STUDIES RELATED TO THE VERATRUM ALKALOIDS.

THE TOTAL SYNTHESIS OF C-NOR-D-HOMO STEROID ANALOGUES

by

ARNOLD WILLIAM BY

B. Sc., The University of British Columbia, 1960
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in the Department
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We accept this thesis as conforming to the
required standard

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November, 1965

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Department of Chemistry

The University of British Columbia
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The University of British Columbia

FACULTY OF GRADUATE STUDIES

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FINAL ORAL EXAMINATION

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IN ROOM 261, CHEMISTRY BUILDING

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STUDIES RELATED TO THE VERATRUM ALKALOIDS. THE TOTAL SYNTHESIS OF C-NOR-D-HOMO STEROID ANALOGUES.

ABSTRACT

A sequence leading to the total synthesis of trans-anti-trans- and trans-syn-cis-C-nor-2-methoxy-8,11-diketo-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11-undecahydrochrysene (LXXXI and LXXXII, respectively) from the known compound, 2-methoxy-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysene (XLIII), is described.

Oxidation of trans-anti-trans-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXV) by means of t-butyl chromate led mainly to the 12-keto derivative (LXVIII). An olefinic bond at the 11,12 position (LXXI) was introduced by mild reduction of LXVIII with sodium borohydride followed by dehydration with phosphorus pentoxide. Subsequent reaction at the olefinic linkage by osmium tetroxide provided mainly the β-diol LXXII which upon treatment with periodic acid gave trans-anti-trans-11,12-seco-11,12-dioxo-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXXIV). Intramolecular aldol condensation of LXXIV with sodium hydroxide gave the C-nor-D-homo diol aldehyde LXXIX. Oxidation of the latter with Jones reagent followed by deformylation of the resulting diketo aldehyde LXXX provided the isomeric diketones LXXXI and LXXXII. It is felt that these latter substances show promise as useful intermediates for the total synthesis of Veratrum alkaloids.

In another sequence designed as a model for the subsequent elaboration of LXXXI and LXXXII to the Veratrum alkaloid system, trans-anti-trans-anti-2-keto-8β-hydroxy-10a-methyl-2,3,4,4a,4b,5,6,6a,7,8,9,10,10a,10b,11,12-hexadecahydrochrysene (XCII) was methylated at C-1 via the pyrrolidyl dienamine XCIII.

A detailed discussion of the nuclear magnetic resonance spectra of the hydrochrysene compounds is also presented.

PUBLICATIONS

J. P. Kutney, W. McCrae and A. By; Total Synthesis of Steroidal Derivatives. I. Synthesis of Hydrochrysene Analogues and Related Compounds; Can. J. Chem., 40, 982 (1962).

J. P. Kutney, J. Winter, W. McCrae and A. By; Total Synthesis of Steroidal Derivatives. II. Synthesis of Hydrochrysene Analogues and Related Compounds; Can. J. Chem., 41, 470 (1963).

J.P. Kutney and A. By; Total Synthesis of Steroidal Derivatives. III. Synthesis of Hydrochrysene Analogues and Related Compounds; Can. J. Chem., 42, 591 (1964).

J. P. Kutney, A. By, T. Inaba and S. Y. Leong; A Totally Synthetic Entry into the Veratrum Alkaloid Skeleton; Tetrahedron Letters, 2911 (1965).

GRADUATE STUDIES

Fields of Study: Chemistry

Topics in Physical Chemistry	A. Bree J. A. R. Coope R. F. Snider
Seminar in Chemistry	J. P. Kutney
Topics in Inorganic Chemistry	N. Bartlett W. R. Cullen
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Physical Organic Chemistry	R. Stewart
Organic Reaction Mechanisms	R. E. Pincock
Structure of Newer Natural Products	J. P. Kutney
Recent Synthetic Methods in Organic Chemistry	G. G. S. Dutton A. Rosenthal

Research Supervisor: Doctor James Peter Kutney

Abstract

A sequence leading to the total synthesis of trans-anti-trans- and trans-syn-cis-C-nor-2-methoxy-8, 11-diketo-10a-methyl-4b, 5. 6, 6a, 7. 8, 9, 10. 10a, 10b, 11-undecahydrochrysene (LXXXI and LXXXII, respectively) from the known compound, 2-methoxy-8-keto-10a-methyl-5, 6, 8, 9, 10. 10a. 11, 12-octahydrochrysene (XLIII), is described.

Oxidation of trans-anti-trans-2-methoxy-8β-acetoxy-10a-methyl-4b, 5, 6, 6a, 7, 8, 9, 10, 10a, 10b, 11, 12-dodecahydrochrysene (LXV) by means of t-butyl chromate led mainly to the 12-keto derivitive of LXV (LXVIII). An olefinic bond at the 11, 12 position (LXXI) was introduced by mild reduction of LXVIII with sodium borohydride followed by dehydration with phosphorus pentoxide. Subsequent reaction at the olefinic linkage by osmium tetroxide provided mainly theβ-diol LXXII which upon treatment with periodic acid gave trans-anti-trans-11, 12-seco-11, 12-dioxo-2 methoxy-8β-acetoxy-10a-methyl-4b. 5, 6, 6a, 7, 8, 9, 10, 10a, 10b, 11, 12-dodecahydrochrysene (LXXIV). Intramolecular aldol condensation of LXXIV with sodium hydroxide gave C-nor-D-homo diol aldehyde, LXXIX. Oxidation of the latter with Jones reagent followed by deformylation of the resulting diketo aldehyde, LXXX, provided the isomeric diketones, LXXXI and LXXXII . It is felt that these latter substances show promise as useful intermediates for the total synthesis of Veratrum alkaloids.

In another sequence designed as a model for the subsequent elaboration of LXXXI and LXXXII to the Veratrum alkaloid system, trans-anti-trans-anti-2-keto-8β-hydroxy-10a-methyl-2, 3, 4, 4a, 4b, 5, 6, 6a, 7, 8, 9, 10, 10a, 10b, 11, 12-hexadecahydrochrysene (XCII) was methylated at C-1 via pyrrolidyl dienamine XCIII.

A detailed discussion of the nuclear magnetic resonance spectra of the hydrochrysene compounds is also presented.

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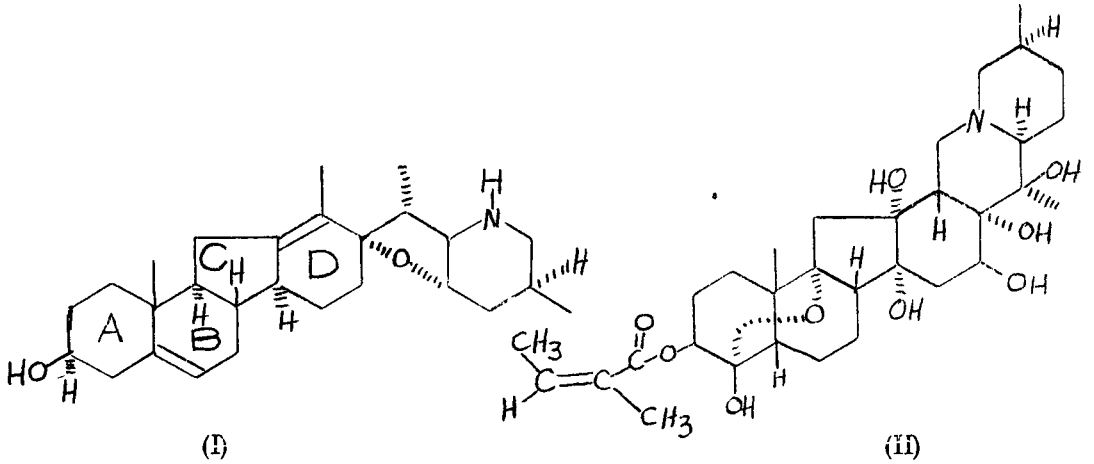
Introduction

Recently many scientists, who have been working in the steroid field have turned their attention to studying nor or homo steroids, or steroids with unnatural stereochemistry. Interest in these compounds has been stimulated to a large extent by reports which state that such unnatural steroidal molecules can have markedly different biological properties from those of the naturally occurring ones. A number of papers (1-11) report on the alterations in the biological activity when the C-18 or C-19 angular methyl group is removed from the steroid molecule. W. S. Johnson and his collaborators (8, 9, 10) have synthesized several D - homo steroids, such as (+) -D-homo-18-norandrostane-3, 17-dione (8), and this compound is as active androgenically as (+) -androstane -3, 17-dione itself. More recently, two papers (12, 13) reported on the synthesis of B-nor-steroids. These latter compounds are somewhat more difficult to prepare. Of pertinence to this discussion was the statement that 9β , 10α- progesterone is approximately five times more active than progesterone as a progestational agent (14).

A large percentage of the above researches have involved the use of the naturally occurring steroids as starting materials. Although these are obviously the logical choice in most cases, they offered certain limitations in synthesizing some of the steroidal derivatives which were of interest in our studies concerned with the relationships between chemical structure and biological activity. For this reason, we initiated investigations directed toward the total synthesis of steroidal analogues

with particular emphasis on intermediates which would readily lend themselves to the introduction of substituents or alterations of the actual skeleton not conveniently possible from the natural steroids. More particularly we were interested in developing a total synthesis of compounds having the modified steroidal skeleton of the C-nor-D-homo type - a system known to be present in the naturally occurring Veratrum alkaloids of which jervine (I) and cevadine (II) are cited as examples.



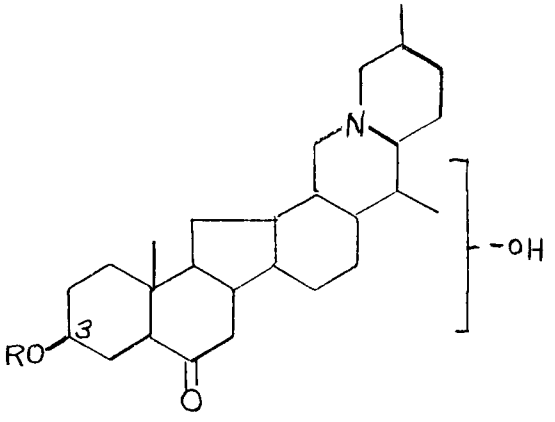
(I) (II)

We felt that if the construction of appropriate C-nor-D-homo steroid intermediates could be realized in the laboratory subsequent extension to the Veratrum series would then be possible. At the present time no total synthesis of the naturally occurring alkaloids is available.

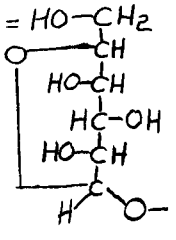
The Veratrum alkaloids are a group of steroidal alkaloids which occur in the plants of the tribe Veratreae. This tribe is part of the subfamily Melanthioideae of the family Liliaceae. Sometimes this subfamily is treated as a separate family, the Melanthiaceae, or the Colchicaceae. The genera which have been investigated are the following: Veratrum (false hellebore), Zygadenus (death camas), Schoenocaulon (Sabadilla), Stenanthium, Amianthium (crow poison), Melanthium (bunch flower) and Fritillaria. The species of the first three genera have received the most attention. Kupchan, Zimmermann and Afonso (15) have recently reviewed

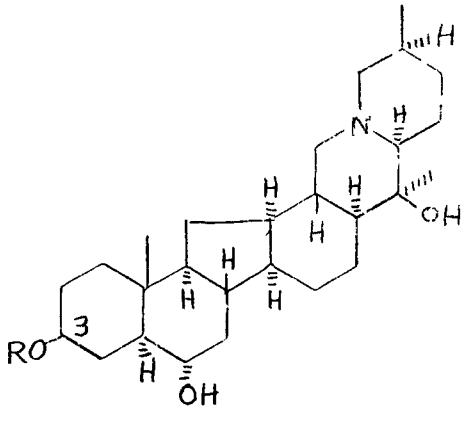
the occurrence and known structures of alkaloids isolated from the Veratreae, the classical botanical taxonomy of the Veratreae, and the implications of alkaloid occurrence and structure to the taxonomy of Veratreae. This review does not cover the work done on the Fritillaria genus.

Veratrum and related plants have been used for medicinal purposes for hundreds of years. Galenical preparations were used in the Middle Ages for purposes of sorcery and mystical rites. Subsequently the crude extracts have been used in the treatment of fevers, as local counterirritants in neuralgia, as cardiac toxics, and as insecticides (16, 17). The use of Veratrum in the control of hypertension, at least in the United States, dates from the report of Baker in 1859 (18). During the late 1930's, purified alkaloidal preparations responsible for the hypotensive activity of Veratrum became available for the first time (19, 20). The group of alkaloids which are mainly responsible for the hypotensive activity are the esters of the ceveratrum alkaloids, such as cevadine (II). These compounds have a heptacyclic skeleton and are highly oxygenated - usually containing 7 to 9 oxygen atoms. Also such molecules have never been found as glycosides but exist as esters of substituted benzoic, acetic and other short chain aliphatic acids. Imperialine (III) (21-25) and verticine ("peimine") (IV) (26, 27) are closely related to these compounds, but, in contrast to the latter, occur naturally as their β-D-glucosides, edpetiline (V) (23, 24, 25) and peiminoside (VI) (26). Kupchan published a review (28) of the hypotensive Veratrum ester alkaloids and, more recently, a series of papers (29-33) on the structure-activity relationships in a series of synthetic protoverine (VII, Figure 1) esters.

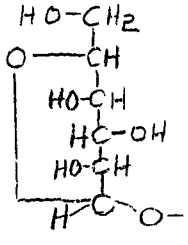


(III) R = H

(V) R = 

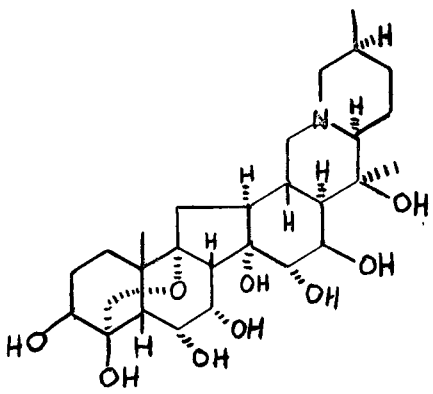


(IV) R = H

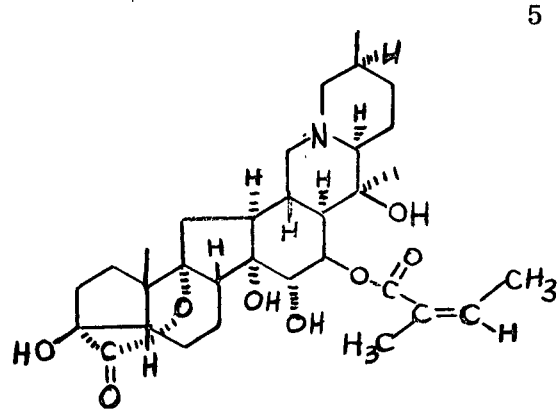
(VI) R = 

The other group of Veratrum alkaloids is the jerveratrum series of which jervine may be cited as an example. Generally these latter substances have only 2 or 3 oxygen atoms in the molecule and possess a penta- or hexacyclic skeleton. These alkaloids occur either as free alkamines or as D-glucosides. Moreover, this group shows very little hypotensive effect (34).

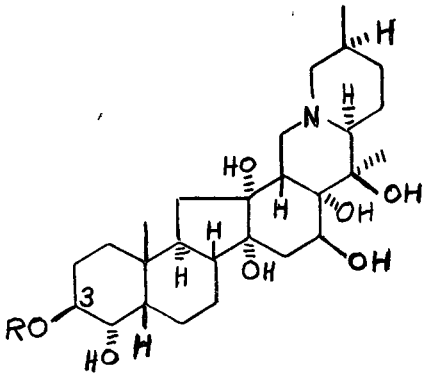
The most recent review of the chemistry of Veratrum alkaloids is by Narayanan (35). However, since then several new alkaloids have been isolated and characterized. Yunusov and Nuriddinov (21, 22) showed that raddeanine (III) from Fritillaria eduardi was identical with sipeimine and imperialine. The latter authors (22) also reported that five new alkaloids were isolated from F. sewerzowi: korseverine ($C_{27}H_{39}O_3N$), alginidine ($C_{27}H_{43}O_4N$), korseverinine ($C_{27}H_{43}ON$), korseveridine ($C_{27}H_{43}O_2N$), and korseveramine ($C_{29}H_{47}O_3N$). In 1962, Yagi and Kawasaki (36) proposed the structure of a new ester alkaloid (VIII, Figure 1, no



(VII)

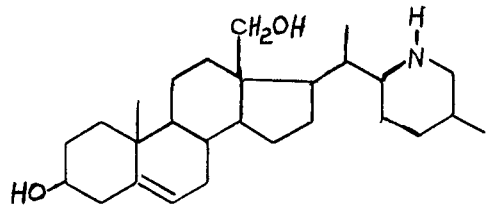


(VIII)

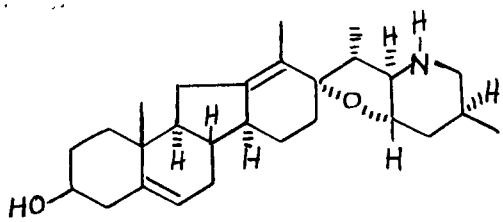


(IX) R = H

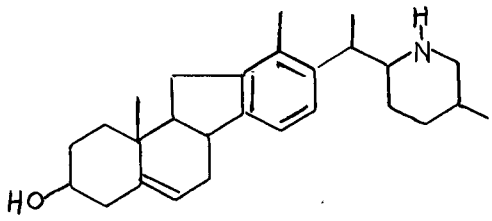
(X) R = Ac



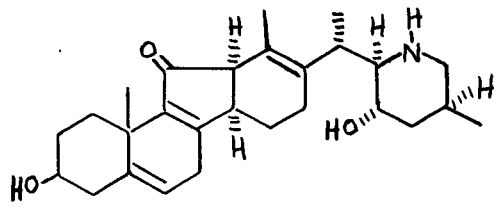
(XI)



(XII)



(XIII)



(XIV)

Figure 1

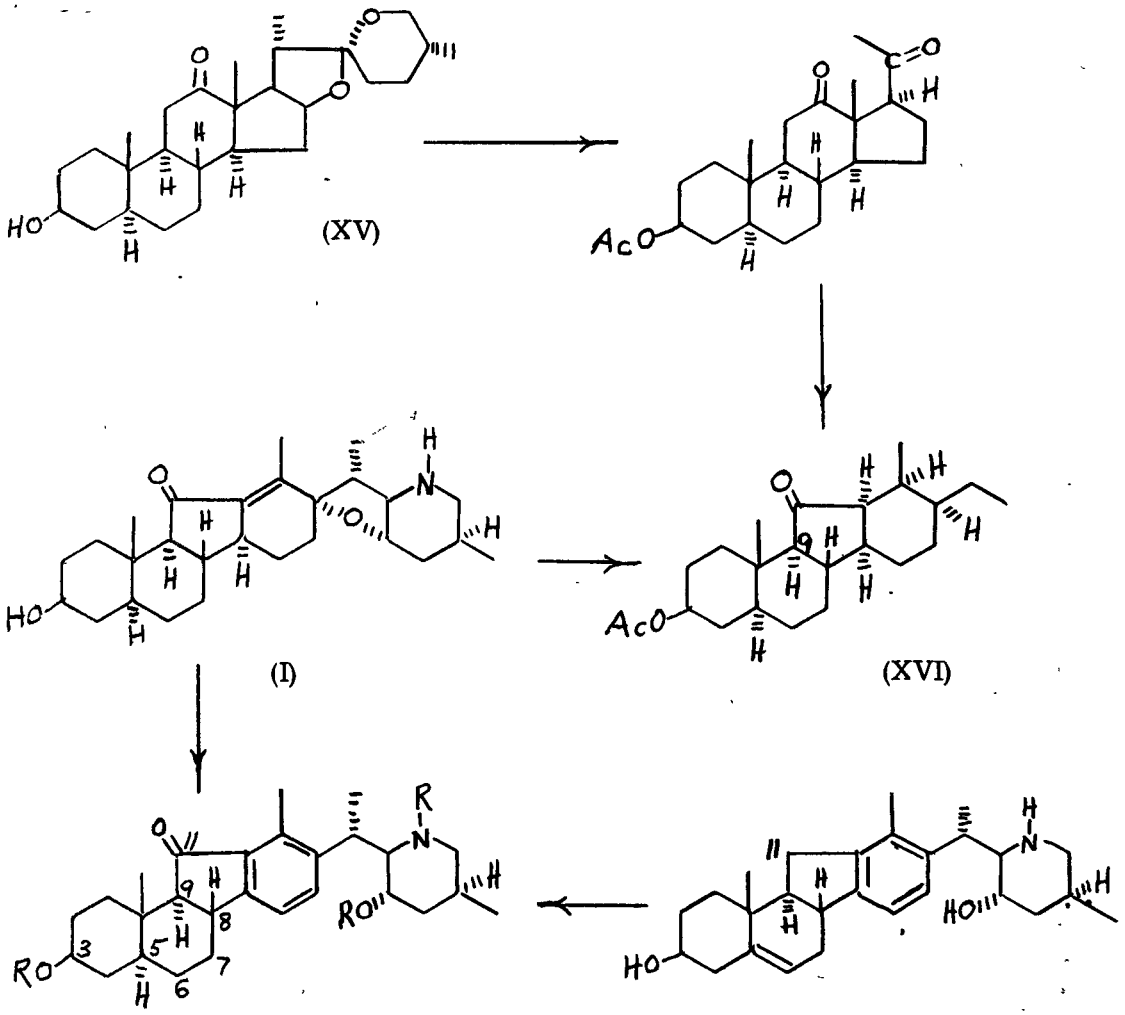
name given) possessing the molecular formula, $C_{32}H_{47}O_8N$, isolated from V. grandiflorum (Maxim.) Loesener fil. In the same year, Kupchan and co-workers (37) gave the structures and configurations of sabine ("neosabadine") (IX, Figure 1) $C_{27}H_{45}O_7N$, and its 3-acetate, sabadine ("sabatine") (X, Figure 1), $C_{29}H_{47}O_8N$. Tomko and Bendik (38) postulated the structure of the jerveratum alkaloid, veralkamine (XI, Figure 1), $C_{27}H_{45}O_2N$. One year later, Ito and collaborators (27) obtained evidence which permitted the assignment of the structure IV for verticine, $C_{27}H_{45}O_3N$, the main alkaloid of Frillaria verticillata var. Thunbergii Baker. Verticine was shown to be identical to peimine. The authors chose the former name over the latter one, since the name "verticine" was first suggested by Fukuda (39) for the pure alkaloid. In 1963, Yunusov (23) isolated from Petilium eduardi the following alkaloids: peimisine, edpetilidine ($C_{27}H_{45}NO_2$), edpetiline, and three unnamed alkaloids (m. pt. 247-51°, 269-71° and 228-31°). Acid hydrolysis (23, 25) of edpetiline produced D-glucose and imperialine. Very recently Yunusov and collaborators (24) synthesized edpetiline from imperialine and tetra-O-acetyl-α-D-glucopyranosyl bromide. In 1964, Masamune and co-workers (40) isolated a new alkaloid, 11-deoxojervine (XII, Figure 1) $C_{27}H_{41}O_2N$, from the roots of V. album L. var. glandiflorum Maxim. It was found to be identical to one of the Wolff-Kishner reduction products of jervine. Tomko (41) has isolated a number of alkaloids from Veratrum album subsp. Lobelianum (BERNH.) Suessenguth including: veralinine ($C_{27}H_{43}ON$), verareine ($C_{27}H_{41}ON$), verasine ($C_{27}H_{43}ON$), veramine ($C_{27}H_{41}O_2N$), veraminine, verarine ($C_{27}H_{39}ON$) and veralkamine ($C_{27}H_{43}O_2N$). He has postulated structure XIII (Figure 1) for verarine (42). Also in 1964, A. G. Smith (43) reported the isolation of a new ester alkaloid, G_9, from Amianthium muscaetoxicum Gray.

Wintersteiner (44) and Masamune (45), in 1962, presented communications on the structural elucidation of isojervine (XIV, Figure 1), an isomer of jervine,

formed in high yield when jervine was treated with hydrochloric acid-methanol solution. More recently, three groups of chemists - Dauben (46), Wintersteiner (47), Masamune (48) and their respective collaborators - have published "final" detailed papers on the structure of isojervine. Fortunately all three groups reached the same conclusion. Wintersteiner and Moore (49) also studied derivatives of isojervine.

The stereochemistry of these molecules has also received recent attention in various laboratories. Mitsuhashi and Shimizu (50, 51) obtained evidence for the 9α configuration of jervine (I) and veratramine (XVIII) by synthesizing the C-nor-D-homo derivative XVI from hecogenin (XV) (Figure 2). In 1963, Johnson (52, 53) published nuclear magnetic resonance and chemical evidence for the 9α configuration of veratramine. He accepts Mitsuhashi's data (50) as being good evidence that the B/C ring fusion of jervine is trans. On the other hand he believes that the C-9 configuration of veratramine is questionable in view of the possibility that the biogenesis of veratramine could well involve 11-keto-veratramine (XVIII with additional keto group at C-11) as an intermediate and this would render C-9 readily epimerizable. The C-19 methyl protons of the derivative XX of 11-keto-veratramine and of the diketone XXI (Figure 2) resonate at exactly the same position (8.81τ). Mitsuhashi (54) and Masamune (55) provided further evidence for the 9α configuration of the jerveratrum alkaloids. Mitsuhashi synthesized the C-nor-D-homo compound XXII (Figure 3) from hecogenin (XV), whereas Masamune synthesized XXII from veratramine (XVIII). Hence the C-9α configuration of veratramine is now well established. Evidence for the 9α configuration in jervine (I) was obtained by Masamune (55) who transformed both jervine and veratramine into compound XXIII (Figure 3). It is now known that 11-deoxojervine (XII) also has the 9α -configuration, since it could be transformed to a compound XXIV (Figure 3) which was a degradation product of veratramine.

W. S. Johnson and co-workers (56, 57) were the first to report on the degradation of veratramine to compound XXII. Their work proceeded further to compound



(XV)

(I)

(XVI)

(XVII) R = H

(XIX) R = Ac

(XVIII)

(XX)

(XXI)

Figure 2

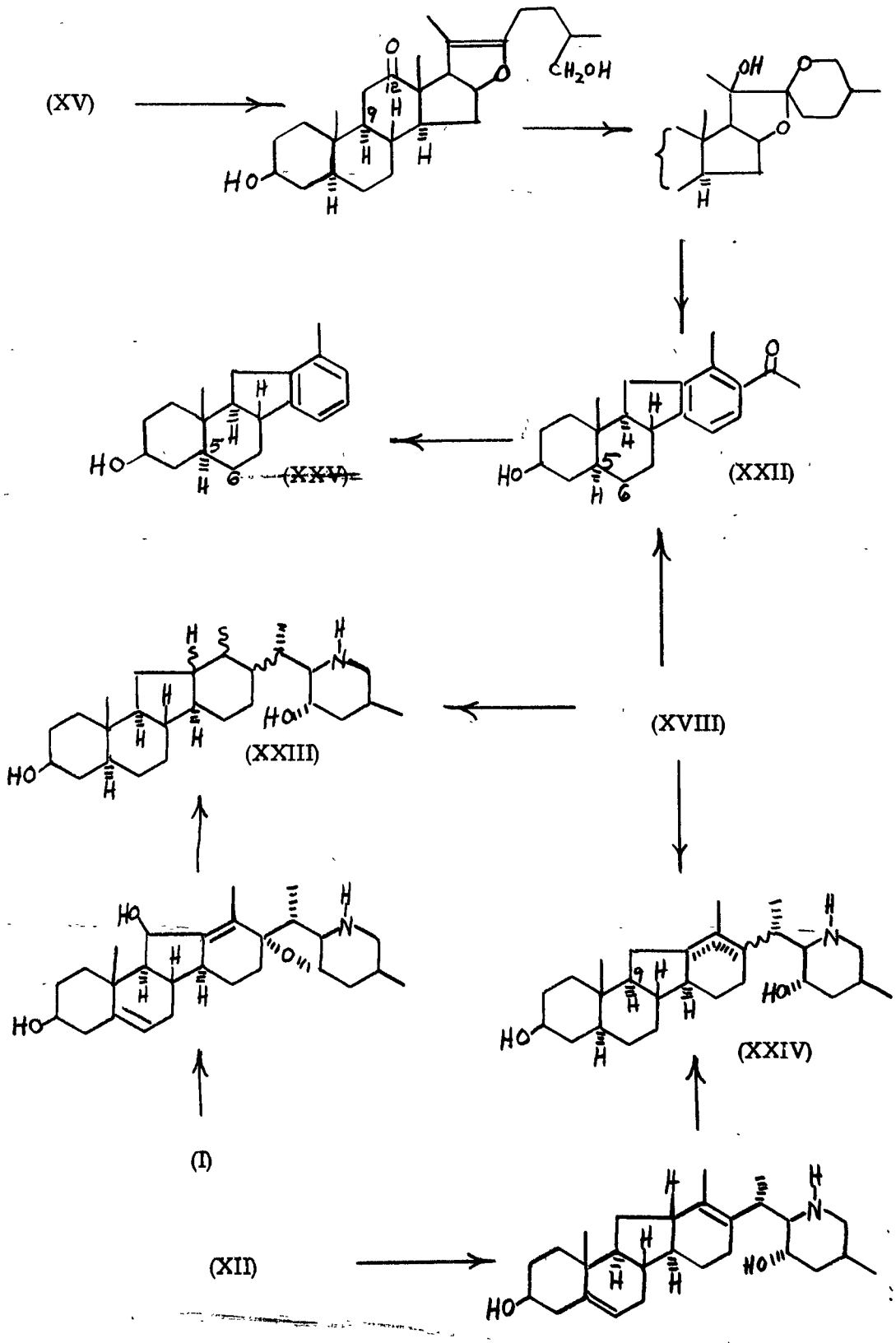
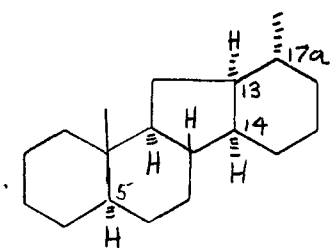


Figure 3

XXV (Figure 3). The reactions leading to XXII were also tried on the compounds having the 5,6-double bond, but the yields were somewhat lower. Compound XXV could possibly be used to determine the stereochemistry of some of our C-nor-D-homo compounds.

Johns (58,59) and Mitsuhashi (60,61) recently published reports on the synthesis of etiojervane derivatives from hecogenin, an abundantly available sapogenin. The designation "etiojervane" will be used to describe 17aα-methyl-C-nor-D-homo-18-nor-5α,13α-androstane (XXVI). Figure 4 and 5 illustrate the sequence employed by Johns. This research is pertinent to our synthesis since our initial goal is to provide a total synthesis of compound XXXIII (Figure 5). It is clear that XXXIII, now available from hecogenin, will allows us to confirm the stereochemistry of our totally synthetic C-nor-D-homo molecules. Mitsuhashi's work is very similar to that of Johns. However in the Japanese paper (60) the compound XXVIII, instead of XXVII, was used to synthesize the C-nor-D-homo compound XXXII. Mitsuhashi's most recent research (61) revealed the synthesis of XXXIII via compound XXXIV (Figure 5).



(XXVI)

It should be noticed that the double bond in XXIX is not in the same position as stated in the above papers. Coxon, in some very recent work (62), gave physical and chemical evidence which indicated that this double bond was at the 13,17a- position and not at the 17,17a -position as previously stated. He also gave proof that the configuration of C-13 in XXX (Figure 4) is α. Etiojervane derivatives have been synthesized from jervine by Kupchan and collaborators (63,64). Some of these compounds are also potentially useful as relay substances in a subsequent synthesis of jervine since they possess an oxygen function at C-11.

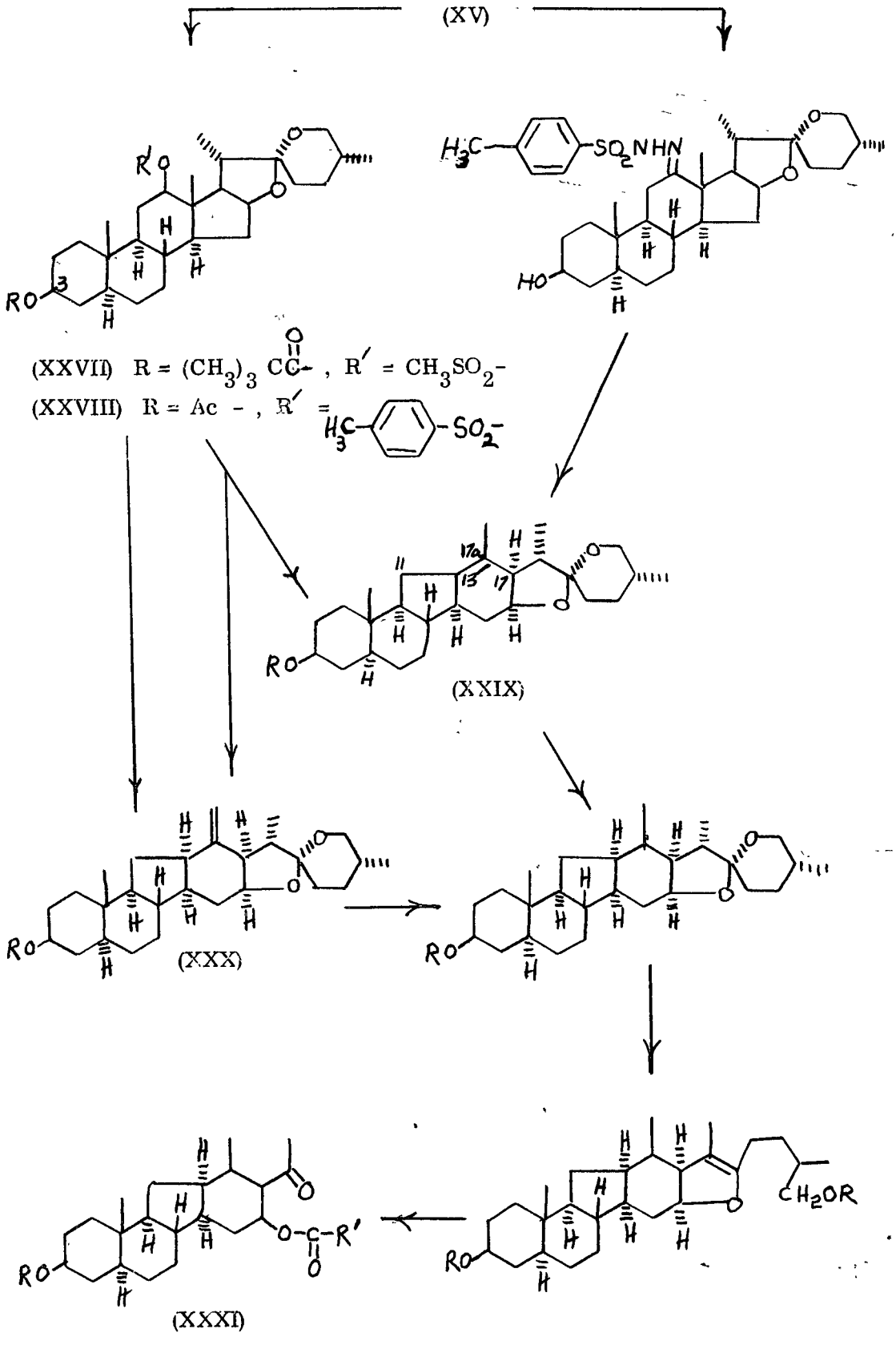

(XV)
(XXVII) R = $(CH_3)_3$ CC(=O)- , R′ = CH_3SO_2-
(XXVIII) R = Ac - , R′ = H_3C-C6H4-SO_2-
(XXIX)
(XXX)
(XXXI)

Figure 4

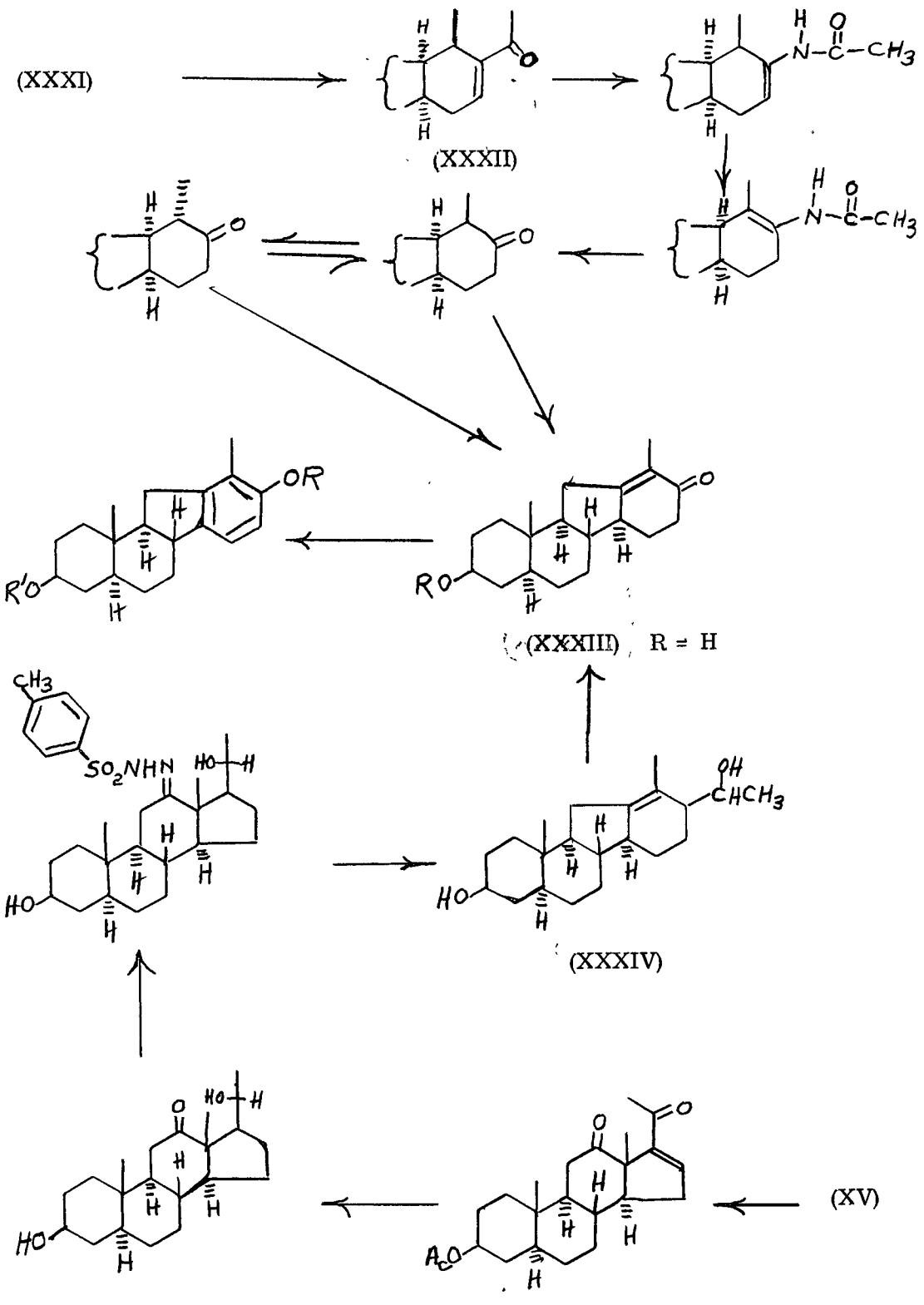


Figure 5

So far I have only discussed the synthesis of etiojervane derivatives which have been obtained by degradation of naturally occurring steroids. Now I would like to consider some the work which has been directed toward the total synthesis of these compounds. In 1961 and 1962, R. A. Barnes published three papers (65, 66, 67) in which attempts at the total synthesis of etiojervane derivatives were reported. Of the several approaches mentioned, none has yet proceeded to its final goal. A more successful method is the one employing the elegant "hydrochrysene approach" already well known from the previous researches of W. S. Johnson. In 1956 and 1960, W. S. Johnson published numerous papers (68-73) in which this approach (see Figure 6) was utilized in the total synthesis of various steroids. More recently, it has been employed in his interest directed at the total synthesis of veratramine (52, 53) (Figure 7).

