x 20 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 3.3 g (81%) of compound 275.

Infrared ($CHCl_3$), 2250, 2100 $cm^{-1}$;

n.m.r. ($CDCl_3$), τca. 6 (multiplet, 2H, C-3 H and C-4 H);

mass spectrum $\frac{m}{e}$ (relative intensity), 276(70),149(100),127(22),107(29), 106(40),80(46),79(46),68(50),67(70),42(57).

Mol. Wt. Calcd. for $C_7H_9N_4I$: 275.9873. Found (high resolution mass spectrometry): 275.9858.

Preparation of (2-azido-1-iodocyclohexyl)-acetonitrile (284)

Sodium azide (1.17 g, 0.018 moles) in acetonitrile (20 ml) was cooled in ice-methanol and then treated with a solution of iodine monochloride (1.46 g, 0.009 moles) in acetonitrile (10 ml). The mixture

was stirred for 5 - 10 min then treated with a solution of cyclohex-1-enylacetonitrile (960 mg, 7.93 mmoles). The reaction mixture was stirred at room temperature for 24 hr then treated with water (20 ml) and extracted with diethyl ether (2 x 20 ml). The combined ethereal extracts were combined and washed with dilute sodium thiosulphate until colourless, then with water (2 x 20 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 1.96 g (85%) of compound 284 as a yellow oil. T.L.C. analysis of this material on silica gel with chloroform as the eluent indicated one compound, $R_f$ 0.85.

Infrared ($CHCl_3$), 2250, 2100 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ6.20 - 5.60 (multiplet, 1H );

mass spectrum $\frac{m}{e}$ (relative intensity), 290(6),163(64),134(75),133(75), 121(64),120(100),119(51),107(80),106(85),105(70),94(75),93(98),42(64).

Preparation of 17β-acetoxy-2-azido-1-iodo-2,3-seco-5β-androstane-3-nitrile (270)

Sodium azide (59.5 mg, 0.9 mmoles) in acetonitrile (4 ml) was cooled in ice-methanol and treated with a solution of iodine monochloride (92.4 mg, 0.57 mmoles) in acetonitrile (2 ml). The mixture was stirred for 5 - 10 min then treated with a solution of 17β-acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (57a, 65 mg, 0.19 mmoles).

The course of the reaction was monitored by t.l.c. and infrared spectroscopy. The reaction mixture was stirred at room temperature for 5 hr, then treated with water (10 ml) and extracted with diethyl ether (2 x 20 ml). The combined ethereal extracts were washed with dilute sodium thiosulphate until colourless, then with water (2 x 10 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 80 mg (80%, crude) of compound 270 as a light yellow oil. T.L.C. analysis of this material on silica gel with a mixture of chloroform and ethyl acetate (1:1, v/v) as the eluent indicated one major compound, $R_f$ 0.71, and baseline contaminants. Attempts to purify the crude product by preparative layer chromatography failed.

Infrared ($CHCl_3$), 2205, 220, 1720 $cm^{-1}$;

n.m.r. ($CDCl_3$), $\tau$9.20 (singlet, 3H, C-18 $C\underline{H}_3$), 8.74, 8.62 (singlets, 3H, C-19 $C\underline{H}_3$), 6.6 - 5.8 (multiplet, 3H, C-1 $\underline{H}$ and C-2 $\underline{H}_2$), 5.37 (triplet, 1 H, C-17 $\underline{H}_\alpha$, J = 9 Hz).

## Attempted preparation of 17β-acetoxy-1,2-imino-2,3-seco-5β-androstane-3-nitrile (242)

To a solution of 17β-acetoxy-2-azido-1-iodo-2,3-seco-5β-androstane-3-nitrile (270, 10 mg, 0.02 mmoles) in isopropanol (5 ml) was added sodium borohydride (5 mg, 0.105 mmoles). The reaction mixture was refluxed for 3 hr and then the solvent was removed by evaporation

under reduced pressure. The residue was dissolved in water (10 ml) and extracted with diethyl ether (3 x 5 ml). The combined ethereal extracts were washed with .1N hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (2 x 2 ml) and sodium chloride (5 ml) solutions. The solvent was removed by evaporation under reduced pressure to afford 4.3 mg of a clear oil. T.L.C. analysis of this material on silica gel with chloroform as the eluent indicated predominantly one compound, $R_f$ 0.65, and minor amounts of starting material, $R_f$ 0.42.

Infrared ($CHCl_3$), 2250, 2125, 1600 $cm^{-1}$.

Attempted preparation of N-(triphenylphosphonium iodide)-17β-acetoxy-1,2-imino-2,3-seco-5β-androstane-3-nitrile (283a)

To a solution of 17β-acetoxy-2-azido-1-iodo-2,3-seco-5β-androstane-3-nitrile (270, 65 mg, 0.11 mmoles) in dry benzene (10 ml) was added triphenylphosphine (31 mg, 0.11 mmoles). The reaction mixture was stirred at room temperature for 24 hr. No phosphonium salt was observed to precipitate. The solvent was removed under reduced pressure to afford a brown oil. T.L.C. analysis of this material indicated a complex mixture of compounds.

Infrared ($CHCl_3$), 2250, 1720, 1600 $cm^{-1}$.

Preparation of 17β-hydroxy-2,3-seco-5β-androst-1-en-3-al (271)

Diisobutylaluminum hydride (87 mg, 0.36 mmoles) in benzene (0.31 mls) was added to a solution of 17β-hydroxy-2,3-seco-5β-androst-1-ene-3-nitrile (57b, 40 mg, 0.14 mmoles) in dry benzene (10 ml) under an atmosphere of nitrogen. The mixture was stirred for 1 hr at room temperature and then the complex was decomposed by careful addition of dilute acetic acid (7 ml, 10%). The resulting mixture was stirred for 30 min at room temperature. The organic layer was extracted with benzene (2 x 25 ml). The combined benzene extracts were washed with saturated sodium bicarbonate (2 x 10 ml) and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 30.3 mg (74%) of olefinic aldehyde 271 as a clear oil. T.L.C. analysis of this material on silica gel with a mixture of chloroform and ethyl acetate (2:1, v/v) as the solvent system indicated essentially one compound, $R_f$ 0.72.

Infrared ($CHCl_3$), 3450, 2750, 1720, 1630, 990, 910 $cm^{-1}$;

n.m.r. ($CDCl_3$), τ9.30 (singlet, 3H, C-18 $C\underline{H}_3$), 8.80 (singlet, 3H, C-19 $C\underline{H}_3$), 6.47 (triplet, 1H, C-17 $\underline{H}_\alpha$), 5.4 - 4.0 (multiplet, 3H, vinyl protons), 4.7 (triplet, 1H, C$\underline{H}$O, J = 2 Hz);

mass spectrum $\frac{m}{e}$ (relative intensity), 291(21),290(95),247(42),246(60), 233(15),231(22),229(16),221(100),220(50),219(100),218(64),202(24), 201(48),200(17).

Mol. Wt. Calcd. for $C_{19}H_{30}O_2$ : 290.2245. Found (high resolution mass spectrometry): 290.2271.

Preparation of 3,3-ethylenedioxy-2,3-seco-5β-androst-1-en-17β-ol (272)

A mixture of 17β-hydroxy-2,3-seco-5β-androst-1-en-3-al (271, 33 mg, 0.11 mmoles), p-toluenesulphonic acid monohydrate (1 small crystal), ethylene glycol (0.6 ml), and dry methylene chloride (5 ml) was shaken in a flask at room temperature for 24 hr, poured into dilute sodium bicarbonate solution (20 ml) and extracted with methylene chloride (2 x 12 ml). The combined methylene chloride extracts were washed with saturated sodium bicarbonate (2 x 10 ml) and sodium chloride (2 x 10 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to give 47.2 mg of a brown oil which was chromatographed on florisil (6 g). Elution with a mixture of chloroform and benzene (1:1, v/v/) afforded 245 mg (71%) of olefinic acetal 272 as a clear oil. T.L.C. analysis of this material on fluorosil indicated one major compound, $R_f$ 0.45.

Infrared ($CHCl_3$), 3500, 1630, 990, 910 $cm^{-1}$; (see Figure VII , Page 252 );

n.m.r. ($CDCl_3$), τ9.37 (singlet, 3H, C-18 $C\underline{H}_3$), 8.93 (singlet, 3H, C-19 $C\underline{H}_3$), ca. 6.3 (multiplet, 5H, C-17 $\underline{H}_\alpha$ and acetal protons), 5.32 (triplet, 1H, $C_2\underline{H}$, J = 5 Hz), 5.3 - 4.0 (multiplet, 3H, vinylic protons); (see Figure X Page 255 );
mass spectrum $\frac{m}{e}$ (relative intensity),335(9),334(40),248(38),175(100), 147(50),125(85); (see Figure XXV , Page 258 );

Mol. Wt. Calcd. for: $C_{21}H_{34}O_5$ : 334.2507. Found (high resolution mass spectrometry): 334.2506.

