SYNTHESIS OF AZA STEROIDS

Part I. The synthesis of 6-aza steroids

Part II. The synthesis of 11-aza steroids

by

ISIDOROS I. VLATTAS

Diploma Chem. The University of Athens - Greece, 1959

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in the Department

of

Chemistry

We accept this thesis as conforming to the
required standard

THE UNIVERSITY OF BRITISH COLUMBIA

April, 1963

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

The writer expreses his appreciation to Dr. James Kutney for his guidance and encouragement during the course of this research.

Financial aid from the National Research Council of Canada and from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, grant No. CY-5037, is very gratefully acknowledged.

PART I

THE SYNTHESIS OF 6-AZA STEROIDS

ABSTRACT

Ozonization of 7-ketocholesteryl acetate has yielded methyl 5-keto-5,7-seco-6-nor-3-cholestene-7-oate in reasonably high yield. This intermediate was converted by catalytic hydrogenation to methyl 5-keto-5,7-seco-6-norcholestan-7-oate which upon treatment with benzyl amine gave N-benzyl-6-aza-4-cholesten-7-one.

INTRODUCTION

In recent years there have been numerous investigations concerned with the effect of substituents attached to the normal steroid skeleton on the biological properties of these important substances. These investigations have brought forth the realization that very dramatic alterations in these properties are indeed encountered when such substituents as halogen, particularly fluorine, hydroxyl and methyl are placed at rather specific positions in the molecule (1-3). These steroidal derivatives still possess the basic steroid skeleton so that the nature of the molecule is not altered to a very significant extent. In this connection it appeared of interest to us to consider a more substantial alteration in the chemical nature of steroidal substances in order to see whether any appreciable differences in the biological activity of these molecules are associated with this change. We therefore considered the replacement of one or more carbon atoms of the cyclopentanoperhydrophenanthrene system by a hetero atom.

The introduction of a nitrogen atom into the steroid nucleus has attracted the interests of chemists for some time. However inspection of the older literature reveals that most of the aza steroids represent analogues in which one of the rings of the skeleton has been expanded from a 6- to a 7- membered ring or in the situation of ring D, from a 5- to a 6- membered cycle. Very recently some successful syntheses of 4-aza steroids possessing the true steroid skeleton have been reported (4) and some interesting biological properties of these compounds have been described (5).

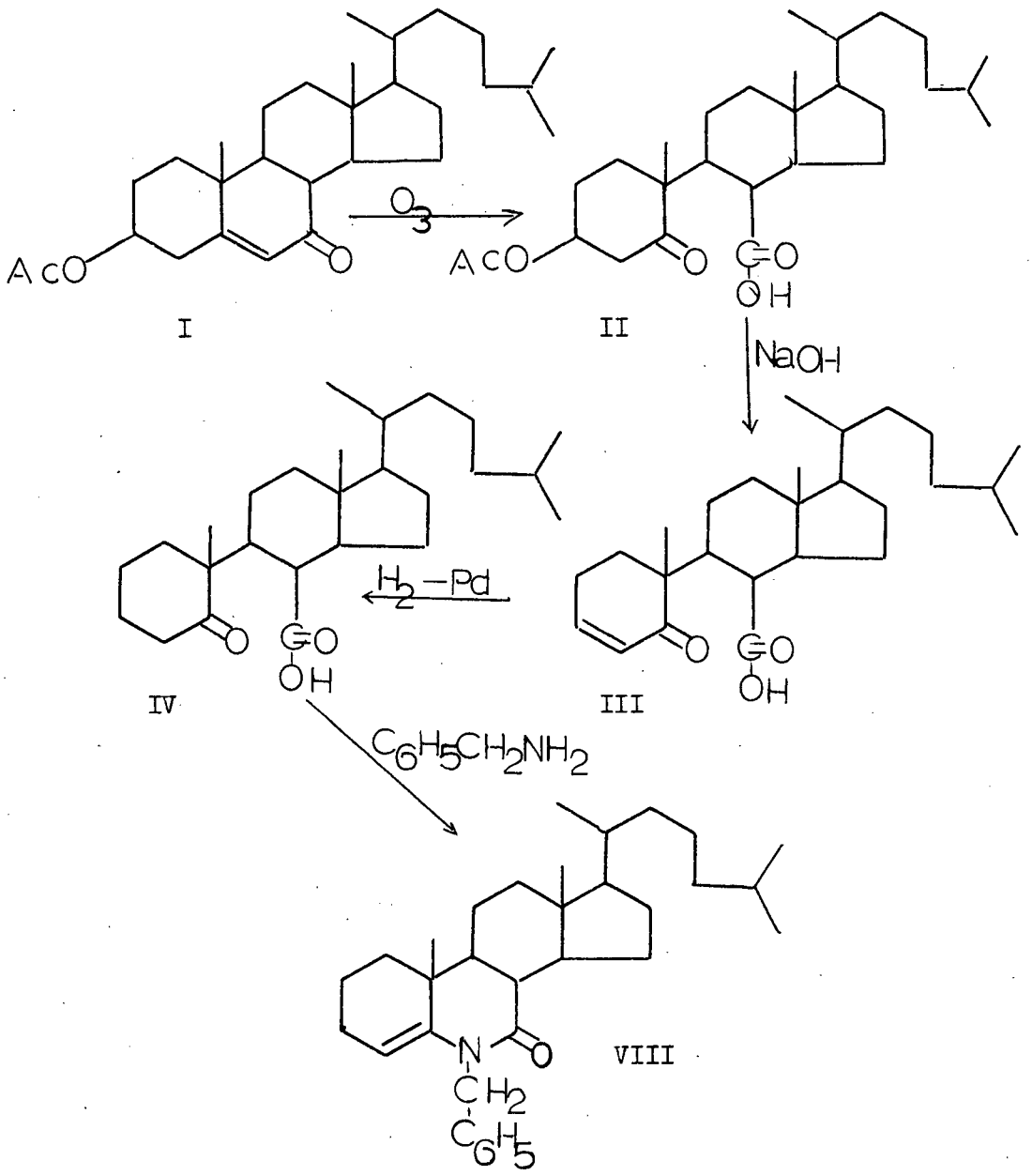


Figure I Synthetic route to 6-aza steroids in the cholestane series

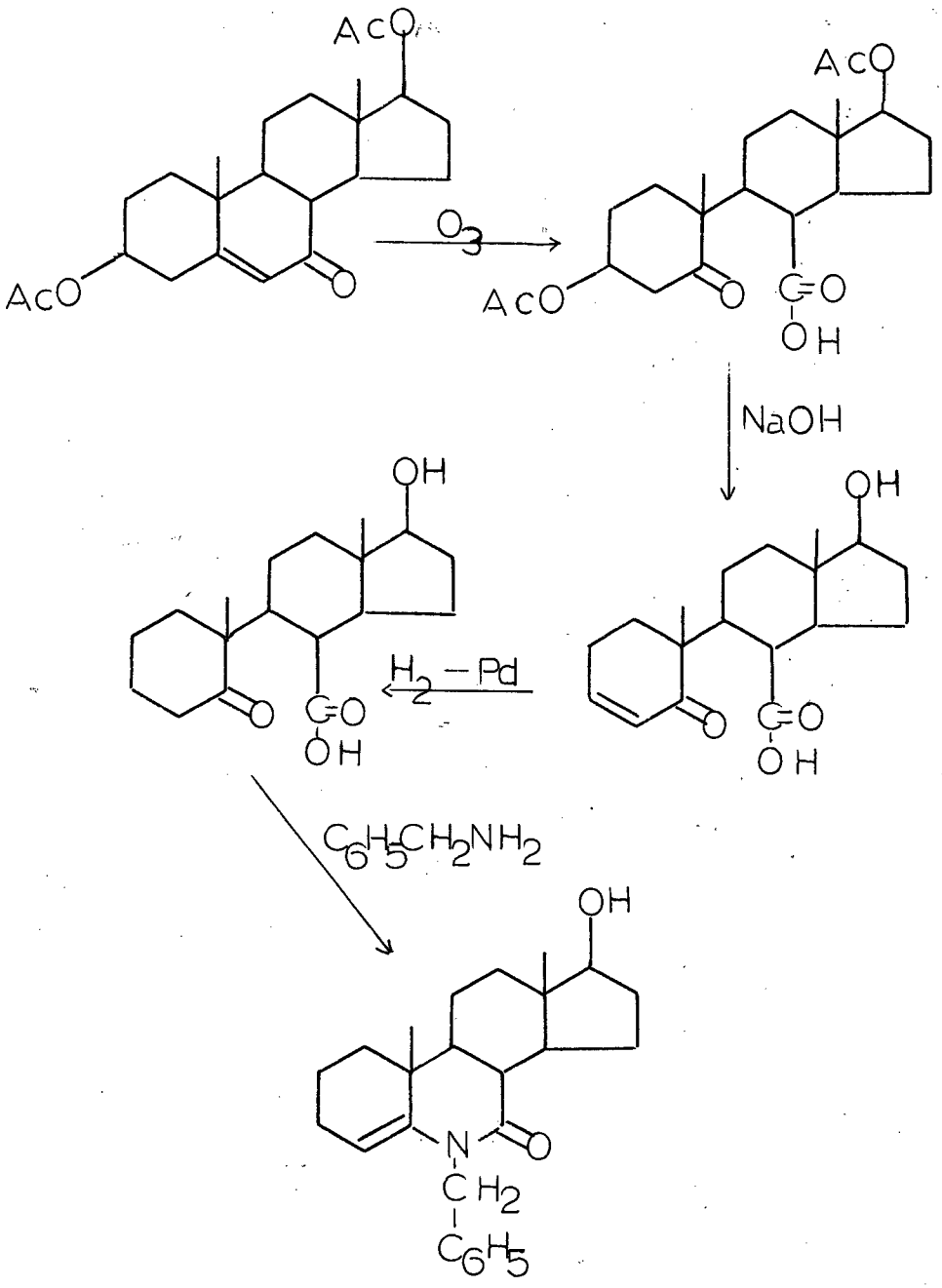


Figure 2 Synthetic route to 6-aza steroids in the androstane series

Interest in the chemistry and biological properties of aza steroids stimulated research in this area in our laboratory. In 1959, Kutney and Johnson considered several approaches which were directed toward the synthesis of ring B aza steroids. It was felt that the introduction of a nitrogen atom in this ring would allow the retention of a Δ^4-3-keto moeity in ring A - a structural feature present in most of the active steroidal hormones. At the time that their work was initiated, there were no ring B aza steroids known although since that time two laboratories have independently reported some work on 6-aza cholestane derivatives (6,7).