I would now like to introduce our previous work as it is relevant to the present thesis. Several years ago our investigations in this laboratory (76-79) and independently by Nagata and collaborators (74, 75) provided a synthetic sequence to the tetracyclic ketone (XLIII, Figure 8). The ketol (XLII) is a very versatile intermediate and not only provides an entry into the cis-syn-cis series (Figure 9) but more recently Roller (80) and Inaba (81) have been successful in converting XLII to B-nor-D-homo steroid derivatives (Figures 10 and 11, respectively).

This thesis presents our work directed toward the total synthesis of C-nor-D-homo intermediates which show promise as useful compounds for the eventual synthesis of the Veratrum alkaloids. The sequence employs the ketone XLIII as the starting material. The initial phases of this research utilize the "hydrochrysene method" to obtain the necessary hydrochrysene derivatives. Dictated largely by the difference in the position of the methoxyl group on the aromatic ring, the differences in the chemical reactivity of our compounds from that of Johnson's hydro-

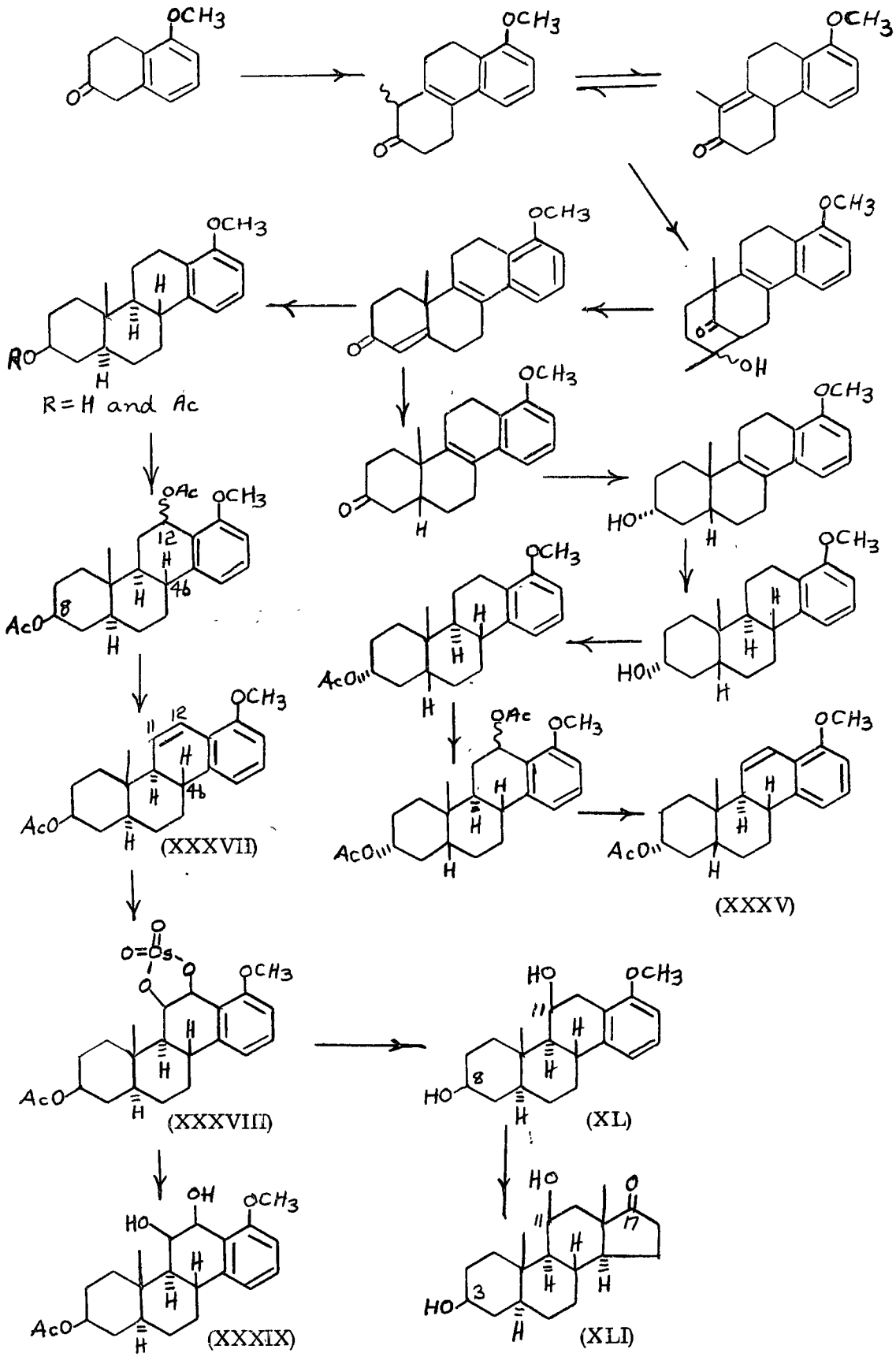


Figure 6

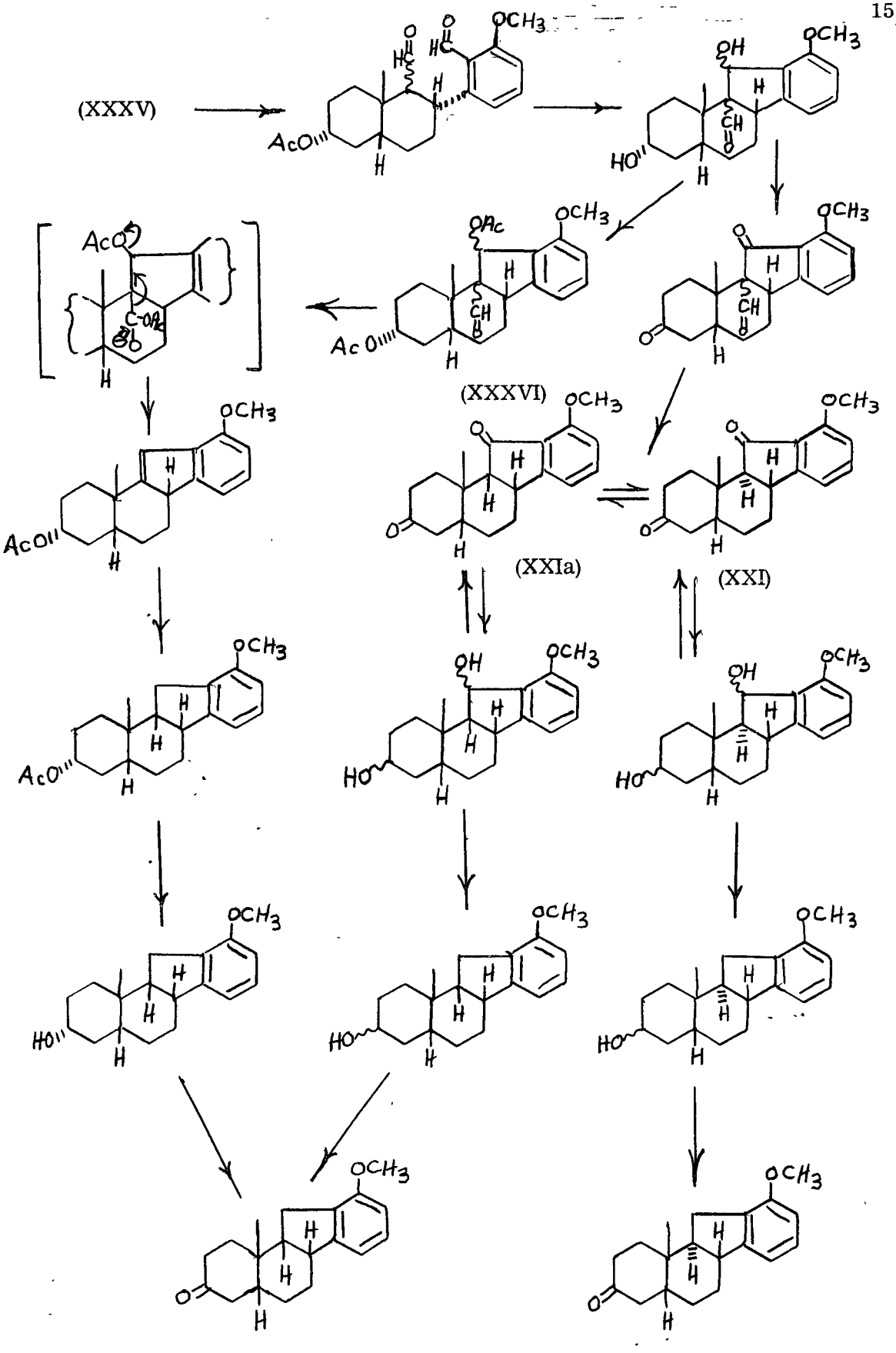


Figure 7

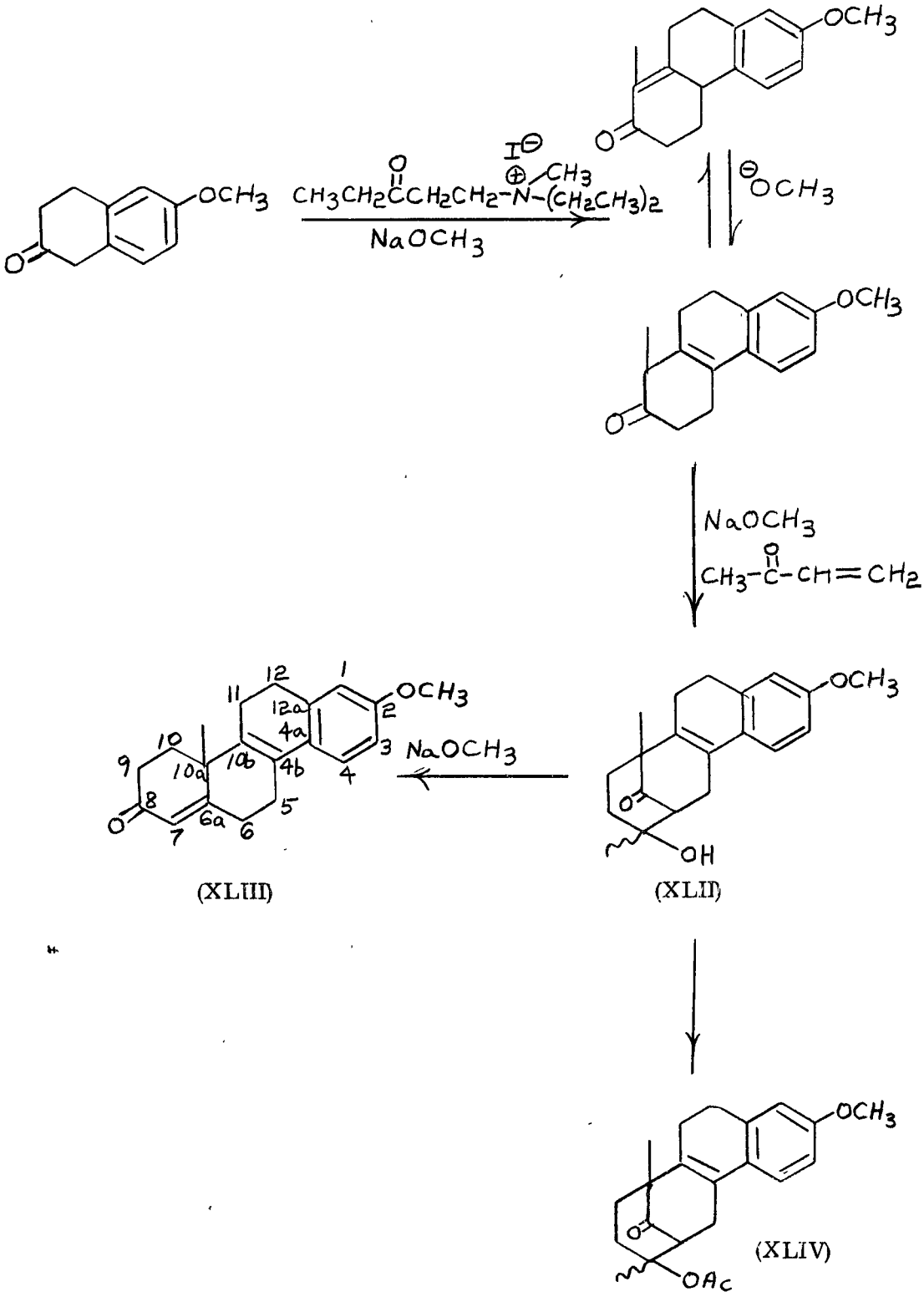

OCH3
CH3CH2CCH2CH2-N-(CH2CH3)2
I⊖
NaOCH3
⊖OCH3
NaOCH3
CH3-C-CH=CH2
NaOCH3
OH
(XLIII)
(XLII)
(XLIV)
OAc

Figure 8

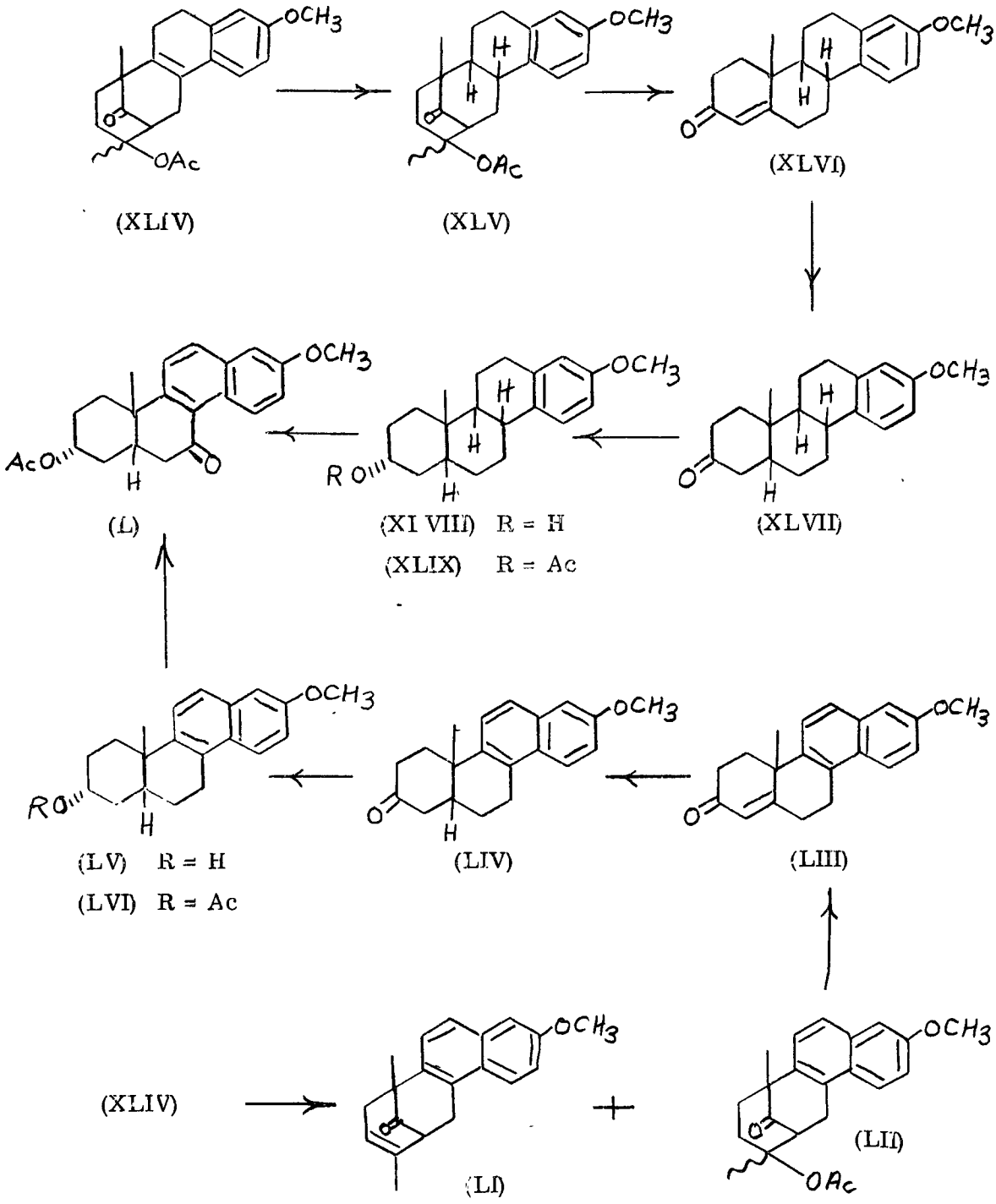

OCH3
OAc
(XLIV)
(XLV)
(XLVI)
AcO
R O
H
O
(L)
(XLVIII) R = H
(XLIX) R = Ac
(XLVII)
(LV) R = H
(LVI) R = Ac
(LIV)
(LIII)
(XLIV)
(LI)
(LII)

Figure 9

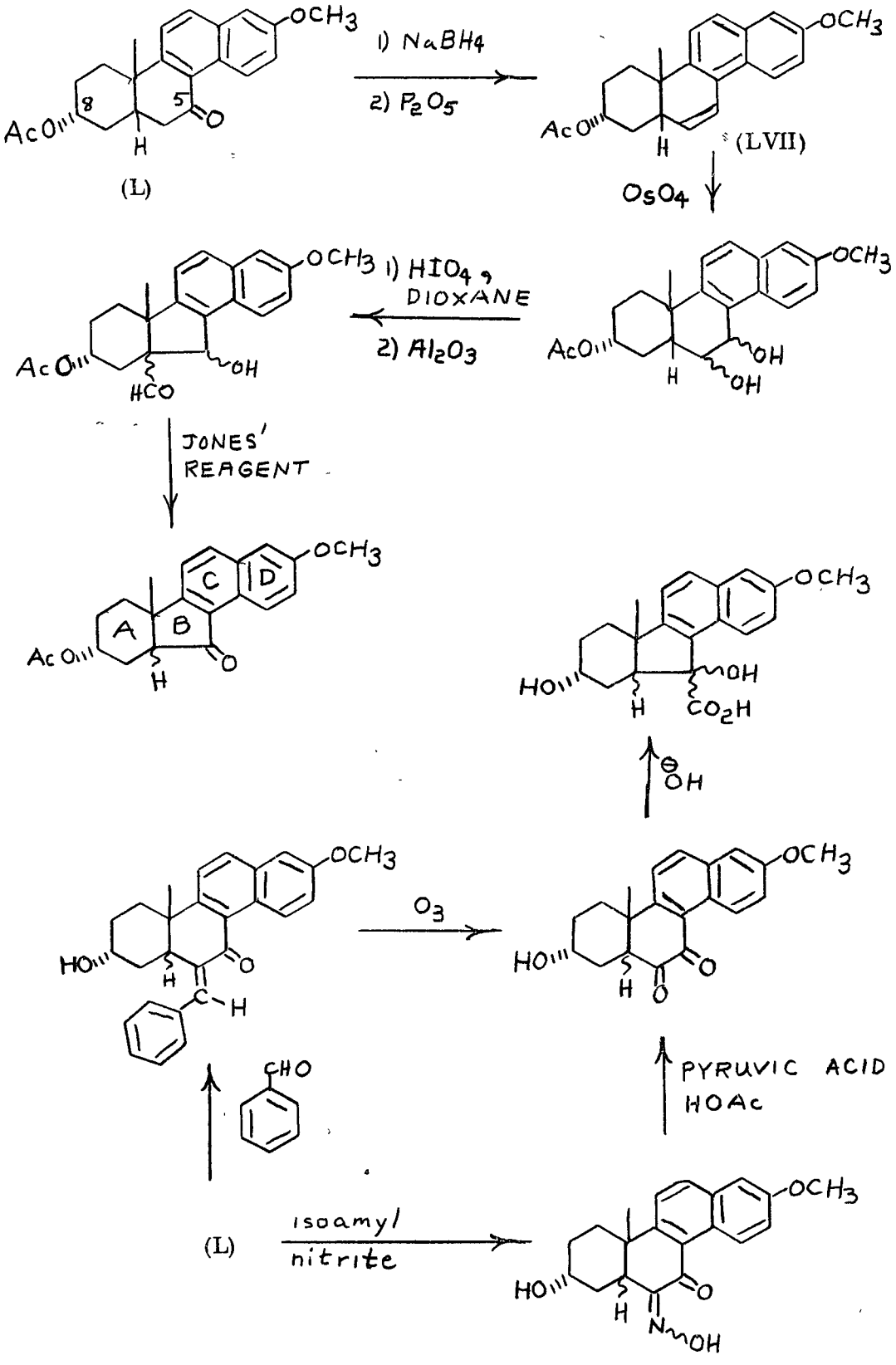

OCH3
1) NaBH4
2) P2O5
AcO
8
5
O
H
(L)
(LVII)
OsO4
1) HIO4, DIOXANE
2) Al2O3
OH
HCO
JONES' REAGENT
A
B
C
D
HO
CO2H
⊖OH
O3
CHO
PYRUVIC ACID
HOAc
isoamyl nitrite
N
OH

Figure 10

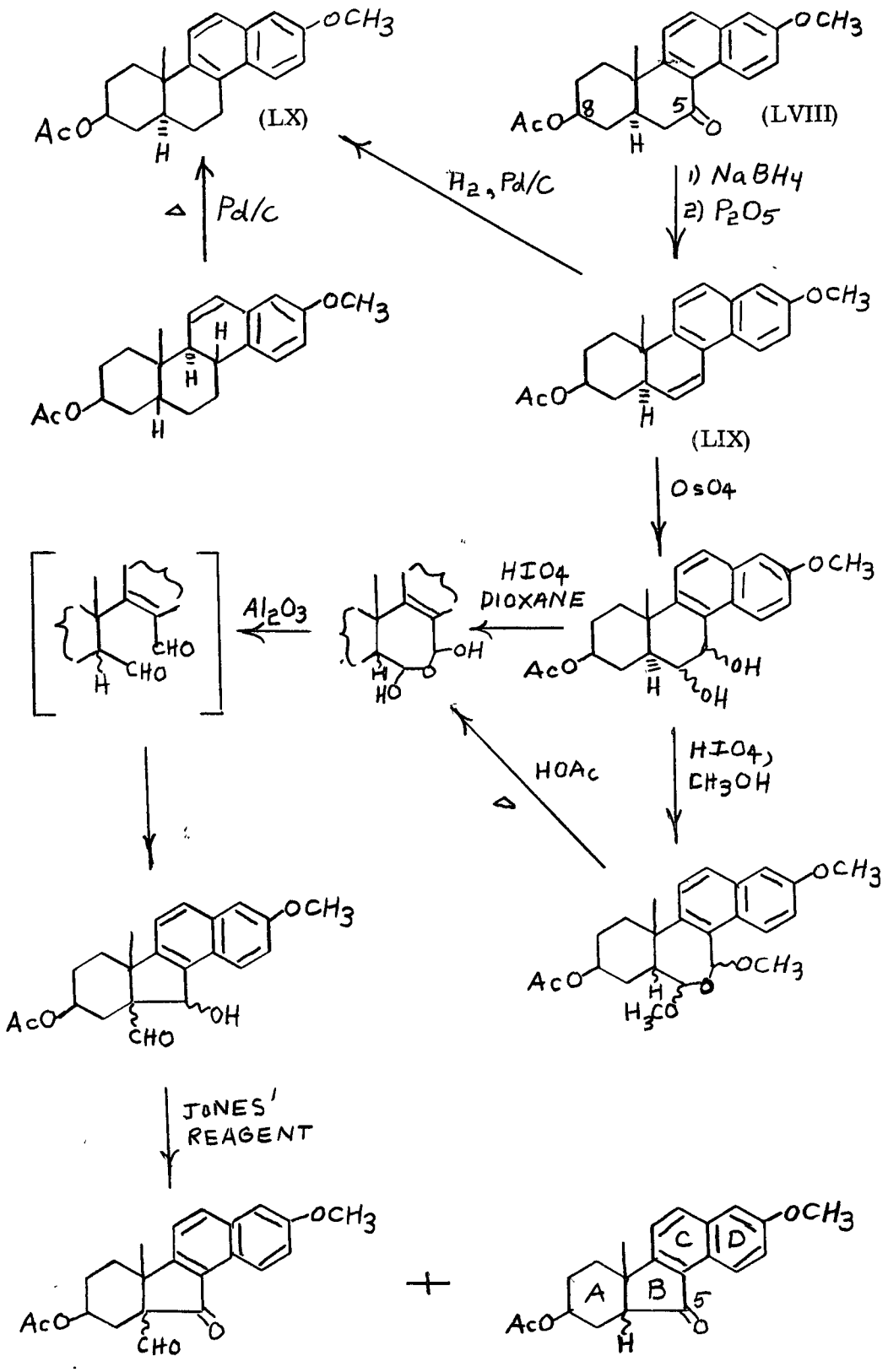

OCH3
AcO
(LX)
H
(LVIII)
8
5
O
Δ
Pd/C
H2, Pd/C
1) NaBH4
2) P2O5
(LIX)
OsO4
HIO4
DIOXANE
Al2O3
CHO
OH
HO
HOAc
HIO4,
CH3OH
OCH3
JONES'
REAGENT
A
B
C
D

Figure 11

chrysene compounds have necessitated modifications in published experimental techniques even in the early stages of the work.

General Discussion

The Veratrum alkaloids of the jervine and veratramine series differ in a number of features. Of particular interest to our synthetic considerations was the fact that the jervine derivatives possess a ketonic function in the C-ring whereas the veratramine compounds do not. It appeared attractive to develop a synthetic sequence leading to C-nor-D-homo intermediates in which a carbonyl group could be on the one hand retained for the jervine series but on the other easily removed for subsequent elaboration to the veratramine system. With this aim in mind we proceeded to develop a synthesis of the C-nor-D-homo compounds LXXXI and LXXXII. The reactions and compounds that will be discussed here are outlined in Figures 12, 13 and 14. Much of this research has appeared in two recent publications (77, 82).

As mentioned previously the tetracyclic ketone (XLIII) was used as the starting material. Catalytic hydrogenation of the latter at atmospheric pressure gave the A/B cis compound LXI (83) (Figure 12) which now exhibited a saturated carbonyl absorption at 5.83μ and 5.85μ in the infrared spectrum and a styrene-type chromophore (λ_{max} 273 mμ , λ_{min} 236 mμ) in the ultraviolet spectrum. As expected the angular methyl protons of LXI registered a peak (8.75 τ) in the n.m.r. spectrum (Figure 25) at higher field ($\Delta\tau$ + 0.18) than the corresponding

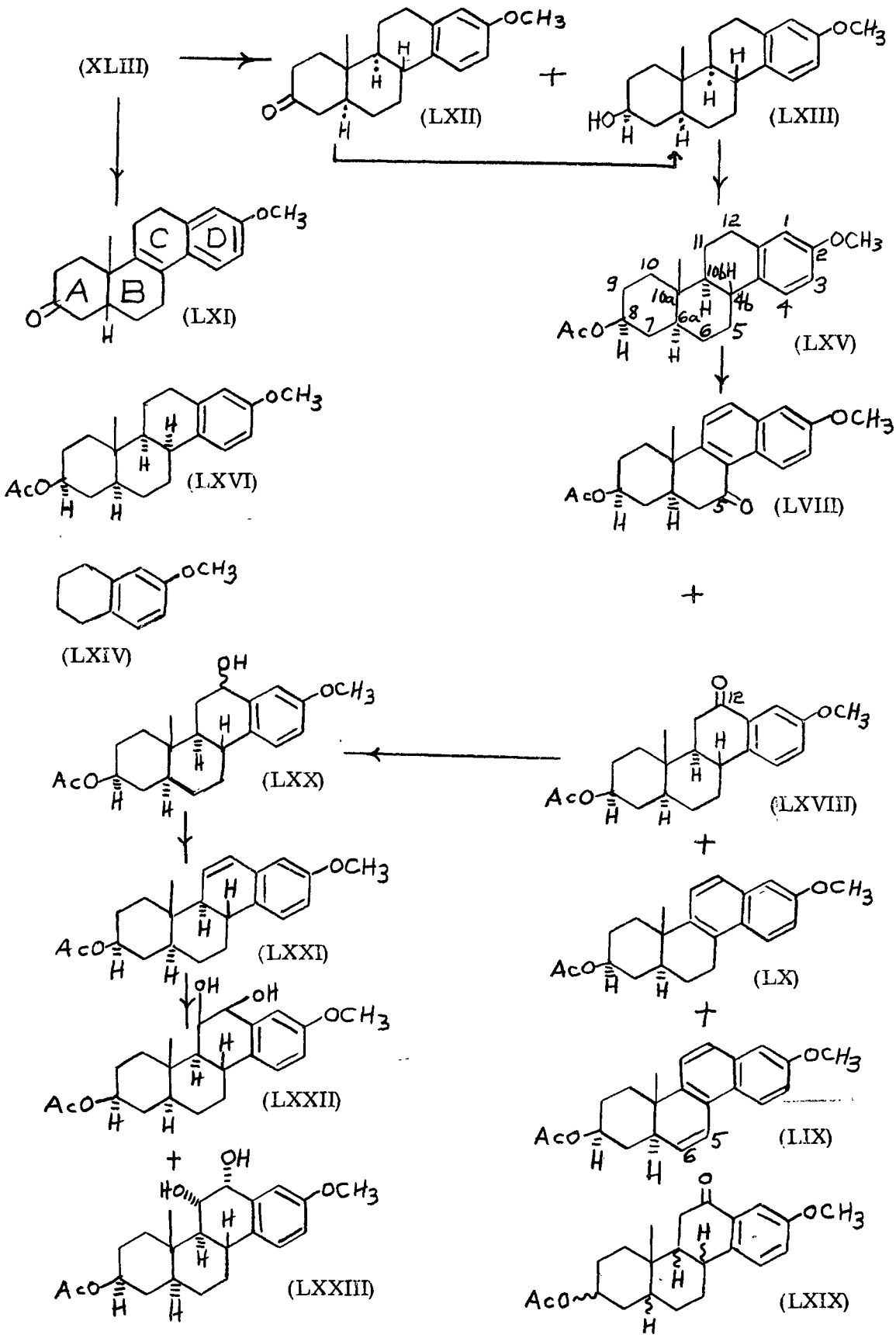

(XLIII)
(LXII)
(LXIII)
(LXI)
(LXV)
(LXVI)
(LVIII)
(LXIV)
(LXX)
(LXVIII)
(LXXI)
(LX)
(LXXII)
(LIX)
(LXXIII)
(LXIX)

Figure 12

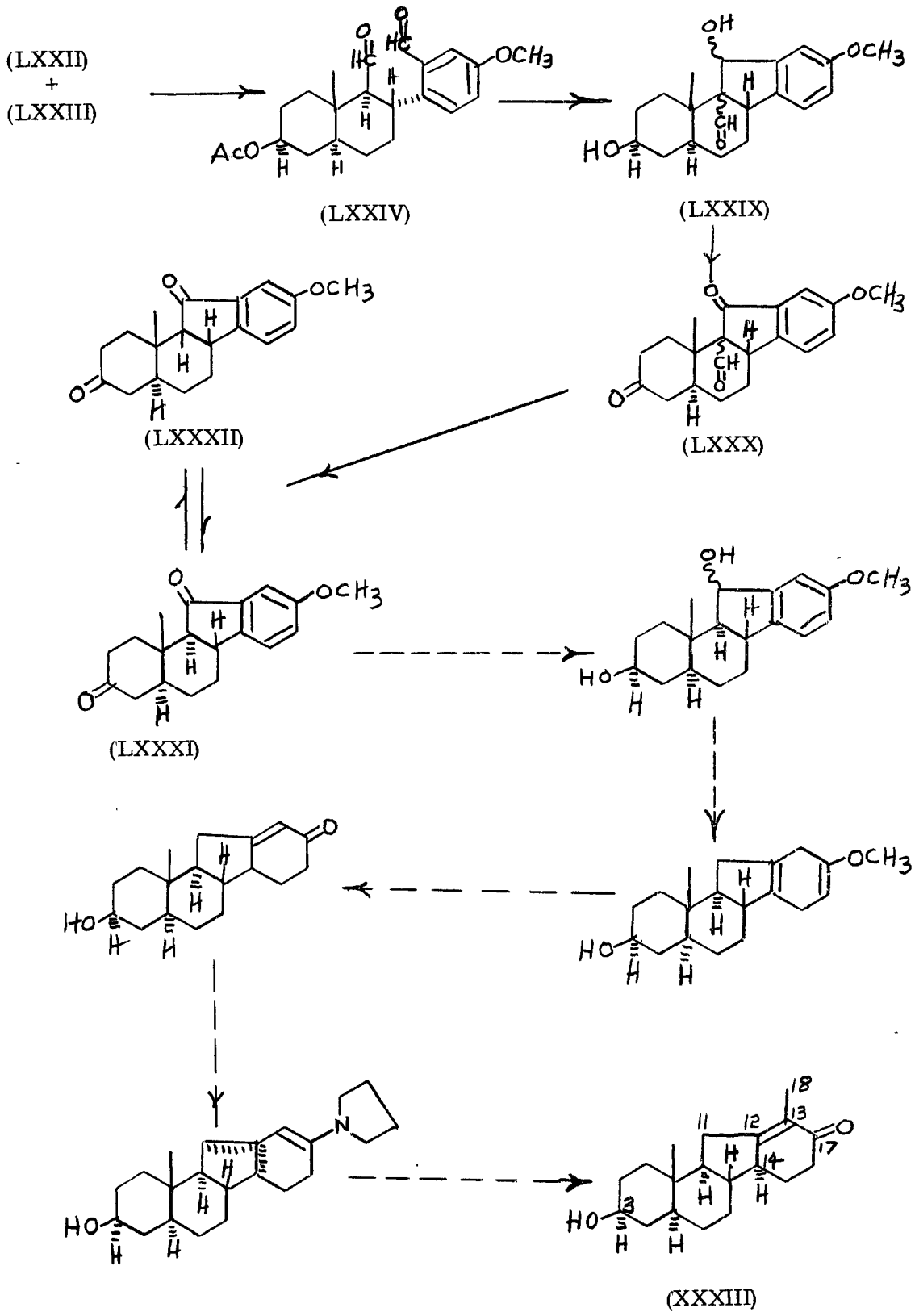
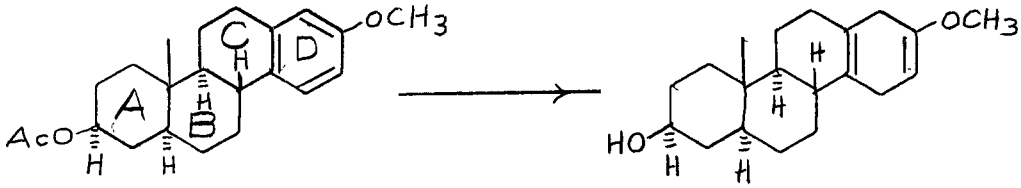
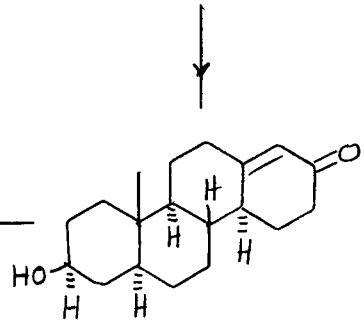


Figure 13

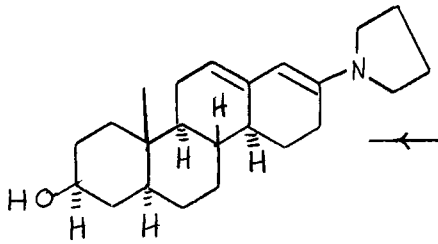


(LXV)

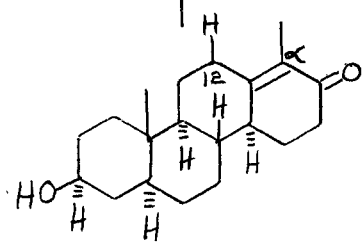
(XC)



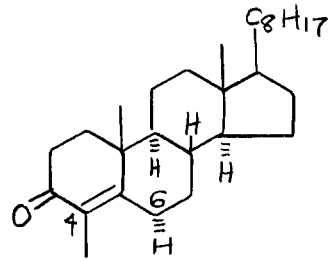
(XCII)



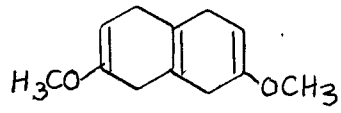
(XCIII)



(XCIV)



(XCV)



(XCI)

Figure 14

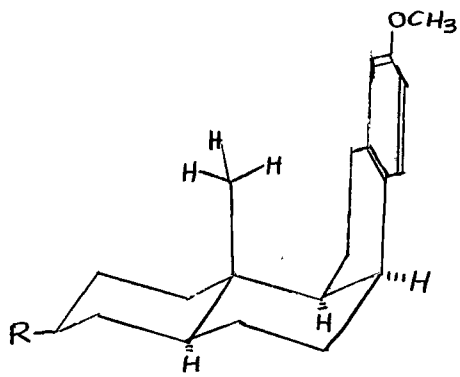
resonance for the tetracyclic ketone. Also, the C-7 olefinic proton signal present in the n.m.r. spectrum of XLIII was now absent. It was therefore established that the A/B cis series could be obtained. However our initial plan to utilize this compound in further investigations was subsequently abandoned and it will not be discussed here any further.