Attempted preparation of 2-azido-3,3-ethylenedioxy-1-iodo-2,3-seco-5β-androstan-17β-ol

Sodium azide (10 mg, 0.15 mmoles) in acetonitrile (4 ml) was cooled in ice-methanol and treated with a solution of iodine monochloride (11.6 mg, 0.071 mmoles) in acetonitrile (4 ml). The mixture was stirred for 10 min, then treated with 3,3-ethylenedioxy-2,3-seco-5β-androst-1-en-17β-ol (272, 20 mg, 0.059 mmoles) in acetonitrile (3 ml). The reaction mixture was stirred at room temperature for 48 hr, then poured into water (5 ml), and extracted with diethyl ether (2 x 10 ml). The combined ethereal extracts were washed with dilute sodium thiosulphate until colourless, then with water (2 x 20 ml), dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to yield 10 mg of a brown oil. T.L.C. analysis of this material on silica gel with a mixture of chloroform and ethyl acetate (2:1, v/v) as the eluent indicated two major compounds, $R_f$ 0.85 and $R_f$ 0.75, several minor compounds, and baseline contaminants. Purification by preparative layer chromatography on silica gel failed.

Infrared ($CHCl_3$), 3400, 2100, 1740, 1620 $cm^{-1}$.

Preparation of 17β-acetoxy-1-hydroxy-2-nitro-2,3-seco-5β-androstane-3-nitrile (291)

A solution of cyanoaldehyde (65.0 mg, 0.19 mmoles) in nitromethane (25.0 ml) at room temperature was treated with triethylamine (6 ml)

under an atmosphere of nitrogen. The solution was stirred at room temperature for five days in the dark. The solvent was removed under reduced pressure to afford 89.3 mg of a yellow oil. This material (89.3 mg) was chromatographed on a 20 x 20 cm silica gel coated plate, adsorbant thickness 0.9 mm, using a mixture of chloroform and ethyl acetate (5:1, v/v) as eluent. After elution, the band lying in the region $R_f$ 0.75-0.85 was removed and extracted with ethyl acetate (50 ml). The solvent was removed by evaporation under reduced pressure to afford a crystalline solid. Recrystallization from ethanol gave 55.2 mg (74%) of compound 291 as a crystalline solid m.p. 186-188°. An analytical specimen was obtained by two recrystallizations from ethanol to afford prisms, m.p. 195-197°.

Infrared ($CHCl_3$), 3450, 2260, 1725, 1560, 1380 $cm^{-1}$ (see Figure VIII Page 252 );

n.m.r. ($CDCl_3$), τ9.21 (singlet, 3H, C-18 $C\underline{H}_3$), 8.95 (singlet, 3H, C-19 $C\underline{H}_3$), 6.36 (doublet, 1H, C-1 $\underline{H}$, J = 3 Hz), 4.60 (multiplet, 3H, C-17 $\underline{H}_\alpha$ and C-2 $\underline{H}_2$) (see Figure XVII , Page 255 );

mass spectrum $\frac{m}{e}$ (relative intensity), 392(1),346(1),303(5),302(15),260(26), 243(20),242(100),107(15),105(10),95(11),93(18),43(100) (see Figure XXVI Page 258 ).

Anal. Calcd. for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.13. Found: C, 64.58; H, 8.35; N, 6.86.

Sodium borohydride reduction of 17β-acetoxy-1-hydroxy-2-nitro-2,3-seco-5β-androstane-3-nitrile (291)

To a solution of compound 291 (12 mg, 0.031 mmoles) in isopropanol (7 ml) was added sodium borohydride (12 mg, 0.31 mmoles). The reaction mixture was refluxed for 26 hr and then cooled to room temperature. The solvent was removed by evaporation under reduced pressure to afford a residue which was dissolved in .1N hydrochloric acid (10 ml) and diethyl ether (20 ml). The organic layer was separated and then the aqueous phase was neutralized with saturated sodium bicarbonate, and extracted with diethyl ether (3 x 5 ml). The combined ether extracts were washed with saturated sodium bicarbonate (2 x 5 ml) and sodium chloride (2 x 5 ml) solutions, dried over sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 9.1 mg of a clear oil. T.L.C. analysis of this material on silica gel with ethyl acetate as eluent indicated predominantly one compound, $R_f$ 0.75. Acid extraction of a solution of the crude product in diethyl ether, followed by neutralization and subsequent diethyl ether extraction was performed. T.L.C. examination of the resulting diethyl ether solution indicated the absence of basic compounds. V.P.C. analysis (column D, 250°, 45 ml/min) indicated one compound (Retention time, 2.8 min). The crude product (8 mg) was chromatographed on a 5 x 20 cm silica gel coated plate, adsorbant thickness 0.6 mm, with ethyl acetate as eluent. After elution the band lying in the region $R_f$ 0.7 was removed and extracted with ethyl acetate. The solvent was removed under reduced pressure to afford 4.5 mg (ca. 50%) of compound 267 as a crystalline solid, m.p. 136-140°.

Infrared ($CHCl_3$), 3400 $cm^{-1}$;

mass spectrum $\frac{m}{e}$ (relative intensity), 294(0.8),277(0.7),276(2.7),259(1.2), 220(1.5),219(1.8),202(3.8),149(13.9),43(100);

Mol. Wt. Calcd. for $C_{18}H_{30}O_3$: 294.2194. Found (high resolution mass spectrometry): 294.2202.

Sodium borohydride reduction of 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262)

To a solution of compound 262 (25.3 mg, 0.076 mmoles) in isopropanol (10 ml) was added sodium borohydride (25 mg, 0.65 mmoles). The reaction mixture was refluxed for 26 hr and then cooled to room temperature. The solvent was removed by evaporation under reduced pressure to yield 21.6 mg (crude, 96% ) of a clear oil. The t.l.c., v.p.c., infrared and mass spectrum of this material were identical with that of 267.

Catalytic hydrogenation of 17β-acetoxy-1-hydroxy-2-nitro-2,3-seco-5β-androstane-3-nitrile (291)

A solution of compound 291 (30.3 mg, 0.077 mmoles) in methanol (25 ml) was hydrogenated over 10% palladium-on-charcoal for 5 hr. The solution was filtered and then the solvent was removed under reduced pressure to afford an oil which was dissolved in diethyl ether (20 ml). The diethyl ether solution was washed with saturated sodium chloride, dried over

sodium sulphate and filtered. The solvent was removed under reduced pressure to afford 21.6 mg of a clear oil. T.L.C. analysis of the crude product on silica gel with a mixture of chloroform and ethyl acetate (5:1, v/v) indicated predominantly two compounds, $R_f$ 0.73 and $R_f$ 0.61, and several minor components. Acid extraction of the crude product, followed by neutralization and subsequent diethyl ether extraction was performed. T.L.C. examination of the diethyl ether solution indicated the absence of any basic compounds. V.P.C. analysis (column D, 250°, 45 ml/min) of the crude product indicated two compounds (Retention times 9 and 18 min).

Infrared ($CHCl_3$), 3450, 2250, 1720 $cm^{-1}$.

Preparation of 17β-acetoxy-1-hydroxy-2,3-seco-A-nor-5β-androstane-3-nitrile (296)

To a solution of 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262, 30.1 mg, 0.0909 mmoles) in ethanol (10 ml) was added sodium borohydride (4 mg, 0.10 mmoles). The reaction mixture was stirred at room temperature for 24 hr and then the solvent was removed under reduced pressure. The resulting residue was dissolved in .1N hydrochloric acid (10 ml) and diethyl ether (20 ml). The organic layer was separated and the aqueous phase was neutralized with saturated sodium bicarbonate, and extracted with diethyl ether (2 x 10 ml). The combined diethyl ether extracts were washed with saturated sodium chloride solution (2 x 5 ml), dried over sodium sulphate and filtered. The solvent was removed

under reduced pressure to yield 28 mg of an oil which was chromatographed on a 5 x 20 cm silica gel coated plate, adsorbant thickness 0.6 mm, with a mixture of chloroform and ethyl acetate (5:1, v/v) as the eluent. After elution, the band lying in the region $R_f$ 0.6 was removed and extracted with ethyl acetate. The solvent was removed under reduced pressure to afford 18.2 mg (60%) of compound 296 as a crystalline solid, m.p. 139-141°.