The successful sequence developed by Kutney and Johnson (8,9) represented a general approach to the synthesis of 6-aza steroids and, in particular, provided the first preparation of a 6-aza derivative in the androstane series. This scheme is outlined in figure 1 .

The generality of the above approach was exemplified by its successful utilization in the first synthesis of N-benzyl-6-azaandrostane as outlined in figure 2 .

DISCUSSION

It was evident to us that although the above approach was of considerable applicability, it suffered from the fact that the ozonolysis reaction provided the desired product in low yield. Consequently a considerable amount of experimentation was done to find optimum conditions for this reaction. Although we have not been able to obtain the corresponding acidic product in substantially higher yields, we have been able to overcome the difficulty by preparing the neutral ester directly from the ozonization. It appeared to us that it may be of advantage to conduct the ozonolysis in non-acidic solvents and in particular, in the presence of an alcohol so that the direct conversion of the ozonide to an ester would be possible. Indeed when 7-ketocholesteryl acetate was treated with ozone at -78°C in a solvent mixture of methylene chloride-methanol followed by oxidative decomposition of the ozonide with hydrogen peroxide and water, only 40% of the material was extracted with sodium carbonate. We did not investigate the nature of this acidic material as we concentrated our attention on the investigation of the remaining neutral residue. This neutral material was treated with base in aqueous dioxane to provide 45% of an oily neutral substance. Chromatography of this neutral product on a silica gel column gave a clear viscous oil (yield 35%) which was characterized as methyl-5-oxo-5,7-seco-6-nor-3-cholestene-7-oate (X). The infrared spectrum of X with absorption bands at 5.81μ and 5.98μ, characteristic of an ester carbonyl and an α,β unsaturated carbonyl respectively was in support for the structural assignment. The n.m.r.

spectrum of X showed a sharp signal at 6.5 τ characteristic of a carbomethoxy function and multiplets at 4.25 τ and 3.8 τ corresponding to the $-\underset{H}{C}=\underset{H}{C}-C=O$ group. Finally the presence of the unsaturated ketone system was shown in the ultra-violet spectrum of this compound which possessed a maximum at 227 mμ (see figure 3). It was therefore obvious that the inital neutral material was mainly the expected intermediate, methyl-3β -acetoxy-5-oxo-5,7-seco-6-norcholestan-7-oate (IX). This compound on treatment with base then readily loses the elements of acetic acid to give X.

In addition to the neutral ester, an acidic material (15% yield) was obtained from the basic aqueous dioxane solution. Chromatography of this acid on a silica gel column gave the unsaturated keto-acid (III) in 5% yield.

The unsaturated keto ester (X) was readily converted by catalytic hydrogenation to the corresponding saturated keto ester, methyl-5-oxo-5,7-seco-6-norcholestan-7-oate (XI), which was a beautifully crystalline, white solid. The success of the hydrogenation was evidenced by a shift of the ketone carbonyl absorption to 5.9 μ in the infrared and by the disappearance of any absorption in the ultra-violet spectrum.

The structure of the unsaturated ester (X) was finally confirmed when the reduction product, XI, was treated with benzyl amine and the enol lactam which resulted was shown to be identical in every respect to N-benzyl-6-aza-4-cholesten-7-one. In this manner, the overall yield of this enol lactam from 7-ketocholesteryl acetate was raised to 40%.

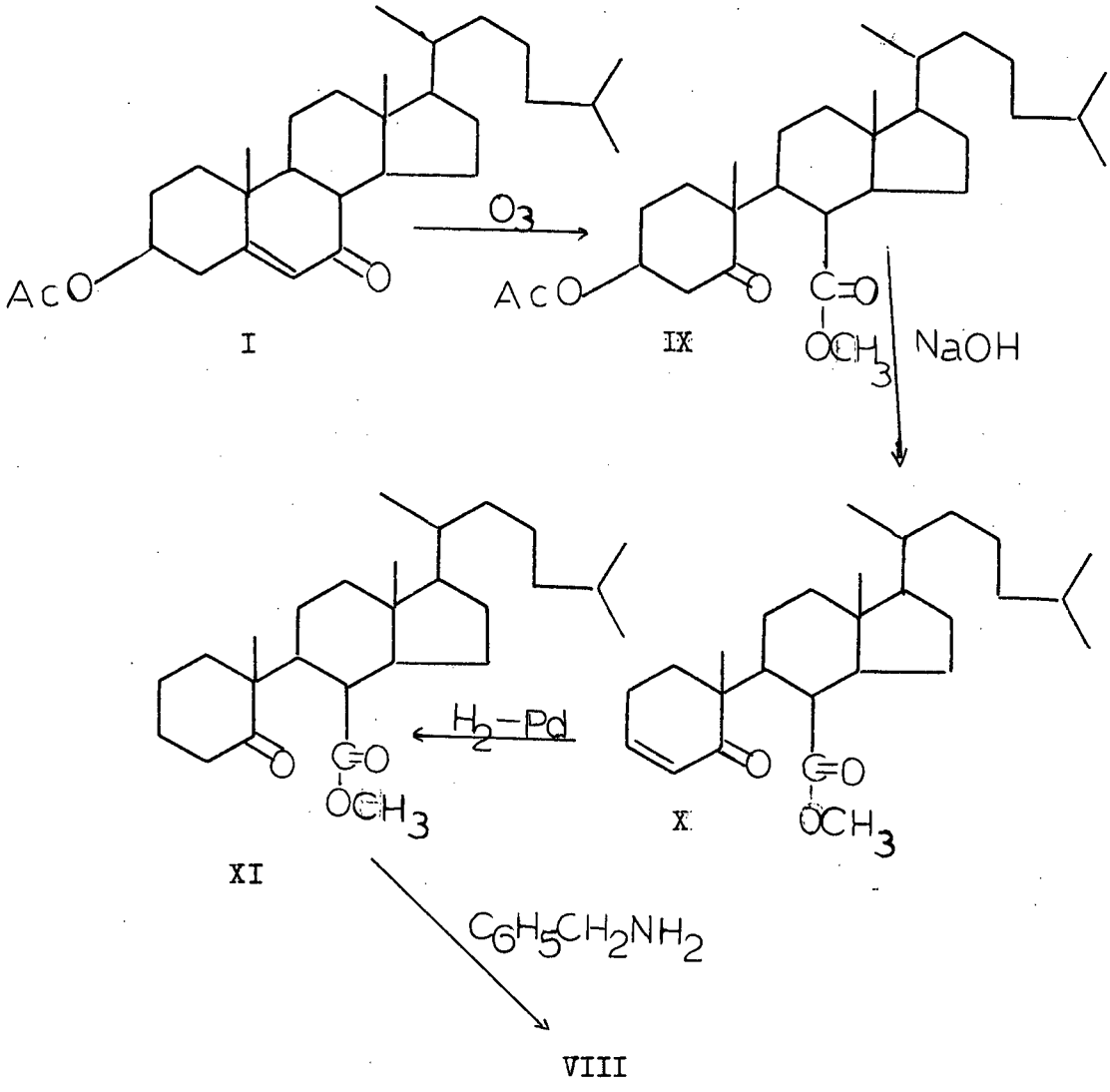


Figure 3 Improved synthetic route to 6-aza steroids in the cholestane series

It was not necessary to extend our studies to the androstane series since at that time that our investigations in the cholesterol series were being conducted, Atwater (10) in his paper on 6-oxa-androstane derivatives, indicated that the analogous ozonolysis reaction provided the corresponding B- nor seco ester in yields up to 73%. It is now clear that the extension to the androstane series is valid.

The above approach as well as the original sequence of Kutney and Johnson have the disadvantage of the loss of the functional group at C_3. For the reintroduction of an oxygen function at C_3, we have concentrated our efforts on the synthesis of N-benzyl-6-aza analogues since the presence of a tertiary nitrogen atom provides more suitable intermediates for this purpose. It would be expected that in the parent 6-aza series, which possess a secondary nitrogen atom, that undesirable double bond migrations might occur. Indeed Jacobs and coworkers (6) have suggested that the reduction of 6-aza-4-cholesten-7-one (XV) with lithium aluminum hydride gives 6-aza-5-cholestene (XVI) rather than 6-aza-4-cholestene. (Figure 5)

In this connection we have put some effort toward the re-introduction of an oxygen function in the allylic C_3 position of the enol lactam. An allylic oxidation was attempted with SeO_2 in a variety of solvents such as absolute ethanol, glacial acetic acid, nitrobenzene and butanol. In all these cases we recovered the starting material. Under drastic conditions (refluxing diethylene glycol for 15 hours) the product from the selenium dioxide oxidation, was an oily material. The spectroscopic data was completely different from that of the starting material. This oily product had no ultraviolet absorption and after chromatographic