Since jervine (I) has the anti-trans-anti configuration, it was felt desireable to reduce the tetracyclic ketone to a compound which had a trans-anti-trans stereochemistry. Of the various methods which were available, the Birch reduction was of distinct advantage since the stereochemistry of this method, when applied to the hydrochrysene analogues, had been studied in considerable detail in the fine researches of Johnson and his co-workers (70). The tetracyclic ketone (XLIII) was therefore subjected to the action of sodium (or lithium) in liquid ammonia in the presence of anhydrous ethanol — reaction conditions which were very successful in a related series (70) (Figure 6). The expected alcohol LXIII, which now possessed four new asymmetric centers, could only be isolated in a very poor yield and even then only after considerable difficulty in separation from the undesirable side products. The side products indicated that the aromatic ring was being reduced, and it was therefore apparent that the reduction of the olefinic bond of the p - methoxystyrene chromophore presented a somewhat different problem to that experienced by Johnson in the m - methoxystyrene series. Hence, a considerable amount of time was spent in attempting to develop optimum conditions for this reduction. The initial efforts were concentrated on varying the amount of alkali metal (sodium or lithium) relative to the amount of ketone used, and on varying the length of the time for the reduction. In all these cases, no substantial improvement to the original yield of the alcohol could be shown. Our attention was then turned to the use of solutions of alkali metals in amine solvents.

An excellent improvement in the yield of the reduction was thus found. When a solution of the ketone in tetrahydrofuran was treated with sodium in liquid ammonia in the presence of aniline, a good yield of the desired reduction product was obtained. Under these conditions the double bond was reduced, while the aromatic ring remained intact. Furthermore, the reduction of the ketonic function in ring A depended on the length of time allowed for the reduction. In other words, it was possible to obtain the ketone LXII or the alcohol LXIII, or a mixture of both products depending upon the reaction conditions utilized (Figure 12). The ultraviolet spectra (λ_{max} 277 and 286 mμ) of both products were virtually superimposable upon the spectrum of an authentic sample of 1,2,3,4 - tetrahydro-6-methoxynaphthalene (LXIV) (Figure 12) indicating that complete reduction of the olefinic double bond had occurred. In the infrared spectrum the ketone had a strong saturated carbonyl peak at 5.88μ, whereas the alcohol had a strong hydroxyl absorption at 2.89μ. The n.m.r. spectra could also be used to differentiate the two compounds, since the latter compound had a singlet for the hydroxyl group at 7.63τ (Figure 29). As expected, this signal disappeared when the spectrum was repeated after deuterium oxide had been added to the solution. A broad multiplet at 6.37τ, which is typical for an axial proton geminal to a hydroxyl group, was also noted in the n.m.r. spectrum of the alcohol LXIII. The n.m.r. data also gave evidence for the A/B trans configuration depicted in the two reduction products, but a more detailed discussion is given in a later section of this thesis. Finally, the alcohol LXIII was shown to be identical with the product derived from the sodium borohydride reduction of ketone LXII thereby confirming the relationship between these two compounds.

Acetylation of the crude saturated alcohol followed by chromatography on alumina yielded two isomeric acetates, LXV, (m. pt. 96.5 - 99^{o}) and LXVI

(m. pt. 142.0 - 142.5°), of which the trans-anti-trans isomer LXV was by far in the greatest abundance. Both of these compounds had typical ester carbonyl absorption in the infrared spectrum (5.80μ and 5.78μ, respectively) and the elemental analyses gave empirical formulae of $C_{22}H_{30}O_3$. The mass spectra of these substances showed a molecular ion peak at m/e 342 thus confirming the molecular formula assigned above. N.m.r. spectral data were very helpful in providing evidence for the stereochemical assignments of these acetates. Figures 30 and 31 reproduce the spectra of these compounds, and particular note should be made of the broad peak centered at 5.3τ which is readily assigned to the C-8 axial proton. As will be seen later, the A/B ring fusion is thought to be trans, and therefore the acetoxyl group will be β oriented. Furthermore, the n.m.r. spectrum of acetate, LXVI, showed an extremely high angular methyl resonance at 9.76 τ compared to the corresponding signal at 9.17τ in the spectrum of LXV. The abnormally high shielding encountered in LXVI allows assignment of the 4bα, 10bα configuration to this molecule, since only in this isomer is the aromatic ring D in such a position as to shield the methyl protons by the diamagnetic field of its π- electrons. Data on the n.m.r. spectrum of the ketone LXVII were published by Nagata (84), and it is of interest that this compound had the highest angular methyl resonance (9.60τ) of the six isomers reported. Brewster and Braden, Jr., (85) and Steele, Cohen and Mosettig (86) also gave examples of such shielding by an aromatic ring in a steroidal molecule.



m/e			
LXV	LXVI	XLIX	estradiol 3-methyl ether
342	43	43	286
147	342	174	186
43	174	342	160
174	160	147	173
187	147	160	174
173	159	173	147
225	173	159	227
160	161	186	199
159	187	161	159
200		187	200

Table 1

R = -OAc (LXVI)

R = =O (LXVII)

It is interesting to discuss briefly the mass spectra of several isomeric compounds prepared in this study. In Table 1 are listed the major peaks (decreasing in relative intensity from top to bottom of each column) in the mass spectra of three isomeric 8-acetoxy-dodecahydrochrysenes. The mass spectrum of XLIX was taken on the A.E.I. MS 9 spectrometer. Except for the peak at m/e 43, all peaks below m/e 147 were not taken into account for this discussion. It is interesting to compare for example the relative intensities of the mass spectral peaks with those of the same peaks of the 3-methyl ether of estradiol previously determined by Djerassi (87). In this latter substance rings A and B are identical to rings C and D of LXV, and similarities in the fragmentation pattern may be expected. The relative intensities in the spectrum of the estradiol derivative are presented in Table 1. The most interesting difference between the spectra appears to be the m/e 147 peak. In the spectrum of the estradiol derivative this peak is quite weak compared to others, whereas in that of LXV it is very strong. A plausible mechanism for the formation of the m/e 147 peak is given in Figure 15.

The real question as to why this peak is weak in the estradiol case is an open one, but perhaps the cleavage of ring A in LXV occurs more easily than cleavage of ring D in the estradiol analogue. Such fragmentation would thus give rise initially to fragments at m/e 228 and therefore in turn more ions at m/e 147. The m/e 228 fragment from the methyl ether of estradiol would differ from that of LXV by having the methyl group at the C-6a rather than at the C-10a position.

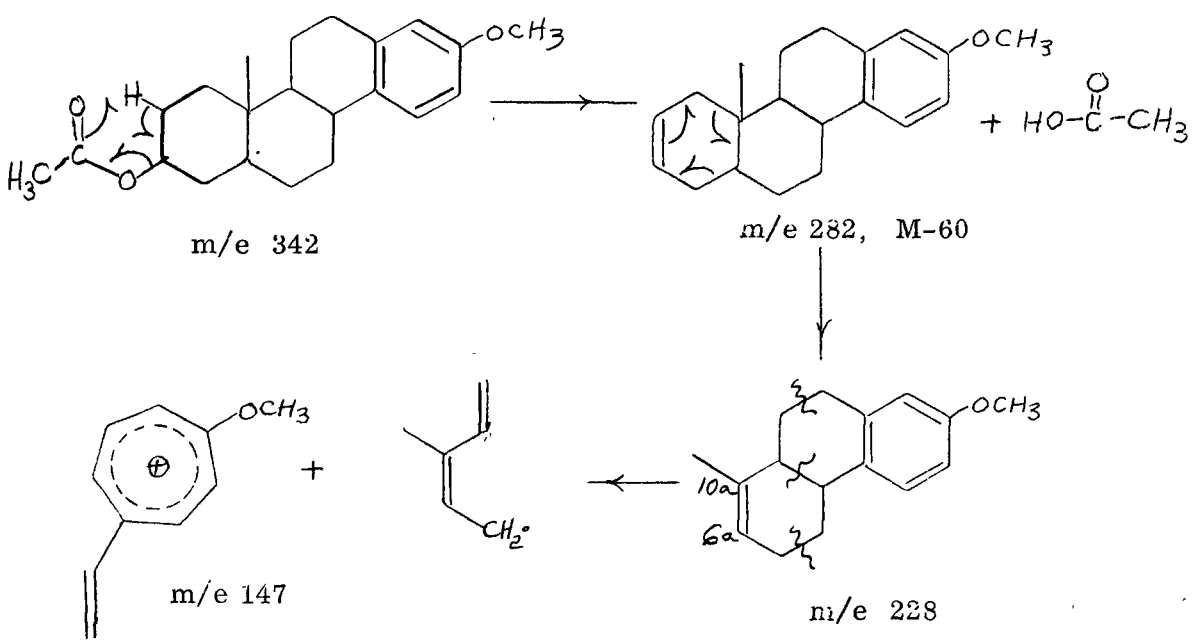


Figure 15

There is literature precedent for the α-cis reduction of the 4b, 10b - double bond. Johnson (70) found that when he reduced trans-1-methoxy-8-ethylenedioxy -10a-methyl-5, 6, 6a, 7, 8, 9, 10, 10a, 11, 12 - decahydrochrysene with lithium and alcohol in liquid ammonia a small yield (1.3%) of the trans-anti-trans-dihydro derivative was obtained.

Now that the trans-anti-trans acetate, LXV, could be obtained in high yield, we considered the introduction of a functional group into ring C of the hydrochrysene skeleton in order to provide an entry into synthetic intermediates where ring C has been opened. A possible approach to this problem was available from the work of W. S. Johnson and collaborators (71) wherein an acetoxyl function was introduced into ring C at C-12 of their hydrochrysene analogues by means of lead tetraacetate (see Figure 6). However, it was recognized at the outset that the methoxyl function in LXV could seriously affect the success of this approach by virtue of its para activation which could favor the introduction of substituents at C-4b instead of the desired position (C-12). It was felt, however, that this activation may be overcome by the ease of reaction at the secondary carbon (C-12) relative to the tertiary center (C-4b). It subsequently became known from the work of Winter and McCrae (77) in our laboratory that the introduction of substituents such as acetate or bromine at the desired C-12 position could not be accomplished successfully, since the predominant reaction which always occurred under the attempted conditions was an aromatization of ring C. This side reaction occurs via initial attack of the reagent at C-4b.

It was then felt that a direct oxidation of this benzylic position (C-12) may prove feasible, since Wintersteiner and co-workers (88) had been successful in preparing 6-keto-estradiol diacetate in this manner. Therefore, the oxidation of LXV with chromium trioxide in acetic anhydride at 0^{o} was attempted. The yield of the desired 12-keto compound was very low, since, as in the above instances, products resulting from the initial oxidation at C-4b were always a complicating factor. It was considered that any oxidation at the tertiary carbon (C-4b) could presumably be eliminated if a sterically large oxidant was used. For this reason the acetate, LXV, was oxidized with t - butyl chromate (89), and indeed a substantial

improvement was realized — one of the reaction products being the desired dodecahydrochrysene analogue LXVIII (77) (Figure 12). The infrared spectrum with bands at 5.84μ, and 5.98μ, and the ultraviolet spectrum with absorption maxima at 222, 254 and 322 mμ presented strong evidence for LXVIII. Further support for the conjugation of the carbonyl function with the aromatic ring was provided by the n.m.r. spectrum (Figure 33) which showed a deshielding of the C-2 methoxyl protons (6.15τ) relative to the corresponding signal in the starting material LXV.

Although the synthetic intermediate for further study at ring C was now available, it was clear that the reaction provided a mixture of several products. The compounds, LVIII, LX and LIX (Figure 12), were subsequently isolated and characterized by T. Inaba (81) (Figure 11) in our laboratory and hence will not be discussed here. Purification of the desired 12-keto compound from the other minor reaction products proved to be the most difficult task of this work. The starting material LXV was easily separated from LXVIII by alumina chromatography, whereas the compounds, LX and LIX, which were very minor impurities, were best separated by fractional crystallization. Unfortunately, product LVIII, which also contaminated the desired 12-keto compound, was difficult to remove. The behaviour of LVIII on silica gel and alumina chromatography made separation in this manner quite difficult, and therefore a combination of very careful chromatography followed by fractional crystallization became necessary. It was interesting to note that LVIII and LXVIII crystallized in different forms, and therefore it was possible on a small scale to purify by means of a physical separation of the crystals. In the instance of large scale separations this latter method was too tedious to be of any value.

A mechanism for the formation of the various C,D-aromatic reaction

products is postulated in Figure 16, although it must be emphasized that this is merely speculation, and we do not have any more direct experimental evidence to support this proposal.

It is interesting at this point to compare these oxidation results with those of the cis-syn-cis-8α-acetoxy isomer, XLIX (Figure 9). The results on the latter oxidation indicated that the cis-syn-cis isomer was oxidized predominantly to the cis-8α- acetoxy-5-keto compound L when the same reaction conditions were used. It is obvious that the reactivity of the tertiary carbon, designated as C-4b, is considerably higher in the cis-syn-cis series than in the trans-anti-trans one. The reasons for this difference are not completely understood, although a study of molecular models of the two isomeric substances does reveal some information. It can be seen from models that C-4b in the cis-syn-cis compound is more accessible to the approach of the oxidant, and it seems reasonable to speculate that it is more easily oxidized.

When the product of acetylation of unpurified compound LXIII was oxidized, an additional compound LXIX, m. pt. 162.5-165°, was isolated. The analysis of this compound indicated that it had the same empirical formula as LXVIII. However, spectral evidence showed that it was not simply a different crystalline form of LXVIII as had been already observed by Winter (77). Its ultraviolet spectrum had absorption maxima at 320, 253.5 and 222 mμ, whereas the infrared spectrum had strong peaks at 5.80μ and 5.94μ thus proving that the compound had a 12-keto group and no olefinic bond in ring C. The n.m.r. spectrum (Figure 34) was most informative. The spectrum was very similar to that of LXVIII therefore providing good evidence that this compound was an isomer of LXVIII. The angular methyl resonance (8.88 τ) was significantly at lower field, while, on the other hand, the methoxyl resonance (6.27 τ) was at higher field than the

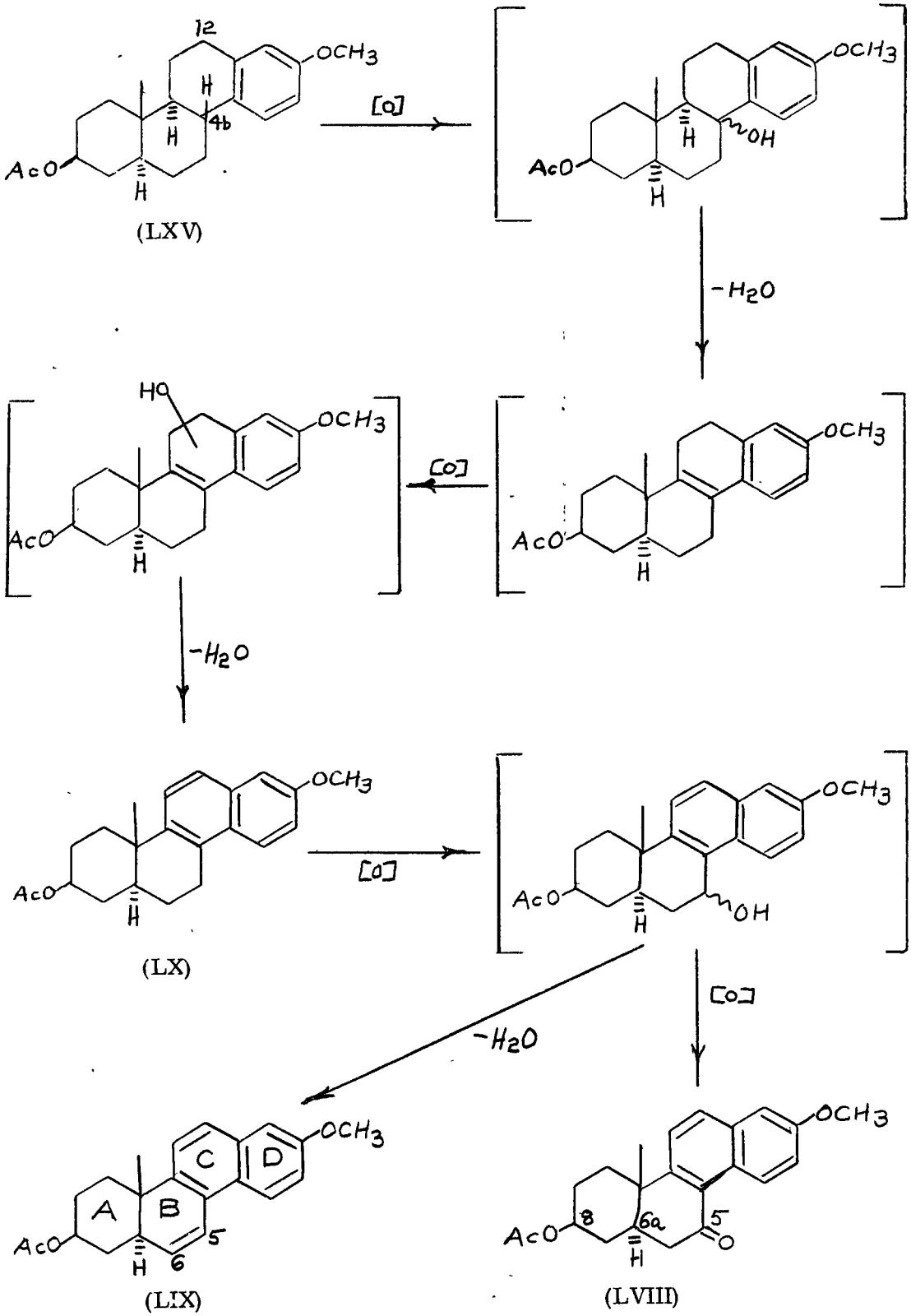


Figure 16

corresponding peaks in the known trans-anti-trans isomer. These large differences indicated that there was probably a different stereochemistry at the B/C ring fusion. Furthermore, there was no olefinic proton signals in the n.m.r. spectrum of LXIX. This compound may prove to be an oxidation product of LXVI, but further work will be necessary before any definite conclusions may be reached.

The trans-anti-trans keto-acetate LXVIII was reduced with sodium borohydride at room temperature to provide a colorless oil. Since this oil could be a mixture of 12α-and 12β-hydroxy compounds (LXX) and the subsequent dehydrations of both of these would give the same final product, the isolation of the pure alcohols was not attempted. As expected, the infrared spectrum of this oil had a strong hydroxyl absorption and no benzoyl carbonyl band, but it still had a strong peak in the carbonyl stretching region associated with the acetoxyl group. The ultraviolet spectrum also indicated the absence of a conjugated carbonyl function, and now was almost identical with the spectrum of the acetate LXV. The n.m.r. spectrum of this reduction product showed three intense singlets at 9.16, 7.99 and 6.23τ which are due respectively to the protons on the angular methyl, acetoxyl and methoxyl groups. Furthermore, two protons resonating at about 5.25τ were also noted and one of the signals in the latter region is assigned to the benzylic hydrogen atom at C-12. It was now obvious that the reduction had proceeded in a very high yield.

The following dehydration of the alcohol LXX (Figure 12) with phosphorus pentoxide was carried out in refluxing benzene. The product obtained was the expected compound LXXI (Figure 12) bearing the 11,12 olefinic bond. The ultraviolet spectrum of the latter substance (λ_{max} 221, 262.5, 270 (shoulder), 302 and 312 (shoulder) mμ) was characteristic for a m-methoxy styrene chromophore, while the infrared spectrum showed only one carbonyl absorption at 5.81μ and a

weaker band at 6.15μ for the 11,12-double bond. The n.m.r. spectrum (Figure 35) as usual was very helpful. In particular one olefinic proton was observed as a doublet ($J_{11,12}$= 10 c.p.s.) at 4.08τ, whereas the other was seen as a quartet ($J_{11,12}$= 10 c.p.s., J = 2.5 c.p.s.) at 3.66τ. It seems reasonable at this time to make a tentative suggestion that the doublet and quartet are due to the C-12 and C-11 protons, respectively, although a more detailed discussion will be presented in the next section. Furthermore, the angular methyl (9.15τ), acetoxyl (8.02τ) and methoxyl (6.29τ) peaks were not shifted to an appreciable extent from those of LXV. It was therefore clear from all of the above evidence that the structure of the dehydration product was the decahydrochrysene analogue as depicted by LXXI.

After introducing the olefinic linkage at the 11,12 - position, our next consideration was centered on the cleavage of ring C in order to provide a pathway for ring contraction to the C-nor-D-homo skeleton. One of the obvious methods involved the ozonolysis of the double bond followed by reductive hydrolysis, but the yield of the expected dialdehyde was very low. Consequently, an alternative approach to this problem was considered. It is well known that osmium tetroxide is capable of hydroxylating olefinic linkages (90), and it seemed the reagent of choice for this purpose. The expected diol could be cleaved by means of periodic acid (91) to the dialdehyde, LXXIV, (Figure 13).

We therefore subjected the olefinic compound, LXXI, to a hydroxylation procedure utilizing osmium tetroxide in ethyl ether at room temperature. The reaction product, which was obtained in good yield, was the expected mixture of cis diols, LXXII and LXXIII. The yield in this reaction was very sensitive to the reaction conditions. Initially a trace of pyridine was used, since it was felt that this compound may catalyze the reaction, but subsequent experiments showed that the yield was higher if no pyridine was present. The optimum yield of the mixture of diols was achieved by keeping the amount of ethyl ether used and the time required for the reaction work-up to a minimum. It is not surprising to expect that these

diols can dehydrate easily. Although the reaction produced two isomeric diols, one of these is by far the predominant isomer and its characterization will be discussed. The minor component, which was not isolated in the pure state, showed on thin-layer chromatography a R_f value slightly greater than that of the major isomer LXXII (Figure 12).

The infrared spectrum of LXXII indicated the presence of a typical carbonyl peak for the acetoxyl group (5.86μ in potassium bromide, 5.81μ in chloroform solution) as well as a maximum at 2.90μ (potassium bromide) or 2.83μ (chloroform) due to the hydroxyl functions. The ultraviolet spectrum (λ_{max} 276 and 282 mμ) was in agreement with the aromatic chromophore present in LXXII. The n.m.r. spectrum (Figure 36) of LXXII (in pyridine) showed no absorption in the olefinic region, but now new signals at 5.24τ (C-12 proton, $J_{12,11}$ = 4 c.p.s.) and 5.61τ (C-11 proton, triplet, half-height width = 9 c.p.s.) confirmed the structural assignment for the diol. Furthermore, the n.m.r. data proved that the stereochemical orientation of the hydroxyl functions at C-11 and C-12 must be β on the basis of several significant features. Firstly, the small coupling (4 c.p.s.) which occurs between the protons at C-11 and C-12 is consistent with the axial - equatorial coupling expected for the cis diol. The relatively narrow half-height width of 9 c.p.s. for the triplet due to the C-11 proton suggests that the coupling constant $J_{11,10b}$ is approximately 5 c.p.s. Therefore, $J_{11,10b}$ would be due to a coupling of the axial C-10b proton to an equatorial C-11 proton thus indicating that the C-11 hydroxyl group is in the axial position and hence is β. Finally, a significant downfield shift of the angular methyl protons (9.13τ, in pyridine) also confirms that the hydroxyl group at C-11 is in the β orientation. It is well known from detailed n.m.r. studies in our laboratory that the chemical shift of the angular methyl groups in this entire series is very sensitive to the effect of substituents in

close proximity to it. For example, it is pertinent to point out that the trans-anti-trans acetate, LXV, which bears no functionality in ring C exhibits a methyl signal (pyridine used as solvent) at 9.26τ. Thus the introduction of the hydroxyl groups at C-11 and C-12 has given rise to a downfield shift of 0.13τ for the angular methyl proton signals. Numerous people have now observed similar effects on the C-19 methyl protons in the steroid series. For example, Tori and Aono (92) have recently given the substituent effects on the chemical shifts of the C-19 methyl groups of many steroidal sapogenins and their derivatives in pyridine: -0.26 to -0.29τ(11α-OH), -0.53 to -0.57τ(11β-OH), -0.03τ(12α-OH) and -0.01τ(12β-OH). However, since none of their compounds were 11,12-diols nor did they have an aromatic ring present in the molecule, a direct comparison is not entirely valid. A more detailed discussion of this n.m.r. data will be presented in the next section of this thesis.

There is a literature precedent in the excellent work by W. S. Johnson (71) (Figure 6) for β-hydroxylation, as suggested above, for the osmium tetroxide reaction. In an analogous reaction in the hydrochrysene series, Johnson demonstrated that the compound, XXXVII, gave the diol acetate, XXXIX. The chemical proof for the β-cis stereochemistry of the hydroxyl functions was established. The osmate ester, XXXVIII, an intermediate in the above hydroxylation reaction, was treated directly with lithium and alcohol in liquid ammonia thus producing the 8β, 11β-diol, XL. The structure and configuration of this diol follows unequivocally from its conversion to the natural product, 3β,11β-dihydroxyandrostane-17-one (XLI) (72). Since the following reaction on our diol mixture destroys the asymmetry at positions 11 and 12, the diol acetate, LXXII, and its 11α, 12α-isomer, LXXIII, were not separated.

The diol mixture was cleaved with periodic acid in methanol to yield the

desired dialdehyde acetate, LXXIV (Figure 13). The extent of the conversion could be followed by withdrawing aliquots of the reaction mixture and measuring the ultraviolet spectrum. Indeed, the ultraviolet spectrum indicated that this reaction took place very rapidly, and the product produced was essentially pure so that a chromatographic purification was not required. It was fortunate that chromatography was not necessary, since subsequent attempts to chromatograph this product on neutral alumina led to poor recovery from the column. Interestingly, the dialdehyde does not cyclize via an internal aldol condensation reaction to provide the C-nor-D-homo skeleton when such a purification attempt is carried out nor does it tend to form cyclic acetals during the periodic reaction in methanol as solvent. Both of these reactions do occur in the analogous situations in the B-nor series as mentioned below.

The spectral data of the 11,12-dialdehyde, LXXIV, was in complete agreement with the assigned structure. The infrared spectrum now showed that there were three carbonyl absorptions at 5.79, 5.87 and 5.97μ as well as a band at 3.63μ for the aldehydic C-H stretching vibration. The ultraviolet spectrum of LXXIV was very similar to that of the 12-keto acetate, LXVIII, and displayed maxima at 225, 255.5 and 321 mμ. Of particular note was the n.m.r. spectrum (Figure 37 which confirmed the presence of two aldehydic protons — a doublet at 0.46τ(-CH-CHO, $J_{11,10b}$ = 4 c.p.s.) and a singlet at -0.30τ (aromatic-CHO) —, an acetate methyl resonance at 7.90τ and the angular methyl peak at 8.85τ. Furthermore, the stereochemistry at positions 4b and 10b was the expected trans as indicated in structure, LXXIV, since $J_{10b,4b}$ = 12c.p.s. and therefore consistent with diaxial coupling (93).

At this point it is of interest to compare briefly these results with those obtained by T. Inaba (81) (Figure 11) and P. Roller (80) (Figure 10) who have been

conducting simultaneously investigations on the synthesis of B-nor-D-homo steroid derivatives which possess aromatic rings C and D. For example, when methanol was used as a solvent for the periodic acid cleavage of LXXV (Figure 17), the expected dialdehyde was not obtained but rather the acetal LXXVI. When a non-alcoholic solvent, such as dioxane, was used in this reaction, the cyclic hemiacetal, LXXVII, was actually isolated.

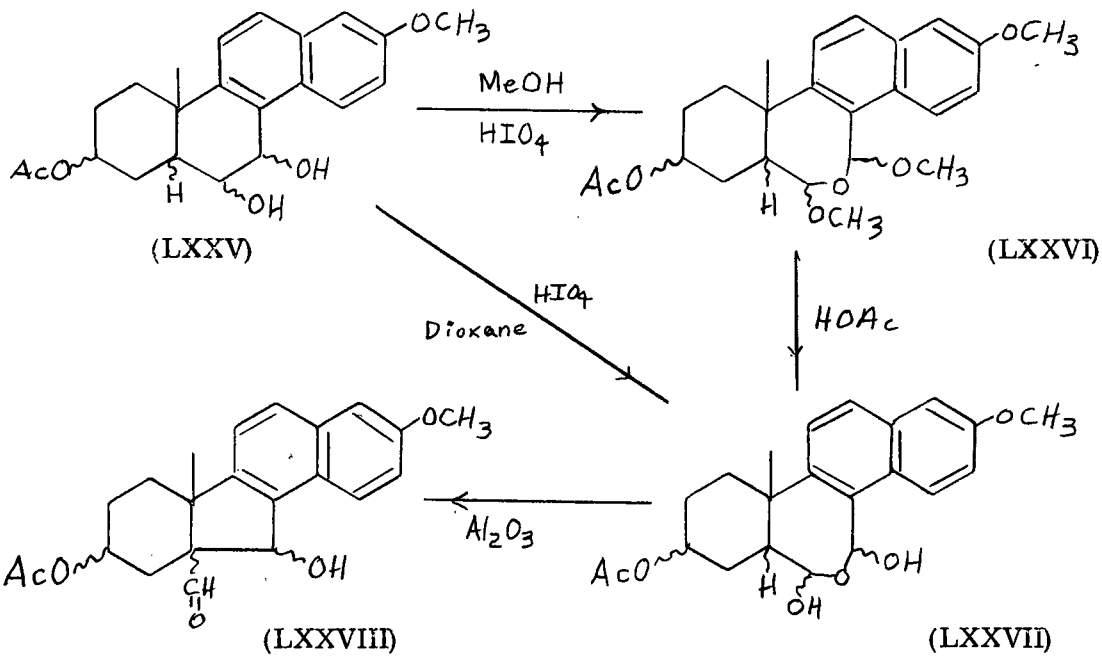


Figure 17

These results indicate that the cyclization of the intermediate dialdehyde occurs very rapidly in this series. Another interesting difference is noted in this series when an attempted chromatographic purification of LXXVII on neutral alumina is carried out. The product obtained from the column was shown to be the B-nor-D-homo compound, LXXVIII, which arises by an internal aldolization of the dialdehyde.

The synthesis of the desired C-nor-D-homo skeleton, which is present in

the veratrum compounds, was accomplished by an internal aldol condensation of the dialdehyde, LXXIV, using sodium hydroxide in refluxing methanol. Again the ultraviolet spectrum of the reaction mixture could be used to follow the cyclization. The reaction product, isolated as a crystalline compound (m. pt. 175-182°), could be assigned the aldol structure, LXXIX (Figure 13), on the basis of the following spectral data. The ultraviolet spectrum (λ_{max} 284 and 289 (shoulder) mμ) of LXXIX was now quite characteristic of the anisole-type chromophore already well known from our previous studies, and the infrared spectrum with peaks at 2.80, 2.89, 3.64 and 5.90μ was in accord with the presence of only hydroxyl and saturated aldehyde functions. Finally, the n.m.r. spectrum (Figure 38) indicated the presence of only one aliphatic aldehydic proton (0.30τ, doublet, $J_{11,10b}$ = 3 c.p.s.), an angular methyl group (8.90τ), a methoxyl function (6.23τ) and the C-11 benzylic proton (4.56τ) thereby confirming the aldol structure LXXIX. We wish to emphasize at this time that this product may still represent a mixture of isomers epimeric at either C-10b or C-11, but this is unlikely since we have made various attempts to try to detect more than one component. The compound is certainly homogeneous to a rather extensive thin-layer chromatography investigation.

The diol aldehyde, LXXIX, was then submitted to a mild oxidation with Jones reagent (94) at room temperature, and the spectral data of the crude product were consistent with the expected diketo aldehyde structure, LXXX (Figure 13). The n.m.r. spectrum revealed the presence of one aldehydic proton (0.32τ, singlet), an angular methyl signal occurring at somewhat lower field (8.78τ) than usual, and a methoxyl signal at 6.19τ. The ultraviolet spectrum of LXXX (λ_{max} 220, 225 and 326 mμ) was immediately reminiscent of the corresponding one exhibited by the 12-keto acetate LXVIII, which possesses the analogous chromophore. Further purification of this product was complicated by its facile loss of the

aldehyde function to provide new compounds possessing the diketo structures LXXXI and LXXXII (Figure 13). For example, chromatography on neutral Woelm alumina converted LXXX to a mixture of ketones which proved identical with the diketones, LXXXI and LXXXII, mentioned below. A n.m.r. spectrum of the mixture indicated that the ketones were in an approximate ratio of 1:1. This type of deformylation reaction is already well known, and a recent example in the sesquiterpene series may be cited (95).

The final conversion in the sequence involved deformylation of LXXX to provide the isomeric diketones LXXXI and LXXXII. Although the alumina method was applicable, a more convenient approach involved deformylation under alkaline conditions (potassium hydroxide in refluxing aqueous dioxane) (52) to an approximate 1:1 mixture separable only by fractional crystallization into two compounds LXXXI, m. pt. 188.5-201.5° (decomposition), and LXXXII, m. pt. 140-142°. Both of these diketones decompose around 200° to give compounds which have different ultraviolet spectra from that of the diketones. The infrared spectrum of LXXXI and LXXXII showed peaks due to carbonyl groups at 5.85 μ, and 5.87 μ, respectively. The ultraviolet spectra of LXXXI (λ_{max} 219, 249 and 319 mμ) and of LXXXII (λ_{max} 218, 249 and 318 mμ) were essentially superimposable. The n.m.r. spectra showed some interesting differences. Of particular note was the angular methyl group region which showed singlets at 8.85τ (Figure 39) and 8.74τ (Figure 41) for LXXXI and LXXXII respectively. This difference in chemical shift allows assignment of the trans-anti-trans stereochemistry to the diketone, LXXXI, and the trans-syn-cis configuration to isomer, LXXXII.

It is well known (96) that protons lying in conical regions extending above and below the plane of the trigonal carbon atom of a carbonyl group will be shielded by this function, while those lying elsewhere and particularly those in the plane

of the trigonal carbon atom will be deshielded. Molecular models of LXXXI and LXXXII reveal that in the former the angular methyl group lies in a plane perpendicular to that of the carbonyl group, whereas in the latter this group lies essentially in the plane of the trigonal carbon atom. Hence, the former methyl proton should be more shielded than the latter. Johnson and co-workers (53), who studied a closely analogous system (see Figure 8), also assigned the higher field angular methyl resonance to the isomer having the B/C trans fusion. The differences observed when the n.m.r. spectra were run with the above diketones in various solvents also supports our assignment of stereochemistry, but this will be discussed in detail in the following section of the thesis.