Infrared ($CHCl_3$), 3450, 2250, 1720 $cm^{-1}$ (see Figure IX, Page 252);

n.m.r. ($CDCl_3$), τ9.22 (singlet, 3H, C-18 $CH_3$), 8.97 (singlet, 3H, C-19 $CH_3$), 7.98 (singlet, 3H, acetate), 6.53, 6.49 (double doublet, 2H C-1 $H_2$, J = 11 Hz), 5.40 (triplet, 1H, C-17 $H_\alpha$, J = 10 Hz) (see Figure XVIII, Page 255);

mass spectrum $\frac{m}{e}$ (relative intensity), 333(1.5),318(1),304(9),303(42), 301(7),286(5),263(39),262(58),260(35),243(20),242(100),203(24),202(47), 201(47),188(6),187(10),186(6),177(8),161(10),107(35),105(23) (see Figure XXVII, Page 258).
Mol. Wt. Calcd. for $C_{20}H_{31}O_3N$; 333.2303. Found (high resolution mass spectrometry): 333.2297.

Preparation of aluminum amalgam[201]

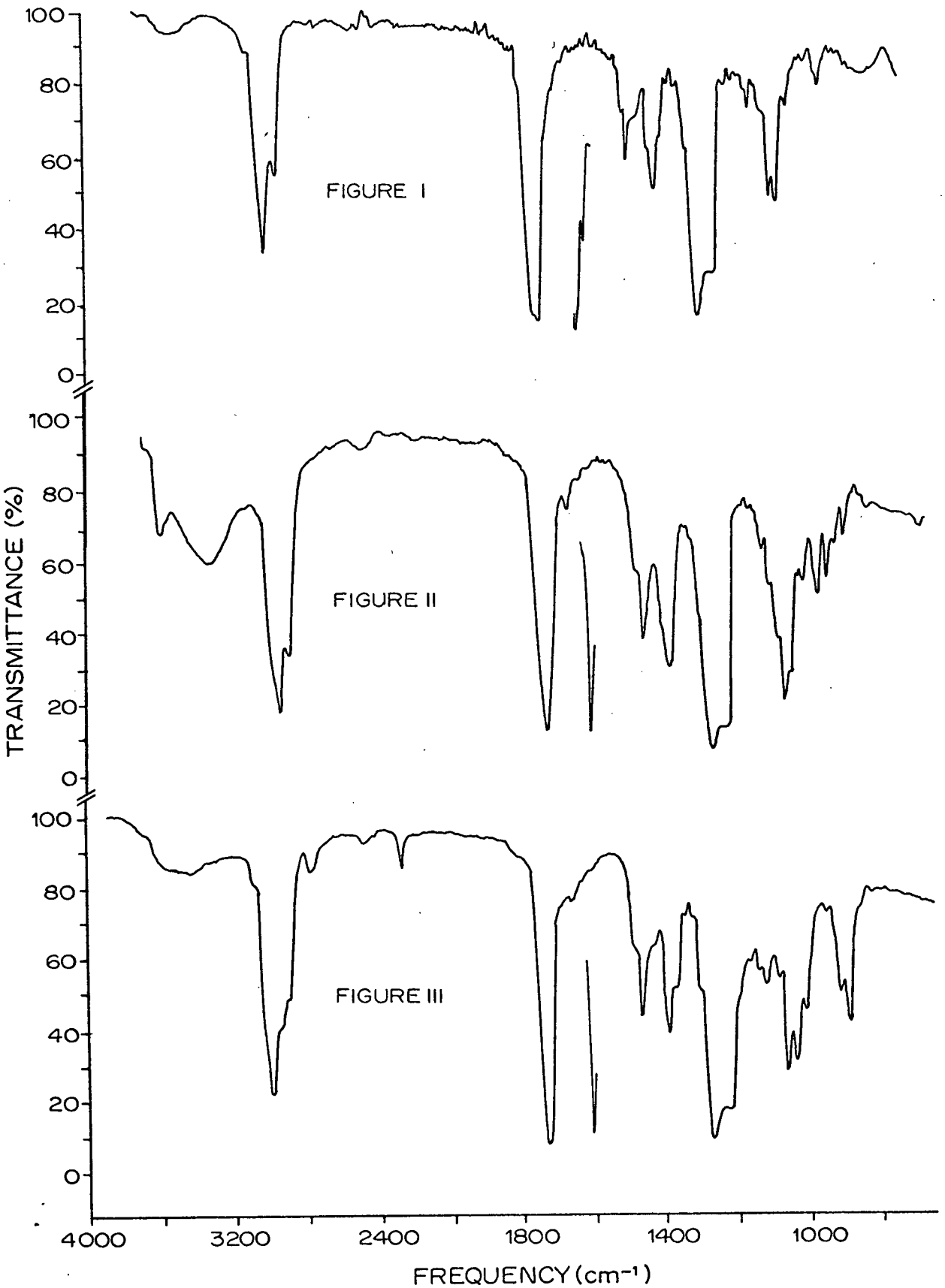
Aluminum (1 g) foil was thoroughly washed with petroleum ether and

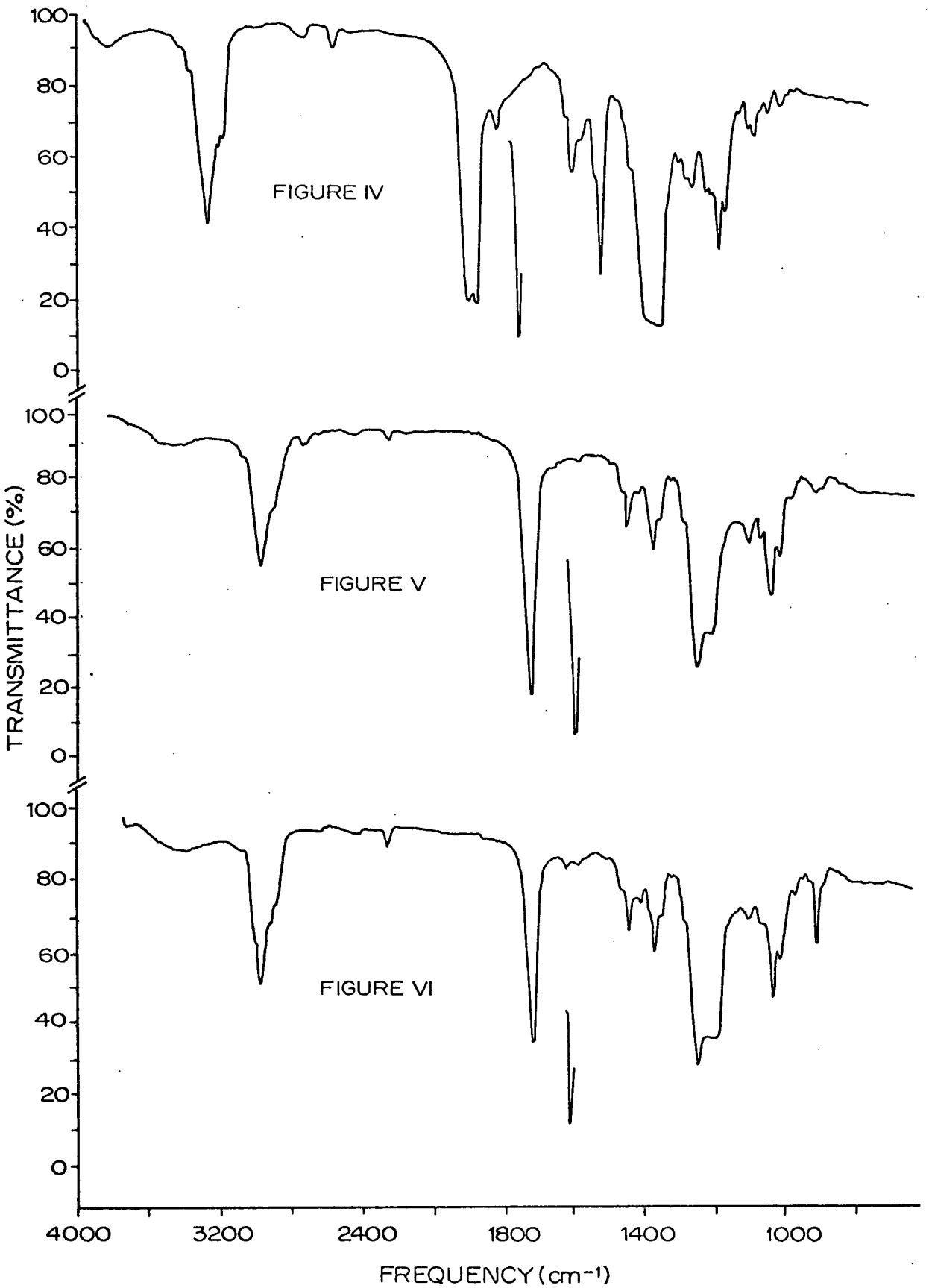
cut into pieces of about 2 x 2 cm. Sufficient 2% aqueous sodium hydroxide to cover the metal (10 ml) was added. After vigorous hydrogen evolution set in, the solution was decanted and the metal washed repeatedly, and quickly, with water; 0.5% aqueous mercuric chloride (20 ml) was added and, after 2 min, the solution was decanted and the metal washed repeatedly, and quickly, with water and then 95% ethanol.