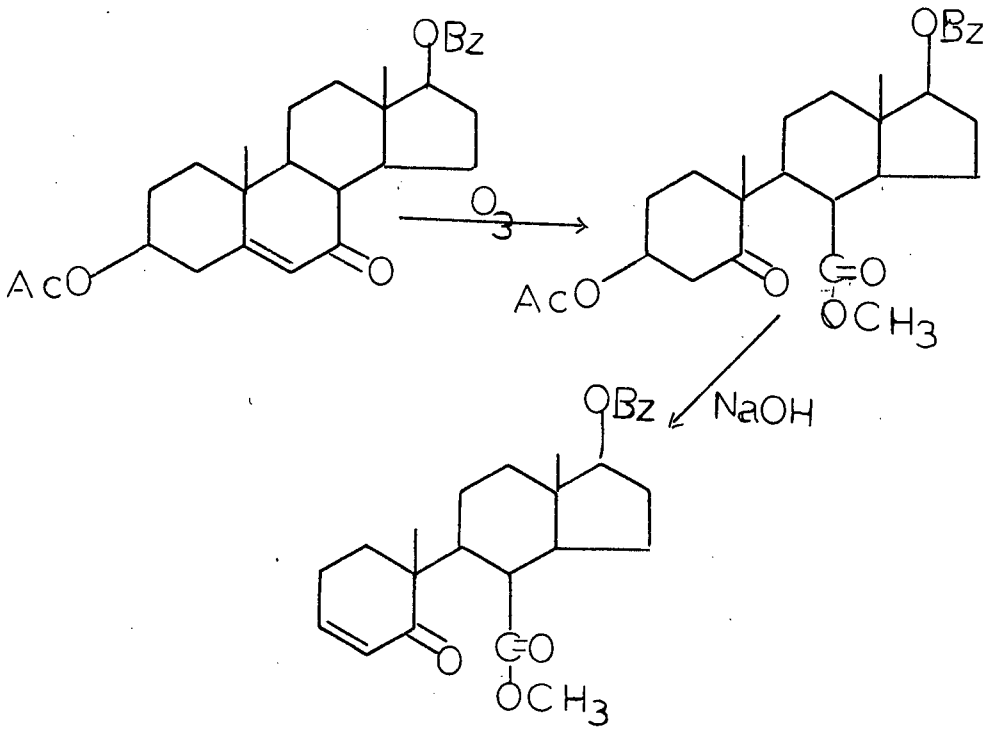
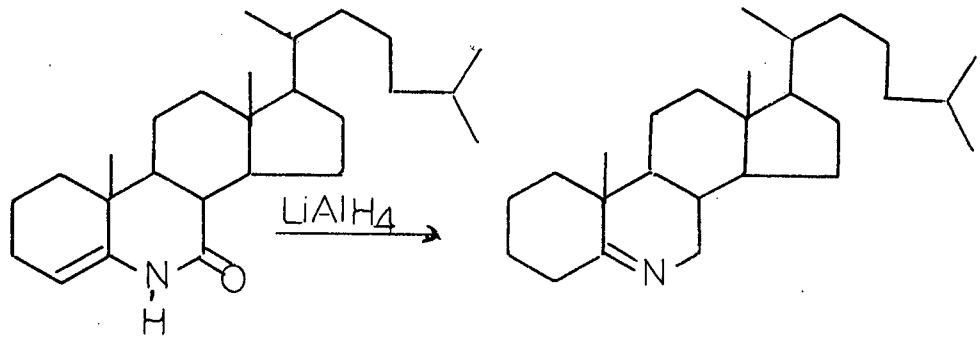


Figure 4 Improved synthetic route to 6-aza steroids in the androstane series



XV XVI

Figure 5 $LiAlH_4$ reduction of the 6-aza-4-cholesten-7-one

purification on a silica gel column, it gave different oily fractions. These fractions possessed infrared absorption maxima at 5.8 μ , 6.0 μ and 6.3 μ while the strong absorption at 6.1 μ corresponding to the lactam carbonyl group had disappeared. However, the oily nature of this material made it difficult to obtain any reliable analytical data and we did not continue this aspect any further.

Bromination of (VIII) with N-bromosuccinimide also gave an oily product which was chromatographed on a silica gel column. The main fraction was an oily material and in spite of numerous attempts, it resisted all efforts to obtain it crystalline. This material had infrared absorption maxima at 6.0 μ and 6.18 μ and an ultra-violet absorption at 242 mμ. Again no characterization was done on this substance. It is clear that further experimentation must be carried out on this aspect of the problem.

CONCLUSION

The synthesis of the N-benzyl-6-aza-4-cholesten-7-one via the above discussed sequence led to an increase of the overall yield of the enol lactam (VIII) from 7-ketocholesteryl acetate to forty percent. This marked improvement now makes the above approach a very attractive one indeed. This work is reported in a recent publication (11).

The introduction of an oxygen or a bromine atom at C_3 of the enol lactam (VIII) was also studied briefly. However the results are not nearly conclusive and further work must still be carried out.

EXPERIMENTAL

All melting points were determined on a Fischer-Johns apparatus and are uncorrected. The ultra-violet spectra were recorded in 95% ethanol on a Cary 14 recording spectrophotometer and the rotations were taken in chloroform. The n.m.r. spectra were taken at 60 Mc on a Varian A60 instrument. The values are given in the Tiers τ scale with the signal of tetramethylsilane, which was used as the internal standard, set at 10.0 τ units. Analyses were performed by A. Bernhardt, Mulheim (Ruhr) Germany and by Mrs. Aldridge, University of British Columbia.

Methyl 5-Oxo-5,7-seco-6-nor-3-cholesten-7-oate (X)

A solution of 7-oxocholesteryl acetate (5.0 g) in dichloromethane (75 ml) and absolute methanol (25 ml) was ozonized at -78° until the solution had attained a blue color (about 20 minutes). The solution was allowed to warm to room temperature, 30% aqueous hydrogen peroxide (0.7 ml) and water (1.7 ml) was added and the mixture was then allowed to stand at room temperature for 16 hours. The organic phase was separated and the aqueous phase was extracted several times with dichloromethane. The organic extracts were combined, washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the solvent after removing the drying agent by filtration, provided a viscous clear oil. This oil was taken up in ether and the ethereal solution was washed with 5% aqueous sodium hydroxide to remove any acidic materials. The workup of this aqueous layer is given below.

The ether layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed to provide a viscous, neutral oil (3.3 g). This neutral oil was taken up in dioxane, treated with 5% aqueous sodium hydroxide (30 ml), and the whole mixture was stirred for 30 minutes. This mixture was then treated with 1.5 liters of water and extracted exhaustively with ether in a continuous extraction apparatus. The resulting ether extract was washed with water, and dried over anhydrous magnesium sulfate. The solvent was removed to yield a viscous oil (2.25 g). This oil was taken up in benzene and chromatographed on silica gel (80 g). The desired, unsaturated keto ester was eluted with benzene as a clear viscous oil (1.76 g) and in spite of numerous attempts, it resisted all efforts to obtain it crystalline. Infrared in CCl_4: 5.98 μ, 5.81 μ; λ_{max} 227 mμ (logε 3.84); $[\alpha]_D^{26}$ + 83; n.m.r. signals (CCl_4): sharp signal at 6.5 τ ($-COOCH_3$), multiplets at 4.25 τ and 3.8 τ ($-\overset{H}{C}=\overset{H}{C}-C=O$). Found: C, 77.52; H, 10.31. Calc. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65.

The aqueous alkaline layer from the potassium hydroxide in dioxane treatment was acidified with hydrochloric acid and the resulting mixture was extracted with ether. The ethereal extract, after washing with water was dried over anhydrous magnesium sulfate. Removal of the solvent yielded an acidic material (0.7 g).

This acidic material (0.7 g) was reduced over 10% palladium on charcoal (0.4 g) in ethanol at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent was removed

under reduced pressure. This crude reduction product was chromatographed on silica gel (16 g) and a solid material (200 mg) which was obtained upon elution with benzene-chloroform turned out to be 5-oxo-5,7-seco-6-norcholestan-7-oic acid (IV).

The original aqueous alkaline extract of the product resulting directly from the ozonization was acidified with hydrochloric acid and this acidic mixture was then extracted with ether. The ether extract was washed with water; and dried over anhydrous magnesium sulfate. Removal of the solvent yielded an acidic material (1.94 g).

Methyl 5-oxo-5,7-seco-6-norcholestan-7-oate (XI)

The unsaturated keto ester, X (1.65 g) was hydrogenated over 10% palladium on charcoal (1 g) in ethanol at room temperature and atmospheric pressure. The catalyst was removed by filtration and the solvent evaporated to yield a white solid. This solid was taken up in benzene and chromatographed on silica gel (60 g). Elution with benzene provided a white crystalline material (1.5 g) which on several recrystallizations from benzene yielded an analytical sample, m.p. 81-83°; $[\alpha]_D^{28}$ + 97°; infrared in KBr: 5.90 μ ; 5.80 μ ; Found: C, 77.30; H, 10.96. Calc. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08.

N-Benzyl-6-aza-4-cholesten-7-one from (XI)

The saturated keto ester, XI, (1 g) was refluxed in benzyl amine (2.5 ml) for 20 hours in a nitrogen atmosphere. The resulting reaction mixture was taken up in ether and the ethereal solution was washed with

dilute hydrochloric acid to remove any benzyl amine. This solution was then washed with 5% aqueous sodium hydroxide, water and finally dried over anhydrous magnesium sulfate. Removal of the solvent gave a white solid (1.1 g) which upon recrystallization from methanol provided a pure sample of the enol lactam, VIII, (0.95 g).

BIBLIOGRAPHY

1. J. Fried and A. Borman, Vitamins and Hormones, 16, 303 (1958).

2. V. A. Drill and B. Riegel, Recent Progress in Hormone Research, 14, 29 (1958).

3. R. Hirshmann, G. A. Bailey, R. Walker and J. M. Chemerda, J. Am. Chem. Soc., 81, 2832 (1959).

4. M. Uskokovic and M. Gut, Helv. Chim. Acta, 42, 2258 (1959).

5. R. I. Dorfman, M. Uskokovic and M. Gut, 137th Meeting of the Am. Chem. Soc., p. 19 N (1960).

6. T. L. Jacobs and R. B. Brownfield, J. Am. Chem. Soc., 82, 4033 (1960).

7. H. Lettre and L. Knof, Ber., 93, 2860 (1960).

8. R. A. Johnson, M.Sc. Thesis in Chemistry, U. B. C., September, 1961.

9. J. P. Kutney and R. A. Johnson, Chem. and Ind., 1713 (1961).

10. N. W. Atwater, J. Am. Chem. Soc., 83, 3071 (1961).

11. J. P. Kutney, R. A. Johnson and I. Vlattas, Can. J. Chem., 41, 613 (1963).

PART II

THE SYNTHESIS OF 11-AZA STEROIDS

ABSTRACT

The ozonization or Lemieux oxidation of 9,11-dehydrohecogenin acetate yielded 3β -acetoxy-9- oxo-9,12-seco-11-norhecogenin-12-oic acid (X) an intermediate useful in the preparation of 11-aza steroids. The keto acid (X), upon treatment with benzyl amine, gave a mixture of two compounds. The minor component was the 3β -hydroxyl-11-aza-5α ,22β -spirost-8,9-ene-12-one (XX) and the major one, was 3β -hydroxy-9-oxo-9,12-seco-11-nor-25-iso-5α ,22β -spirostan-12-N-benzyl carboxamide (XI).