Finally, to confirm the isomeric nature of LXXXI and LXXXII, we submitted these compounds to a mass spectrometric analysis. The mass spectra of LXXXI and LXXXII are reproduced in Figures 18 and 19, respectively. The isomeric nature of these compounds was established beyond any doubt by the presence of an identical molecular ion peak (m/e 298) and the virtually complete identity of their mass spectra in the range m/e 80-225. Furthermore, only minor intensity differences occur in the range m/e 225-280. One significant difference is noted in the two spectra and this occurs in the region m/e 280-298. Both compounds exhibit relatively intense molecular ion peaks and also appreciable signals at m/e 280 (M-18, loss of water), but only the trans-anti-trans diketone, LXXXI, possesses a significant M-15 peak (m/e 283) which indicates loss of the angular methyl group. It is interesting to note that the trans-anti-trans 8-ketone, LXII, also possesses significant M-15 and M-18 peaks in its mass spectrum (Figure 20). It, therefore, appears that the loss of the angular methyl group, at least in the 8-keto series, is a more significant process when the normal steroid stereochemistry prevails, but further work is necessary before any

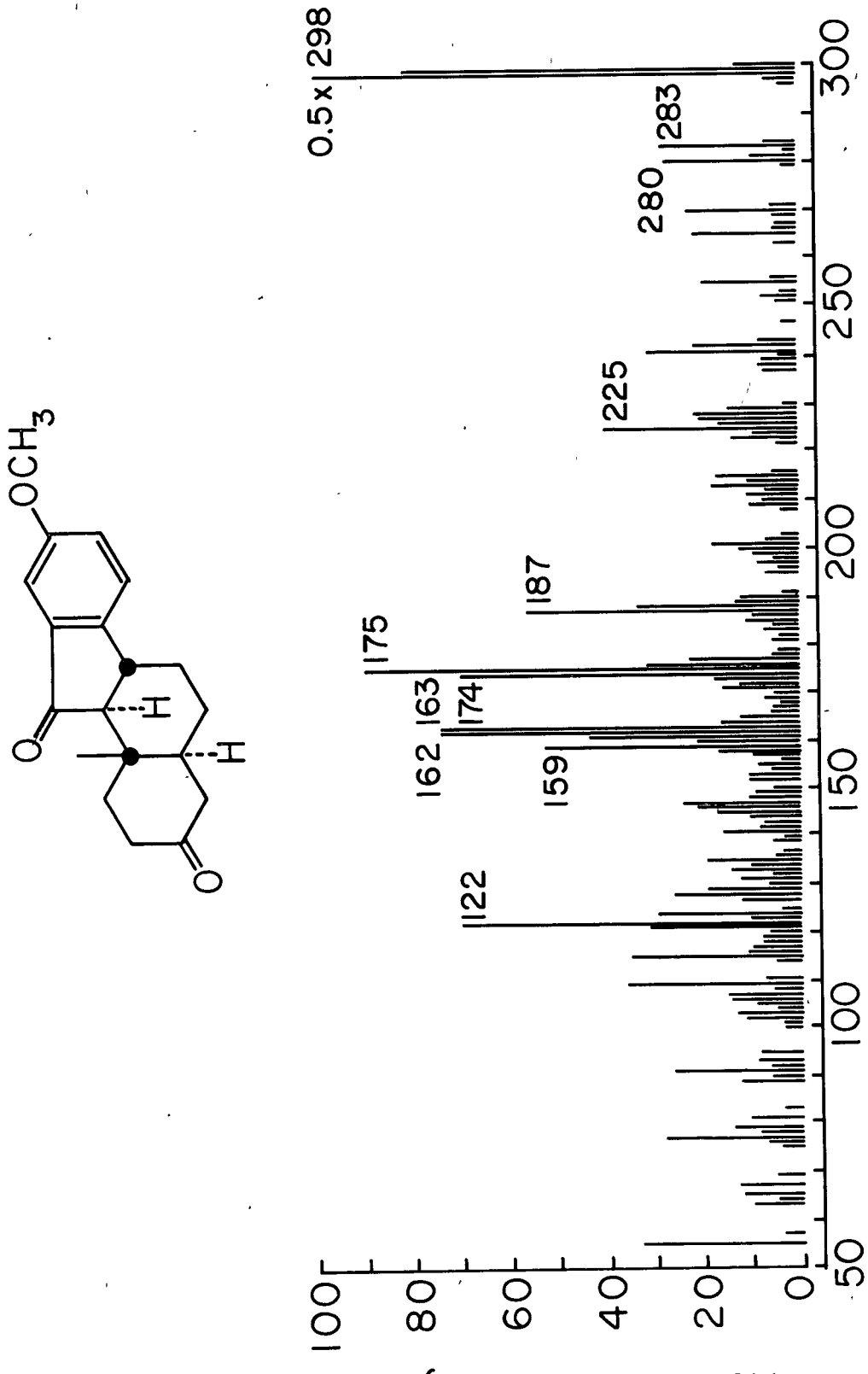

OCH3
O
H
H
O
Relative intensity
100
80
60
40
20
0
50
100
150
200
250
300
m/e
0.5x 298
283
280
225
187
175
163
162
174
159
122

Figure 18

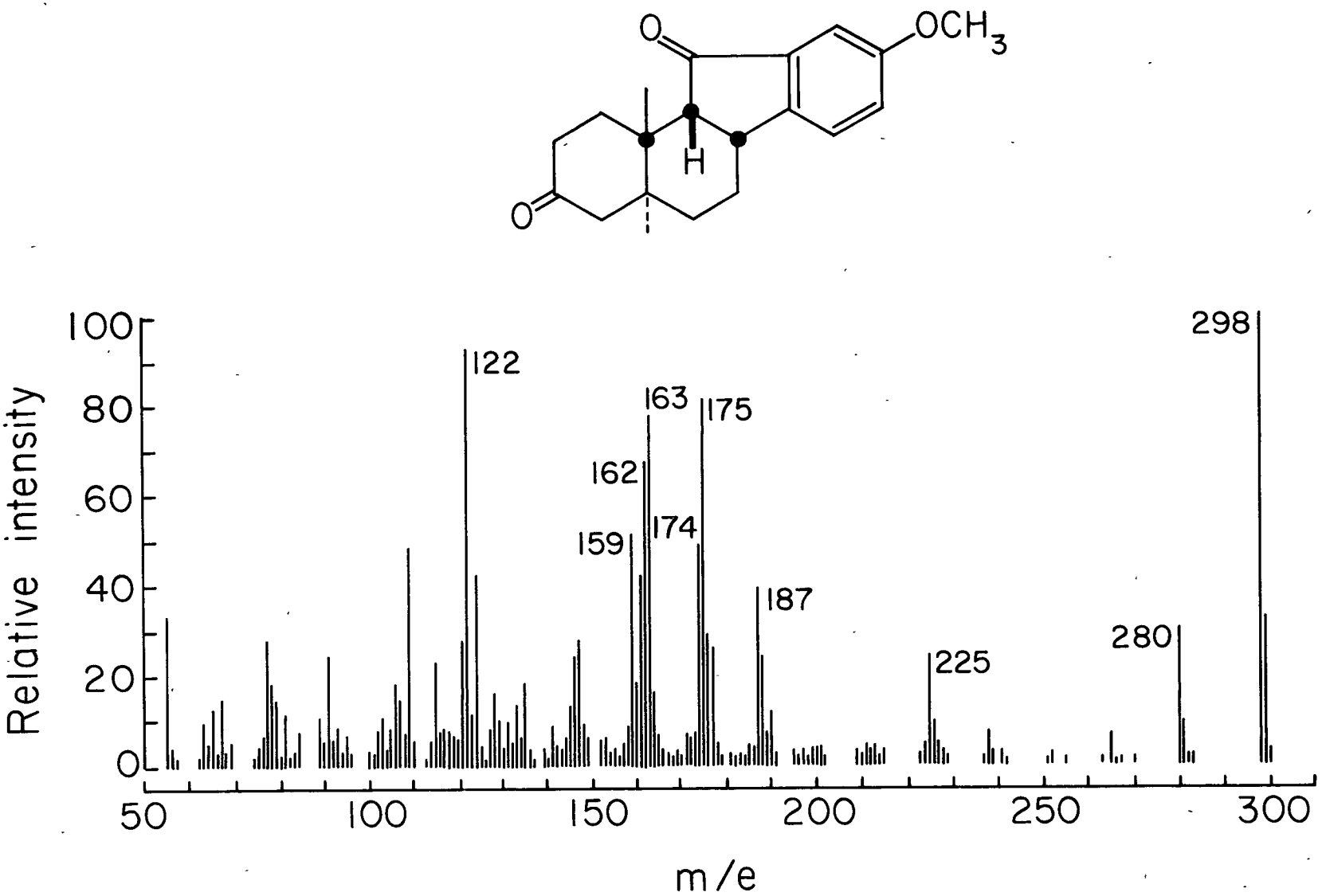

O
OCH3
H
O
Relative intensity
100
80
60
40
20
0
122
163
175
298
162
174
159
187
225
280
50
100
150
200
250
300
m/e

Figure 19

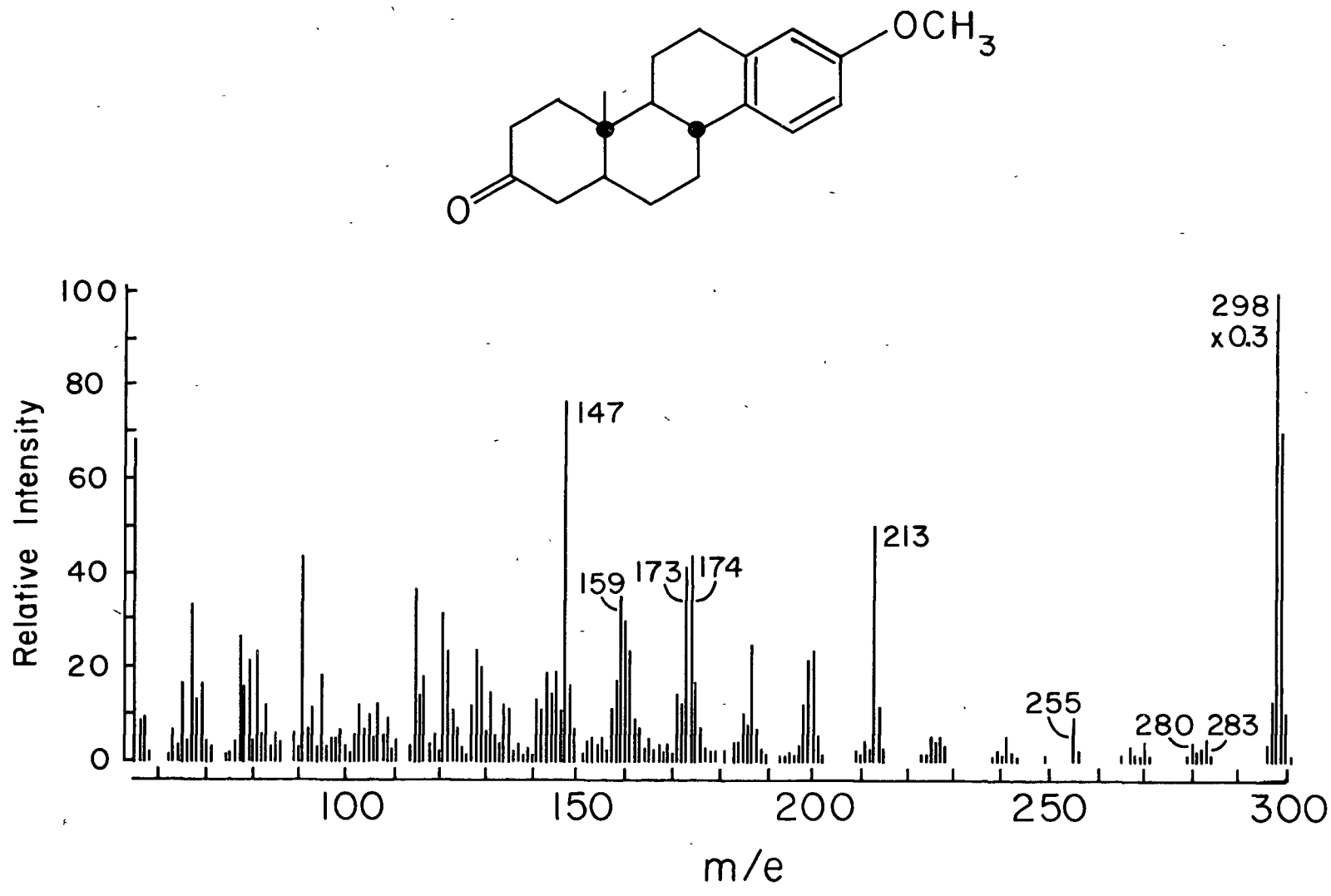

OCH3
O
100
80
60
40
20
0
Relative Intensity
147
159
173
174
213
255
280
283
298
x0.3
100
150
200
250
300
m/e

Figure 20

more definitive evidence can be provided. Also, it is pertinent to mention that the fragmentation process observed in the above diketones, particularly in the case of LXXXI, is in good agreement with the detailed investigations of Djerassi and collaborators (97) on steroidal ketones in which significant M-15 and M-18 peaks are noted.

It is of interest that a strong peak occurs at m/e 147 in LXII. This peak is also present in the mass spectrum of the trans-anti-trans acetate, LXV, and therefore this fragment must contain the aromatic portion of the molecule.

In 11-keto steroids it is well known that cleavage of bonds 9, 10 and 6, 7 take place quite easily (97). By analogy with this, cleavage of bonds 10a, 10b and 5, 6 will give rise to two charged fragments which may explain the strong intensity of the m/e 122 and 175 peaks. The mechanism for formation of the m/e 187 species is probably closely linked with that of the m/e 175 fragment. On the other hand, in order to explain the formation of the m/e 163 signal one needs to cleave the 4b, 10b bond. The hypothetical mechanisms and structures for the above fragments are depicted in Figure 21, although of course no direct evidence is available from our work.

Before proceeding to the next series of reactions, it is appropriate to discuss the interesting problem of cis-trans isomers in the indanone series and subsequently compare these results with our C-nor-D-homo compounds. House and co-workers (98) have shown unequivocally by equilibration studies that the cis benzindanone, LXXXVII, is considerably more stable than the trans epimer, LXXXVIII.

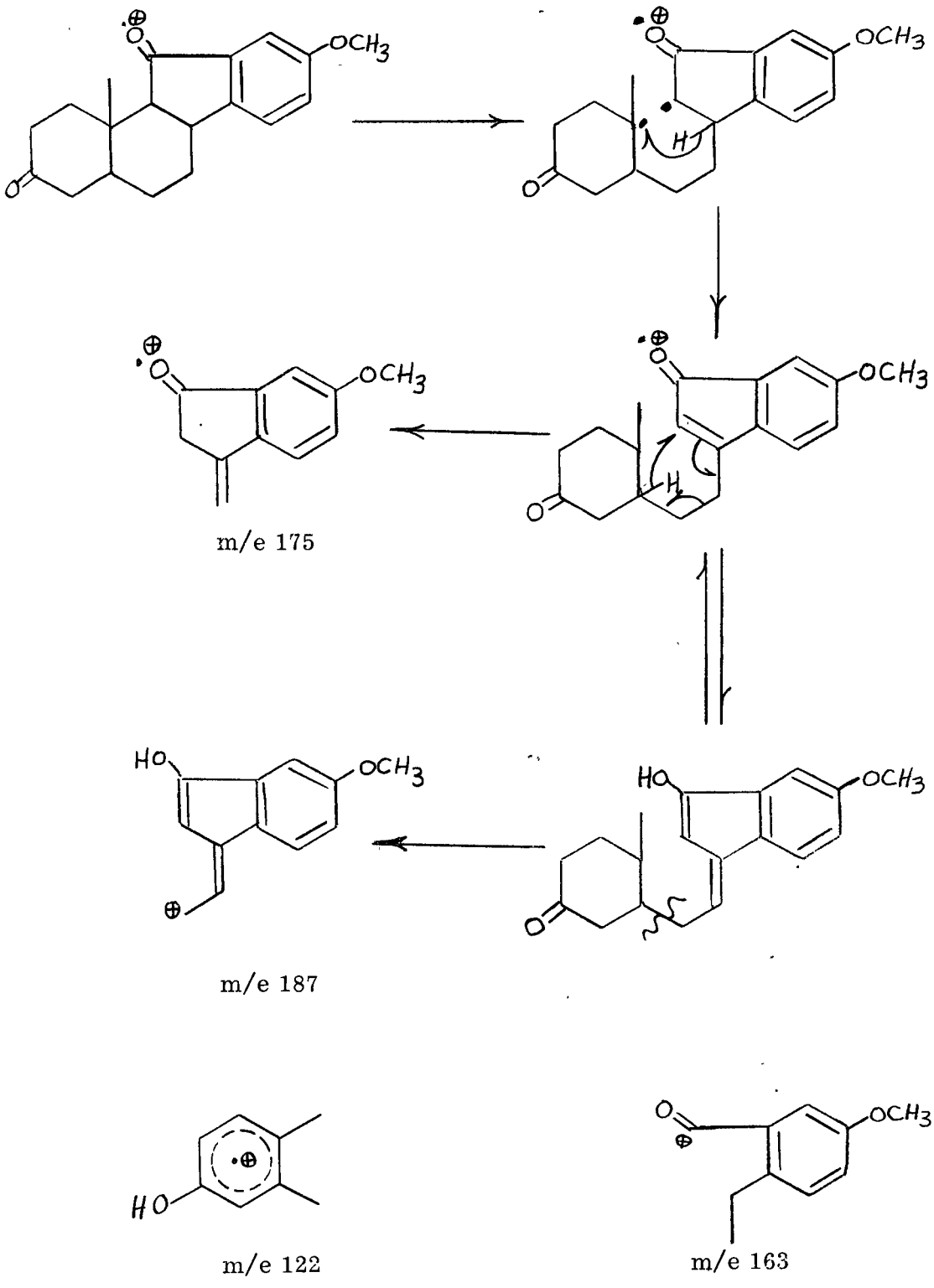
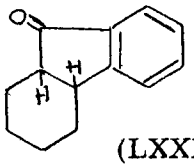
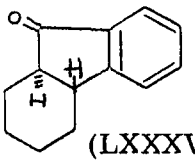


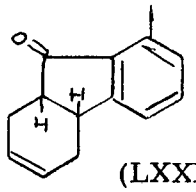
Figure 21



(LXXXVII)



(LXXXVIII)



(LXXXIX)

Under equilibrating conditions it was established that the equilibrium lies 85 percent in favor of the cis substance LXXXVII. Moreover, W. S. Johnson and collaborators (53) have synthesized the cis-anti-trans diketone, XXI, and its cis-syn-cis epimer, XXIa (Figure 7), and have shown that at equilibrium the ratio of cis to trans was about 7 to 3. Very recently, House and Carlson (99) found that LXXXIX was stable to refluxing methanolic sodium methoxide indicating that in this instance the cis isomer is very much more stable. All of these observations are consistent with the general predilection of hydrindanones for the cis configuration (100-104). There are also several examples in the literature (105-109) where the trans fused hydrindanones are more stable. In contrast to the benzindanones mentioned above, 11-keto-veratramine (XVIII with 11-carbonyl group, Figure 2) is very stable in the trans configuration (53).

Ourisson, House and Wintersteiner explained their observations by stating that the most unstable isomer is obviously the one which has the most steric interactions. With this is mind, the models of 11-keto-veratramine, Johnson's diketones and our diketones were examined. It was apparent that two interactions, apart from the usual types associated with these molecules, seemed to require consideration. These are as follows: (a) the interaction between the oxygen atom of the carbonyl group and the hydrogen atoms on C-10 (using hydrochrysene nomenclature), and (b) the interaction between the angular methyl group and the hydrogen atom on C-4b. A study of Johnson's cis-syn-cis diketone, XXIa, which

can exist with rings A and B in a non-steroidal conformation (angular methyl group is equatorial to ring B), indicates that the above interactions are not appreciable. On the other hand, the cis-anti-trans diketone XXI shows the "b" type interaction. Therefore one would expect much more cis isomer than trans isomer at equilibrium. In the trans-anti-trans diketone, LXXXI, the "b" type interaction is also present, but in the trans-syn-cis diketone, LXXXII, where no appreciable "b" type interaction exists, a more serious "a" type interaction is noticed. Thus, the approximate ratio of 1:1 which was found for LXXXI and LXXXII is in good agreement with what one would expect from molecular models. In the case of 11-keto-veratramine the 5, 6-double bond appears to decrease the interaction of the methyl group with the C-4b proton thus making the B/C trans isomer more stable with respect to the cis one.

In order to achieve the final synthesis of the relay compound, XXXIII (Figure 5 and 13), which could be used to confirm the stereochemistry of diketones LXXXI and LXXXII, the reaction sequence illustrated by dotted arrows in Figure 13 is proposed. To evaluate this sequence, it was felt preferable to develop some of these reactions by utilizing a readily available model substance, and these experiments are presented in Figure 14.

Treatment of the trans-anti-trans acetate, LXV, with a large excess of lithium and ethanol in liquid ammonia led to XC. Reduction of the anisole system was easily shown by the disappearance of the characteristic ultraviolet absorption. The infrared spectrum of XC indicated absorption bands at 3.09, 5.89 and 6.00μ — the last two maxima being typical of the type of 1, 4-diene chromophore seen in ring D (110). The n.m.r. spectrum (Figure 43) was also very informative. The methoxyl, vinyl (C-3) and allylic methylene protons (C-1 and C-4) absorbed respectively at 6.47, 5.37 and 7.34τ which is in good agreement with the corresponding signals

(6.50, 5.47 and 7.42τ) (111) published for the enol ether XCI (Figure 14). Furthermore, the angular methyl protons were found to resonate at 9.22τ, whereas the hydroxyl proton absorbed at 8.07τ. The trans-anti-trans alcohol, LXIII, which was a contaminant in the Birch reduction, was difficult to separate from the enol ether, XC, since the former compound had the same R_f value as XC and was more insoluble than the latter. For this reason, the crude Birch reduction product was treated with dilute methanolic sulphuric acid, and in this way the enol ether was hydrolyzed to the conjugated ketone, XCII. Sulphuric acid was used instead of hydrochloric acid, which is most often employed in this type of reaction, because it did not cleave the anisole system of LXIII so readily. It was now possible to separate XCII easily from LXIII by simple column chromatography. The melting point (182-185.5°), infrared spectrum (2.91, 2.98, 5.99, 6.06, 6.16 and 6.19μ) and ultraviolet spectrum (λ_{max} 239.5 and 308 mμ; λ_{min} 284.5 mμ) of XCII are in good agreement with those reported by Nagata and collaborators (74, 112). The n.m.r. spectrum of XCII (Figure 44) showed resonances at 4.19τ (C-1 olefinic proton, singlet), 6.38τ (C-8 axial proton, half - height width = 22 c.p.s.), 7.65τ (HO-), and 9.24τ (angular methyl protons).

The pyrrolidyl enamine XCIII was prepared next by refluxing the conjugated ketone, XCII, with pyrrolidine in benzene. The ultraviolet spectrum of crude product (λ_{max} 276 mμ, λ_{min} 224 mμ (methanol); λ_{max} 274.5 mμ (methanol, HCl) was in agreement for a heteroannular diene system as depicted in structure XCIII (Figure 14) (113).

In the subsequent step the crude enamine, XCIII, was refluxed in methanol with methyl iodide and then hydrolyzed with an aqueous sodium acetate - acetic acid mixture. Since the product showed a saturated carbonyl absorption in the infrared spectrum, it was necessary to reflux with aqueous methanolic hydrochloric acid to rearrange the isolated double bond into conjugation with the 2-keto group. Unfort-

unately the final desired material XCIV (Figure 14) was obtained in poor yield. This was not entirely unexpected since, for example, Babcock and Pedersen (114, 115) likewise observed low yields (about 10%) when they carried out the analogous reactions on androst-4-en-3-one derivatives. When anhydrous dioxane was used instead of methanol even poorer yields of XCIV were realized. Further experiments on developing optimum reaction conditions, or perhaps the use of more active alkylating agents must be done in the future. It was merely necessary at this time to demonstrate that such a reaction sequence was indeed feasible.

The spectral results were in good agreement for compound XCIV. The ultraviolet spectrum of the alkylation product (λ_{max} 250 and 309 mμ; λ_{min} 287 mμ) showed the expected bathochromic shift of 10 mμ relative to the spectrum of the starting ketone XCII. Such a shift complies with the empirical Woodward rules and shows that an alkyl substituent is now present in the α-position (116). The infrared spectrum showed a typical conjugated carbonyl absorption and a peak for the hydroxyl group. Furthermore, the n.m.r. spectrum confirmed the structure of XCIV. The C-1 methyl group by virtue of its attachment to an olefinic carbon atom, resonates at lower field (8.22 τ) than the angular methyl group (9.25 τ) and is clearly evident in the spectrum. Also no olefinic signals are present, but peaks at 6.38 τ (broad) and 8.11 τ (singlet) could be assigned to the C-8 and hydroxyl protons, respectively. In addition to the above signals, a very interesting doublet was observed at 7.10 τ (J_{gem} about -12 c.p.s.). The starting conjugated ketone XCII has no peaks in the region 6.7 to 7.3 τ, and it was obvious that this absorption must be characteristic of the alkylation product. Pertinent to this last observation, Tomoeda, Inuzuka and Furuta (117) have noted a doublet at about 7.21 τ (J_{gem} = -14.5 c.p.s.) in the n.m.r. spectrum of 4-methyl-cholest-4-en-3-one (XCV) (Figure 14). They were able to assign this absorption to the C-6α equatorial proton and indicated that a

spatial interaction between the C-4 methyl group and the C-6α proton is the cause of the deshielding. As may be expected the C-6α proton of the parent compound, cholest-4-en-3-one, does not absorb below 7.58τ in the n.m.r. spectrum. A comparison with the system of XCIV reveals that the C-12β equatorial proton is identically oriented with respect to the methyl group at C-1. On this basis we assign our low field doublet to this proton.

Finally, a comparison of the mass spectra of XCII and XCIV (Figure 22 and 23, respectively) also supports the structure of the latter molecule. First of all, the molecular ion peak at m/e 302 in the mass spectrum of XCIV relative to the corresponding peak at m/e 288 for XCII established an addition methyl group in the former compound. Since both compounds have a C-8 hydroxyl group, it is not surprising to see strong M-18 peaks in the spectra (m/e 270 and 284, respectively; $M-H_2O$) of both substances and similarly weaker M-17 peaks representing loss of •OH (m/e 271 and 285, respectively). Moreover, the M-42 peaks (m/e 246 and 260, respectively) are due to the loss of ketene, $CH_2=C=O$, and are indicative of a compound having the system, $-\overset{|}{C}=CR-CO-CH_2-$ (118, 119). Steroids bearing the Δ^4-3-keto chromophore and their corresponding 19-nor analogues have prominent peaks at m/e 124 and 110, respectively (118, 119, 120). These fragments are due to cleavage of the 9,10 and 6,7 bonds (steroidal nomenclature) plus the transfer of two protons to the charged fragment. In the mass spectrum of XCIV an intense peak is observed at m/e 124, while in that of XCII, one is noted at m/e 110. It is seen that these latter facts are in excellent agreement with the steroid series and offer further confirmation that the relationship between XCIV and XCII is as suggested above. Suggested mechanisms for the fragmentation process of the above compounds are displayed in Figure 24. The mass spectrum of XCIV, however, has also a strong m/e 123 peak which was not observed in any of the above steroid spectra. This fragment may very well evolve from a mechanism similar to that proposed for the m/e 124 fragment.

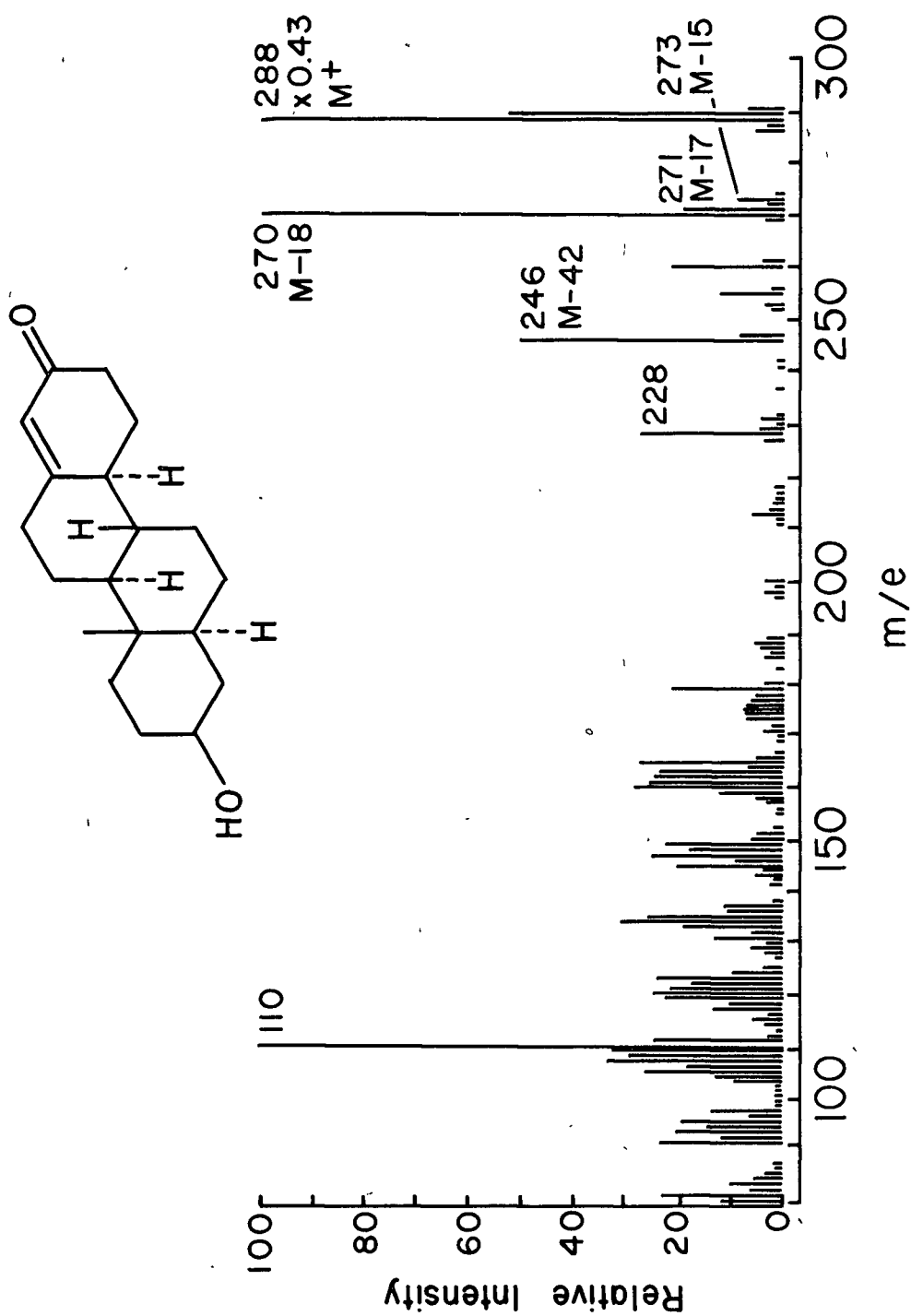

Relative Intensity
m/e
110
228
246
M-42
270
M-18
271
M-17
273
M-15
288
x0.43
M+
HO
H
O

Figure 22

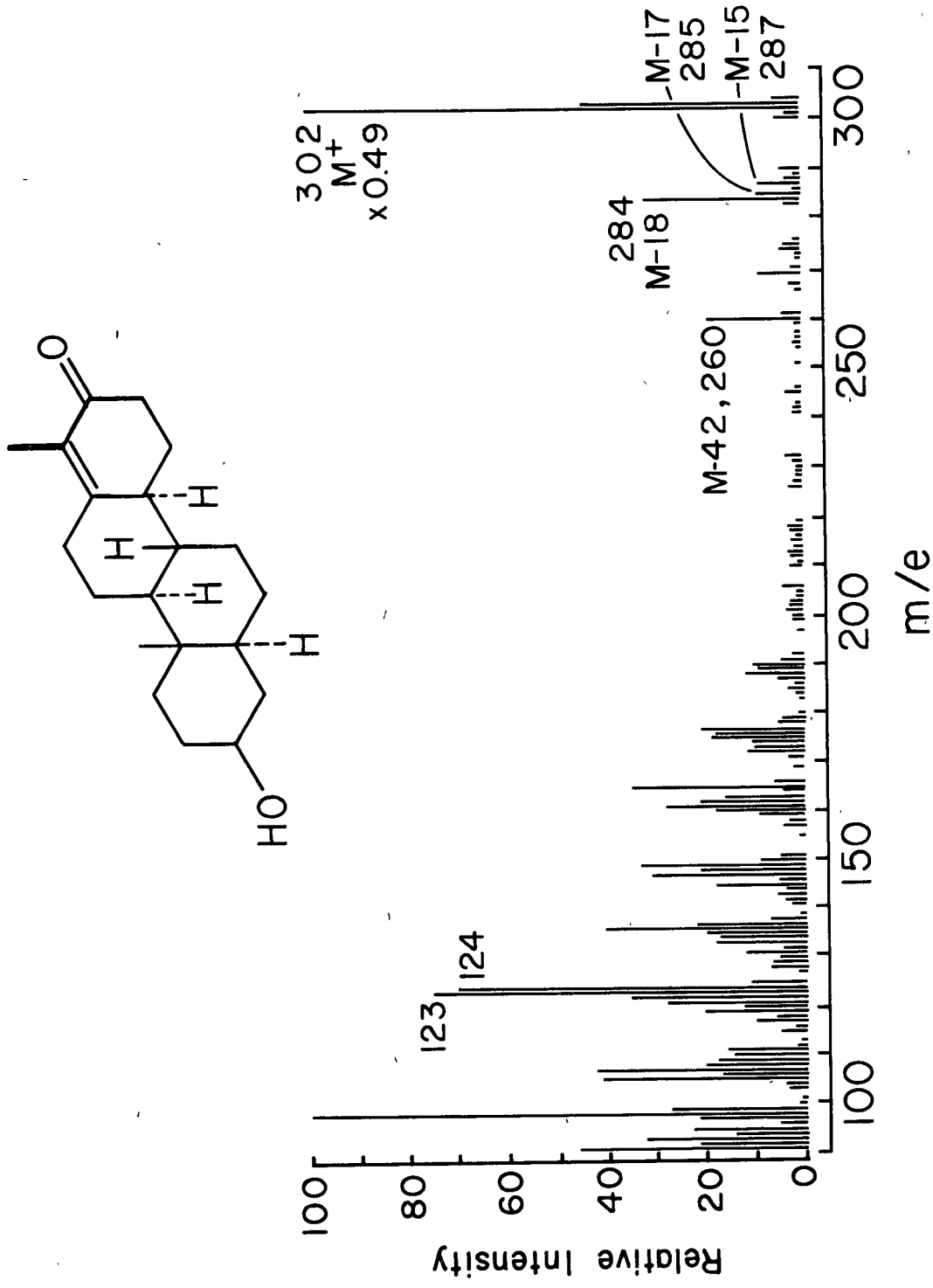

O
H
H
H
H
HO
302
M+
x0.49
M-17
285
M-15
287
284
M-18
M-42, 260
124
123
Relative Intensity
100
80
60
40
20
0
100
150
200
250
300
m/e

Figure 23

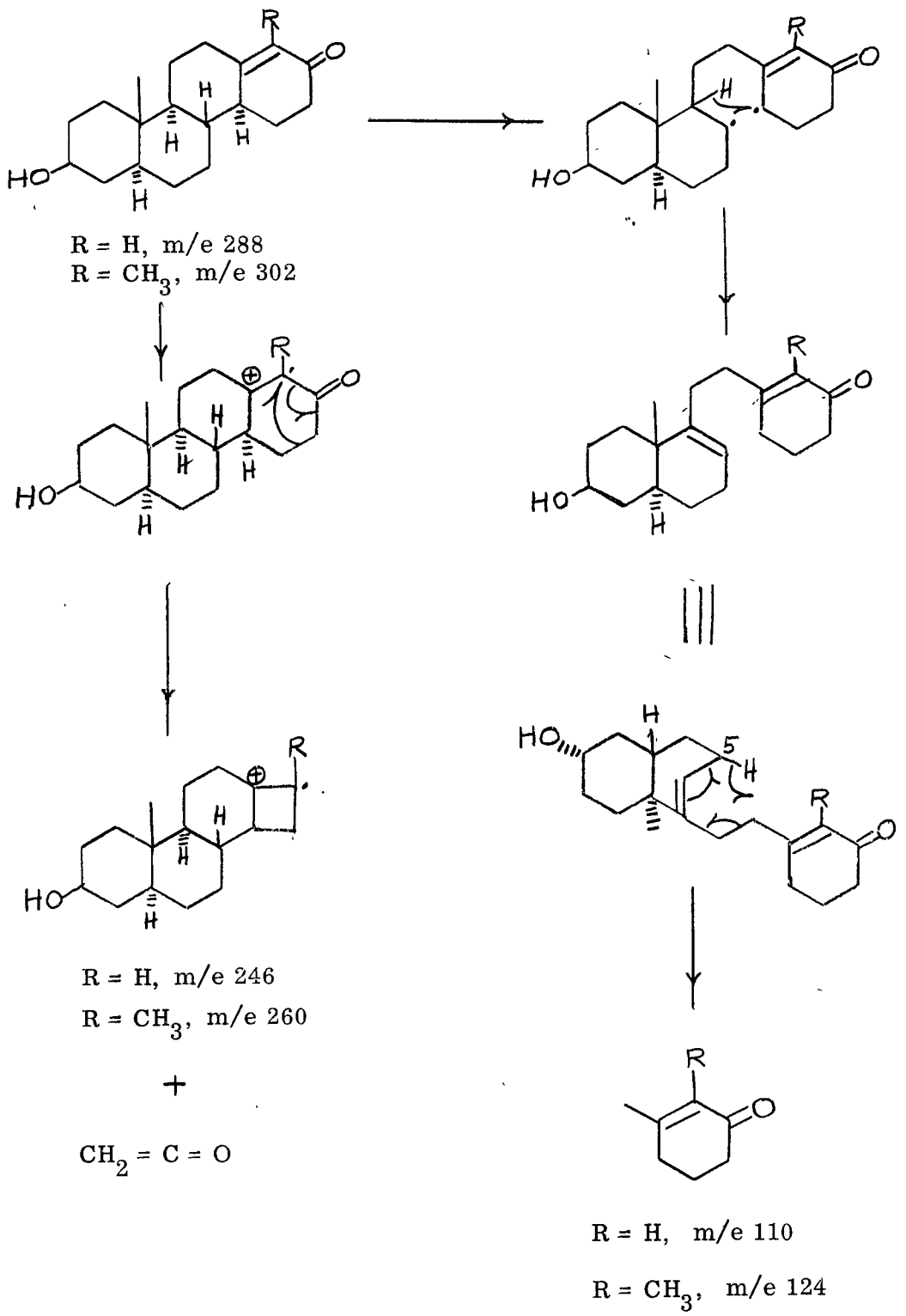

R
O
H
HO
R = H, m/e 288
R = CH3, m/e 302
R = H, m/e 246
R = CH3, m/e 260
+
CH2 = C = O
R = H, m/e 110
R = CH3, m/e 124

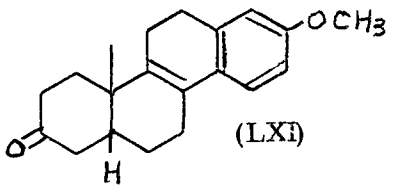
Figure 24

Interpretation of the Nuclear Magnetic Resonance Data

Most of the novel hydrochrysene compounds, which have been made in our laboratory, have their n.m.r. spectra recorded. A number of the most obvious features in the n.m.r. spectra have been presented in the previous section of the discussion, but there are a number of interesting points which evolve from a closer scrutiny of the n.m.r. data. It is the purpose of this section of the thesis to present a more detailed examination of the n.m.r. data of the various hydrochrysene derivatives.