Attempted reduction of 17β-acetoxy-1-hydroxy-2-nitro-2,3-seco-5β-androstane-3-nitrile (291) by employing aluminum amalgam

To a solution of compound 291 (5 mg, 10.2 mmoles) in diethyl ether (5 ml) and methanol (3 ml) was added 100 mg of aluminum amalgam. The reaction mixture was allowed to stand at 0° for twenty four hr and then the reaction solution was decanted. The solvent was removed under reduced pressure to afford a yellow oil. T.L.C.,

V.P.C. and infrared studies indicated 17β-acetoxy-1-oxo-2,3-seco-A-nor-5β-androstane-3-nitrile (262) as the predominant product.


100
80
60
40
20
0
FIGURE I
100
80
60
40
20
0
TRANSMITTANCE (%)
FIGURE II
100
80
60
40
20
0
FIGURE III
4000
3200
2400
1800
1400
1000
FREQUENCY (cm⁻¹)


100
80
60
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20
0
FIGURE IV
100
80
60
40
20
0
TRANSMITTANCE (%)
FIGURE V
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60
40
20
0
FIGURE VI
4000
3200
2400
1800
1400
1000
FREQUENCY (cm-1)

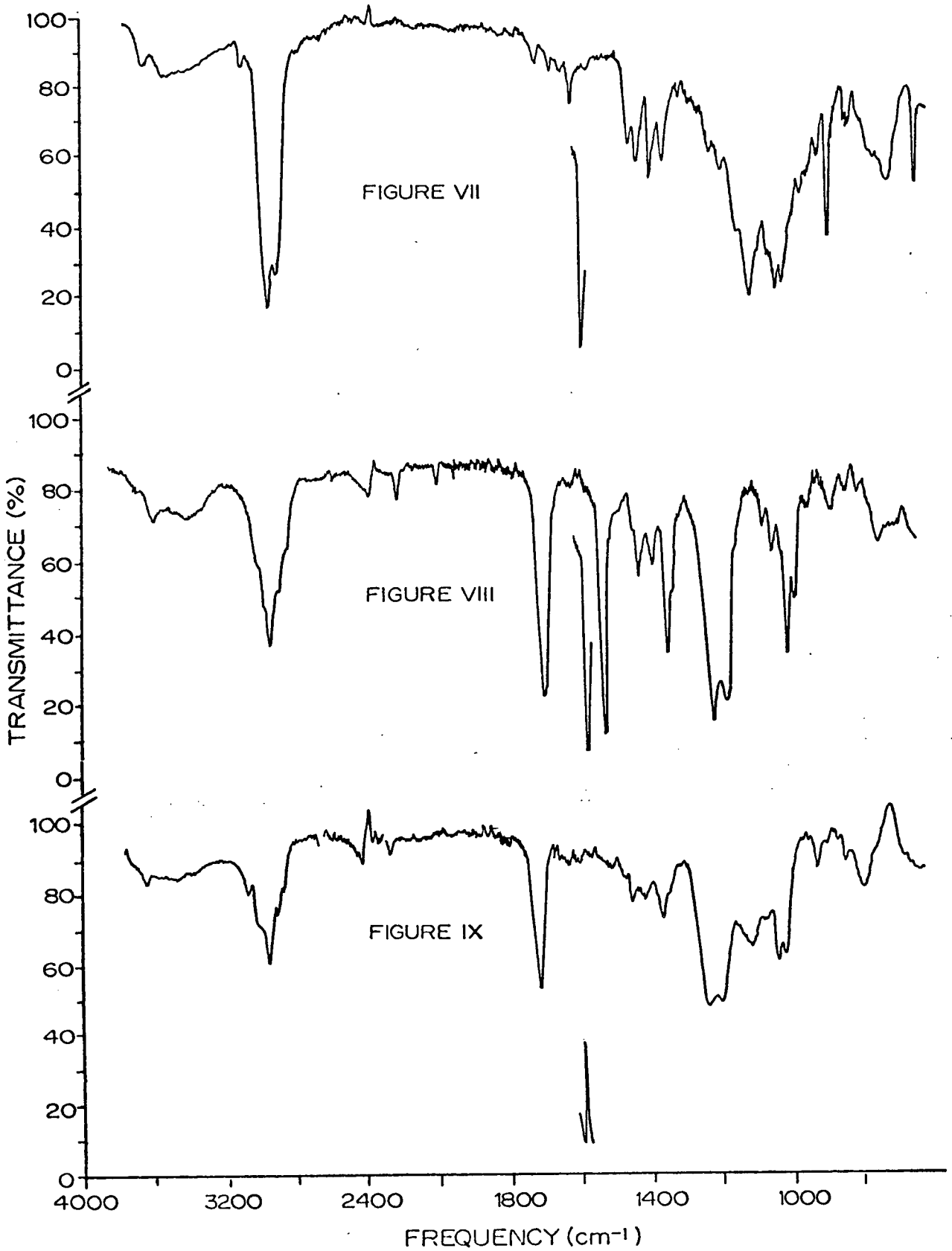

100
80
60
40
20
0
FIGURE VII
100
80
60
40
20
0
TRANSMITTANCE (%)
FIGURE VIII
100
80
60
40
20
0
FIGURE IX
4000
3200
2400
1800
1400
1000
FREQUENCY (cm⁻¹)