The enol lactam (XX) was also prepared from the keto acid (X), upon treatment with ammonia. It was subsequently shown that the steroid enol lactam (XX) could be prepared in essentially quantitative yield by treatment of the keto acid with anhydrous ammonia at 150°C.

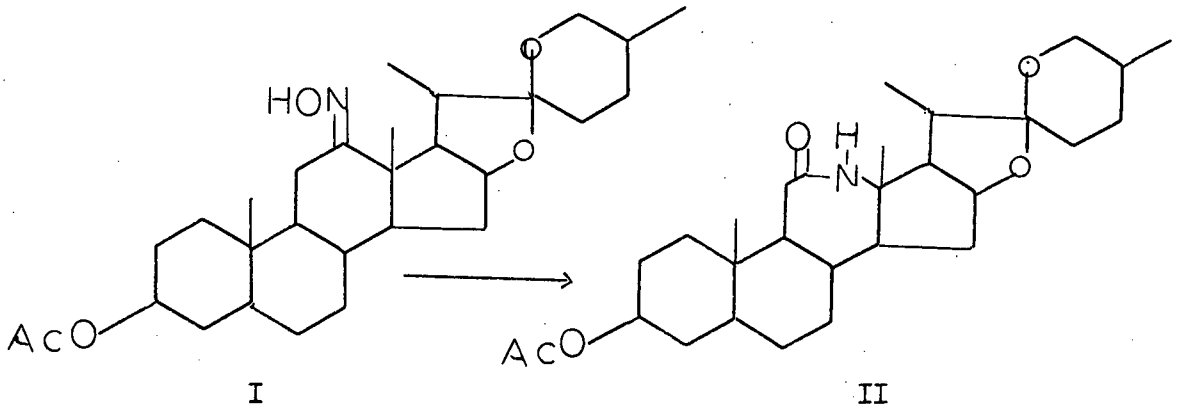
Acetylation of the enol lactam (XX) provided 3β -acetoxy-11-aza-5α ,22β -spirost-8(9)-ene-12-one (XIX) which is the first 11-aza steroid in the sapogenin series.

INTRODUCTION

After the successful synthetic sequence leading to the introduction of a nitrogen function into ring B of the steroid skeleton was initiated in 1959 by Kutney and Johnson in our laboratory (1,2), we decided to extend our studies to the synthesis of ring C-aza steroids. The investigation of such compounds appeared attractive not only from a chemical standpoint but also in consideration of the possible biological importance of certain aza derivatives of steroid hormones.

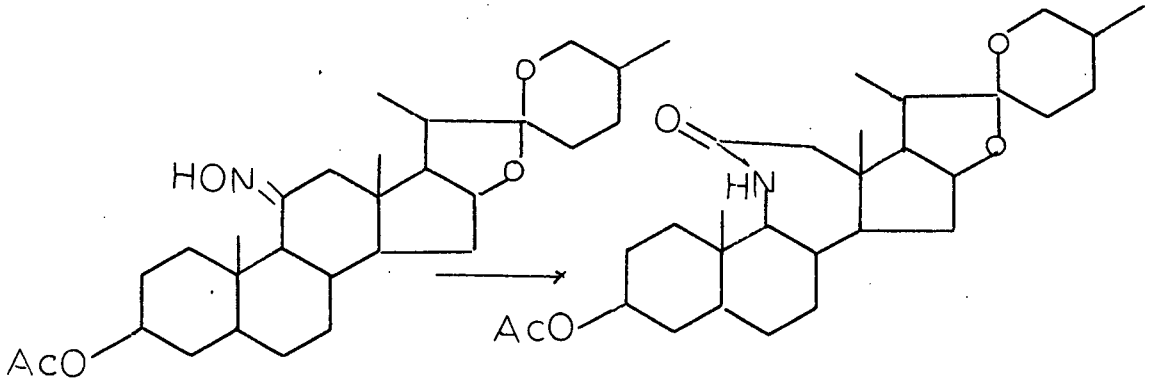
At the time when our work was initiated, no ring C-aza steroids with an unexpanded C ring system were known. The synthesis of 9,11 and 12-aza-C-homo steroids has been reported recently (3,4,5), but these analogues possess a seven membered C-ring and not the true steroid skeleton. However, since this work represents the only instances of preparation of any type of ring C-aza steroids prior to our own, it is appropriate to discuss it briefly at this point.

In 1959, Mazur (3) described the preparation of several 12-aza-C-homo steroids by applying a Beckman rearrangement on the oxime of a 12-keto steroid. The oxime of hecogenin acetate (I) was used and the main product of the reaction was 12α -aza-C-homo hecogenin-12-one-3-acetate (II). This was only one of the two possible lactams and its formation was explained by the fact that the configuration of the oxime possessing the hydroxyl group anti to ring D has no serious steric effects. (Fig. 1).



I II

Figure 1 Synthesis of 12-aza-C-homo steroids



III IV

Figure 2 Synthesis of 9-aza-C-homo steroids

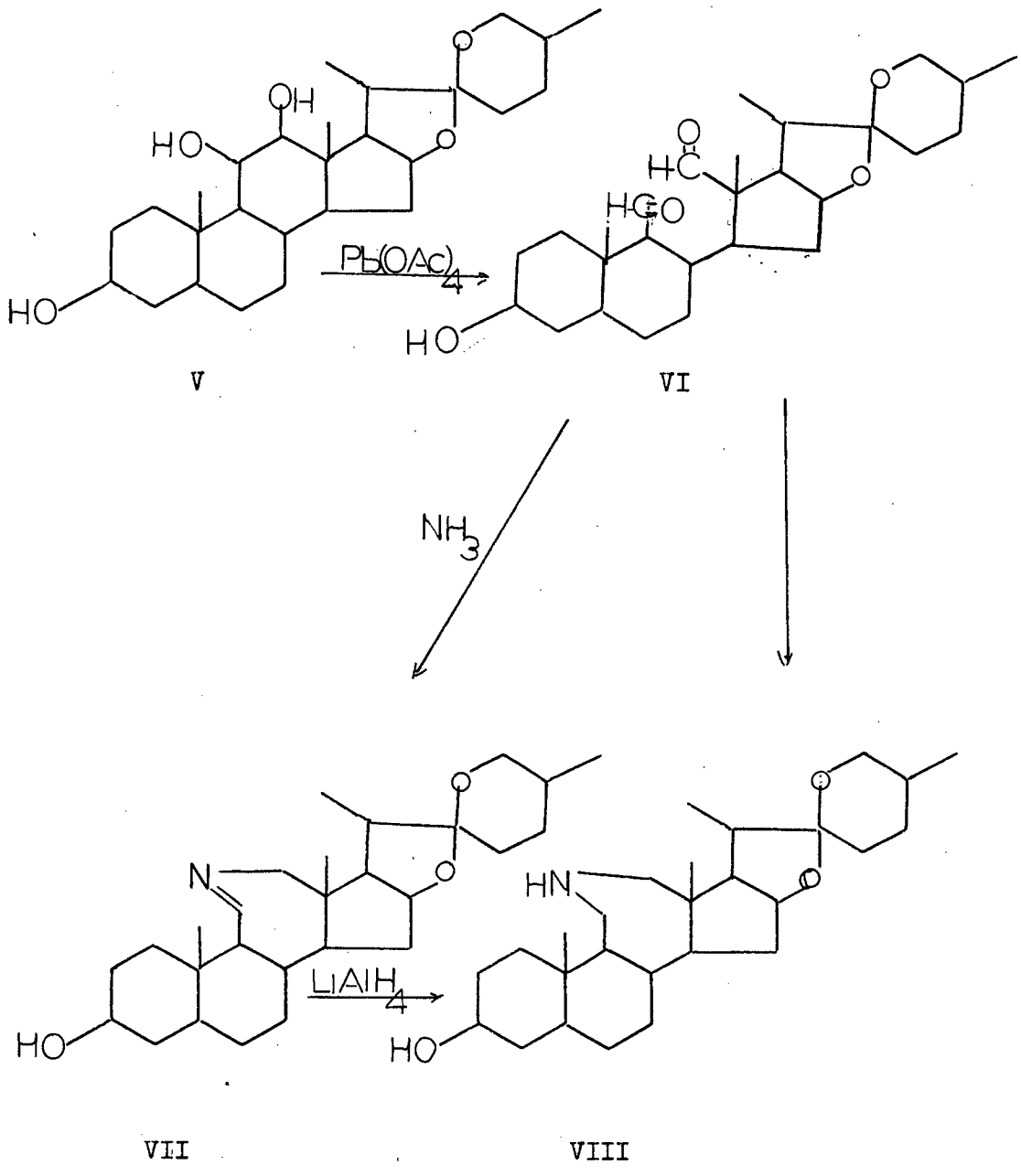


Figure 3 Synthesis of 11-aza-C-homo steroids

In an analogous manner, Zderic et al (4) recently described the synthesis of 9α -aza-C-homo steroids, by carrying out a Beckman rearrangement on the oxime of an 11-keto steroid (6). In this case, the main product was the expected 9-aza-C-homo derivative (IV) because in the configuration of the oxime, with the hydroxyl group anti to ring A, steric effects are at a minimum. (Fig. 2).

It is apparent from the above approach to 9 and 12 aza-C-homo steroids, that 11-aza steroids cannot be synthesized directly by a simple Beckman rearrangement. In 1961, Zderic and his coworkers (5) reported the synthesis of 11-aza-C-homo steroids by a different reaction sequence. Their starting material, 11β ,12β -dihydroxy tigogenin V (7), was treated with lead tetraacetate to yield the 11,12-seco-tigogenin-11,12-dialdehyde (VI). This compound was then treated, under reductive conditions, in the presence of ammoniated ethanol to give 11-aza-C-homo tigogenin (VIII) in good yield. An alternative preparation of VIII was achieved by heating the dialdehyde (VI) at the reflux temperature with a saturated solution of ammonia in ethanol to yield the Schiff base (VII), which was subsequently reduced by lithium aluminum hydride to (VIII).(Fig. 3).