The synthetic sequence as outlined in the previous section provided successive alterations in certain portions of the hydrochrysene molecule and also made available several stereoisomers of the various intermediates along the synthetic pathway. Consequently, it was possible to make meaningful correlations of spectral behaviour with structural features in this series.

It was felt preferable to make comparisons of the n.m.r. data by correlating the results in tabular form. The tables present the position of the proton resonances in τ values and in cycles per second (c.p.s.), the latter values being given in parenthesis. The coupling constant J is recorded as usual in c.p.s. units. All spectra were run with the sample at room temperature and with tetramethylsilane as the internal reference.



(LXi)

Solvent: $CDCL_3$

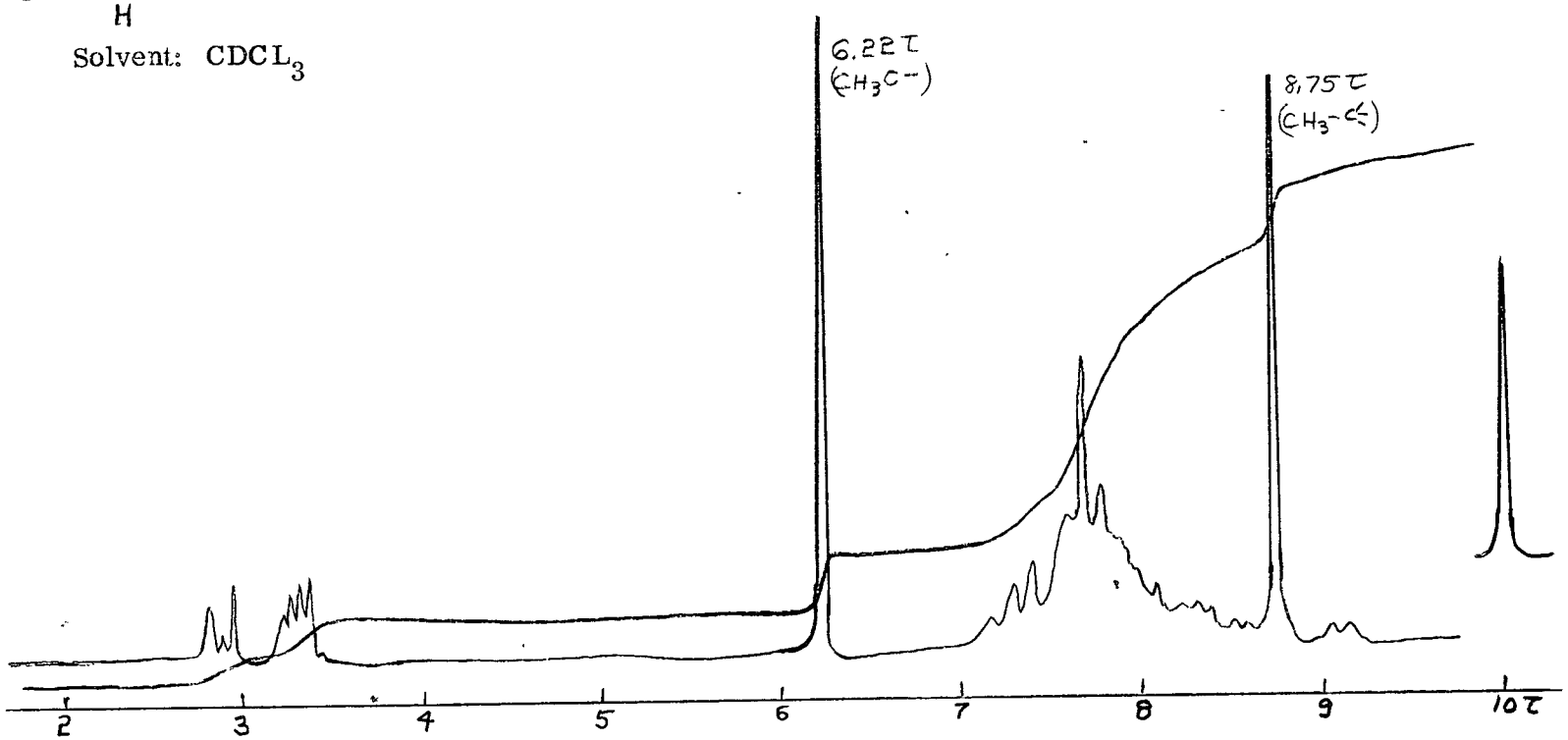
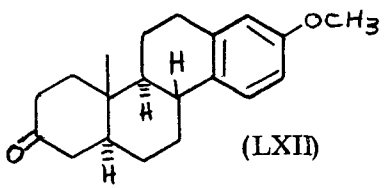


Figure 25.



(LXII)

Solvent: $CDCL_3$

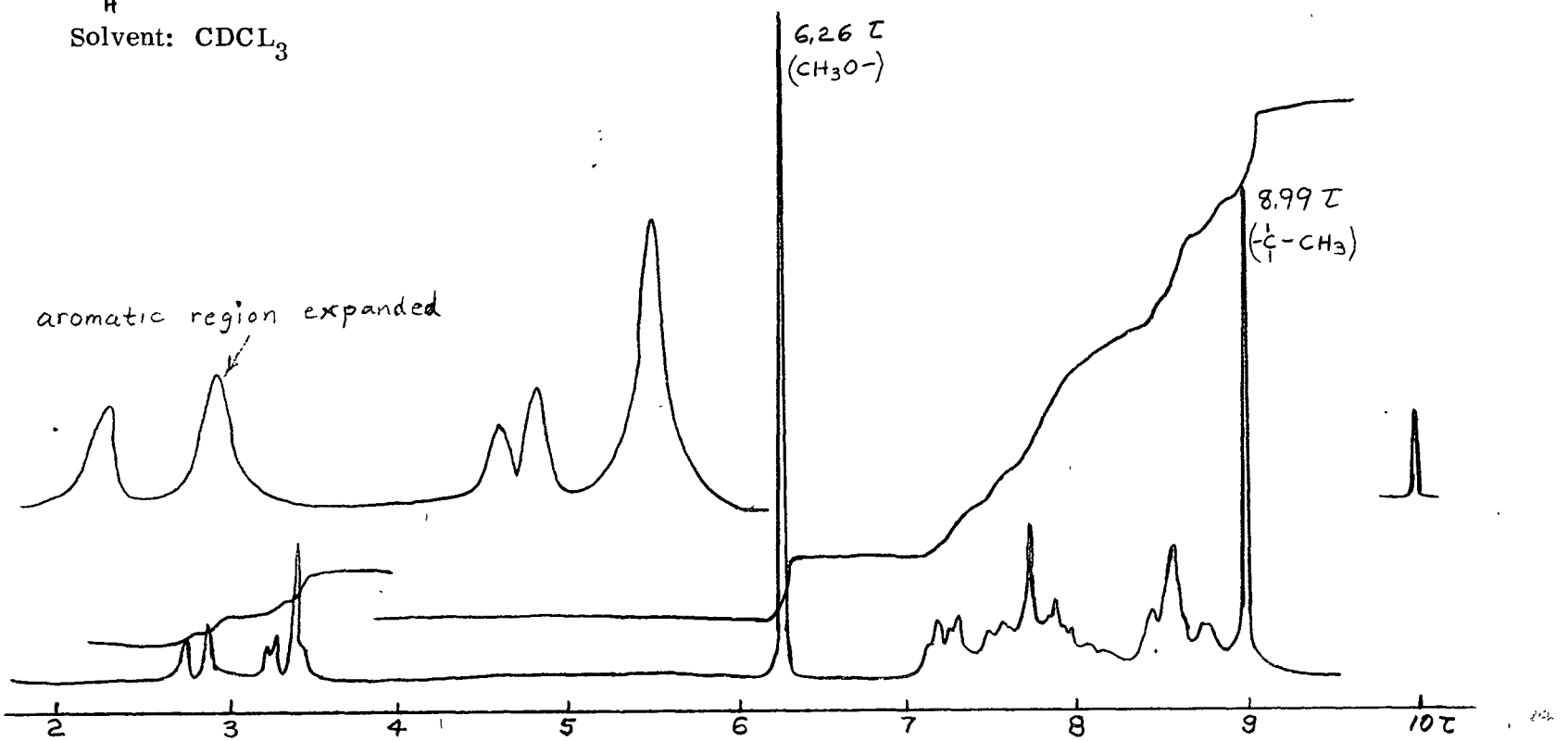
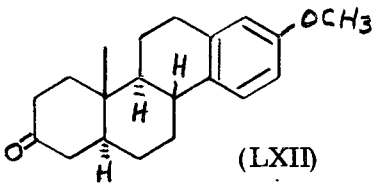


Figure 26



(LXII)

Solvent: C_6H_6

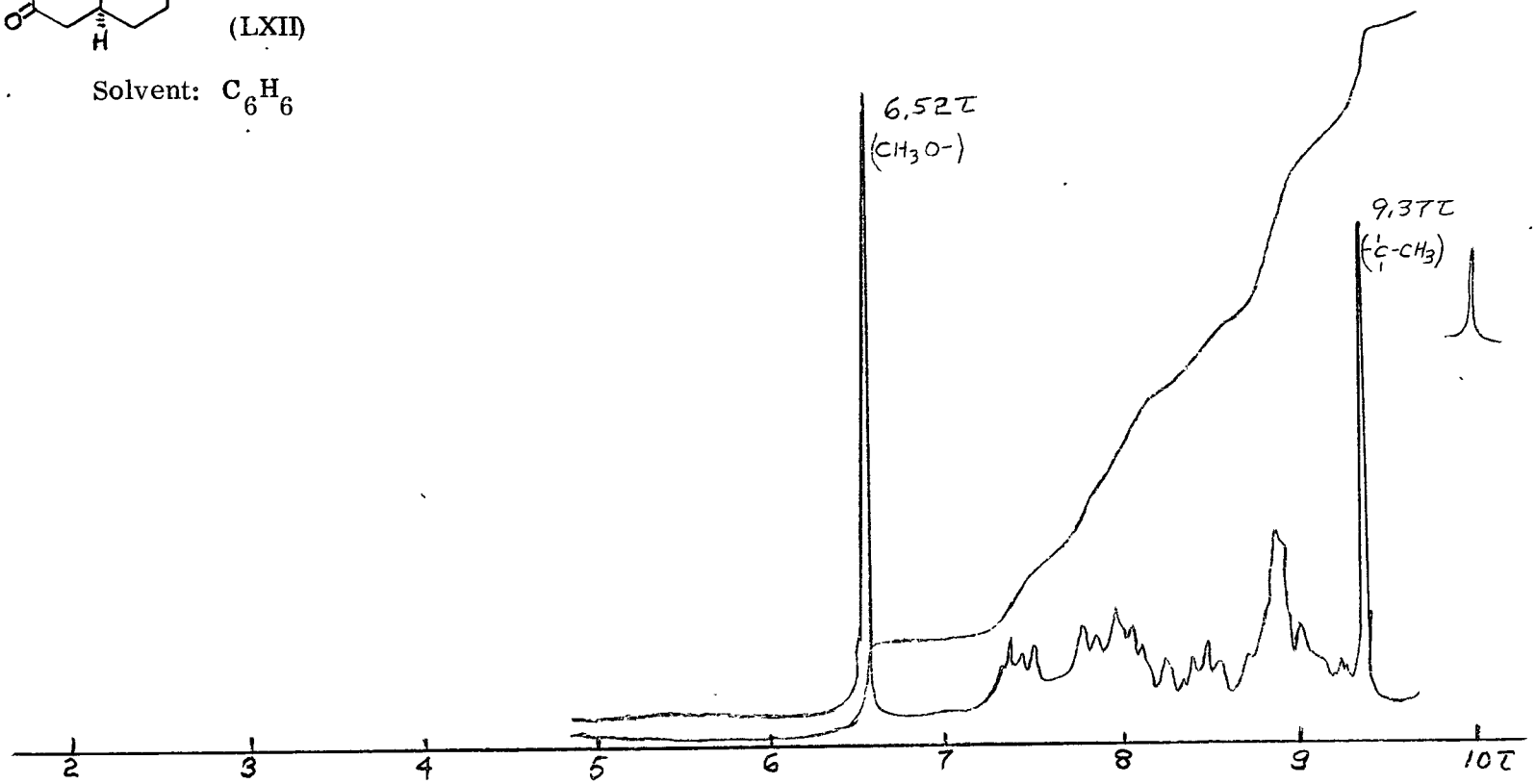
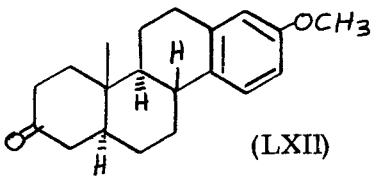


Figure 27



(LXII)

Solvent: C_5H_5N

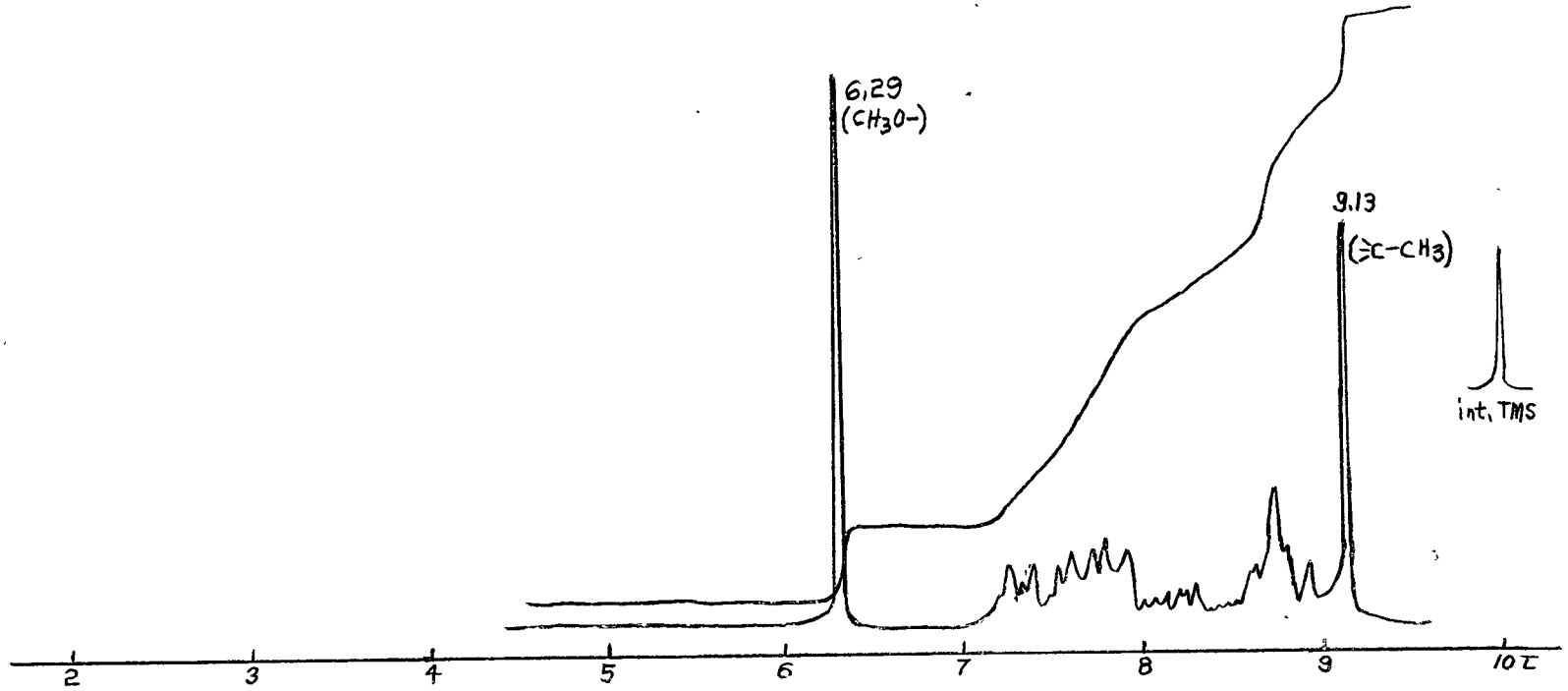
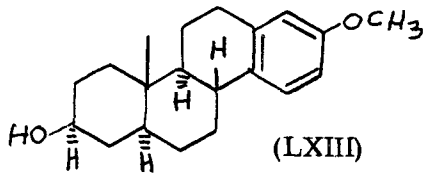


Figure 28



(LXIII)

Solvent: $CDCL_3$

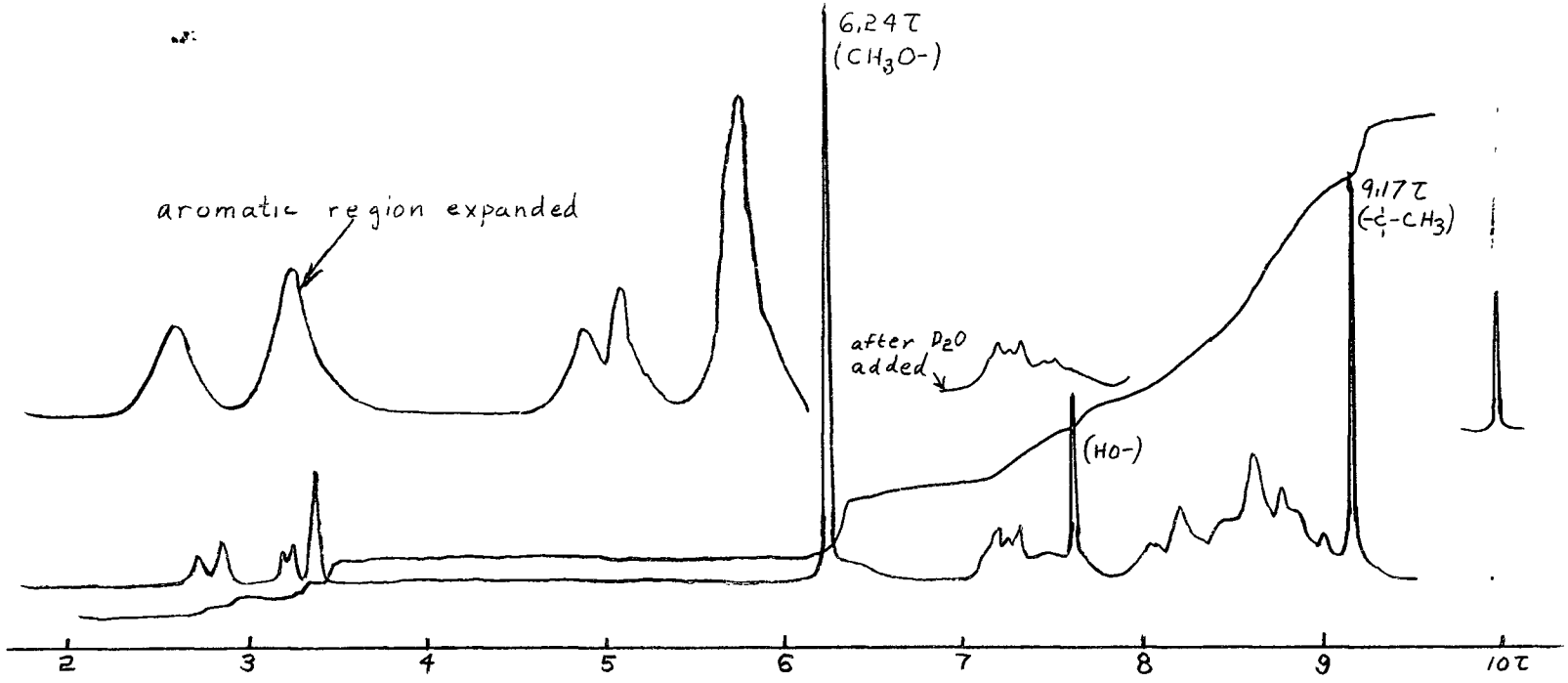
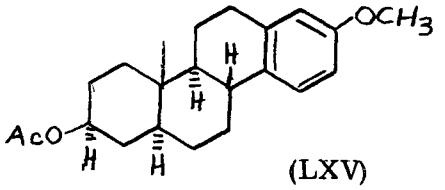


Figure 29



(LXV)

Solvent: $CDCL_3$

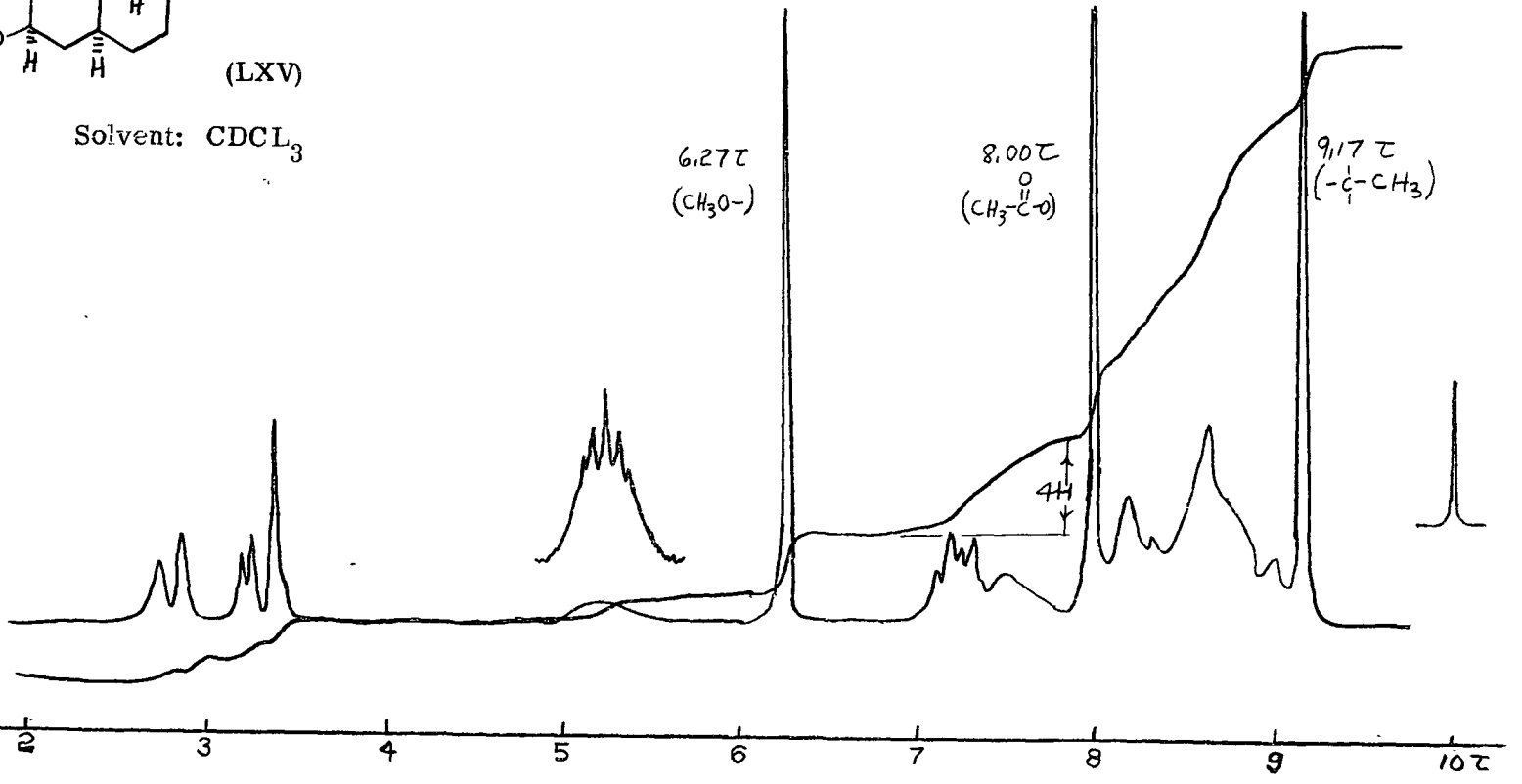
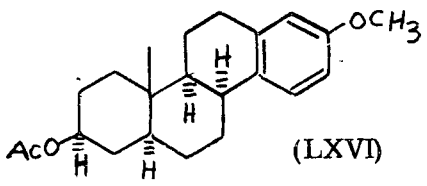


Figure 30



(LXVI)

Solvent: $CDCL_3$

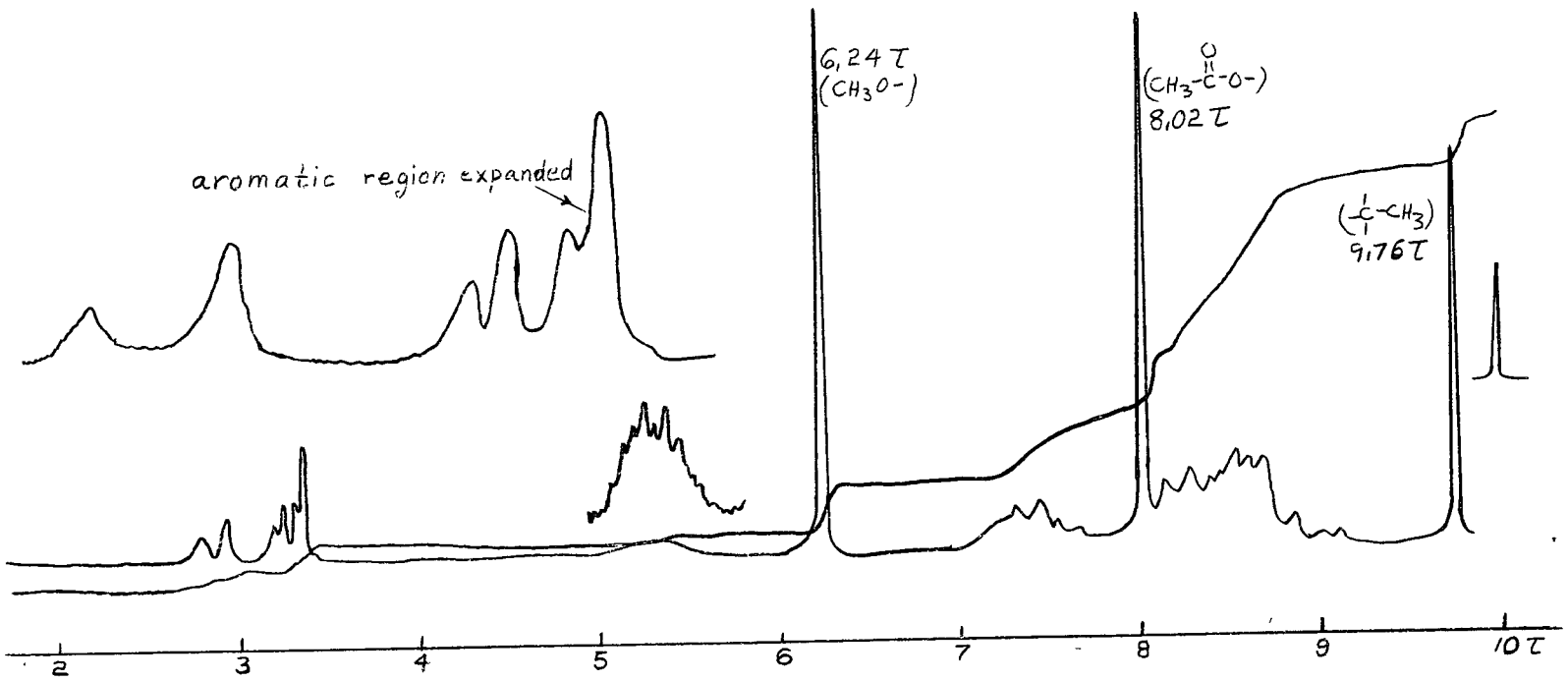
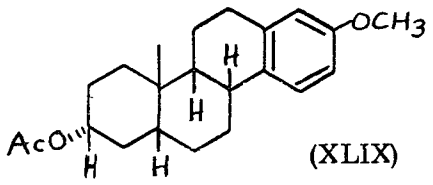


Figure 31



(XLIX)

Solvent: $CDCL_3$

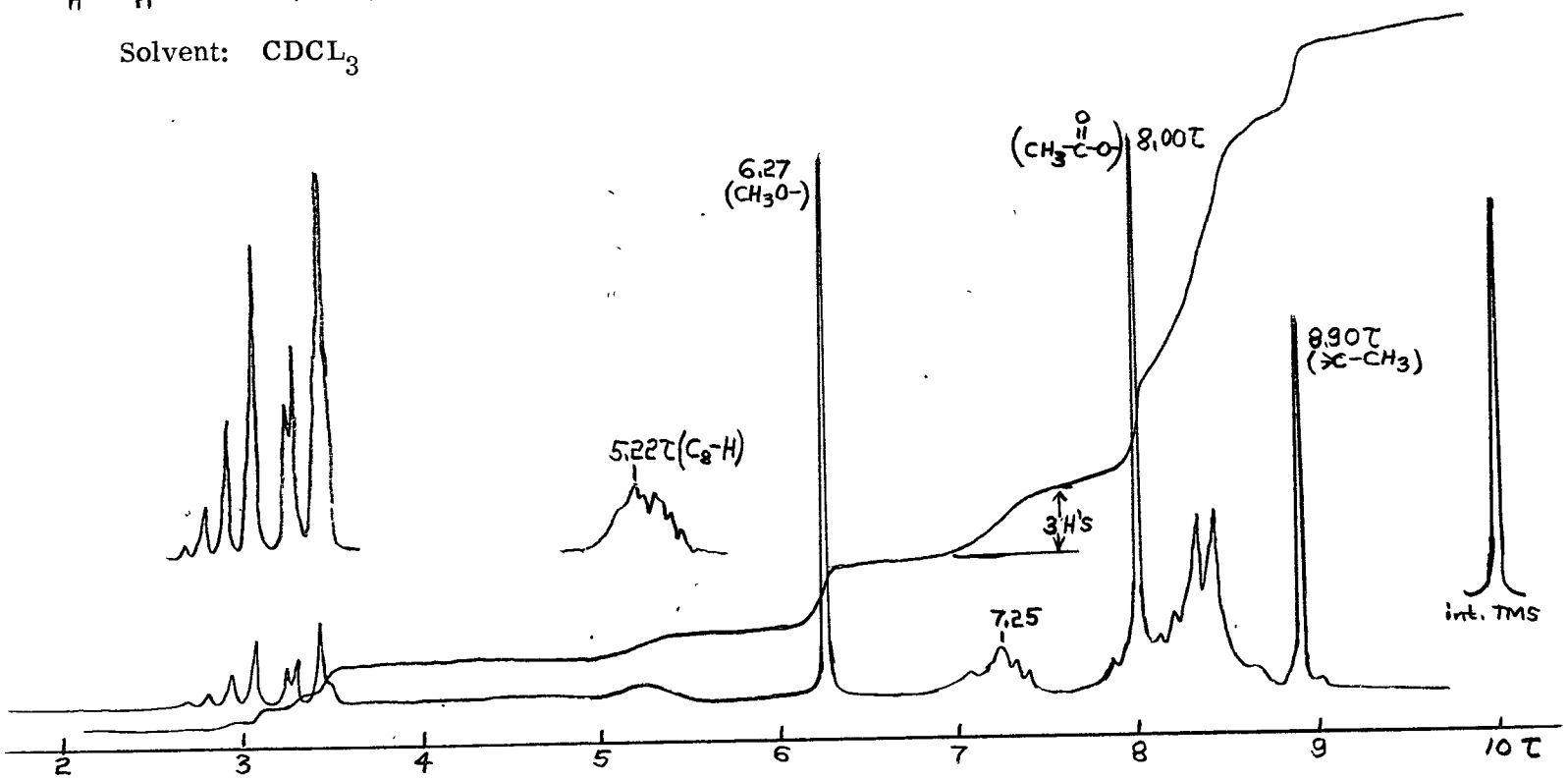
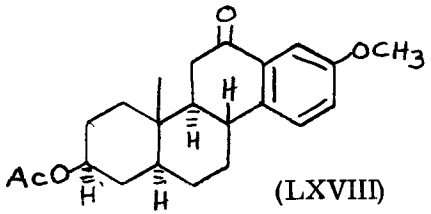


Figure 32



(LXVIII)

Solvent: $CDCL_3$

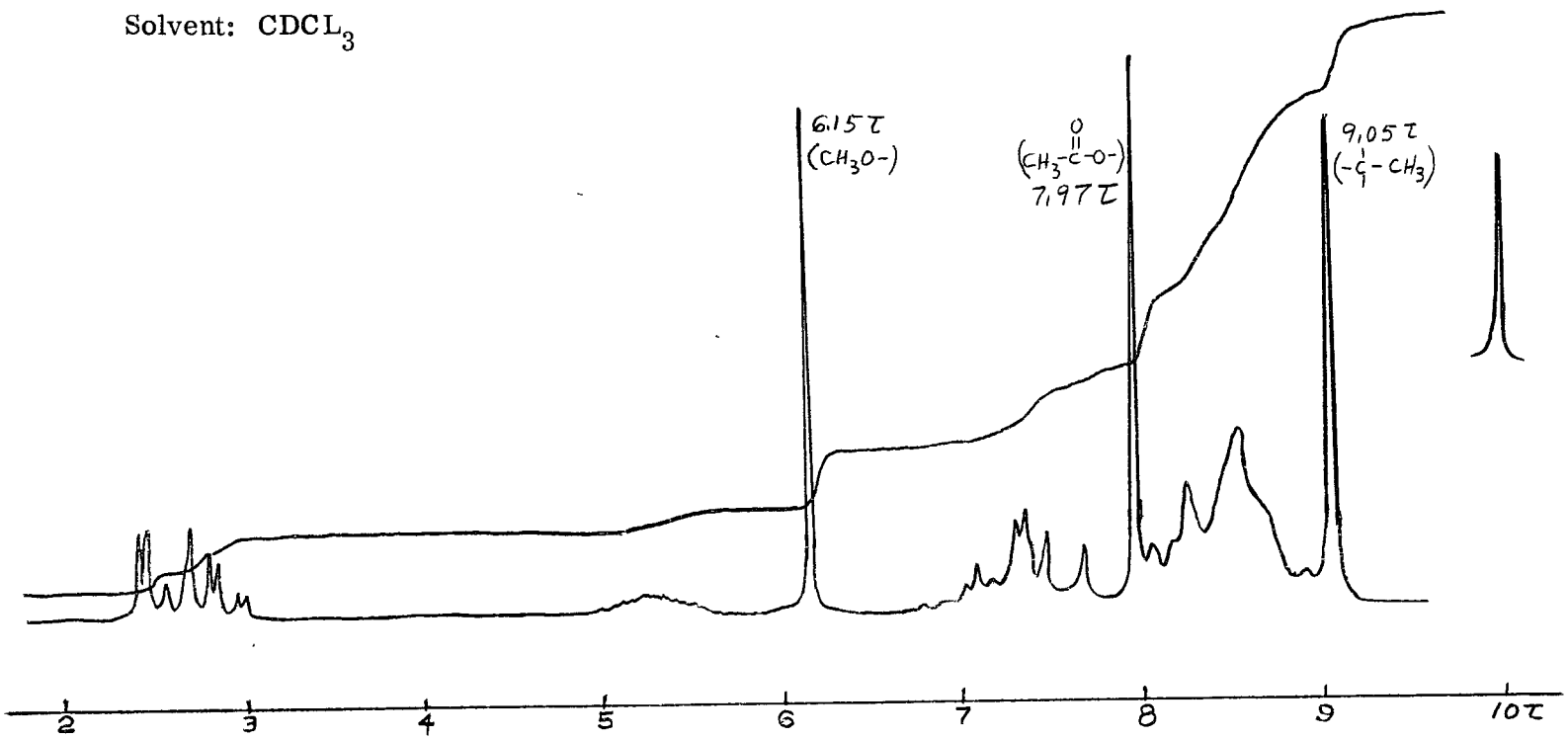
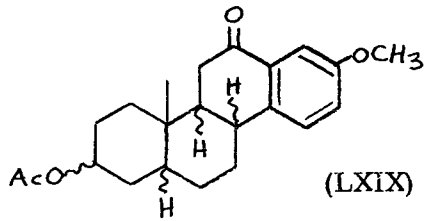