FIGURE X

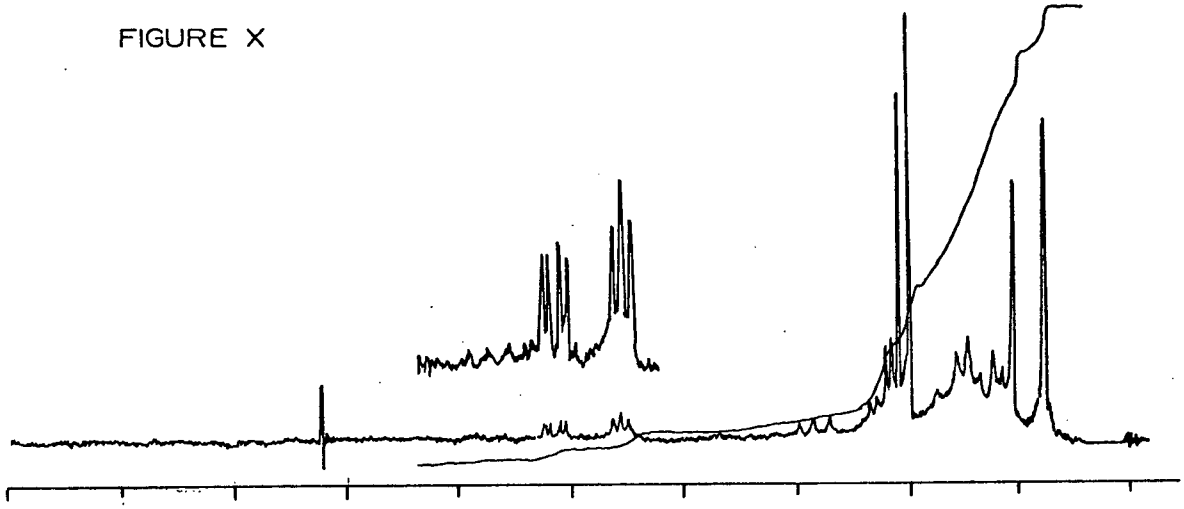


FIGURE XI

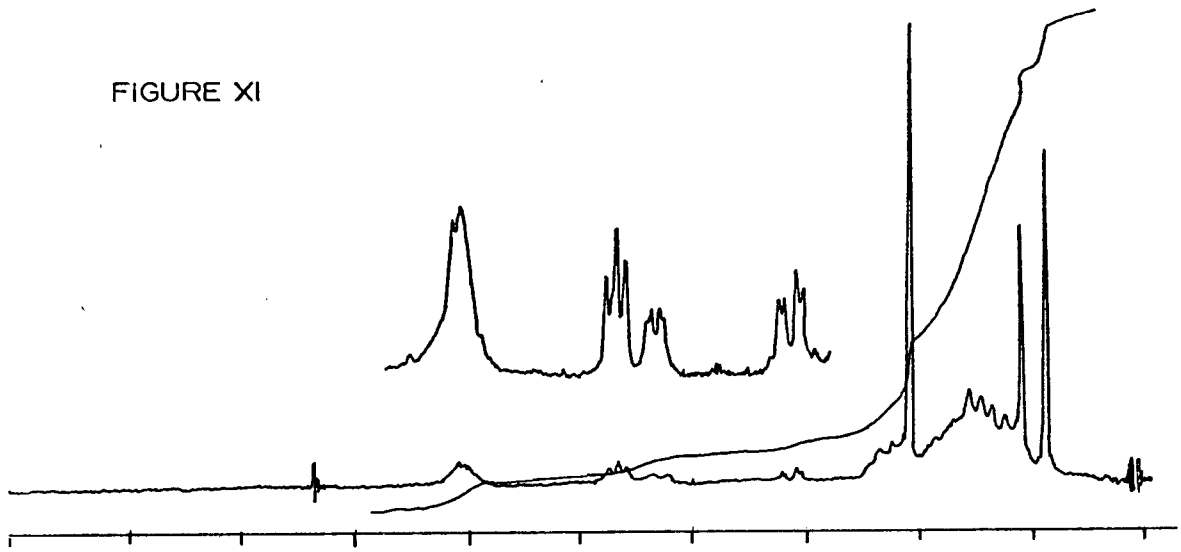


FIGURE XII

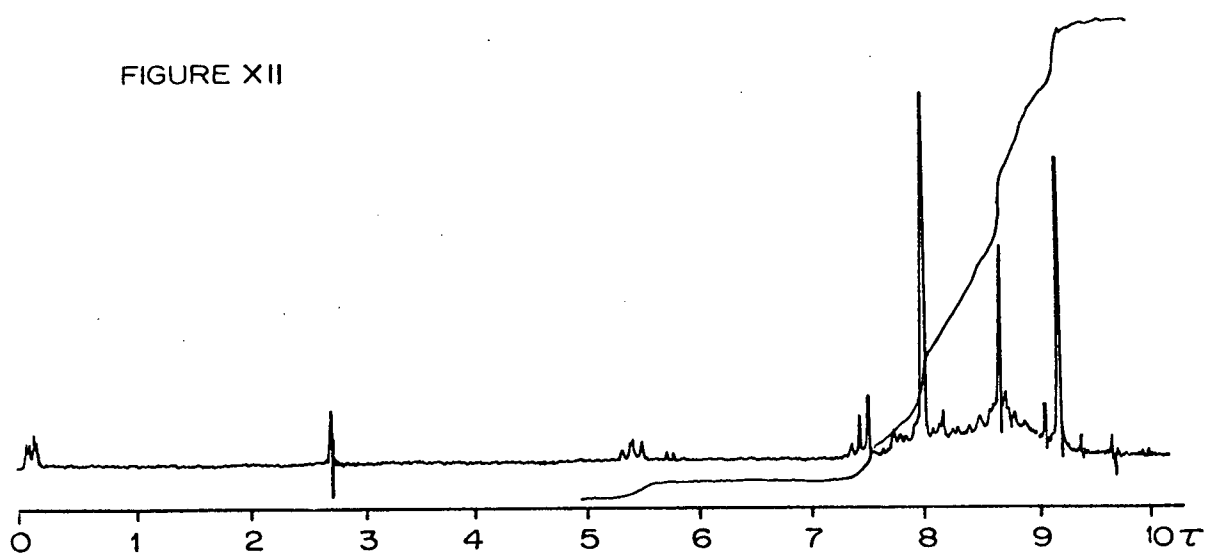


FIGURE XIII

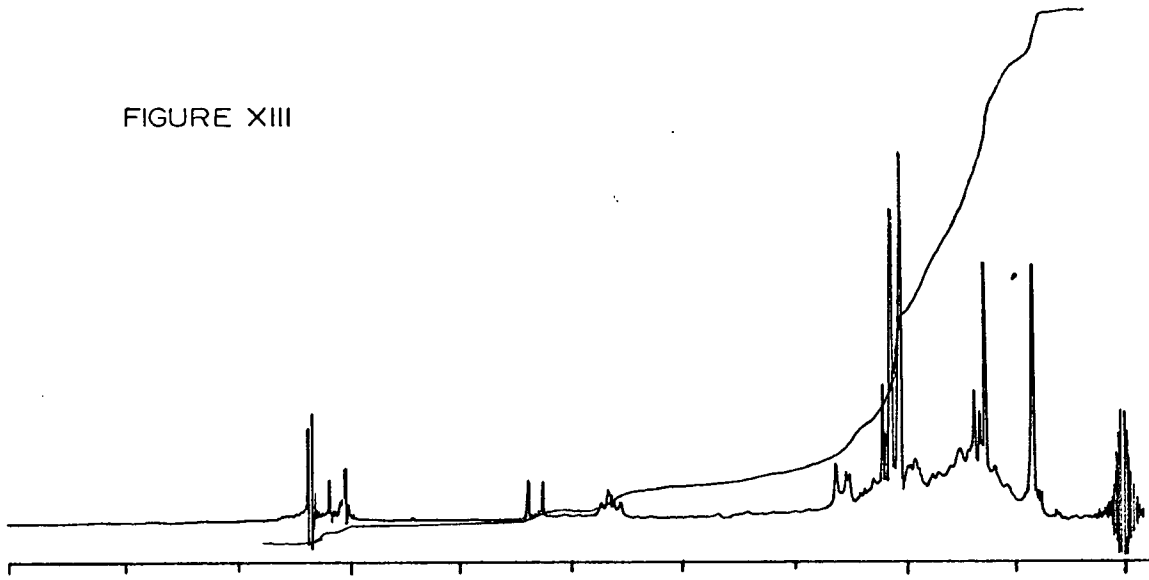


FIGURE XIV