Since the above investigations do not provide the desired aza steroids, it was necessary to develop a new synthetic pathway to the preparation of the normal C-aza steroids. Our own work which leads to the first synthesis of a true 11-aza steroid in the steroidal sapogenin series is discussed in the next section of this thesis.

DISCUSSION

In considering a synthetic sequence leading to 11-aza steroids, it was obvious that an extension of our work in ring B should provide an entry into this series. It was therefore necessary to prepare the appropriate 9,12-seco steroidal intermediates which, in turn, could be cyclized in the presence of an amine to provide the 11-aza steroid. The most direct approach to the desired 9,12-seco steroids involved ozonolysis of a 9,11-unsaturated 12-keto steroid since this type of reaction had been successfully employed in our laboratory (1,2) and by Jacobs and Brownfield (8) in the synthesis of ring B seco derivatives and by Engel and coworkers (9) in the synthesis of some 9,12-seco steroids. An attractive starting material for the ring opening reaction was 9,11-dehydrohecogenin acetate, which was readily available from hecogenin acetate (10). When we subjected this substance to ozonolysis we obtained in low yield from the acidic fraction of the reaction product, a crystalline high melting compound which exhibited the expected properties of the desired 9,12-seco keto acid (X). The infrared spectrum indicated two bands in the carbonyl region (5.80 μ, 5.93 μ) and still retained the characteristic spiroketal bands (11, 12) indicating that the spiroketal side chain remained unaffected under these conditions. In spite of numerous experiments, we were not able to improve the yield in this reaction and we turned to consider another approach to this problem. An attractive alternative was the use of the Lemieux reagent (13,14) since just at this time, Edward (15) published some work which indicated that this reagent was superior to

ozone in the instance of cholest-4-en-3-one. Consequently, 9,11-dehydrohecogenin acetate was treated with this reagent and a crystalline acidic product was obtained from this reaction. This substance was shown to be identical with the ozonolysis product (X). In addition, another crystalline compound was obtained from the acidic fraction of the reaction product which on the basis of its infrared spectrum (5.68 μ), is tentatively assigned an enol lactone structure (XIII). Our present evidence does not fully establish this structure and further investigation will be necessary. The overall yield of the desired keto acid (X) was substantially higher in the Lemieux reaction particularly since a large proportion of the neutral fraction in this reaction was unreacted starting material. In addition to the improved yield, it was also more convenient to utilize this reagent in large scale preparations of (X) and we have used this procedure in all our subsequent preparations. After this phase of the work was completed, a detailed study of the ozonolysis of $\Delta^{9,11}$-12-keto steroids was reported by Engel (16).

Because of our success with benzyl amine in our previous work on ring B aza steroids, we decided to study the cyclization of the keto acid (X) with this amine. When the keto acid was reacted with refluxing benzyl amine and the reaction mixture extracted with ether, there was obtained from the neutral portion of the reaction product, two crystalline compounds. The minor component was a high melting substance which exhibited strong absorption at 6.01μ and 6.06μ in the infrared spectrum and also possessed an absorption maximum of 255 mμ in the ultraviolet spectrum. This spectral data initially led us to believe that the desired

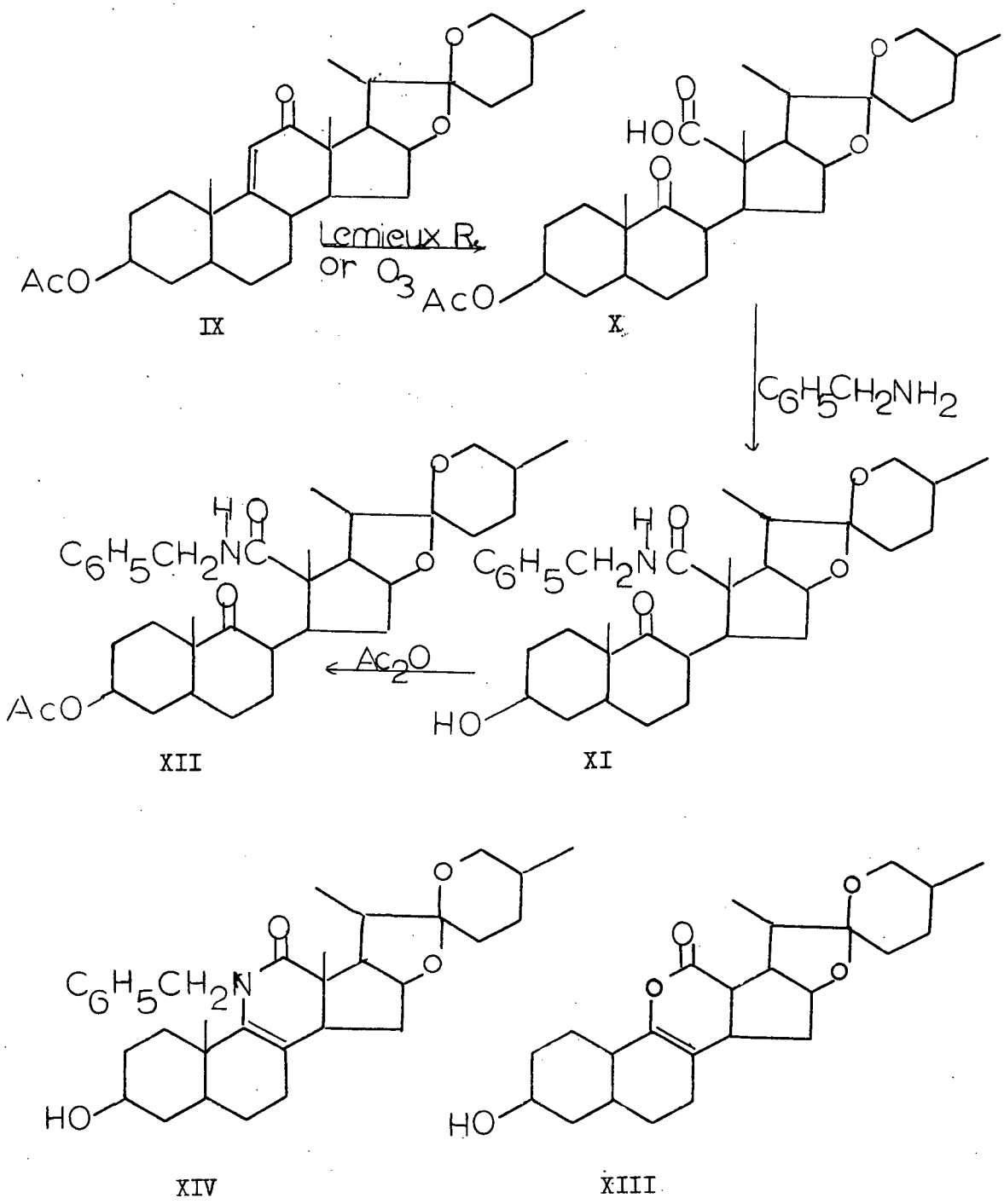


Figure 4 Investigation of the benzylamine reaction with the keto acid (X)

enol lactam (XIV) had been obtained but the subsequent analytical data was not in agreement with this structure. The structure of this product will be discussed in a later portion of this discussion. The major product of the benzyl amine reaction was a lower melting crystalline compound which possessed strong carbonyl absorption in the infrared at 5.88μ and 6.15μ . The substance did not possess any absorption in the ultraviolet and the n.m.r. spectrum of this material showed an intense signal in the aromatic proton region (2.75τ). It was therefore clear that this substance did not represent a cyclic enol lactam structure but was most probably the keto amide (XI). The analytical data supported this structure for the substance. In view of the apparent difference in reaction of the keto acid (X) when compared to the corresponding keto acid in the ring B series (1,2), it was necessary to establish fully the assigned structure (XI) for this keto amide. The following results provided conclusive proof of the structure (XI).

The presence of the hydroxyl group at C_3 was readily demonstrated by the formation of a monoacetate (XII) which now showed, apart from the ketone and amide absorption, a new band at 5.80 μ in its infrared spectrum. In addition, the n.m.r. spectrum indicated a new signal for the acetate methyl group (8.0τ). Reduction of the keto amide with sodium borohydride or, with lithium aluminum hydride under mild conditions, provided a dihydroxy amide (XV) in good yield. Chromatographic purification of this reduction product indicated a predominance of only one isomer. The infrared spectrum of this compound indicated a disappearance of the acetate and ketone absorptions but still

indicated the amide band at 6.15 μ . Similarly, a disappearance of the acetate methyl signal was likewise noted in the n.m.r. spectrum for this substance. A similar reduction of the acetate provided a mixture of the hydroxy acetate (XVI) and the dihydroxy amide (XV). The hydroxy acetate (XVI) was also obtained from a mild acetylation of XV. This last reaction demonstrated that it was possible to obtain preferential acetylation at C_3 without affecting the hydroxyl function at C_9. Acetylation of XV under drastic conditions (refluxing isopropenyl acetate or acetic anhydride in pyridine) provided a crystalline, high melting compound which had no band at 6.15 μ in the infrared spectrum, corresponding to the amide group. Further reduction of XV with lithium aluminum hydride in boiling tetrahydrofuran, provided the amine (XVIII) in good yield. The infrared spectrum of this compound indicated the disappearance of the amide band, while a sharp absorption at 3.1 μ indicated the presence of the N-H group. The analysis of XVIII was not satisfactory, however, we were able to characterize this material as the N-acetyl-3β ,9ξ -diacetate (XIX). The presence of the three acetyl groups in XIX was indicated by the appearance of two strong bands at 5.8 μ and 6.05 μ in the infrared spectrum and three sharp signals at 7.93, 8.03 and 8.19 τ in the n.m.r. spectrum. This series of reactions served to demonstrate the functionality present in the major reaction product from the benzyl amine reaction and allowed us to assign structure XII to this substance.

It was now clear that the cyclization of 9,12-seco keto-acids of the type indicated above could not be accomplished under the influence of refluxing benzyl amine to provide N-benzyl 11-aza steroid analogues.