Figure 33



(LXIX)

Solvent: $CDCL_3$

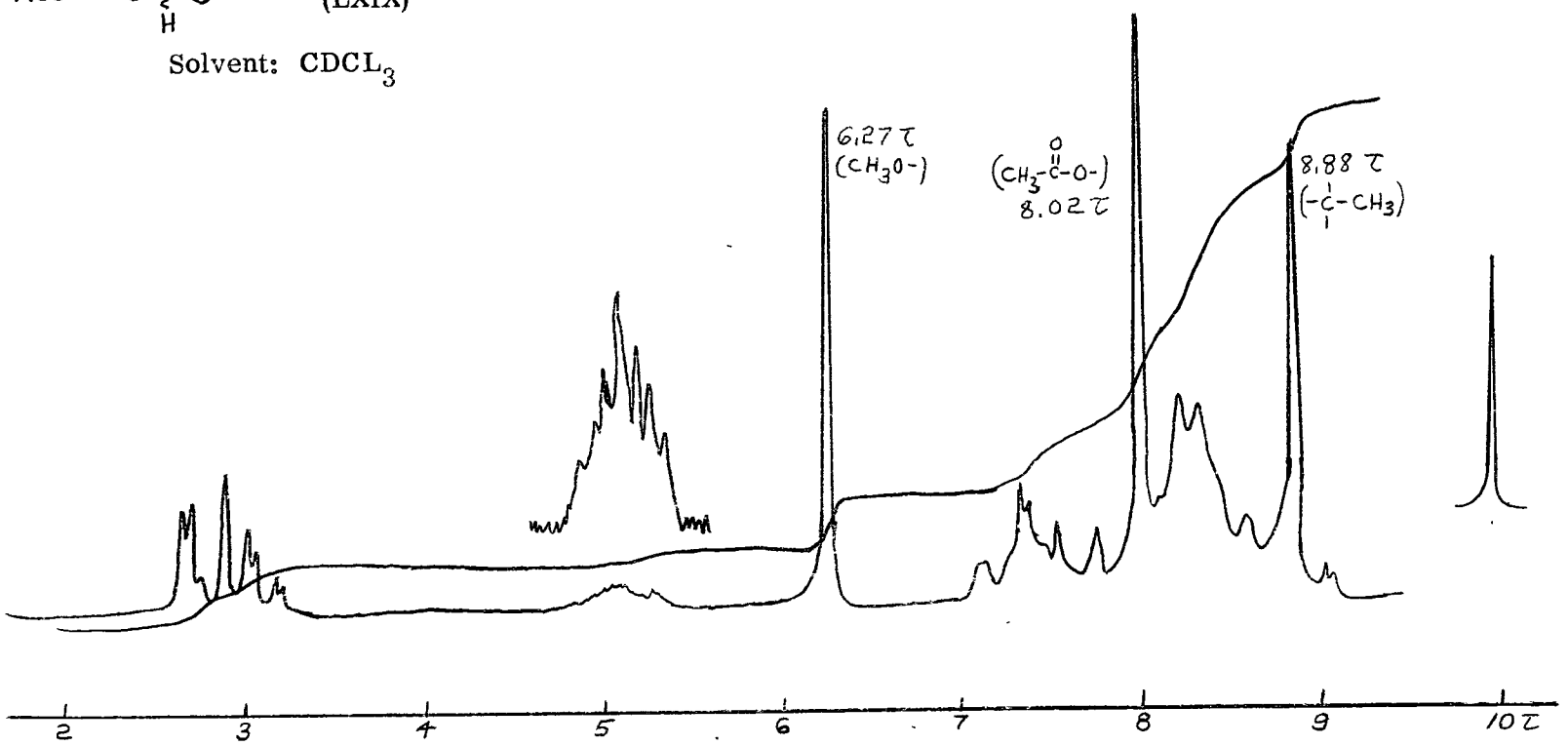
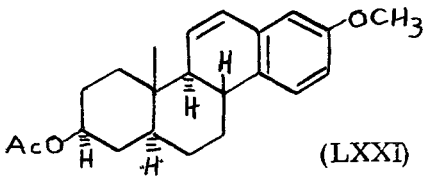


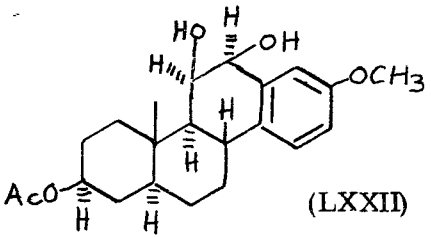
Figure 34



(LXXI)

Solvent: $CDCL_3$

Figure 35



(LXXII)

Solvent: C_5H_5N

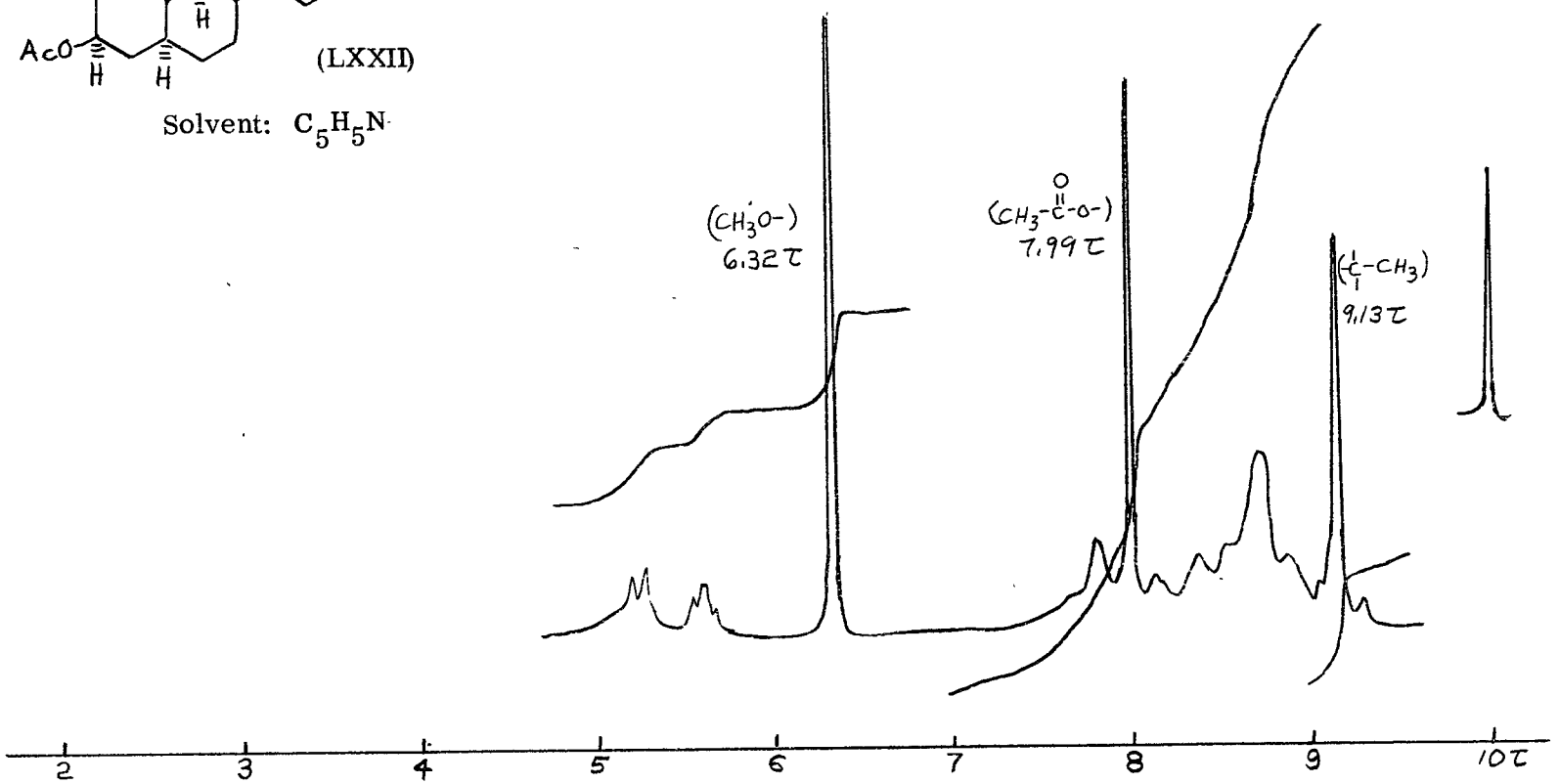


Figure 36

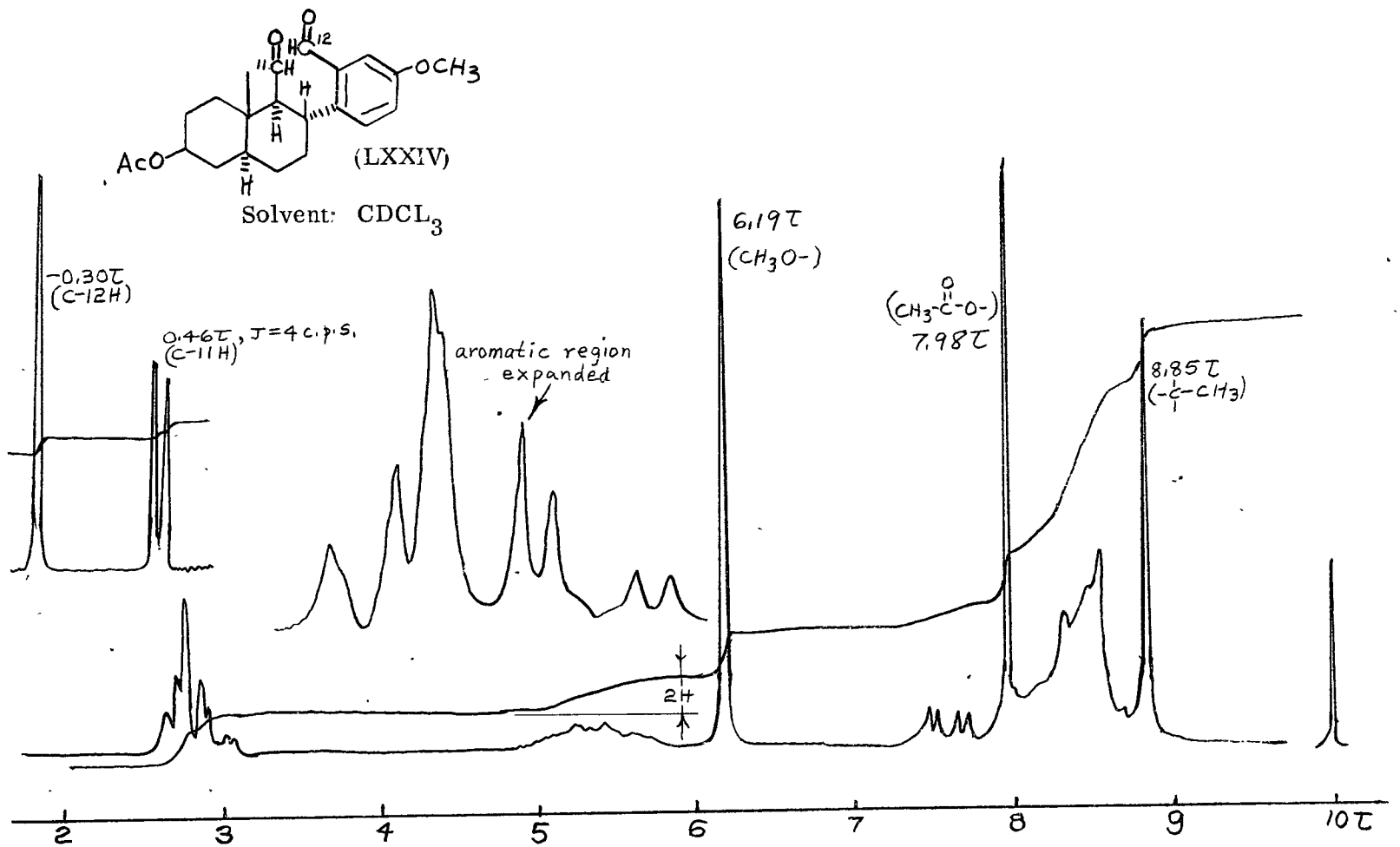
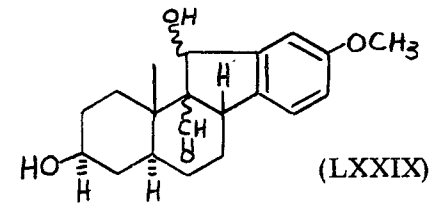

(LXXIV)
Solvent: $CDCL_3$
-0.30τ
(C-12H)
0.46τ, J=4 c.p.s.
(C-11H)
aromatic region
expanded
6.19τ
(CH_3O-)
(CH_3-C(=O)-O-)
7.98τ
8.85τ
(-C-CH_3)
2H
2
3
4
5
6
7
8
9
10τ

Figure 37



(LXXIX)

Solvent: $CDCL_3$

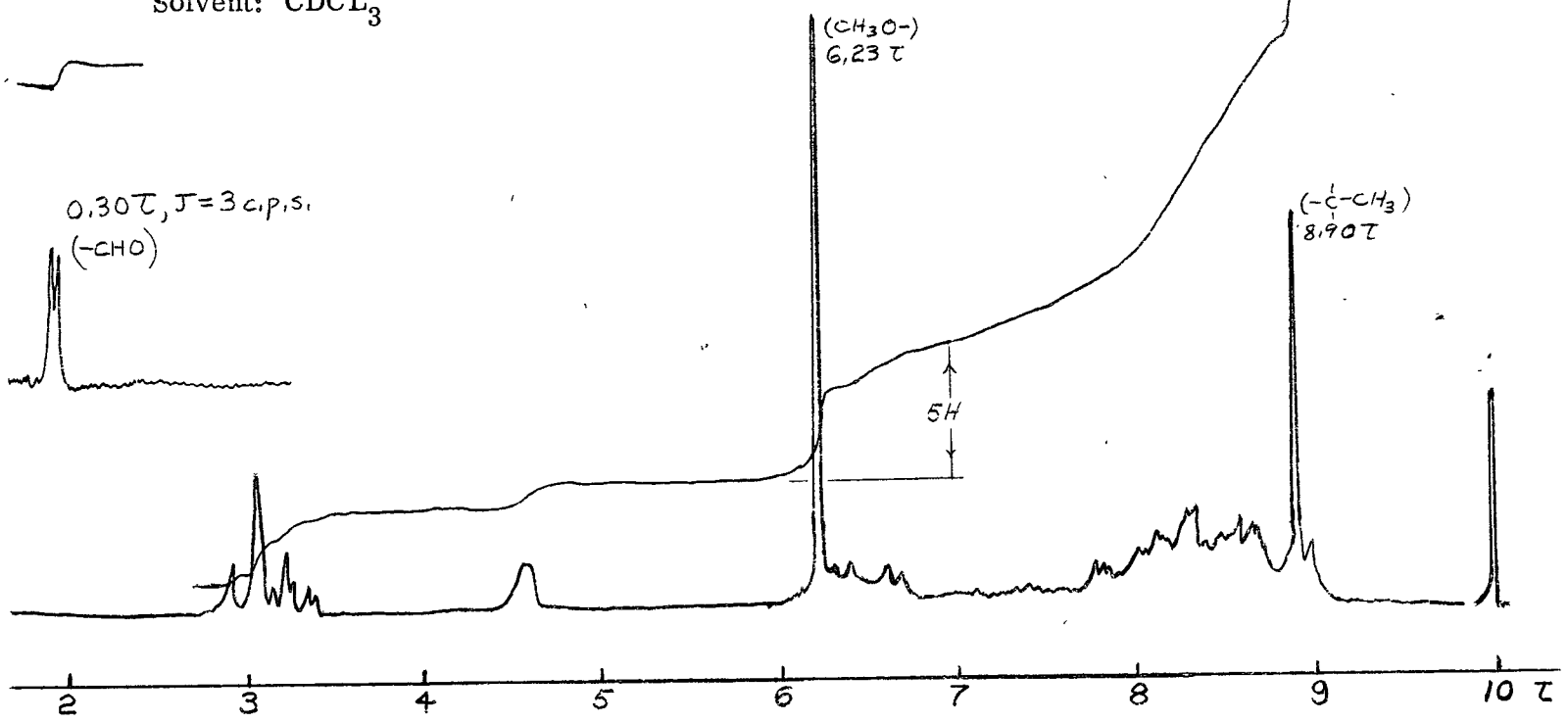
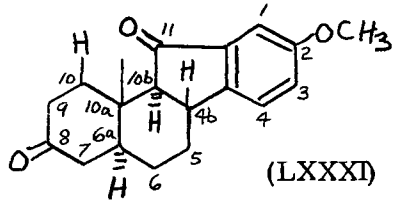


Figure 38



(LXXXI)

Solvent: $CDCL_3$

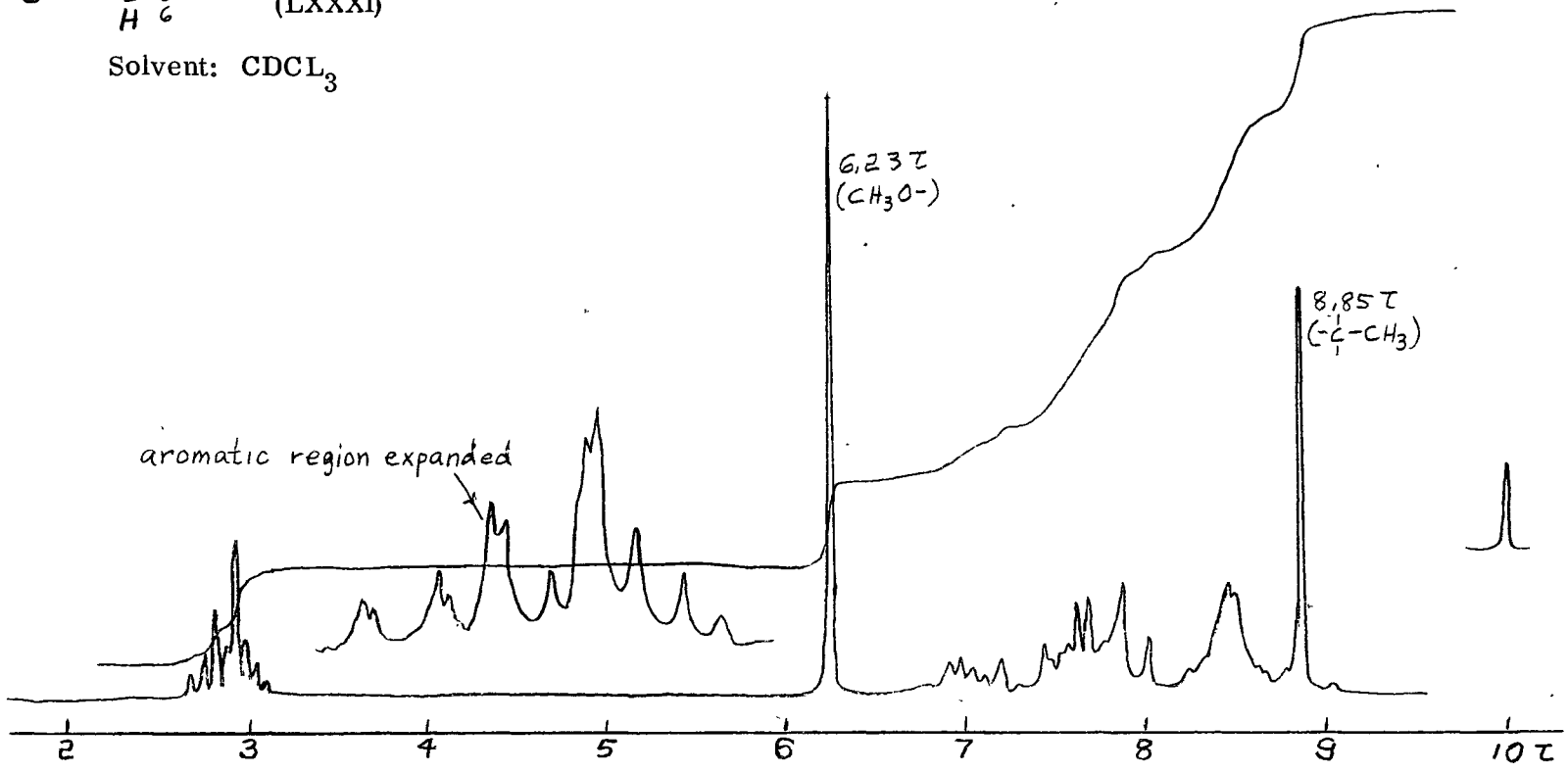
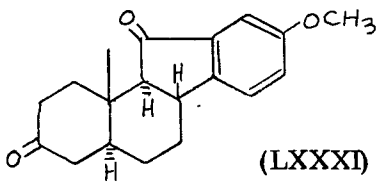


Figure 39



(LXXXI)

Solvent: C_6H_6

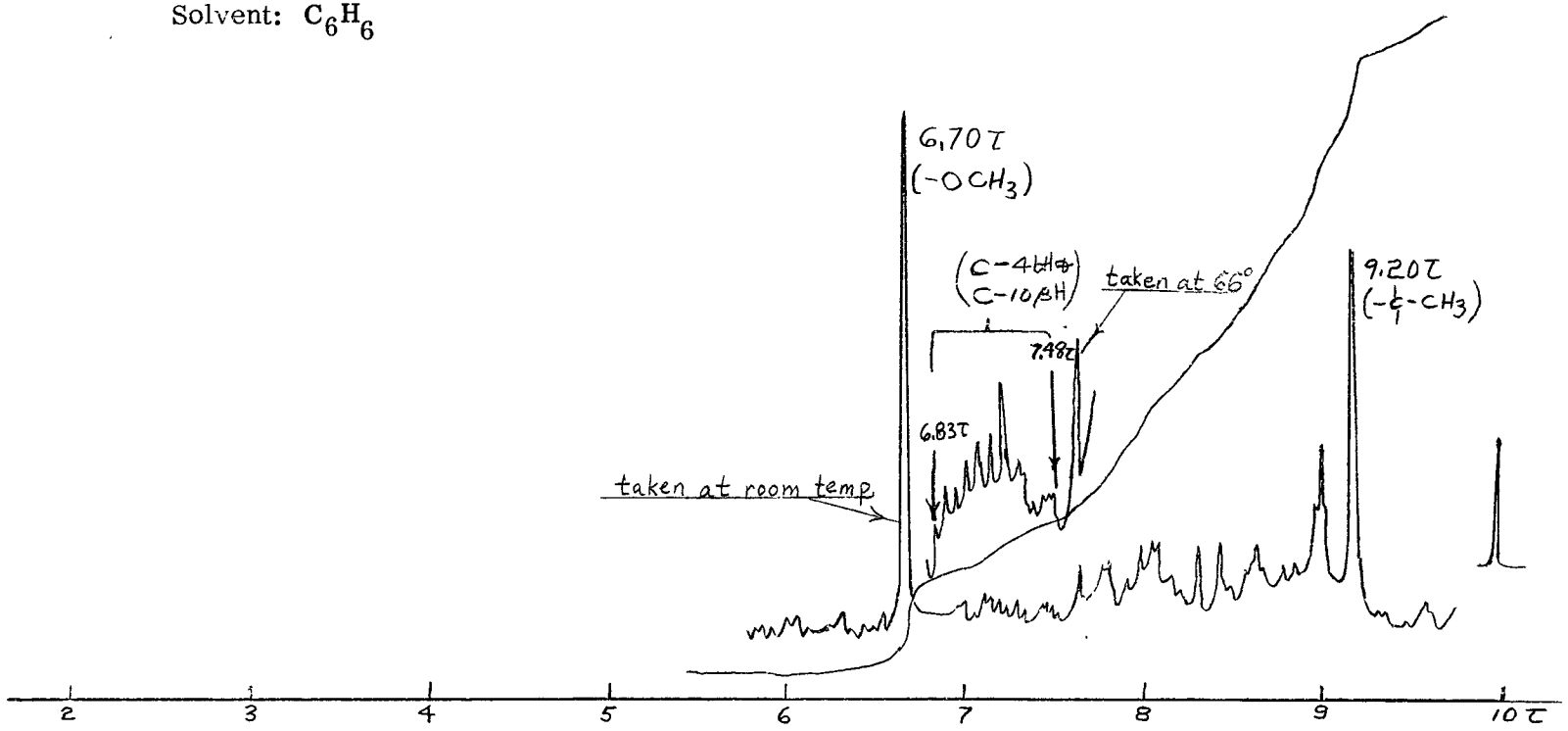
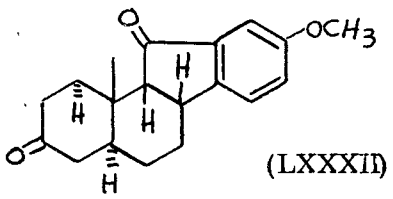


Figure 40



(LXXXII)

Solvent: $CDCL_3$

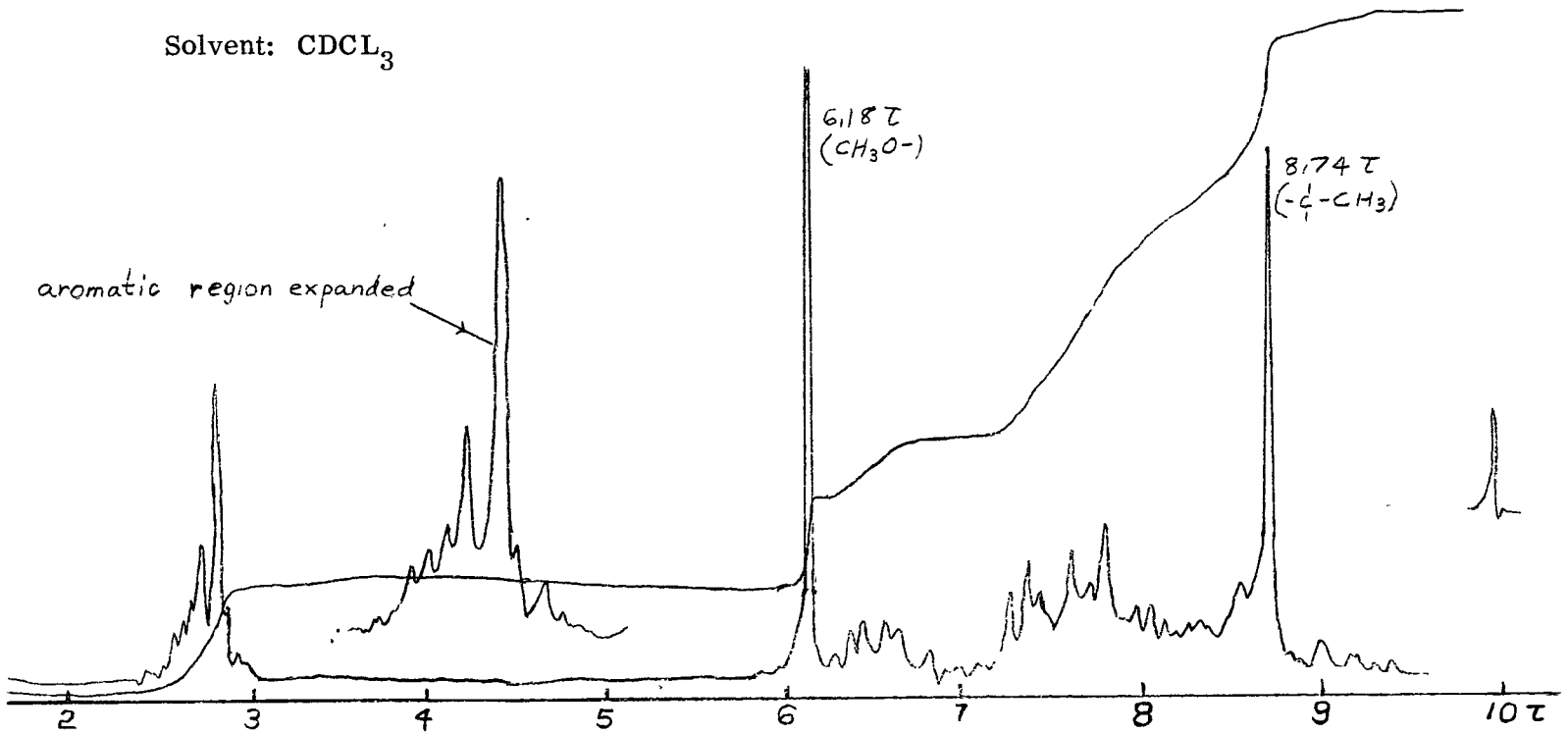
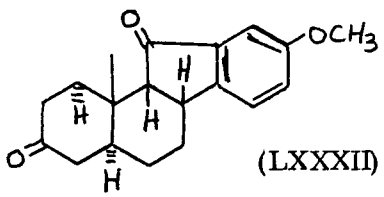


Figure 41



(LXXXII)

Solvent: C_6H_6

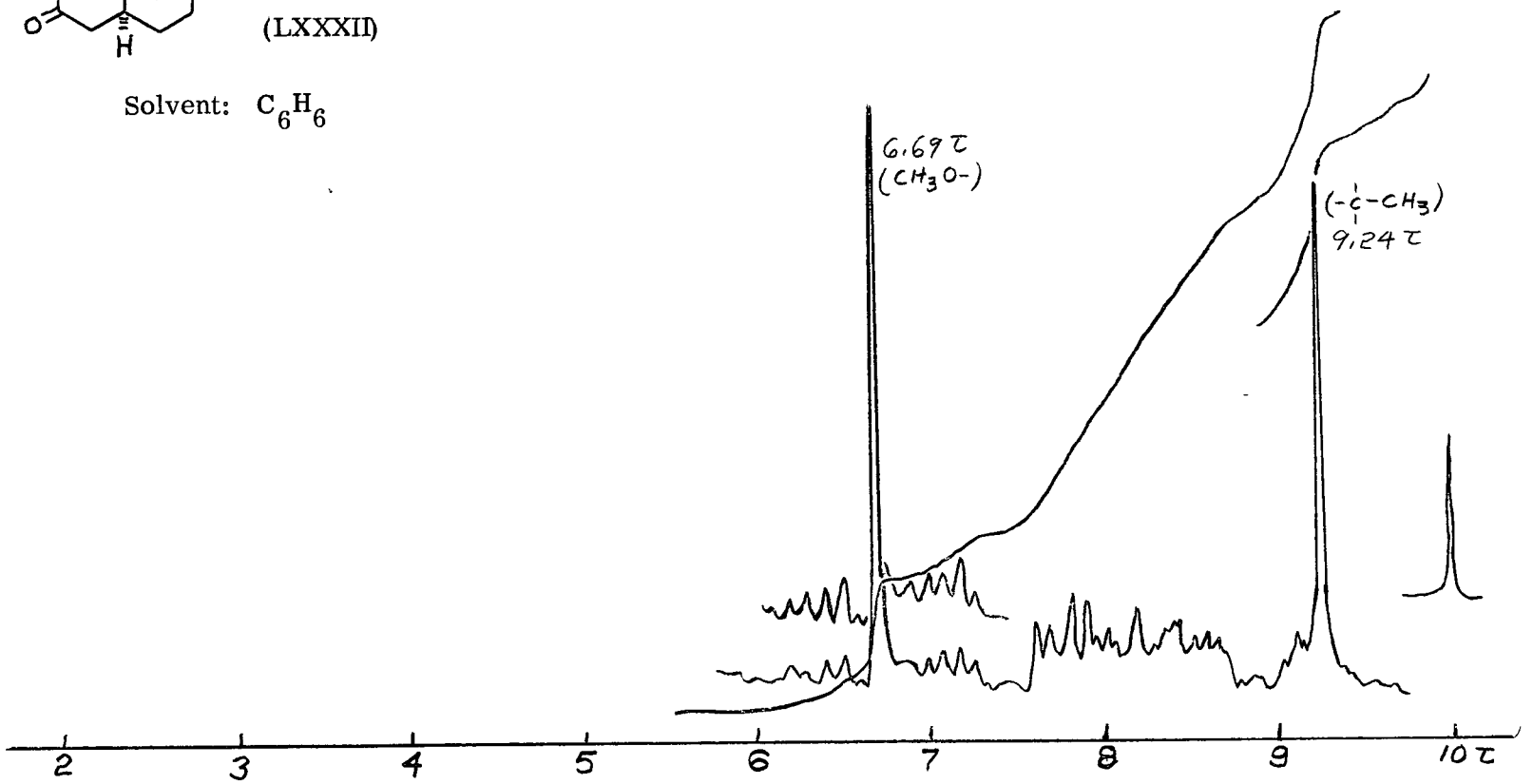
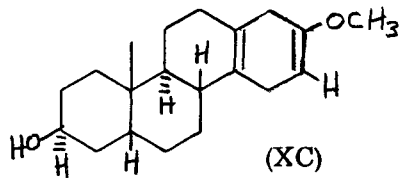


Figure 42



(XC)

Solvent: $CDCL_3$

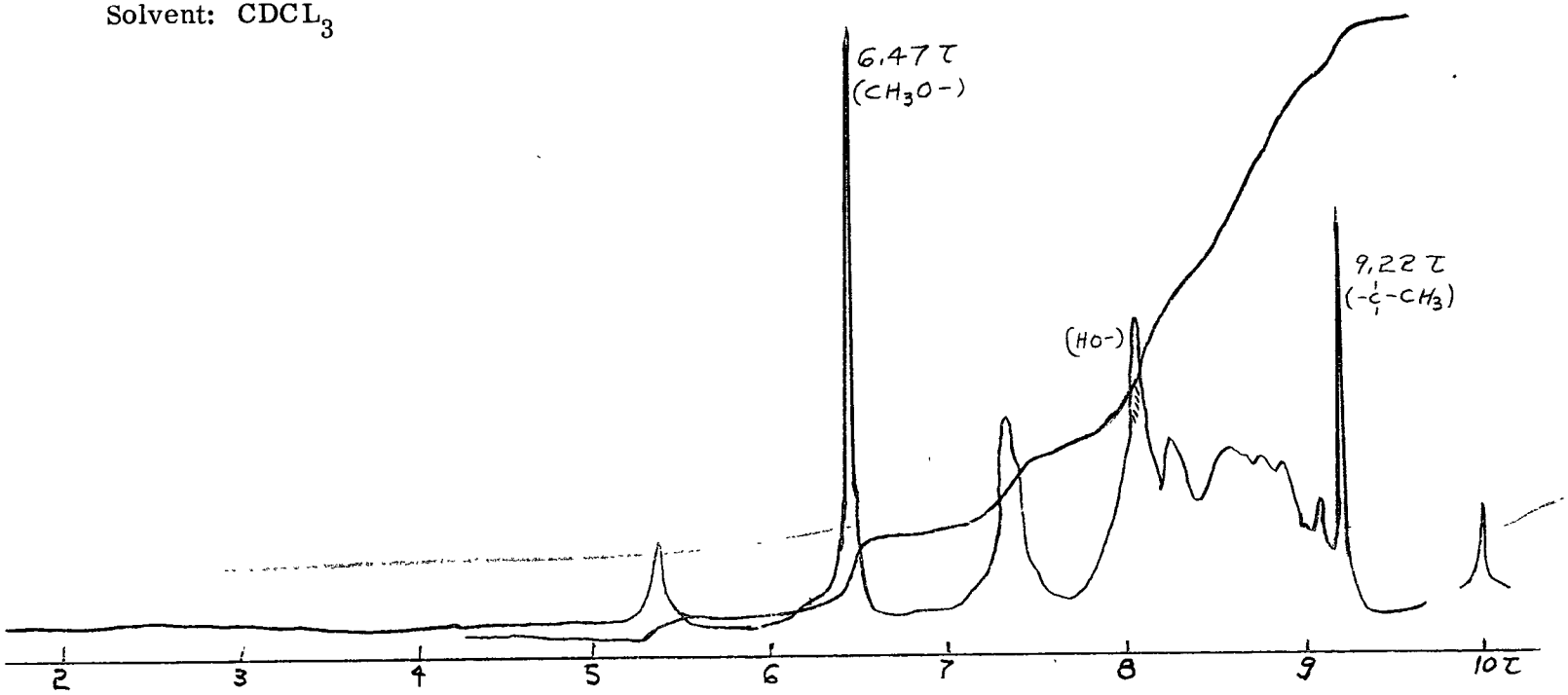
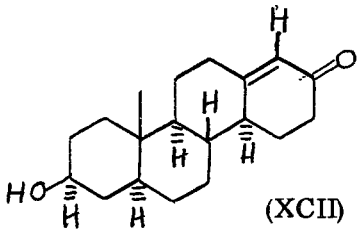