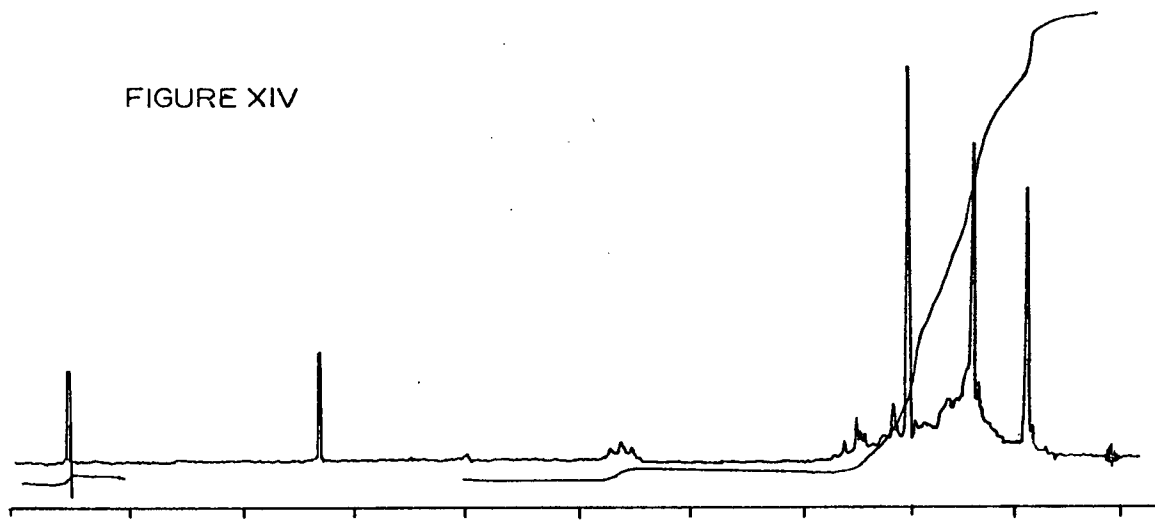


FIGURE XV

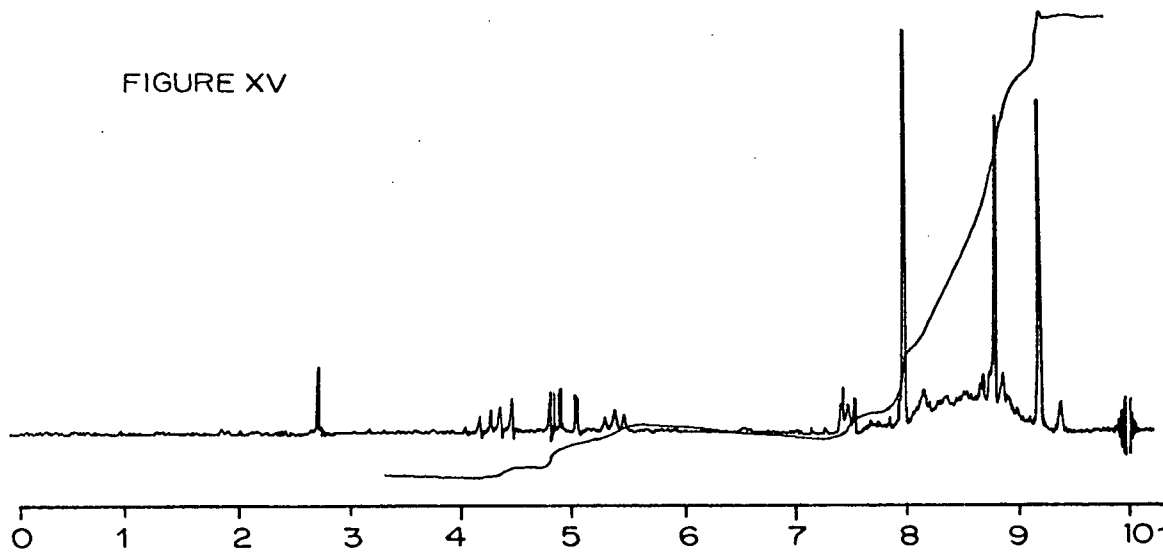


FIGURE XVI

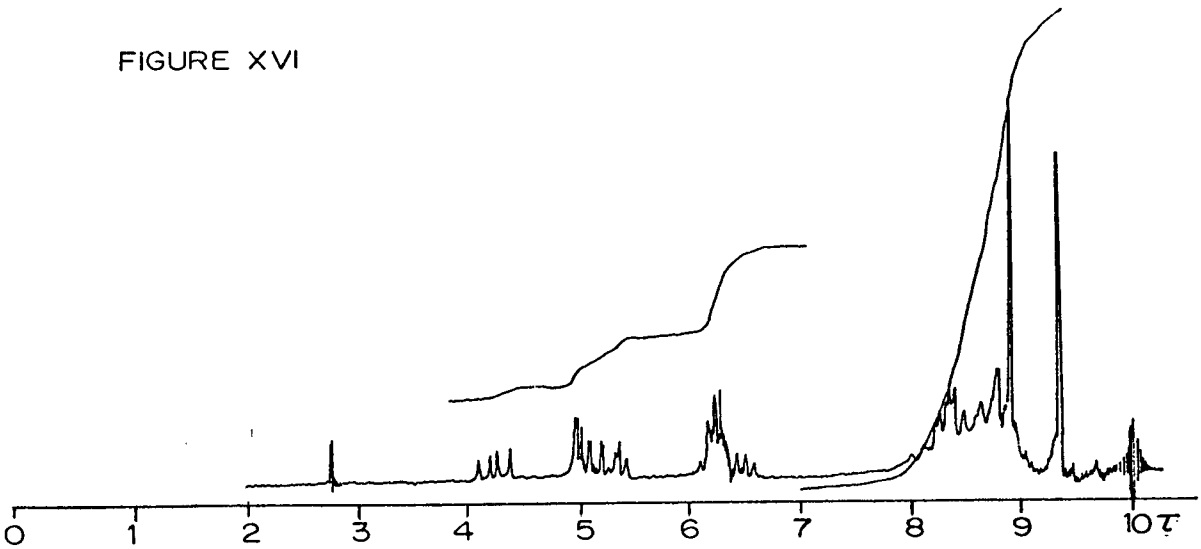



FIGURE XVII

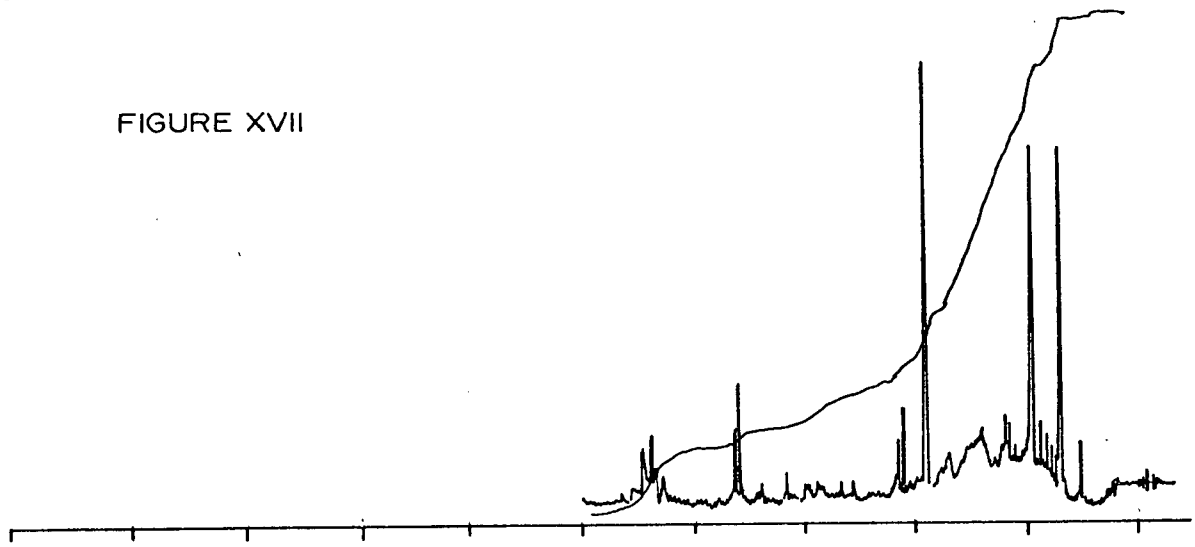
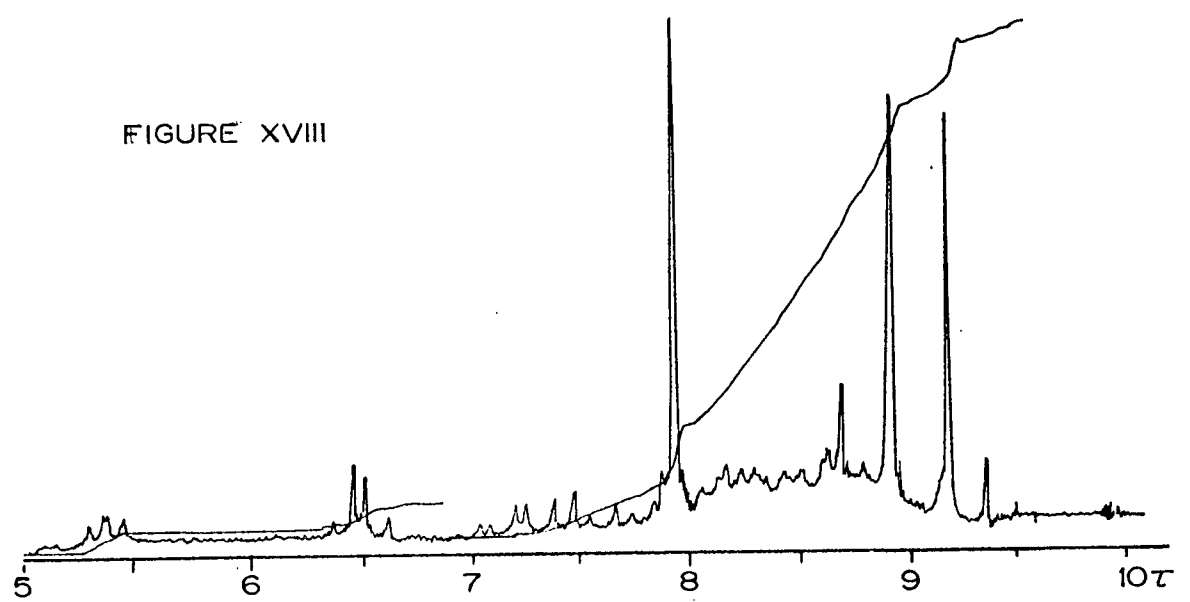