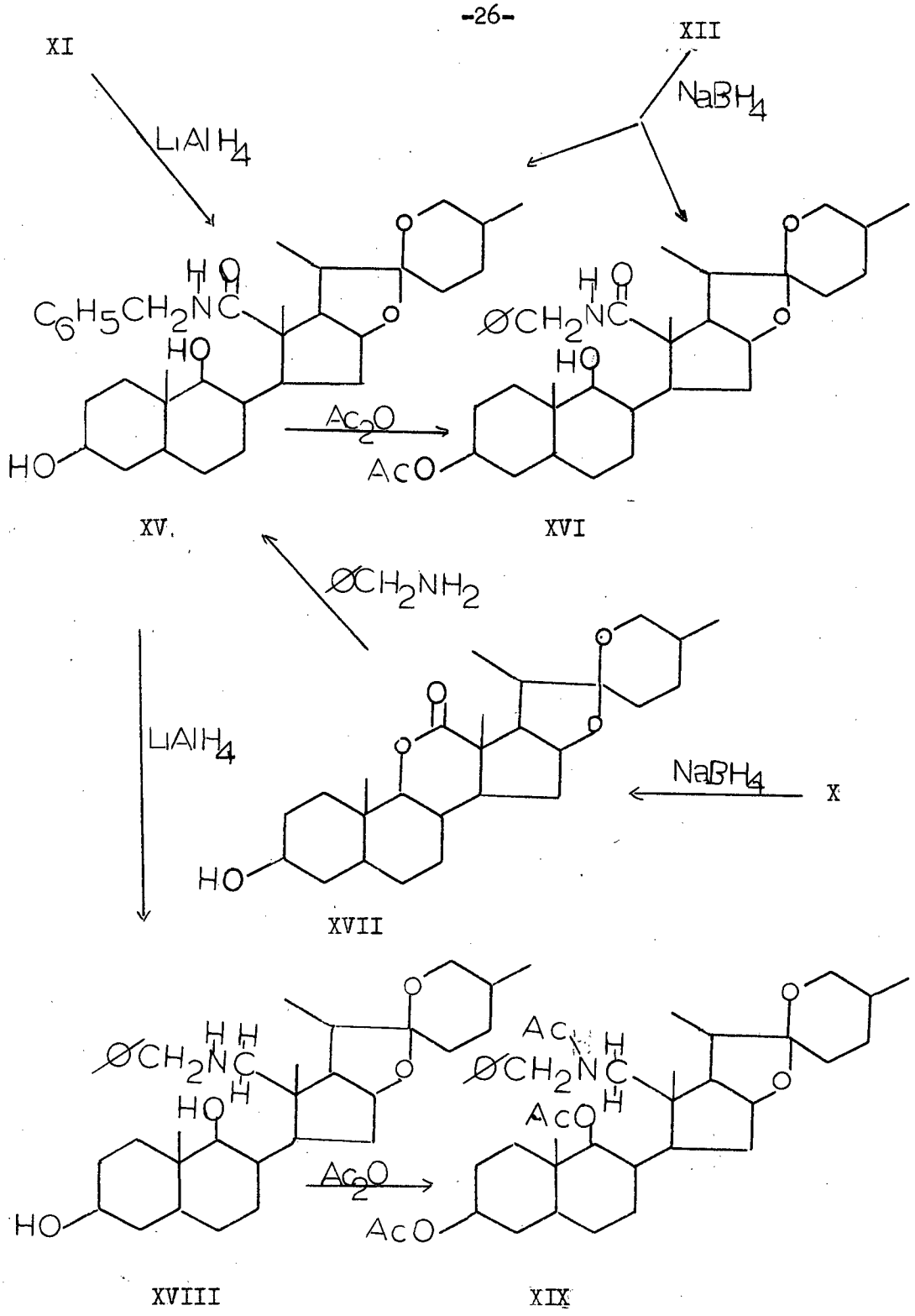


Figure 5 Investigation of the benzylamine reaction with the keto acid (X)

We felt that the steric influence of the angular methyl group at C_{10} was probably the reason why the cyclization with relatively large N-benzyl function had failed. In order to obtain more information about the cyclization reaction, we subjected the keto-acid (X) to a reduction with sodium borohydride in the hope that the resulting hydroxy acid could be cyclized to provide a δ-lactone structure (XVII). Indeed when we completed this reduction we obtained as one of the reaction products, a crystalline substance which showed only one carbonyl absorption in the infrared spectrum (5.81 μ). The n.m.r. spectrum of this material showed the absence of a carboxylic proton and the analytical data was in good agreement with a lactone structure. Consequently, we tentatively assign the lactone structure XVII to this reduction product although it is necessary to carry out a more careful study of this reaction. It is to be noted that Atwater, in his paper on oxasteroids (17), has reported a complex mixture of lactones and lactols in his work on ring B seco steroids and it would be of some interest to see whether similar results are also obtained in ring C. However, as far as the present phase of the investigation was concerned, it was merely necessary to realize that the cyclization of 9,12-seco steroids could indeed be successfully accomplished.

With the above information at hand, we reacted an alcoholic solution of the keto acid (X), with anhydrous ammonia in a sealed tube at 150°C for 15 hours (8) and obtained an excellent yield of the expected enol lactam (XX). This compound possessed an absorption at 255 mμ in its ultraviolet spectrum as expected for this type of chromophore (1,2,8) and its high melting point was immediately reminiscent of the minor

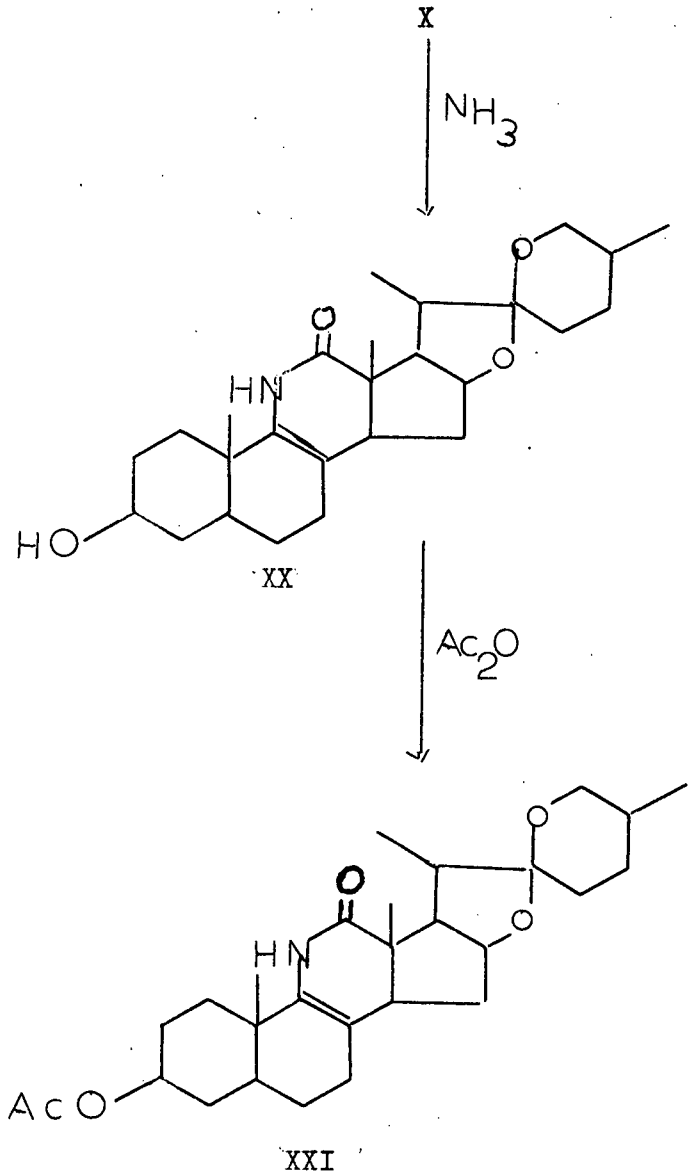


Figure 6 Synthetic route to 11-aza steroids

product which we had previously isolated in the reaction of benzyl amine with X. Indeed, infrared, n.m.r. and mixed melting point comparison of these two products and of their acetylation products (XXI) established beyond any doubt that they were identical. This very interesting result revealed several important aspects of the cyclization reaction. First, the cyclization of 9,12-seco keto-acids can be accomplished very successfully with ammonia and, most probably, with relatively small amines to generate 11-aza steroid derivatives. As already mentioned above, Engel has recently reported this reaction in another series of compounds (18) and our results amplify the generality of this type of reaction. Secondly, if a sterically larger amine such as benzyl amine is employed, the reaction path takes an unusual course wherein an unexpected cyclic product is obtained. It is not knownat this time whether the mechanism of the benzyl amine reaction involves debenzylation at some stage or whether perhaps ammonia possibly formed by prolonged heating of the benzyl amine is the actual reactant.

CONCLUSION

A synthesis of 11-aza steroids with the true steroid skeleton has been developed. This represents the first synthesis of an 11-aza steroid in the steroidal sapogenin series. The sequence employs hecogenin acetate as the starting material to provide the necessary 9,12-seco keto-acid. This latter substance could be cyclized in the presence of ammonia to 11-aza steroidal analogues. Attempts to cyclize the keto acid with benzyl amine led to some interesting results. The major product from this reaction was a keto amide which indicated that cyclization with this amine did not occur. A minor product from the benzyl amine reaction was shown to be identical to the substance obtained from the ammonia cyclization. The isolation of this material reveals that steric effects are important in determining the course of the reaction. Further investigation will be necessary before any accurate evaluation of this steric factor can be made.

A portion of this work has been submitted for publication (19).

EXPERIMENTAL

All meltingpoints were determined on a Fischer-Johns apparatus and are uncorrected. The ultra-violet spectra were recorded in 95% ethyl alcohol on a Cary 14 recording spectrophotometer and the rotations were taken in 1% chloroform solutions except where stated otherwise. The infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. The n.m.r. spectra were taken at 60 Mc on a Varian A60 instrument. The values are given in the Tiers τ scale with the signal of tetramethylsilane, which was used as the internal standard, set at 10.0 τ units. Analyses were performed by Mrs. Aldridge, University of British Columbia and by A. Bernhardt and his associates, Mulheim (Ruhr) Germany.