Figure 43



(XCII)

Solvent: $CDCL_3$

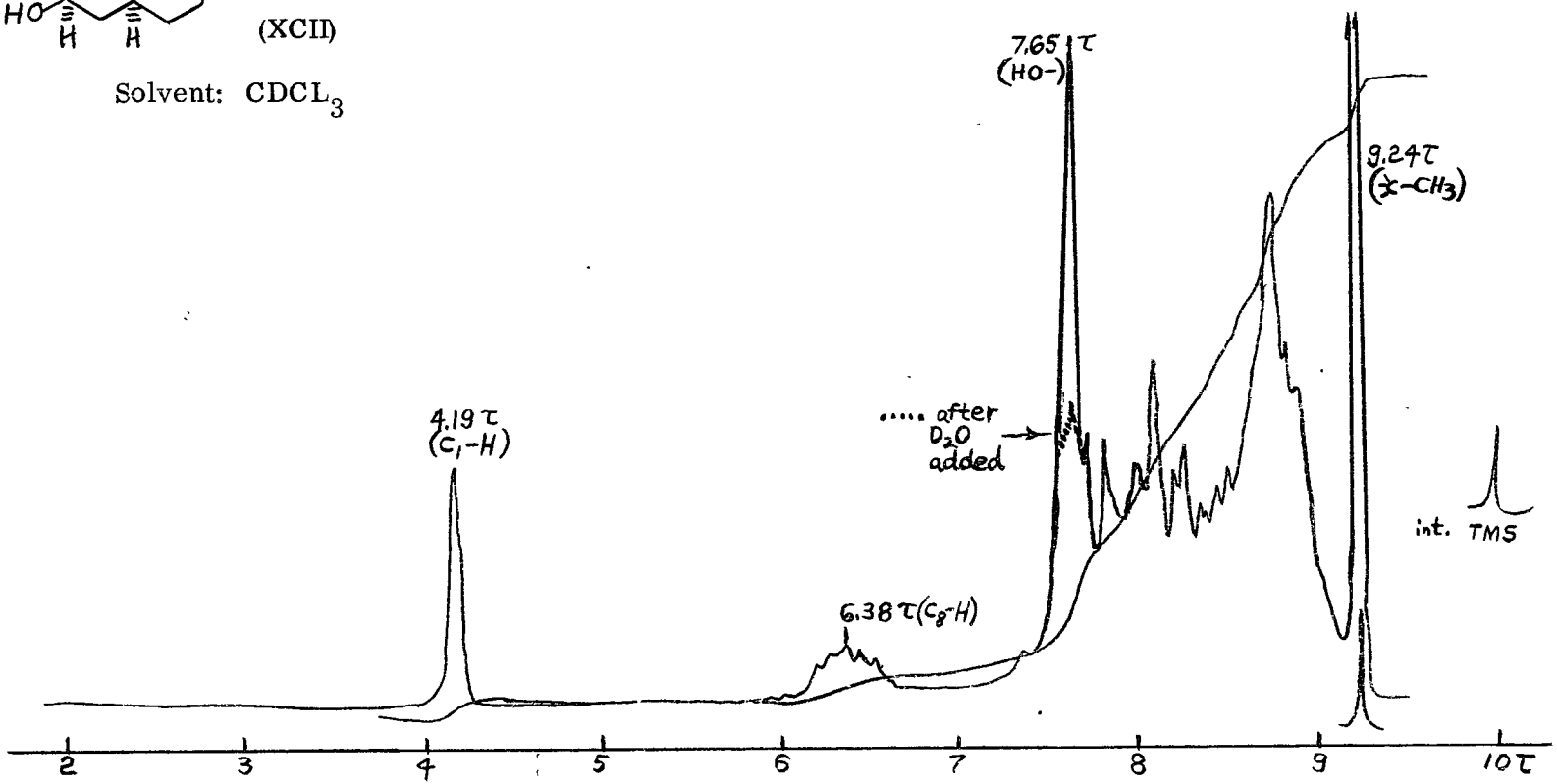


Figure 44

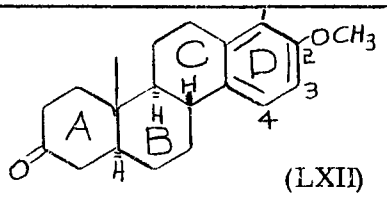
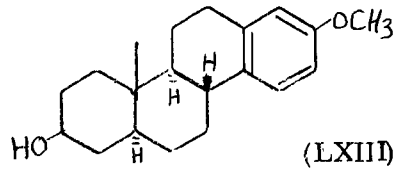
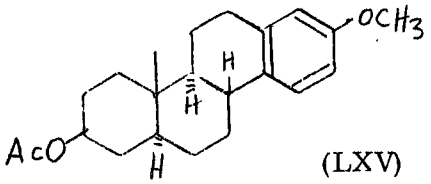
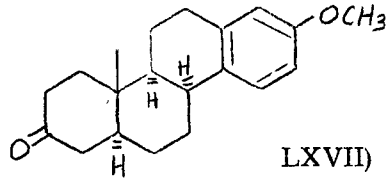
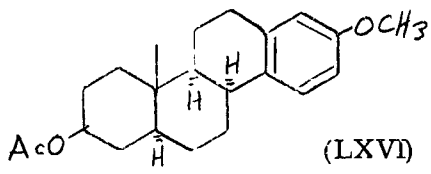
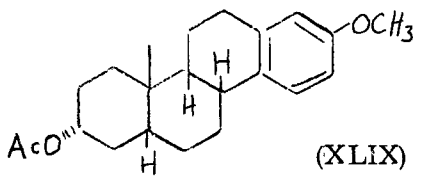
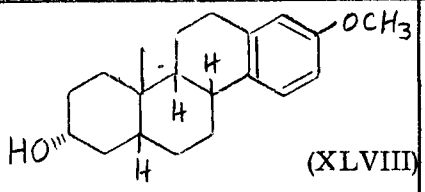
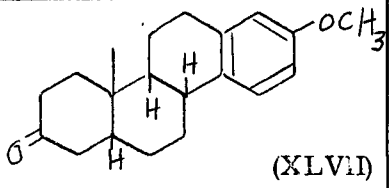
Compound	C-1 H	C-3 H	C-4 H	$\Delta\tau_{1,4}$
 (LXII)	3.37 (397) 3.39 *	3.28 (406.1) 3.31 * $J_{2,1} = 2.8$	2.81 (431) 2.79 * $J_{4,3} = 7.9$	0.56 0.60 *
 (LXIII)	3.36 (398.5)	3.26 (404.6) $J_{3,1} = 2.6$	2.80 (432) $J_{4,3} = 7.8$	0.56
 (LXV)	3.39 (396.5)	3.30 (401.8) $J_{3,1} = 2.8$	2.83 (430.5) $J_{4,3} = 8.5$	0.57
 LXVII)	3.34 *	3.27 *	2.84 *	0.50 *
 (LXVI)	3.34 (399.6)	3.27 (403.9) $J_{3,1} = 2.5$	2.87 (428.0) $J_{4,3} = 9.2$	0.47
 (XLIX)	3.41 (394.5)	3.30 (401.6) $J_{3,1} = 2.7$	3.01 (419.7)	0.40
 (XLVIII)	3.45 (393)		3.02 (418.6)	0.43
 (XLVII)	3.35 *	3.27 *	2.88 *	0.47 *

Table 2. Aromatic Proton Assignments of Various Hydrochrysene Derivatives. * Refers to values as given in reference (84).

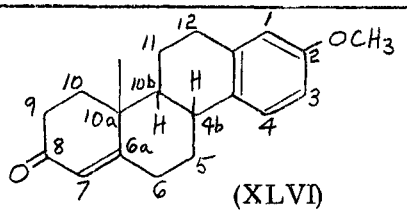
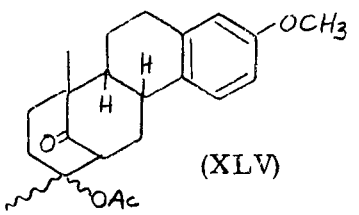
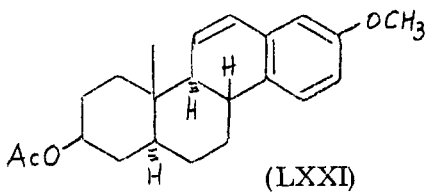
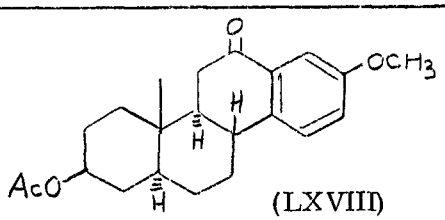
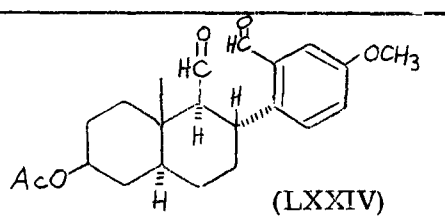
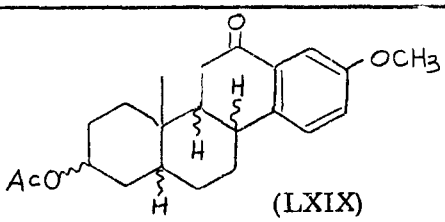
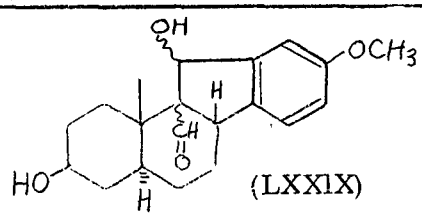
Compound	C-1 H	C-3 H	C-4 H	$\Delta\tau_{1,4}$
 (XLVI)	3.42 (394.6)	3.31 (401.2) $J_{3,1}$ = 2.8	3.01 (419) $J_{4,3}$ = 8.1	0.41
 (XLV)	3.40 (396)	3.29 (402.3) $J_{3,1}$ = 2.8	3.01 (419) $J_{4,3}$ = 8.2	0.39
 (LXXI)	3.44 (393.5)	3.34 (399.3) $J_{3,1}$ = 2.6	2.99 (420.7) $J_{4,3}$ = 8.1	0.45
 (LXVIII)	2.42 (454.6) $J_{1,3}$ = 2.6	2.86 (428.4) $J_{3,4}$ = 8.7 $J_{3,1}$=2.7~3.0	2.64 (441.6) $J_{4,3}$ = 8.6	
 (LXXIV)	2.74 (435.3)	2.93 (424) $J_{3,4}$ = 8.8 $J_{3,1}$=2.4~2.5	2.74 (435.3)	
 (LXIX)	2.67 (440.0) $J_{1,3}$ = 2.9	3.08(415.0) $J_{3,4}$ = 8.7 $J_{3,1}$=2.6~3.1	2.85 (429.0) $J_{4,3}$ = 8.8	
 (LXXIX)	3.05 (417)	3.28 (403.0) $J_{3,1}$ ~ 2.5-3.0	3.00 (419.7) $J_{4,3}$ ~ 8	

Table 3. Aromatic Proton Assignments of Various Hydrochrysene Derivatives.

A study of a series of n.m.r. spectra of the aromatic ring D compounds has allowed us to assign the complex multiplet in the region 2.4 - 3.5τ to specific aromatic protons. This low field region is characteristic of aromatic protons, and the downfield shift relative to the olefinic or methylenic proton resonances is ascribed to the effect of the ring current associated with the aromatic system (121). Since there was no substitution or alteration of the aromatic protons throughout the synthetic sequence, the interesting variations occurring are the direct effect of structural or conformational changes in rings A, B and C.

The assignments of the aromatic proton resonances for the various compounds prepared in this investigation are summarized in Tables 2 and 3. The aromatic chromophore present in these compounds is close to an ABX type and it can be correlated to the 3,4-disubstituted anisole system or the closely related 3,4-disubstituted phenol system which occurs in the naturally occurring steroids such as estradiol. The former system has been recently studied in some detail by Nagata (84), whereas Bhacca and Williams (122) have discussed the latter in terms of its n.m.r. characteristics. Considering at first compounds which have no extra functionality in ring C, it is seen that all the aromatic proton signals are at higher field than those of normal benzenoid protons (2.73 τ). This diamagnetic shift is due to the presence of electron donating substituents attached to the aromatic ring (123). As expected the strongly electron donating methoxyl substituent at C-2 shields the ortho C-1 and C-3 protons and these absorb 0.4 to 0.6τ to higher field than the C-4 proton. Furthermore, it was possible to establish that the C-1 protons signal is at slightly higher field than that of the C-3 proton.

It is appropriate at this point to discuss Nagata's recent paper (84) as it relates directly to some of our work. Nagata showed in a n.m.r. study of an octahydrophenanthrene series in which one aromatic ring was present (for examples see

Figure 45) that a strong deshielding of the aromatic C-4 protons had occurred.

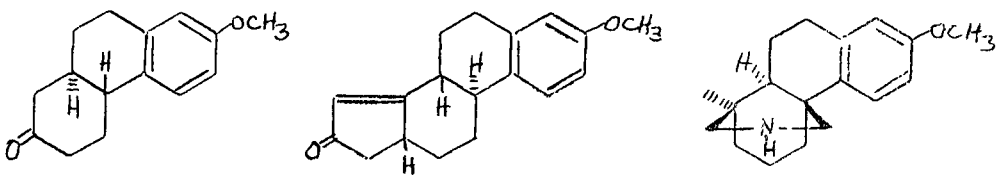
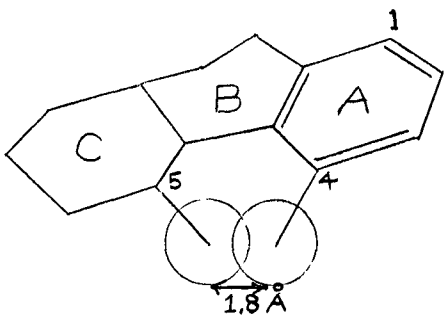
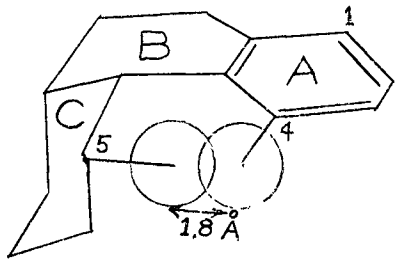


Figure 45

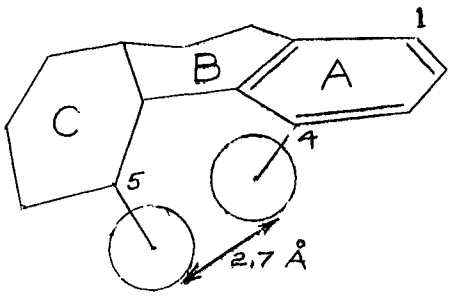
He attributed this result as being due to the steric effect of an equatorial C-5 proton. The degree of this deshielding, which is represented by the difference in the chemical shifts between the C-1 and C-4 protons, was correlated to the van der Waals compression between the C-4 and C-5 protons which is represented by the interatomic distance between them. Nagata stated further that Dreiding models showed that the distance between the atoms is closely related to both B/C ring fusion and the conformation of the molecule. The four possible situations in which this molecule can be pictured are illustrated below (Figure 46). In considering these various conformations it must be noted that the deshielding of the C-4 proton is greatest when the steric interaction is most severe. The reference compound that was chosen was 2-methoxy-5, 6, 7, 8-tetrahydronaphthalene (LXIV, Figure 12) which has no hydrogen atom capable of interacting with the C-4 proton, and in this case the difference in chemical shift between the C-1 and C-4 signals ($\triangle \tau_{1,4}$) was 0.39. This result, when compared to the $\Delta\tau$ values indicated above, reveals an interesting relationship between chemical shift and steric interactions.



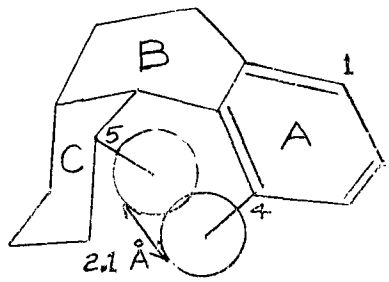
Type A (B/C trans)



Type B (B/C cis)



Type C (B/C cis)



Type D (B/C cis)

Figure 46

The data presented in Table 2 reveal a close agreement between the various measurements conducted in our laboratory and those of Nagata (84).

A comparison of the $\Delta\tau_{1,4}$ values for the compounds XLVI (0.41) and XLV (0.39) (Tables 3) is interesting. These values are very similar to those obtained for the cis-syn-cis compounds presented in Table 2. In these latter compounds the C-4 proton signal occurs at highest field relative to the above compounds. An inspection of a molecular model of compound XLVI reveals that the unsaturated carbonyl system eliminates the interaction between the C-5 and C-4 protons. The above conformations illustrated above in Figure 46 do not apply to the bridged compound XLV, since ring A

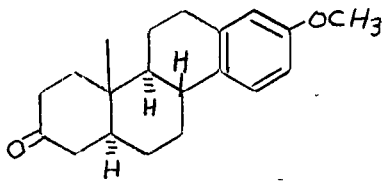
exists in a plane perpendicular to the rest of the molecule and therefore groups on ring A interact too strongly with those on rings C and D, particularly when ring B exists in a chair conformation. However, if ring B adopts a boat conformation, no steric interaction between the protons on C-4 and C-5 exists. The $\Delta\tau_{1,4}$ value of 0.39 obtained from the n.m.r. spectrum of XLV suggests that such a boat conformation may be present in solution. In contrast, an inspection of molecular models in which ring B exists in a chair conformation leads one to speculate that the severe steric interaction between these protons should provide a $\Delta\tau_{1,4}$ value of 0.5-0.6 regardless of the conformation of ring C.

It must be emphasized that, although such speculations are of interest, one must exercise considerable caution in attaching any conclusive significance to them.

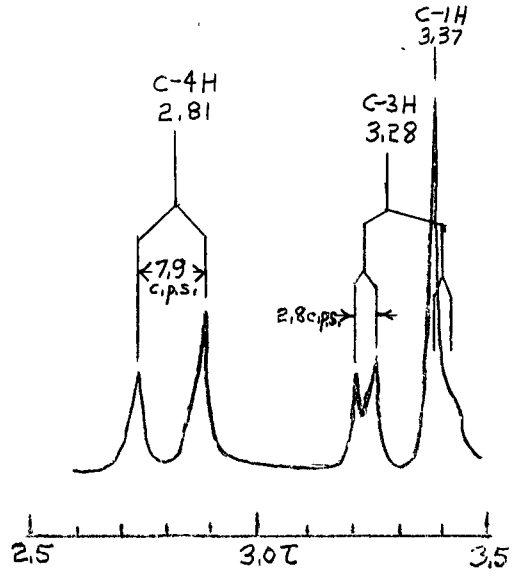
It is of interest to comment on the effect that the introduction of a 11,12-double bond has on the chemical shift of the aromatic protons. If one compares the values obtained for LXV and LXXI as given in the tables, it will be noticed that protons at C-1 and C-3 are affected less than the C-4 proton. Since the former protons are situated ortho and para, respectively, to the conjugated double bond, one may expect to observe changes in the chemical shifts of these atoms if electronic effects played a significant role. The experimental results indicated that the C-4 proton signal moves upfield by 0.16τ in the spectrum of LXXI — a situation again in agreement with the steric argument proposed by Nagata for the cases quoted above. A molecular model of LXXI shows that the olefinic bond in ring C has the overall effect of increasing the interatomic distance between the C-4 and C-5 protons so that they are now about 2.3 Å apart. Hence, one would expect considerably less deshielding in compound LXXI than in LXV if this steric interaction were taken into account.

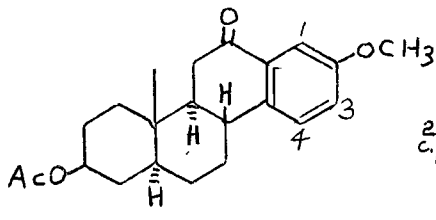
By putting a carbonyl group into position C-12 of XLV, all aromatic peaks are shifted downfield. This is expected since this group is strongly electron withdrawing. The relative magnitude of the shift of the resonances are in the normal order — ortho>para>meta. Hence, in this case, the C-1 proton signal is at lower field than that of the C-4 proton. In this respect it is interesting to compare the n.m.r. spectra of the 12-ketone LXVIII and the ring-opened dialdehyde, LXXIV. The latter compound also possess a carbonyl function in conjugation with the aromatic ring, but now this function is free to rotate and the amount of deshielding of the aromatic protons in the latter is considerably less than in the former. Clearly the rigidity of the cyclic 12-ketone fixes the orientation of this carbonyl group so that it lies essentially in the plane of the aromatic ring, and therefore one observes a significant influence in this case (see Figure 47 which compares the aromatic regions of the n.m.r. spectra of LXVIII and LXII). The 12-keto compound LXIX, which has unknown stereochemistry, has the aromatic protons absorbing in the same order as in the trans-anti-trans isomer, LXVIII. Interestingly, the differences of the chemical shifts between like protons of LXIX and LXVIII are almost the same — 0.25τ for C-1, 0.22τ for C-3, and 0.21τ for C-4 protons. The difference of about 0.2τ probably means that the B/C ring fusion is different for the two molecules.

One other group of compounds, which we also studied, has been omitted from Tables 2 and 3, because either poor resolution or the complexity of the aromatic proton region prevents any definitive assignments at this time. All of the compounds possess a 4b,10b-double bond, and examples which may be cited are the tetracyclic ketone (XLIII, Figure 8), ketol acetate XLIV (Figure 8) and the A/B cis dihydro XLIII (LXI, Figure 12). The aromatic regions of all these latter spectra are very similar and show in each instance two sets of multiplets — a lower field triplet and a higher field quintet (or sextet) which integrate for one and two protons, respectively.

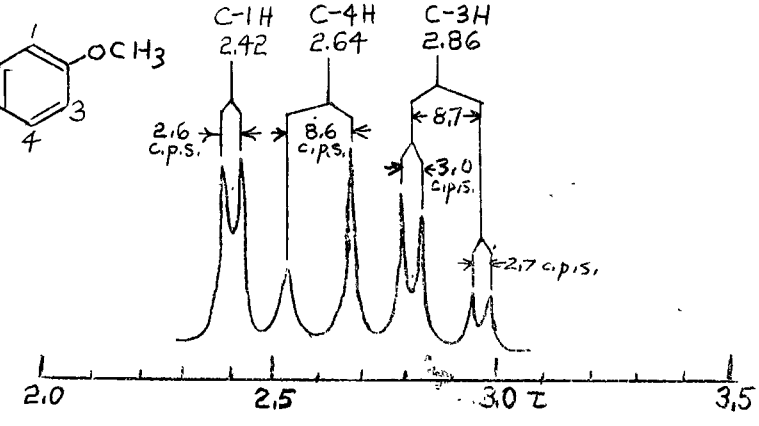


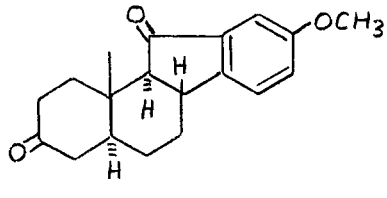
(LXII)





(LXVIII)





(LXXXI)

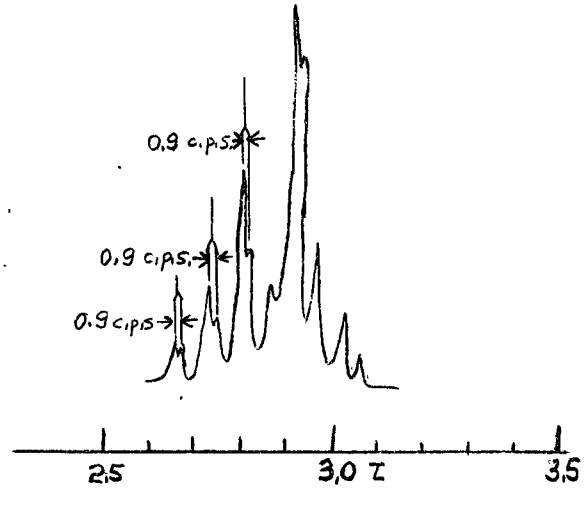


Figure 47

I would like now to discuss very briefly the aromatic region of the C-nor-D-homo compounds, LXXIX, LXXXI and LXXXII. Firstly, only the signals in the aromatic region of LXXIX can be assigned with confidence. As expected, the n. m. r. spectrum of the latter shows that the C-1 proton signal occurs at low field with respect to the C-3 resonance, since the C-1 proton is in close proximity to the C-11 hydroxyl group. The actual influence of contracting ring C cannot be ascertained at this time, since insufficient data is available at present. Unfortunately the aromatic region of the trans-syn-cis diketone LXXXII is poorly resolved, but the corresponding region for the trans-anti-trans diketone LXXXI is resolved into two sets of multiplets. The lower field multiplet, which integrates for one proton, shows six lines (J about 0.9 c.p.s.) as shown in Figure 47. The upper field multiplet is also split into six lines but integrates for two protons. It is clear from Figure 47, which shows the corresponding aromatic region for the 12-keto compound LXVIII, that the contraction of ring C can have a profound effect on the splitting patterns in this region. However, no generalizations can be made until further studies become available.

Having considered the aromatic region of the 3,4-disubstituted anisole system, it is now appropriate to extend our discussion to the more complex 2,5,6-trisubstituted naphthalene system which is present in the 2-methoxy-hydrochrysene compounds in which rings C and D are aromatic. These substances were available from my own previous studies as well as from investigations conducted by P. Roller and T. Inaba in this laboratory. The assignments of aromatic proton resonances in this latter series are summarized in Tables 4 and 5. The n. m. r. spectra in the above compounds are quite unique, and, although no unambiguous methods were sought to confirm the assignments, the justifications presented here conform well with arguments put forward by earlier authors. In this regard special attention is directed to an excellent article by Dudek (124) wherein he discusses the n. m. r. spectra of

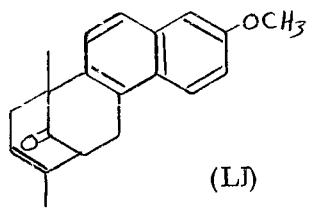
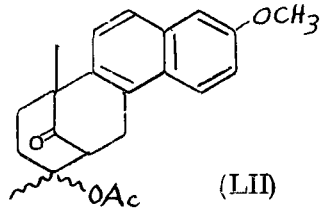
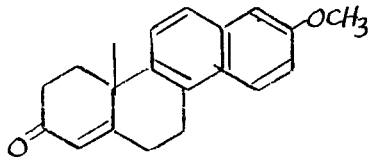
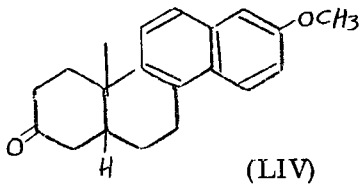
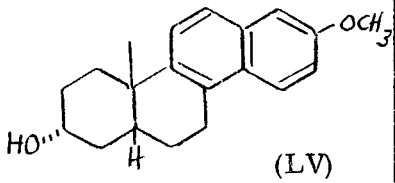
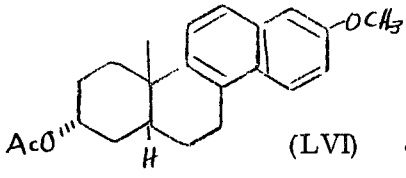
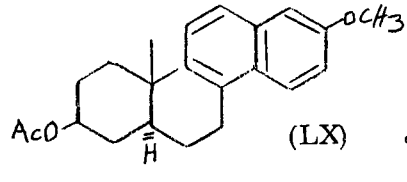
Compound	C-4 H	C-12 H	C-11 H	C-3 H	C-1 H
 (LJ)					2.87 (428)
 (LII)					2.85 (429.2)
 (LIII)	$J_{4,3}=10.4$	$J_{12,11}=9.5$			2.89 (427)
 (LIV)	2.22 (466.6) $J_{4,3}=10$	2.47 (451.9) $J_{12,11}=8.5$	2.62 (442.5) $J_{11,12}=9$	$J_{3,1}=2.3$	2.98 (421.3)
 (LV)	2.24 (465.5) $J_{4,3}=9.7$	2.53 (448.4) $J_{12,11}=8.6$	2.70 (438) $J_{11,12}=9.2$	$J_{3,1}=2.3$	3.00 (420)
 (LVI)	2.21 (467.3) $J_{4,3}=9.8$	2.50 (450) $J_{12,11}=8.8$	2.66 (440) $J_{11,12}=9.0$	$J_{3,11}=2.8$	2.98 (421)
 (LX)	2.16 (470.1) $J_{4,3}=10.2$	2.48 (451.0) $J_{12,11}=8.8$	2.59 (444.6) $J_{11,12}=8.8$	$J_{3,1}=2.3$	2.94 (423.3)

Table 4. Aromatic Proton Assignments of Various Hydrochrysene Derivatives.

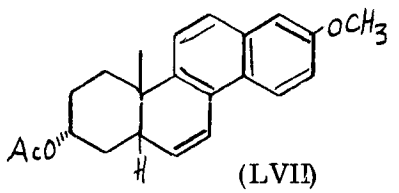
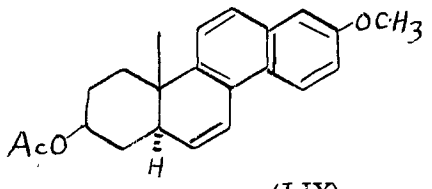
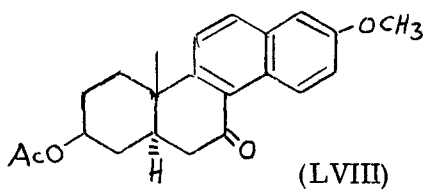
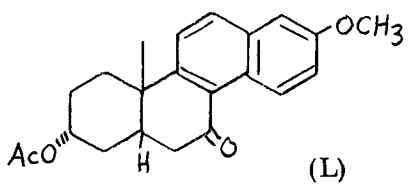
Compound	C-4H	C-12H	C-11H	C-3H	C-1H
 (LVII)	2.01 (479.4) $J_{4,3}$=10.3	2.37 (458.1) $J_{12,11}$=8.8	2.59 (444.7) $J_{11,12}$=8.7		2.93 (424.5)
 (LIX)	2.01 (479.3) $J_{4,3}$=10.3	2.40 (456.0) $J_{12,11}$=8.3	2,62 (443.0) $J_{11,12}$=8.8		2.93 (424.1)
 (LVIII)	0.93 (545) $J_{4,3}$=9	2.16 (470.5) $J_{12,11}$=8.7	2.55 (446.8)		
 (L)	0.78 (554) $J_{4,3}$=9.2	2.16 (470.3)	2.61 (443.3) $J_{12,11}$=8.4		

Table 5. Aromatic Proton Assignments of Various Hydrochrysene Derivatives.

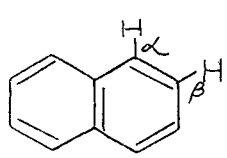
Unsaturated Compound	$\Delta\tau = \tau_{saturated} - \tau_{unsaturated}$					olefinic protons	
	C-4H	C-12H	C-11H	C-3H	C-1H		
LXXI	+.16			+0.04	+.05	3.66 (380.5) J = 10, 2.5	4.08 (355.0) J=10
						C-5H	C-6H
LVII	-.20	-.13	-.07		-.05	~ 2.9	3.92 (364.8) J = 9.9, 6.1
LIX	-.15	-.08	+.03		-.01	~2.9	4.20 (348) J=10, 2.5

Table 6, Effects of Double Bond on the Aromatic Proton Resonances in Some Hydrochrysene Analogues.

polysubstituted naphthalenes, and, in particular, the polysubstituted 2-methoxy-naphthalene systems. Some rationalizations presented in the following paragraphs lend meaning to the assignments made in Tables 4 and 5 (Figures 48 and 49).

The intense broad signal appearing in the region 2.8-3.0τ was assigned to the C-1 proton, and the partially hidden quartet ($J_{3,1}$ about 2 c.p.s., $J_{3,4}$ about 9 c.p.s.) for the C-3 proton appears at slightly lower (about 0.1τ) field. The reason for these two protons absorbing at higher field than the other aromatic protons is the same as was given in the previous discussion on the ring D aromatic compounds. In the 5-keto compounds, LVIII and L, the C-1 proton signal is split to such an extent that one cannot distinquish it from the C-3 proton resonance, and hence no assignment was given. It is interesting to note that in general the C-1 protons signal in this series appears at lower field (about 0.4-0.6τ) than the corresponding signal in the n.m.r. spectra of compounds with the aromatic system in ring D only (see Tables 2 and 3, excluding compounds with a carbonyl or olefinic function at C-12). This shift is due to the additional paramagnetic effect created by an extra aromatic ring in the octahydrochrysene system.

Before proceeding to a more detailed discussion, it is necessary to review the n.m.r. data already available for the unsubstituted naphthalene system (XCVI). It is known that the β-proton signal is usually 0.34τ to higher field than the α-proton signal, because the latter is more proximate to the center of the extra aromatic ring. However, substitution of a methoxyl group at C-2 alters the resonance frequencies for the C-1 and C-3 protons. Although the electron donating methoxyl group has an overall shielding effect on all ring protons, the resulting effect was found to be one in which the α-proton (C-1H) signal appears about 0.1τ higher than the β-proton (C-3H) resonance. This can be rationalized in the following way: using valence bond structures with the second ring fully aromatic (see p), any inductive effect of a 2-methoxyl substituent can appear at the C-1 position.