FIGURE XVIII



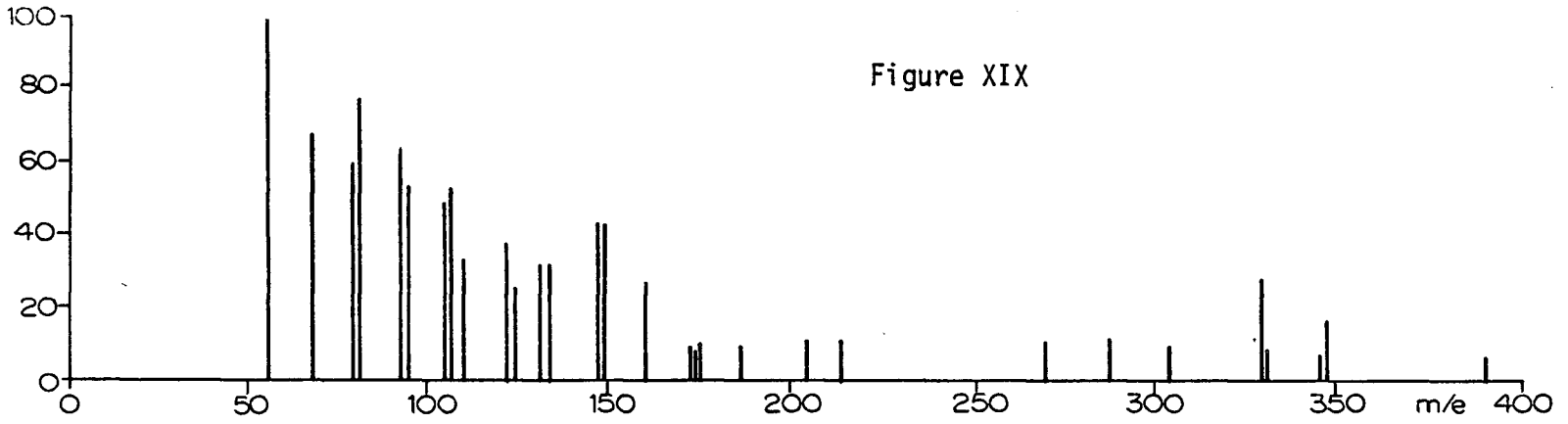



Figure XIX

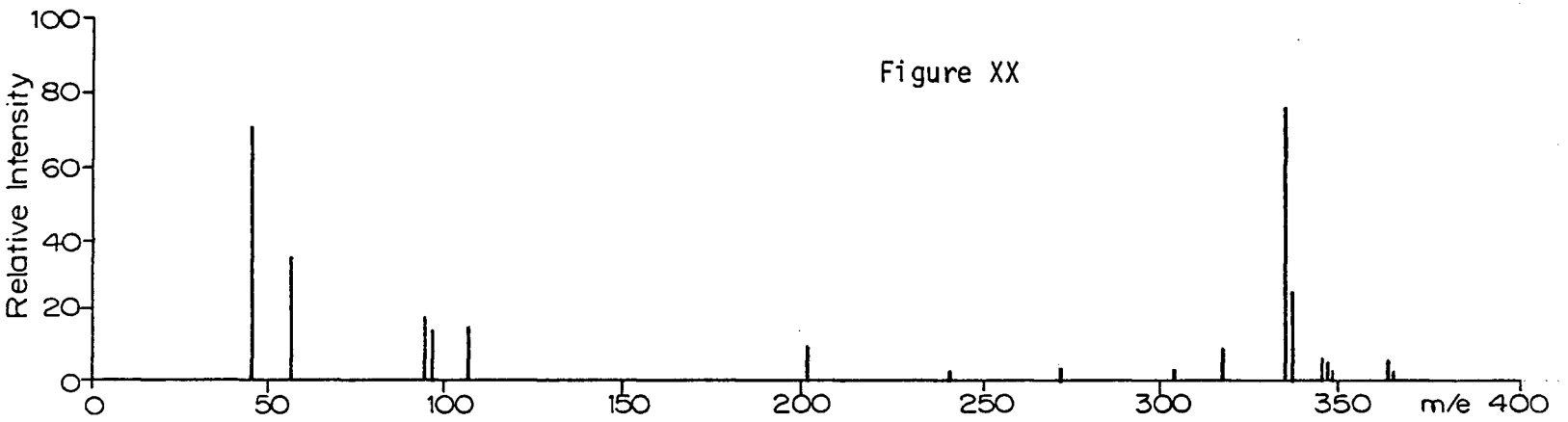



Figure XX

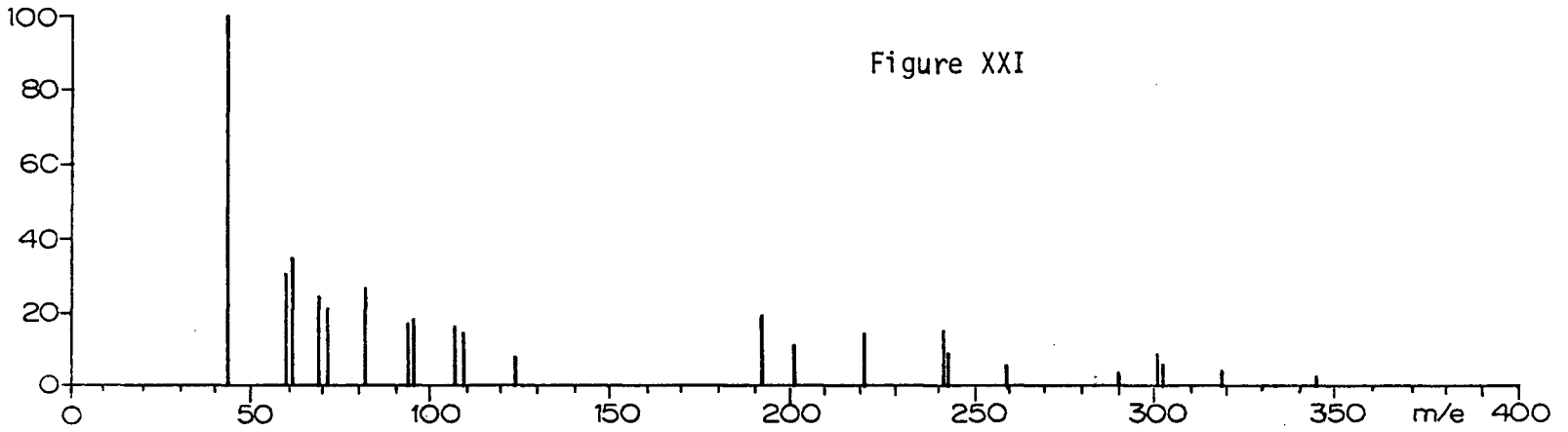



Figure XXI

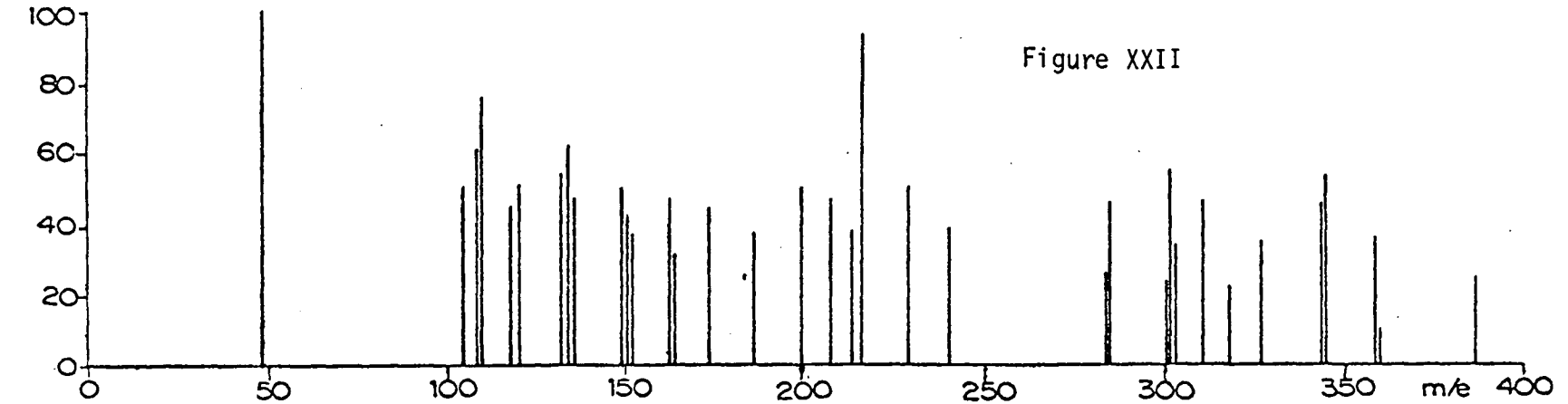



Figure XXII

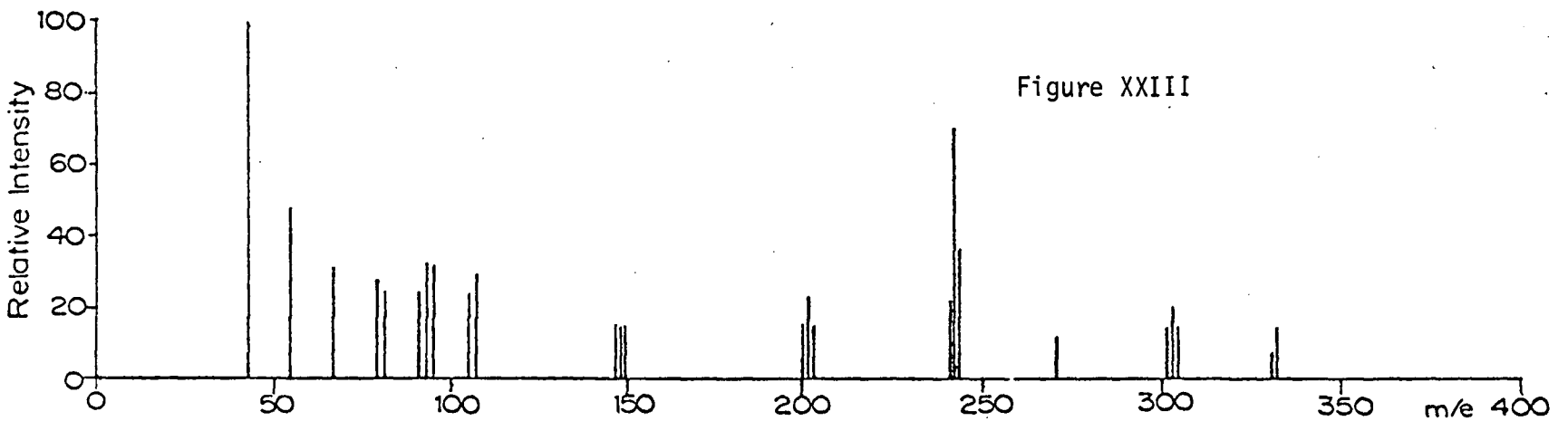