Ozonolysis of 9,11-Dehydrohecogenin Acetate

This experiment was initially done by Dr. Ganti Verkat Rao of this laboatory.

A solution of 9,11-dehydrohecogenin acetate (2.7g, prepared according to the procedure of Bowers et al (10)) in methylene chloride (100 ml) was ozonised at -78°C over a period of one hour with an ozone stream producing 0.1 mole ozone per hour. The reaction mixture was then brought to room temperature and water (5 ml) and 30% hydrogen peroxide (5 ml) were added. The reaction mixture was stirred for 4 hours at room temperature and then the organic layer was separated. The aqueous layer was extracted with several small portions of methylene chloride and the combined organic extracts were evaporated to dryness. The residue was taken up in ether (250 ml) and washed with a saturated

solution of sodium bicarbonate (100 ml) to remove acidic components. The sodium bicarbonate layer was then made acidic with dilute hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and the solvent removed to yield an insignificant amount (0.15g) of a solid, acidic material.

The original ether extract, which had been washed with the sodium bicarbonate solution, was now washed with cold aqueous 7% sodium hydroxide to remove any remaining acidic products. The alkaline layer was then acidified with hydrochloric acid and this mixture now extracted exhaustively with ether. The ether extract was dried over anhydrous magnesium sulfate and the solvent removed to yield 0.73 g (total, 0.88 g) of crystalline, acidic product with a melting point of 262-264°. Several recrystallizations from methanol-chloroform provided a pure sample (0.7g) of 3β -acetoxy-9-oxo-9, 12-seco-11-nor-25-iso-5α , 22β -spirostan-12-oic acid (X), m.p. 261-265°; $[\alpha]_D^{26}$-87°; infrared (KBr): 5.80 μ , 5.93 μ . Found: C, 68.94; H, 8.89; O, 22.53. Calc. for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63; O, 22.83.

Lemieux Oxidation of 9,11-Dehydrohecogenin Acetate

A solution of 9,11-dehydrohecogenin acetate (3.0g) in a t-butanol-water mixture (220.6 ml, prepared from 200 ml t-butanol and 20.6 ml water) was treated with an aqueous solution of potassium carbonate (1.375 g) in water (39 ml). This stirred mixture was then treated with an aliquot (25 ml) of a stock solution of sodium metaperiodate (prepared from sodium meta periodate (9.81 g) in water (123 ml)) and 0.8% aqueous potassium permanganate (2.5 ml) and the stirring was continued.

The remainder of the periodate solution was added slowly to the reaction mixture over a period of 10 minutes and after this time, another portion (2.5 ml) of 0.8% aqueous permanganate was added. The whole mixture was stirred at room temperature for another 30 minutes, a third portion (3.75 ml) of permanganate was added and the mixture stirred at room temperature for 4 hours. The excess permanganate was destroyed by the addition of sodium bisulfite and the resultant brownish reaction mixture was concentrated on a steam bath in vacuo to about one-half the original volume (until most of the volatile materials had been removed). The reaction mixture was cooled in ice, acidified with ice-cold 50% aqueous sulfuric acid and extracted with ether. The ether extract was then washed several times with cold, dilute aqueous sodium hydroxide and finally with water. The alkaline and water washings were combined and treated with concentrated hydrochloric acid until the solution was acidic and then extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and the solvent was removed to provide a crystalline, acidic product (1.1 g). Several recrystallizations from methanol-chloroform (1:1) provided the pure product (0.75 g). Infrared and mixed melting point comparison established that this product was identical with the ozonolysis product (X). The mother liquors from the above crystallizations were concentrated and another crop (300 mg) of crystals was collected, m.p. 230-240°. Repeated recrystallization of this material from aqueous methanol provided a crystalline substance (200 mg) which exhibited a somewhat improved melting point (235-238°) but it was clear that this sample was not analytically pure. The infrared spectrum of this substance with only one strong carbonyl absorption at 5.68 μ

suggests an enol lactone structure XIII but further work will be necessary before any definite conclusions can be made.

The original ether extract which had been washed with sodium hydroxide and water was dried over anhydrous magnesium sulfate. The solvent was removed to yield 1.3 g of a crystalline, neutral product which proved to be unreacted starting material.

Because of the recovery of a significant amount of starting material in this reaction indicating a much improved overall yield of the desired keto-acid, X, and the convenience of handling larger quantities under these oxidation conditions, we have utilized this procedure in all subsequent preparations of X.

Benzyl Amine Reaction on Keto Acid

The keto-acid (X, 2.57 g) was dissolved in benzyl amine (10 ml) and refluxed for 26 hours under a nitrogen atmosphere. The cooled reaction mixture was then taken up in ether (200 ml) and the ethereal mixture was washed several times with 5% aqueous hydrochloric acid solution, water and finally with 5% aqueous potassium carbonate. The ether extract was dried over anhydrous magnesium sulfate and the solvent removed to provide a semi-solid neutral material (1.9 g). This material was taken up in a small amount of ether and a small amount of white solid which remained undissolved was removed by filtration. On allowing the ether solution to stand at room temperature for one hour, a second crop of the white solid precipitated out. Both crops of the solid were combined and weighed (0.7 g). This substance was recrystallized from benzene to provide pure, white needles (0.55 g) melting at 274-276°

(with some decomposition). This compound was subsequently shown to be identical with the enol lactam, XX, by means of infrared, ultraviolet, nuclear magnetic resonance and mixed melting point comparison. The preparation and complete characterization of XX is given in a later portion of this experimental part.

The ether solution remaining after the removal of the enol lactam, XX, was diluted with petroleum ether and after standing overnight deposited another crop of crystals. Several more crops of crystals were obtained upon concentration of this solution and a total of 1.0 g of this compound melting at 172-174° was obtained. Two further recrystallizations from ether-petroleum ether provided an analytical sample (0.85 g) of 3β-hydroxy-9-oxo-9, 12-seco-11-nor-25-iso-5α, 22β-spirostan-12-N-benzylcarboxamide (XI), m.p. 174-175°; $[\alpha]_D^{26}$ -143°; infrared (KBr): 5.88 μ, 6.15 μ; infrared ($CHCl_3$): 5.90 μ, 6.08 μ, and spiroketal bands at 10.19 μ, 10.85 μ, 11.11 μ, 11.50 μ (8,9); NMR ($CDCl_3$): 2.75 τ (aromatic H). Found: C, 73.32; H, 8.83; O, 15.48; N, 2.70. Calc. for $C_{33}H_{47}O_5N$: C, 73.70; H, 8.81; O, 14.88; N, 2.61.

3β-Acetoxy-9-oxo-9, 12-seco-11-nor-25-iso-5α, 22β-spirostan-12-N-benzylcarboxamide (XII)

The keto-amide (XI, 300 mg) was treated with pyridine (8 ml) and acetic anhydride (5 ml) and the reaction mixture was allowed to stand at room temperature for 24 hours. The excess anhydride was destroyed by the cautious addition of water and the reaction mixture was extracted with ether. The ether extract was first washed with 5% aqueous hydrochloric acid and then with ice-cold 5% aqueous sodium carbonate and

finally dried over anhydrous magnesium sulfate. The solvent was removed and the crystalline solid (310 mg) was recrystallized from ether-petroleum ether to provide the analytical sample of the acetate (XII, 300 mg), m.p. 168-170°; $[\alpha]_D^{26}$ -132°; infrared (KBr): 5.80 μ, 5.87 μ, 6.15 μ; NMR ($CDCl_3$): 2.74 τ (aromatic H), 8.0 τ ($-\overset{O}{\overset{\|}{C}}-CH_3$). Found: C, 72.09; H, 8.42; N, 2.67. Calc. for $C_{35}H_{49}O_6N$: C, 72.51; H, 8.52; N, 2.92.

3β, 9ξ-Dihydroxy-9, 12-seco-11-nor-25-iso-5α, 22β-spirostan-12-N-benzylcarboxamide (XV)

a) By lithium aluminum reduction of keto-amide (XI)

The keto-amide (XI, 140 mg) was dissolved in anhydrous tetrahydrofuran and refluxed for 6 hours with lithium aluminum hydride (400 mg) which was initially placed in a Soxhlet extractor and gradually brought into the vessel by the refluxing solvent. The excess hydride was destroyed by careful addition of water and the ether layer was separated. After drying the ether extract over anhydrous magnesium sulfate, the solvent was removed to yield a white solid (150 mg). This solid was recrystallized several times from ether to provide an analytical sample of the dihydroxy amide (XV) (120 mg), m.p. 223-224°; $[\alpha]_D^{26}$ -108°; infrared (KBr): 2.86 μ, 2.91 μ, 3.01 μ, 6.15 μ; NMR ($CDCl_3$): 2.75 τ (aromatic H), complete disappearance of signal at 8.0 τ present in the spectrum of XII. Found: C, 73.37; H, 9.32; N, 2.78. Calc. for $C_{33}H_{49}O_5N$: C, 73.43; H, 9.15; N, 2.66.

b) By sodium borohydride reduction of acetoxy keto-amide (XII)

A solution of the acetoxy keto-amide (XII, 110 mg) in methanol (8 ml) was treated with a solution of sodium borohydride (65 mg) in methanol (6 ml) and the mixture was stirred at room temperature for one hour. After this time, more sodium borohydride (75 mg) was added to the reaction mixture and the stirring was continued at room temperature for a further 3 hours. The mixture was concentrated in vacuo, water was added and the whole mixture was acidified by the addition of 10% aqueous acetic acid. The organic product was extracted from the reaction mixture with ether and the ether extract was then washed with ice-cold 5% potassium carbonate solution and finally with water. The ether layer was dried over anhydrous magnesium sulfate and the solvent removed to yield an oily product (110 mg) which did not crystallize too well. This product was taken up in benzene and chromatographed on silica gel (50 g). Elution with benzene-chloroform (1:1) provided 35 mg of the 3-acetoxy-9-hydroxy amide, XVI, which is characterized below. Elution with chloroform-benzene (9:1) yielded 65 mg of another solid which was shown to be completely identical to the lithium aluminum hydride reduction product, XV, by infrared and mixed melting point comparison.

3β -Acetoxy-9ξ -hydroxy-9, 12-seco-11-nor-25-iso-5α, 22β -spirostan-12-N-benzylcarboxamide (XVI)

The dihydroxy amide (XV, 100 mg) was dissolved in pyridine (5 ml) and treated with acetic anhydride (3 ml) and the reaction mixture was left to stand at room temperature for 24 hours. The excess anhydride

was destroyed by the addition of water and the resulting reaction mixture was extracted with ether. The ether extract was washed with 5% aqueous hydrochloric acid, then with 5% aqueous sodium carbonate and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a white solid (100 mg) which on recrystallization from ether-petroleum ether provided an analytical sample of the acetate, XVI, (90 mg) as white needles, m.p. 166-167°; $[\alpha]_D^{26}$-59°; infrared (KBr): 5.80 μ, 6.17 μ; NMR ($CDCl_3$): 2.78 τ (aromatic H), 8.0 τ ($-\overset{O}{\overset{\|}{C}}-CH_3$). Found: C, 72.50; H, 8.75; N, 2.70. Calc. for $C_{35}H_{51}O_6N$: C, 72.25; H, 8.84; N, 2.41.

3β,9ξ-diacetyl-9,12-seco-11-nor-12(-N-benzyl acetimide)-25-iso-5α,22β-spirostane (XIX)

The hydroxyl amide (XV, 900 mg) was dissolved in anhydrous tetrahydrofurane and refluxed for 22 hours with lithium aluminum hydride (1 gr) which was initially placed in a Soxhlet extractor and gradually brought into the vessel by the refluxing solvent. The excess hydride was destroyed by careful addition of water and the ether layer was separated. After drying the ether solution over anhydrous magnesium sulfate, the solvent was removed to yield an oily material. This was taken with ethyl ether and the ethereal solution was extracted with 5% hydrochloric acid solution. The aqueous acidic extracts were made basic with 10% sodium hydroxide solution and the resulting mixture was extracted with ether. The ethereal extract, after washing with water, was dried over anhydrous magnesium sulfate. Removal of the solvent yielded a basic oily material (200 mgr). This material was crystallized

from ether-pet-ether (30° - 60°) and represented 3β ,9ξ -dihydroxy-9,12-seco-11-nor-12-N-benzyl-5α ,22β -spirostane (XVIII). The initial ether solution, after washing with water and drying over magnesium sulfate, provided a neutral material (650 mgr) which was found to be starting material (XV).

The compound (XVIII) was dissolved in 12 cc of pyridine and treated with 8 cc of acetic anhydride at room temperature for 24 hours. The excess of acetic anhydride was decomposed with water and the mixture was extracted with ether. The ether solution was washed with 5% hydrochloric acid solution and then with water. The ether layer was dried over magnesium sulfate and provided, after removal of the solvent, a neutral material (180 mgr) which on several recrystallizations from ether-petroleum ether (30° - 60°) yielded an analytical sample (XIX), m.p. 157-159°; $[\alpha]_D^{27}$-115°; infrared (nujol): 5.8 μ and 6.05 μ ; NMR signals ($CDCl_3$): sharp signals at 7.93, 8.03 and 8.19 τ ($COOCH_3$); multiplet at 2.7 τ (aromatic H). Found: C, 71.96; H, 8.59; N, 2.4. Calc. for $C_{39}H_{57}O_7N$: C, 71.86; H, 8.81; N, 2.15.

3β -Hydroxy-11-aza-5α , 22β -spirost-8(9)-ene-12-one (XX)

The keto-acid (X, 500 mg) was taken up in 95% ethyl alcohol (50 ml) and anhydrous ammonia was bubbled through the solution for one hour at 0°C. The mixture was then heated in an autoclave kept at 150°C for 15 hours. At the end of this heating period, the mixture was allowed to come to room temperature and a small amount (50 mg) of a yellowish solid which had precipitated was removed by filtration. The filtrate

was concentrated on a steam bath in vacuo to yield a yellowish solid (460 mg). Both crops of the solid material were combined and recrystallized from benzene to provide the enol lactam, XX, as yellowish needles. Further recrystallization from benzene, after treatment with Norite, provided the pure enol lactam as white needles (450 mg), m.p. 274-276° (with some decomposition); $[\alpha]_D^{26}$ +163° (due to solubility difficulties, this rotation was done on 1% tetrahydrofuran solution); ultraviolet: λ_{max} 255 mμ (log ε 3.68); infrared (KBr): 6.01 μ, 6.06 μ; Found: C, 73.11; H, 9.10; N, 3.45. Calc. for $C_{26}H_{39}O_4N$: C, 72.69; H, 9.15; N, 3.26.

3β-Acetoxy-11-aza-5α, 22β-spirost-8(9)-ene-12-one (XXI)

The enol lactam (XX, 100 mg) was dissolved in pyridine (5 ml) and the solution was treated with acetic anhydride (4 ml) and then allowed to stand at room temperature for 24 hours. The excess anhydride was destroyed by addition of water and the reaction mixture was then extracted with ether. After washing the ether extract with 5% aqueous hydrochloric acid and ice-cold 5% aqueous sodium carbonate solution, it was dried over anhydrous magnesium sulfate. Evaporation of the solvent provided a white solid (105 mg) which on recrystallization from methyl alcohol yielded the pure acetate, XXI, as white needles (95 mg) m.p. 283-285° (dec); $[\alpha]_D^{26}$ +132°; ultraviolet: λ_{max} 255 mμ (log ε 3.69); infrared ($CHCl_3$): 5.81 μ, 6.0 μ and spiroketal bands at 10.18 μ, 10.85 μ, 11.11 μ and 11.53 μ. Found: C, 71.05; H, 8.60; N, 2.85. Calc. for $C_{28}H_{41}O_5N$: C, 71.30; H, 8.76; N, 2.97.

3β-Hydroxy-11-oxa-5α, 22β-spirostan-12-one (XVII)

The keto-acid (X, 230 mg) was dissolved in a mixture of wet methyl alcohol (18 ml) and chloroform (10 ml) and treated with a solution of sodium borohydride (150 mg) in methyl alcohol (10 ml). The reaction mixture was stirred at room temperature for one hour and then more sodium borohydride (300 mg) was added and stirring continued for a further 2.5 hours. After this time the solvent was removed in vacuo and the residue treated with a small amount of water and then acidified by the addition of 10% aqueous acetic acid. The reaction mixture was extracted with ether and the ether extract dried over anhydrous magnesium sulfate. Evaporation of the solvent left a white solid which was recrystallized from aqueous methanol to provide a first crop (150 mg) of the lactone, XVII. Concentration of the mother liquors provided an additional crop (20 mg) of the same material but subsequent concentrations of the mother liquors provided small crops (total 50 mg) of solid materials which were obviously mixtures and still remain to be characterized.

The first two crops (170 mg) were combined and recrystallized from aqueous methanol to yield the pure lactone, XVII (140 mg), m.p. 274-276°; $[\alpha]_D^{26}$ -22°; infrared (KBr): 5.81 μ; infrared ($CHCl_3$); 5.78 μ and spiroketal bands at 10.18 μ, 10.83 μ, 11.11 μ and 11.53 μ; NMR ($CDCl_3$): complete absence of any signals for acetate methyl group and carboxylic proton. Found: C, 72.46; H, 9.20; O, 18.27. Calc. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32; O, 18.49.

Benzyl Amine Reaction on Lactone (XVII)

The lactone (XVII, 115 mg) was dissolved in benzyl amine (2 ml) and refluxed for 22 hours under a nitrogen atmosphere. The cooled reaction mixture was taken up in ether and the ethereal mixture was washed with 5% aqueous hydrochloric acid and then with 5% aqueous sodium carbonate solution. After drying the ether extract over anhydrous magnesium sulfate, the solvent was removed to yield a white solid (130 mg). Crystallization of this substance from ether yielded a pure sample (105 mg), m.p. 222-224°. Subsequent comparison of the infrared spectrum of this product with the spectrum of the dihydroxy amide, XV, indicated that the two substances were identical. This identity was further confirmed by a mixed melting point determination and comparison of the nuclear magnetic resonance spectra.

BIBLIOGRAPHY

1) J. P. Kutney and R. A. Johnson, Chem. and Ind., 1713 (1961).

2) J. P. Kutney, R. A. Johnson and I. Vlattas, Can. J. Chem., 41, 613 (1963).

3) R. H. Mazur, J. Am. Chem. Soc., 81, 1454 (1959).

4) J. A. Zderic and J. Iriate, J. Org. Chem., 27, 1756 (1962).

5) J. A. Zderic, H. Carpio, D. Chavez Limon and A. Ruiz, Ibid, 26, 2842 (1961).

6) E. B. Hezshberg, E. P. Oliveto and R. Rausser, Chem. and Ind. (London), 1477 (1958).

7) C. Djerassi, C. H. Martiner and C. Rosenkranz, J. Org. Chem., 16, 1278 (1951).

8) T. L. Jacobs and R. B. Brownfield, J. Am. Chem. Soc., 82, 4033 (1960).

9) Ch. R. Engel and W. W. Huculak, Can. J. Chem., 37, 2031 (1959).

10) A. Bowers, E. Denot, M. B. Sanchez, F. Neuman and C. Djerassi, J. Chem. Soc., 1859 (1961).

11) C. R. Eddy, M. E. Wall and M. K. Scott, Anal. Chem., 25, 266 (1953)

12) R. N. Jones, E. Katzenellenbogen and K. Dobriner, J. Am. Chem. Soc., 75, 158 (1953).

13) R. U. Lemieux and E. von Rudloff, Can. J. Chem., 33, 1701, 1710 (1955).

14) E. von Rudloff, Ibid, 33, 1714 (1955); 34, 1413 (1956).

15) J. T. Edward, D. Holder, W. H. Lunn and I. Puskas, Ibid, 39, 599 (1961).

16) Ch. R. Engel, S. Rakhit and W. W. Huculak, Ibid, 40, 921 (1962).

17) N. W. Atwater, J. Am. Chem. Soc., 83, 3071 (1961).

18) Ch. R. Engel and S. Rakhit, Can. J. Chem., 40, 2153 (1962).

19) J. P. Kutney, I. Vlattas and Ganti Venkat Rao, Ibid, in press (1963).