Figure XXIII

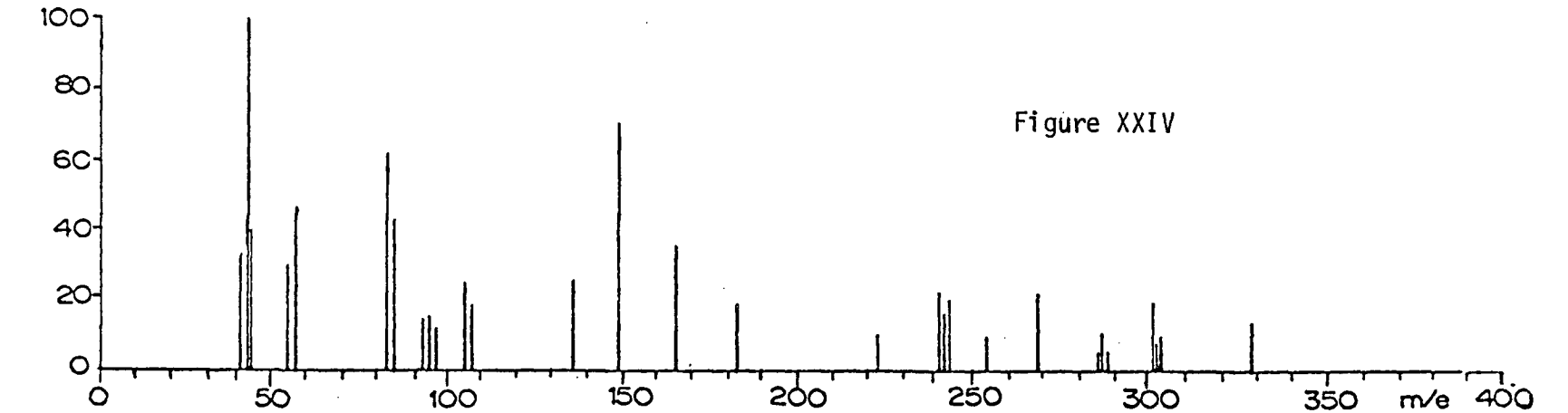



Figure XXIV

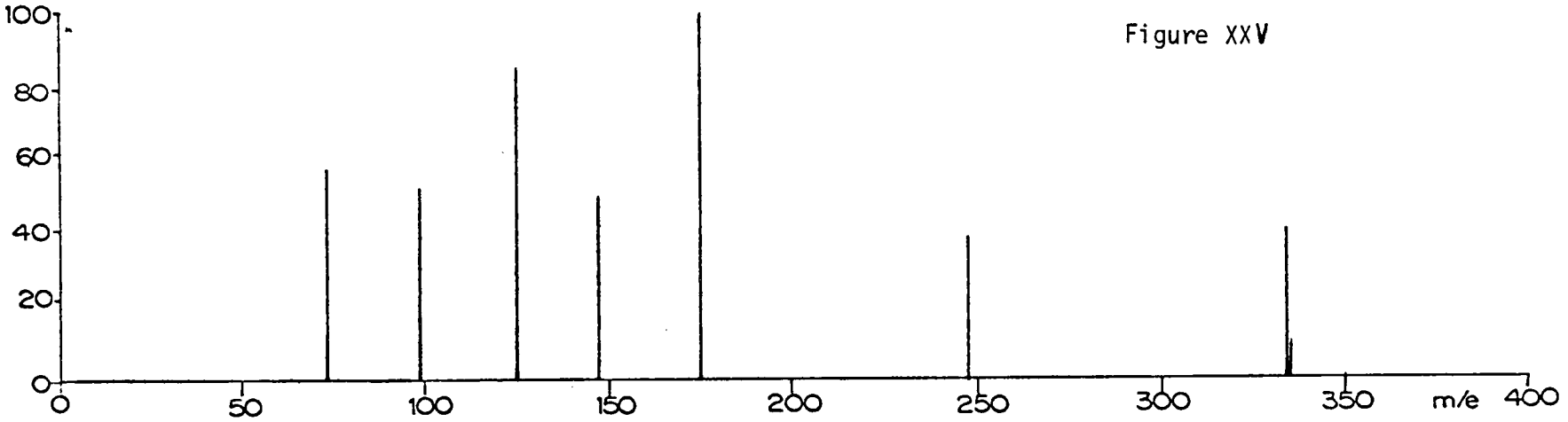



Figure XXV

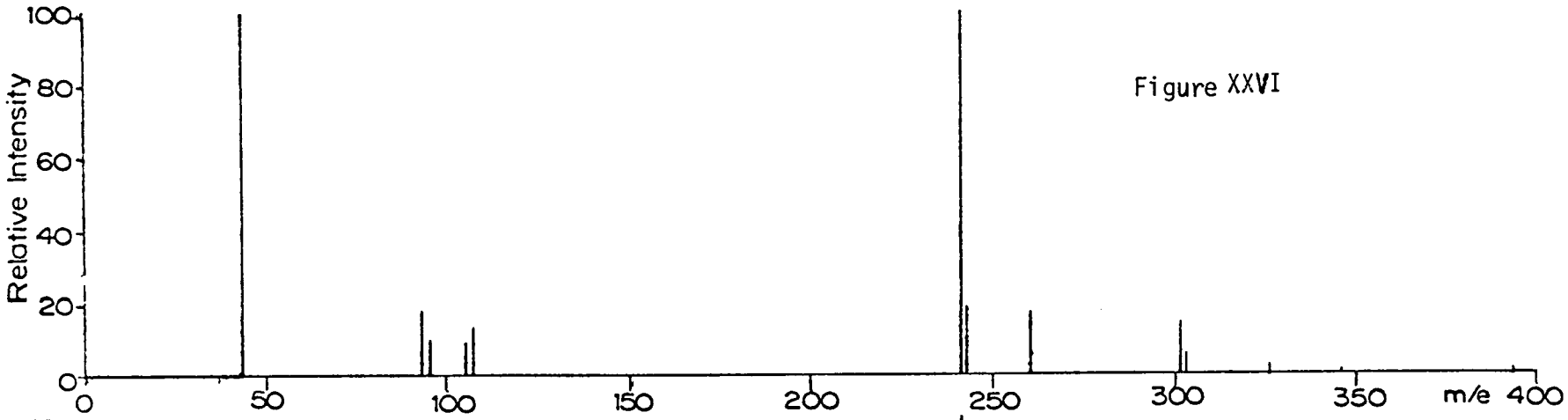



Figure XXVI

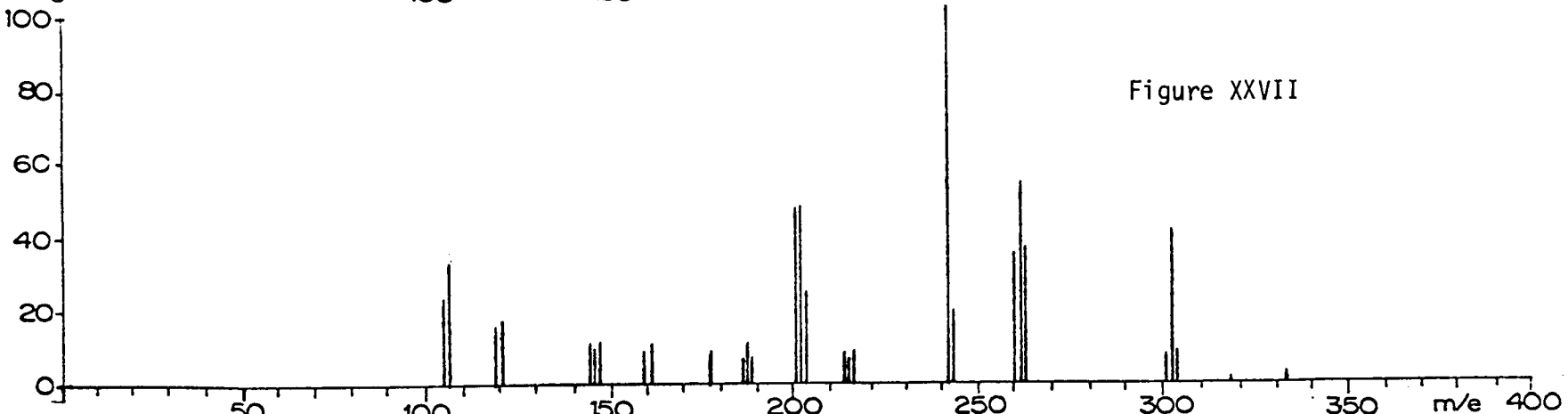



Figure XXVII

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