(XCVI)

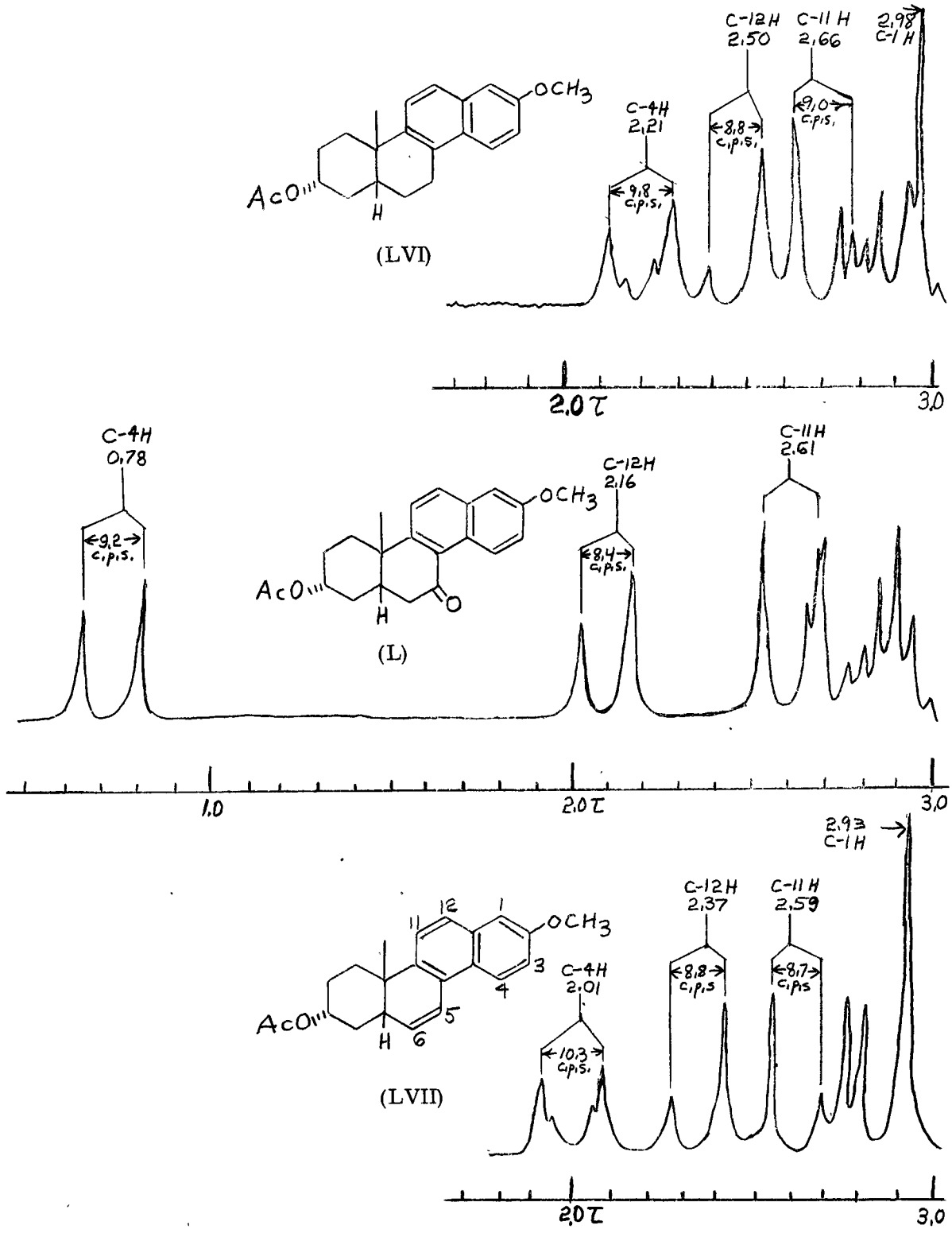

OCH3
AcO
H
(LVI)
C-12H
2,50
C-11H
2,66
2,98
C-1H
C-4H
2,21
9,8
c.p.s.
8,8
c.p.s.
9,0
c.p.s.
2.0τ
3.0
C-4H
0,78
9,2
c.p.s.
C-12H
2,16
8,4
c.p.s.
C-11H
2,61
O
(L)
1.0
2.0τ
3.0
2,93
C-1H
C-12H
2,37
C-11H
2,59
12
1
11
3
4
5
6
C-4H
2,01
10,3
c.p.s.
8,8
c.p.s
8,7
c.p.s
(LVII)
2,0τ
3,0

Figure 48

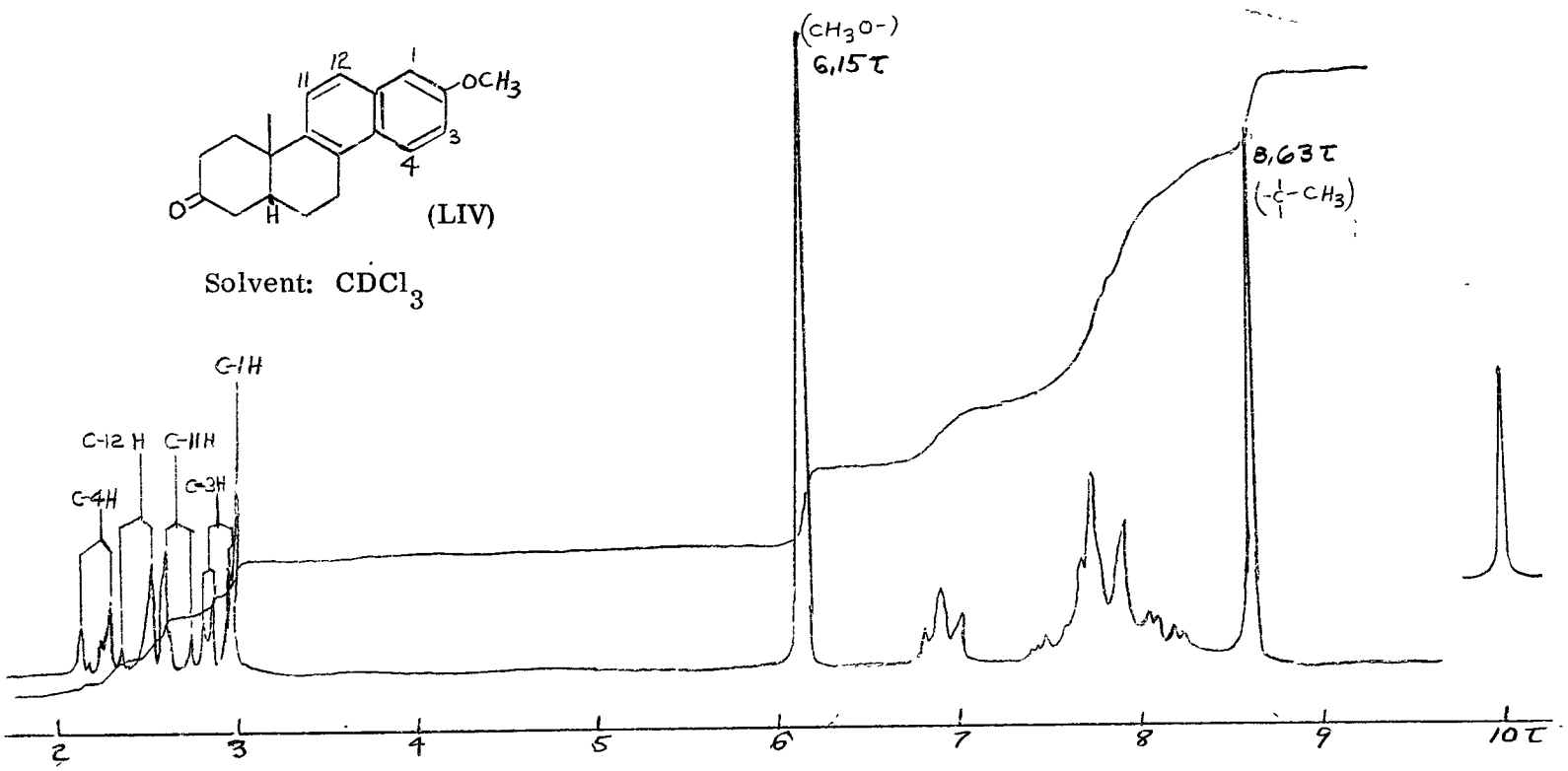
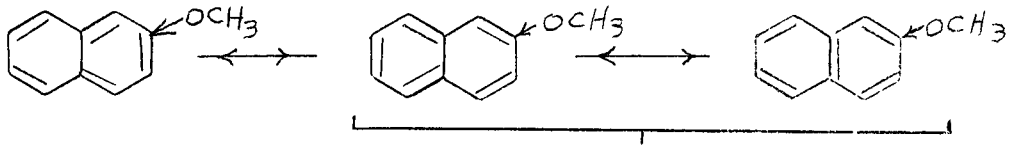

12
11
1
OCH3
3
4
O
H
(LIV)
Solvent: CDCl3
(CH3O-)
6,15 τ
8,63 τ
(-C-CH3)
C-1H
C-12 H
C-11H
C-4H
C-3H
2
3
4
5
6
7
8
9
10 τ

Figure 49



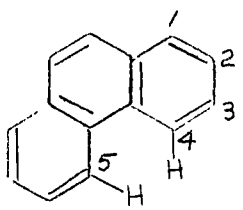
q p

but for the inductive effect to be transmitted to the C-3 position the second ring must be quinonoid (see q). These observations are in good agreement with results expressed by Dudek (124) on methoxy substituted naphthalenes.

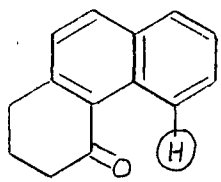
With the above data on hand it is now possible to consider the remaining aromatic protons in the octahydrochrysene compounds. As expected the C-11 and C- 12 protons gave rise to an AB quartet with a splitting constant, $J_{11,12}$ of about 9 c.p.s. Since the C-11 proton is a β-type the higher field doublet was assigned to this proton. The difference in chemical shift between the two doublets was found to be 0.11 to 0.17τ for compounds like LV, 0.22τ for 5,6-dehydro derivatives, and 0.39-0.45τ for the octahydrochrysene analogues possessing a keto group at C-5. The introduction of a double bond or carbonyl function into ring B has a deshielding effect on both protons, but a greater effect on the para C-12 proton. As a result a wider separation of doublets occurs. A paramagnetic shift of an aromatic proton situated para to a carbonyl group has been reported in the literature (125.)

The C-4 hydrogen atom was found to resonate at lowest field in the octahydrochrysene structure examined. This proton appears as a clean doublet in the instances where a functional group in ring B lowers its position of absorption. This situation prevails in the n.m.r. spectra of 5-keto compounds LVIII and L.

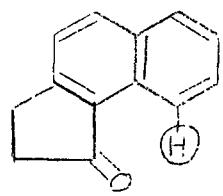
Previously, Reid (126) had related the deshielding observed for protons C-4 and C-5 of phenanthrene (XCVII) and its 1,2- and 3,4-dihydro derivatives to the change in electron distribution in the C-H bond which must occur when repulsive forces come into play between sterically close hydrogen atoms. Also the re-entrant position of hydrogen atoms at C-4 and C-5 brings these protons close to aromatic rings



(XCVII)



(XCVIII)



(XCIX)

other than those to which they are attached. More recently Nagata in his publication (84), which was mentioned earlier in the discussion, arrived at the same conclusion in his study of aromatic ring A protons in the octahydrophenanthrene series.

Also recently a series of articles by Martin (125) have dealt with the n. m. r. spectra of numerous fused aromatic hydrocarbon systems. Of significance to the present discussion are the n. m. r. results obtained for compounds of the types XCVIII and XCIX. Martin was able to show that the signals for the "peri" hydrogen atoms (circled) occurred at 0.58 τ (565 c.p.s.) and 0.85 τ (549 c.p.s.), respectively.

I would now like to return to the discussion of our results in the octahydrochrysene series. First of all, the abnormal deshielding of the C-4 proton in the molecules having a C-5 carbonyl function deserves comment. This effect is due to the diamagnetic anisotropy of this function (Figure 50) where protons so positioned as to be inside the cone will be shielded, and those close to the plane of the trigonal carbon atom of the carbonyl group will be deshielded (127). Secondly, the distance between the oxygen atom and the C-4 proton is certainly less than the normal hydrogen bond distance in many strong hydrogen bonds (usually

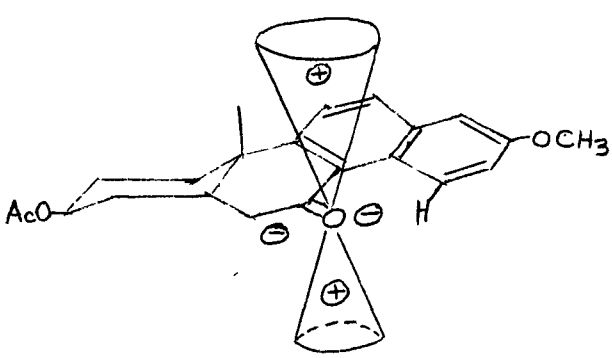


Figure 50

about 2.7 Å). It should be noted that the resonances of the C-4 hydrogen atom are also considerably lowered by the presence of a 5,6-double bond as shown in the spectra of LVII and LIX (Table 5). According to the literature (128), a double bond acts like a carbonyl group in that the former can also deshield protons which are in the same plane as the trigonal carbon atoms. As expected this deshielding is smaller than that of the carbonyl group, because the carbon atoms of the double bonds are further removed from the C-4 hydrogen atom than the oxygen atom of the carbonyl function.

It is interesting to compare the general effect of placing a double bond in conjugation to the aromatic system in the hydrochrysene series studied above. There is a striking difference in the n.m.r. spectra of compounds having a double bond at the 11,12 position, as for example in LXXI, and those in which the olefinic linkage is at the 5,6 position, as in compounds LVII and LIX. For comparison purposes, the changes in the chemical shift ($\Delta\tau$) of the aromatic protons created by introduction of a double bond, and the data on the resonances of the olefinic protons are recorded in Table 6. Firstly, it will be noted that in compound LXXI, in which a 11,12-double bond is present, the aromatic protons are shielded; that is, $\Delta\tau$ is positive. On the other hand, the 5,6-double bond in compounds LVII and LIX causes the aromatic protons to resonate at lower field so that $\Delta\tau$ is a negative value (except C-11 of LIX). These data would suggest that caution is needed in predicting the effect that a vinyl substituent would have on an aromatic system. As may be expected, the substituent on C-4b exerts a more pronounced effect on the C-12 proton than on the C-11 proton. This is reasonable since C-12, by virtue of its para relationship to the double bond, would be influenced if resonance effects played any role. It is also of interest to note the relatively large deshielding of the C-4 aromatic proton caused by the introduction of the 5,6-double bond into LVI and LX. The principle reason for the deshielding of this proton is unknown at this time.

It is now appropriate to make a few comments about the olefinic protons of

compounds LXXI, LVII and LIX. In the previous section of the thesis I had suggested that the low field quartet at 3.66τ in the n.m.r. spectrum of LXXI was due to the C-11 proton, while the high field doublet at 4.08τ was associated with the C-12 proton. Although this suggestion appears most reasonable at the present time there is an alternate possibility which I would like to mention presently. The above assignments were made in consideration of vicinal and allylic coupling constants as they are normally observed. It is known from the published literature that under normal circumstances the vicinal coupling constant (as for example between protons at C-11 and C-10b) is greater than the allylic coupling constant (for example between protons at C-12 and C-10b). In general, allylic coupling is in fact very small and is often not observable. On this basis one would therefore expect that the C-11 proton should appear as a quartet since it is spin coupled to the protons on C-12 and C-10b, whereas the C-12 proton should appear as a doublet since it couples with the vicinal C-11 proton. In actuality these splitting patterns are observed in the n.m.r. spectrum of LXXI, and it is tempting to make the assignments as quoted above. However, one must exercise caution in eliminating the possibility of significant allylic coupling, since Collins, Hobbs and Sternhell have stated that an allylic coupling may be as large as 3.1 c.p.s. (129). Since one of the J values of the above quartet was less than 3.1 c.p.s. (J = 2.5 c.p.s.), the reverse assignment of olefinic protons is not entirely unreasonable. Further n.m.r. data on deuterated derivatives of LXXI would be needed to prove unambiguously the assignments of these resonances. The situation is quite clear in the assignments of the olefinic signals in the spectra of LVII and LIX. From Reid's n.m.r. data of 1,2-dihydrophenanthrene (126) and its 4-deuterio derivative it can be seen that the high field quartets at 3.92τ and 4.20τ in the n.m.r. spectra of LVII and LIX, respectively, must be assigned to the C-6 proton. Moreover, the C-5 proton, like the corresponding proton (C-4) in 1,2-dihydrophenanthrene, resonates in the aromatic region (about 2.9τ). The vicinal coupling constant,

$J_{6,6a}$ = 6.1 c.p.s. in the A/B cis compound LVII, whereas it is only 2.5 c.p.s. in the spectrum of the A/B trans isomer, LIX. This difference in coupling between the two compounds is to be expected. Molecular models reveal that the dihedral angle between the C-6a and C-6 protons in the A/B cis case is small, whereas the corresponding angle in the A/B trans case approaches 90^{o}. The relationship between coupling constants and dihedral angle is discussed by Bhacca and Williams (93).

I would now like to mention several other pertinent regions in the n.m.r. spectra of the hydrochrysene series. Tables 7-10 record the τ values of the angular methyl and methoxyl proton resonances of a large number of compounds. The signals of the methyl groups attached to olefinic carbon atoms (XCIV and LI) as well as the secondary methyl proton signals of XLV, XLIV and LII are also recorded for comparison. Of course the latter two types of methyl protons resonate at lower field than those of the angular methyl groups.

The methoxyl resonances may be grouped into three regions: the protons absorbing in the vicinity of 6.15 τ, those at 6.25 τ and finally those at 6.47 τ. The latter group absorbs at higher field than the first two, because the methoxyl function is only attached to a olefinic bond whereas in the other cases it is joined to an aromatic ring. Finally, it will be noted that the methoxyl protons in the C,D-ring aromatic series resonate at lower field than the methoxyl protons in the compounds in which only ring D is aromatic. This situation is analogous to the one encountered in comparing the chemical shifts of the aromatic protons in the two series.

Since the angular methyl proton resonances are much more sensitive than the methoxyl signals to stereochemical changes or substituent effects, it is appropriate to discuss them in greater detail. A considerable number of papers (130-139) have been published on the n.m.r. behaviour of angular methyl groups, and hence, for the

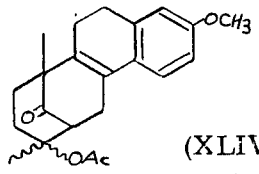
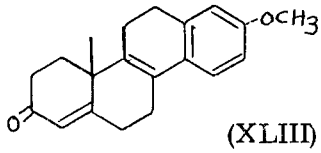
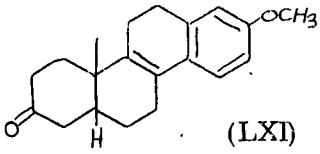
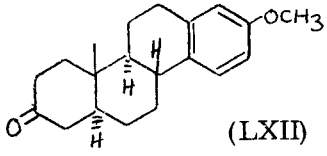
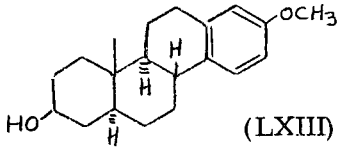
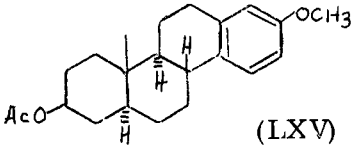
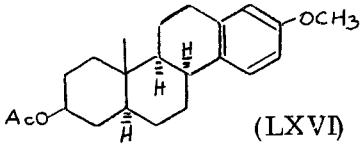
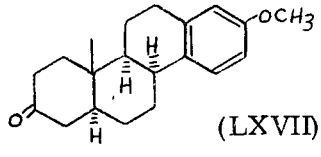
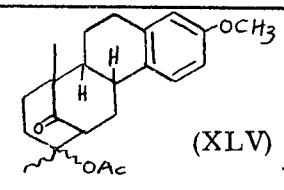
Compound	$CH_3-\overset{C}{\underset{C}{|}}-C$, τ(c.p.s.)	CH_3O- , τ(c.p.s.)
 (XLIV)	8.85 (69) 8.38 (97)	6.22 (227)
 (XLIII)	8.57 (86)	6.23 (226)
 (LXI)	8.75 (75)	6.22 (227)
 (LXII)	8.99 (60.5) 8.97 (62) *	6.26 (224.5) 6.25 (225) *
 (LXIII)	9.17 (49.5)	6.24 (225.5)
 (LXV)	9.17 (50)	6.27 (224)
 (LXVI)	9.76 (14.5)	6.24 (225.5)
 (LXVII)	9.60 (24) *	6.22 (227) *
 (XLV)	8.95 (63) 8.50 (90)	6.27 (224)

Table 7. N.M.R. Data on the Angular Methyl and Methoxyl Protons of Hydrochrysene Analogues. *Refers to values as given in ref. (84).

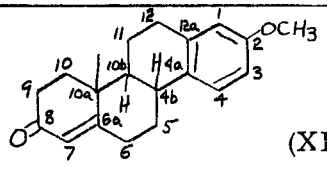
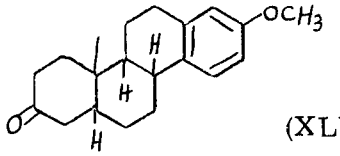
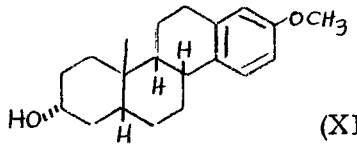
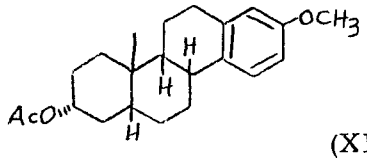
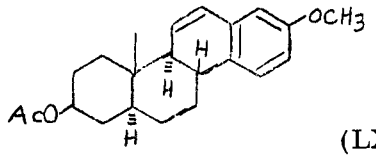
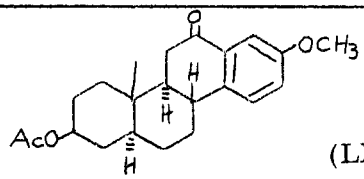
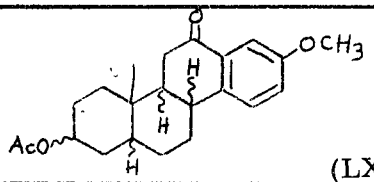
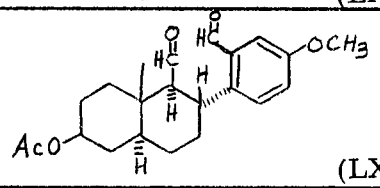
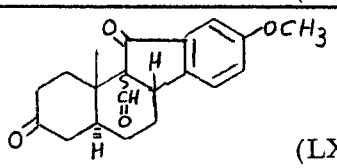
Compound	$CH_3-\overset{C}{\underset{1}{C}}-C$, τ(c,p,s,)	CH_3O- , τ(c,p,s,)
 (XLVI)	8.58 (85)	6.27 (224)
 (XLVII)	8.80 (72) *	6.23 (226) *
 (XLVIII)	8.92 (65)	6.27 (224)
 (XLIX)	8.90 (66)	6.27 (224)
 (LXXI)	9.15 (51)	6.29 (222.5)
 (LXVIII)	9.05 (56.7)	6.15 (231)
 (LXIX)	8.88 (67)	6.27 (224)
 (LXXIV)	8.85 (69)	6.19 (228.5)
 (LXXX)	8.78 (73)	6.19 (228.3)

Table 8. N. M. R. Data on the Angular Methyl and Methoxyl Protons of Hydrochrysene Analogues. *Refers to values as given in ref. (84).

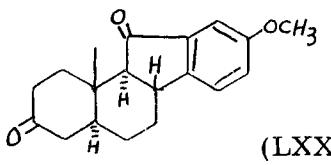
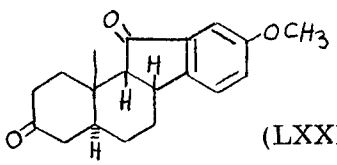
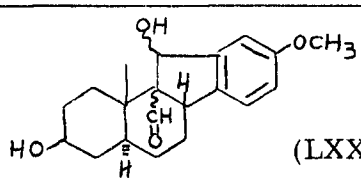
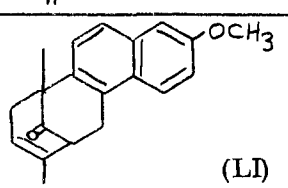
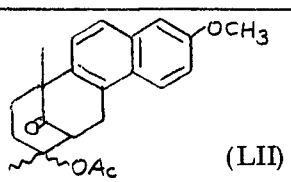
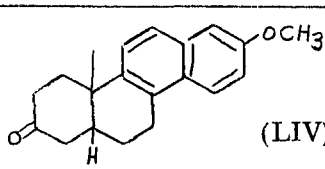
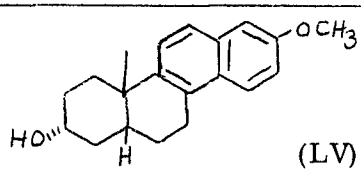
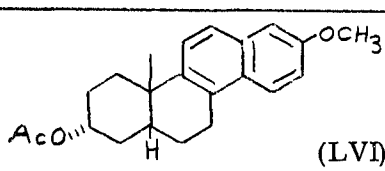
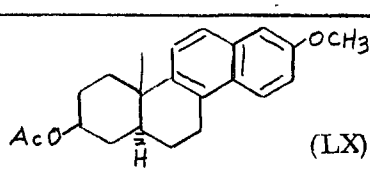
Compound	$CH_3-\overset{C}{\underset{1}{C}}-C$, τ(c.p.s.)	CH_3O-, τ(c.p.s.)
 (LXXXI)	8.85 (69)	6.23 (226)
 (LXXXII)	8.74 (75.5)	6.18 (229)
 (LXXIX)	8.90 (65.5)	6.23 (226)
 (LI)	8.48 (91) 8.32 (101)	6.12 (233)
 (LII)	8.47 (92) 8.32 (101)	6.10 (234)
 (LIV)	8.63 (82)	6.15 (231)
 (LV)	8.83 (70)	6.17 (230)
 (LVI)	8.78 (73)	6.17 (230)
 (LX)	8.81 (71.4)	6.11 (233.5)

Table 9. N. M. R. Data on the Angular Methyl and Methoxyl Protons of Hydrochrysene Analogues.

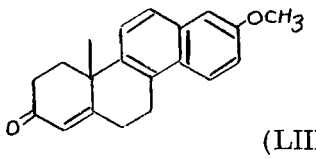
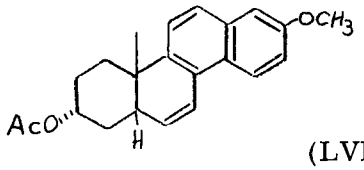
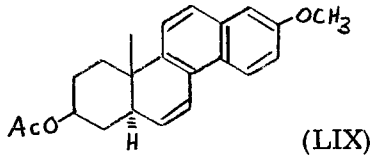
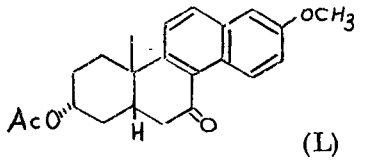
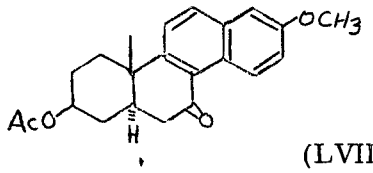
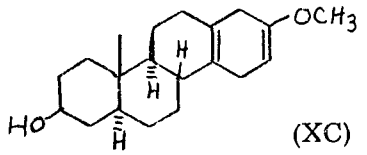
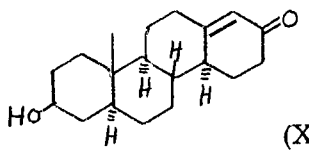
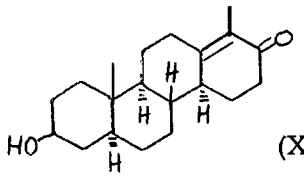
Compound	$CH_3-\overset{C}{\underset{I}{C}}-C$, τ(c.p.s.)	CH_3O-, τ(c.p.s.)
 (LIII)	8.37 (98)	6.10 (234)
 (LVII)	8.90 (66)	6.14 (231.6)
 (LIX)	8.93 (64)	6.10 (234)
 (L)	8.63 (82)	6.12 (233)
 (LVIII)	8.76 (74.4)	6.10 (234)
 (XC)	9.22 (47)	6.47 (212)
 (XCII)	9.24 (45.5)	
 (XCIV)	9.25 (45) 8.22 (107)	

Table 10. N. M. R. Data on the Angular Methyl and Methoxyl Protons of Hydrochrysene Analogues.

purpose of comparison, the $\Delta\tau$ values between the methyl resonances of different compounds are tabulated in Tables 11 and 12. The changes found in the trans-anti-trans or trans-anti-cis compounds, and the cis-syn-cis molecules upon reduction of the 8-carbonyl group to the equatorial 8-hydroxyl function are the same as those in the 5α- and 5β -steroids, respectively, (137). This data lends further support to the assignment of stereochemistry in the rings A and B of our compounds. It is interesting to see that the angular methyl protons of the β-cis compounds have a tendency to absorb at lower field than those of the trans isomers. This observation is in accord with the fact that the C-19 and C-18 angular methyl resonances of the 5β- and 14β-androstanes are at lower field than those of the trans epimers (140).

A brief mention should be made of the acetate methyl proton signals in the C-8 acetoxy compounds. As expected these protons absorb in the 8 τ region, and, as Table 13 indicates, there are small but significant differences in the various compounds studied. It will be noted that these proton resonances fall roughly into three groups. The signals in the compounds, LXV to LXXIV, in which only ring D is aromatic are relatively unaffected by a change in stereochemistry, but the C, D-ring aromatic molecules, LX to L, are quite sensitive to such a change. The A/B trans molecules (LX, LIX and LVIII) exhibit the acetate methyl signals at slightly lower field perhaps because the acetoxyl function is in the plane of the naphthalene system. On the other hand, the higher τ values of this group in the A/B cis compounds (LVI, LVII and L) are due to the shielding caused by the protons being out of the plane of the above aromatic system. It is obvious that this is not an entirely satisfactory explanation and other unknown factors may be operative.

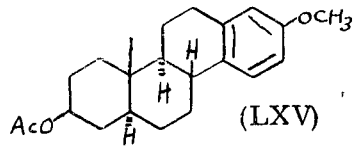
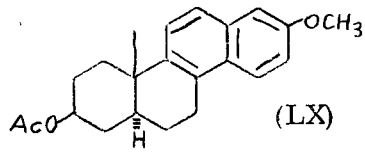
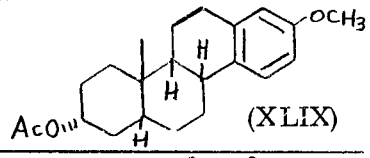
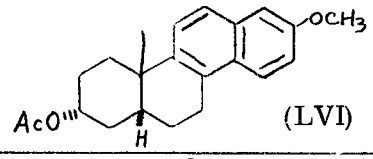
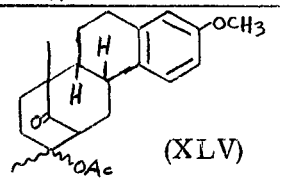
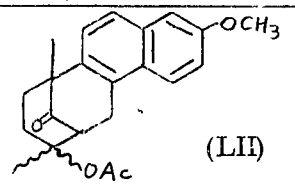
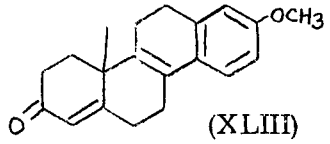
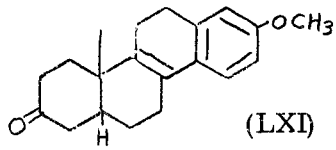
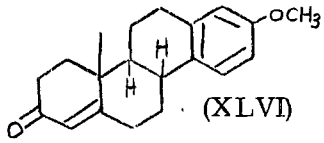
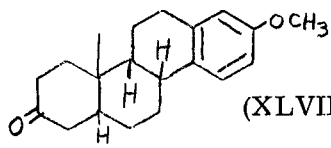
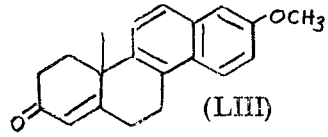
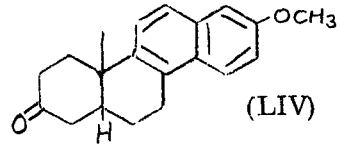
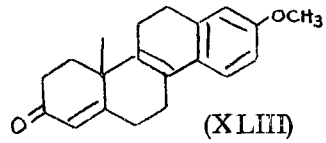
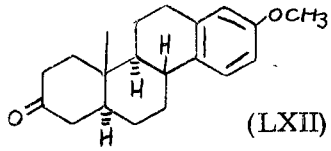
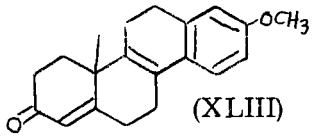
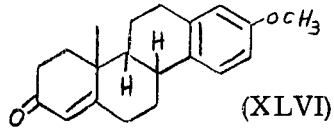
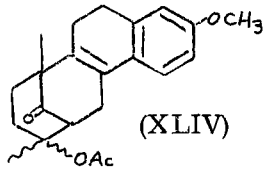
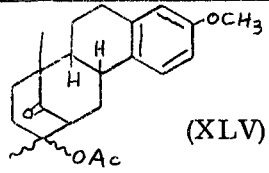
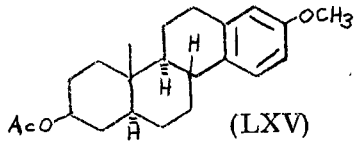
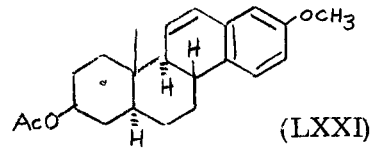
Compound a	Compound b	change of $CH_3-C<$ $\Delta\tau = \tau_b - \tau_a$
 (LXV)	 (LX)	-0.36
 (XLIX)	 (LVI)	-0.12
 (XLV)	 (LII)	-0.48
 (XLIII)	 (LXI)	+0.18
 (XLVI)	 (XLVII)	+ 0.22
 (LIII)	 (LIV)	+0.26
 (XLIII)	 (LXII)	+0.40
 (XLIII)	 (XLVI)	+0.01
 (XLIV)	 (XLV)	+0.10
 (LXV)	 (LXXI)	- 0.02

Table 11. Effects of Structural Variations on Proton Resonances in Some Hydrochrysene Analogues.

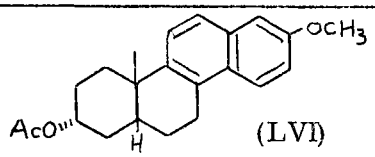
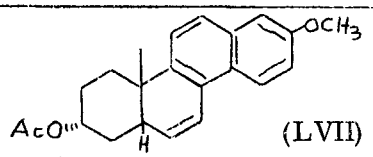
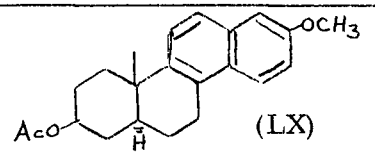
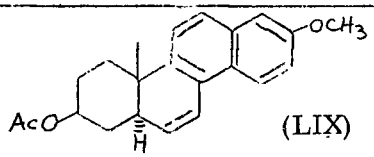
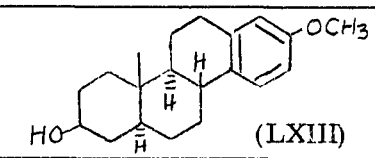
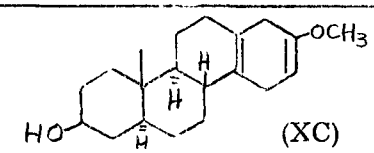
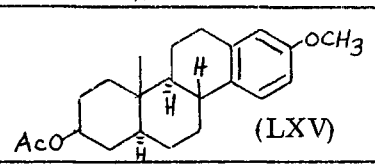
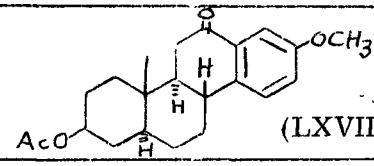
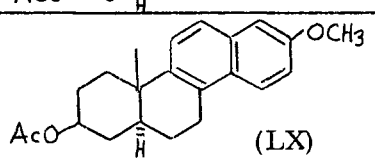
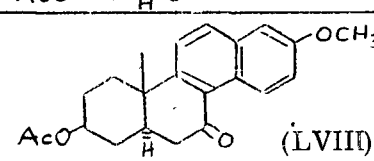
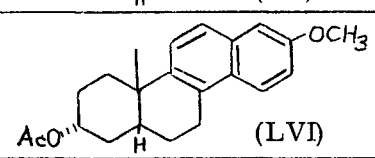
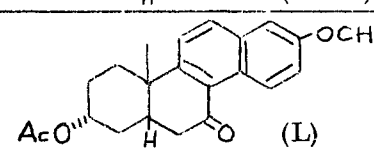
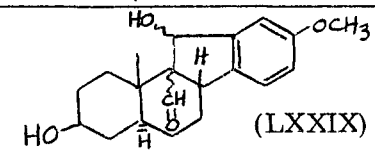
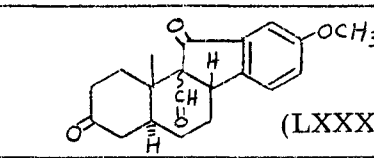
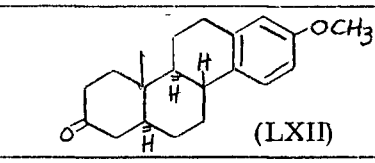
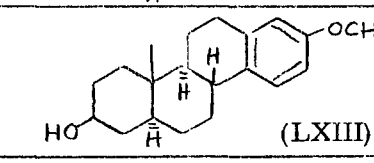
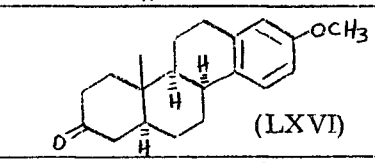
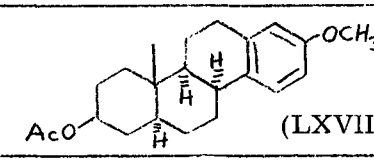
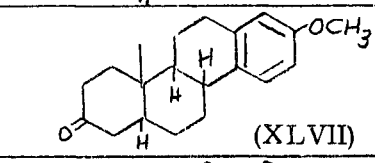
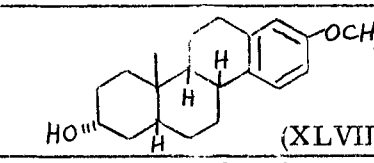
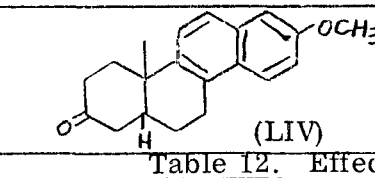
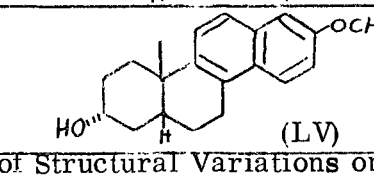
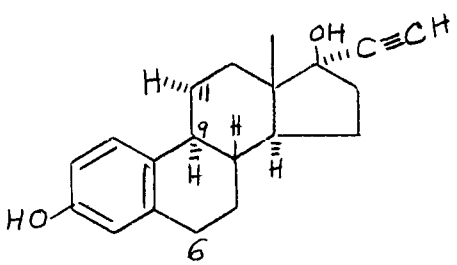
Compound a	Compound b	change of CH_3-C< $\Delta\tau = \tau_b - \tau_a$
 (LVI)	 (LVII)	+ 0.12
 (LX)	 (LIX)	+ 0.12
 (LXIII)	 (XC)	+ 0.05
 (LXV)	 (LXVIII)	- 0.12
 (LX)	 (LVIII)	- 0.05
 (LVI)	 (L)	- 0.15
 (LXXIX)	 (LXXX)	- 0.12
 (LXII)	 (LXIII)	+ 0.18
 (LXVI)	 (LXVII)	+ 0.16
 (XLVII)	 (XLVIII)	+ 0.12
 (LIV)	 (LV)	+ 0.20

Table 12. Effects of Structural Variations on Proton Resonances in Some Hydrochrysene Analogues.

Ring D aromatic compounds	AcO- , τ (c.p.s.)	C,D-ring aromatic compounds		AcO- , τ (c.p.s.)
LXV	8.00 (120)	A/B trans.	LX	7.95 (123)
XLIX	8.00 (120)		LIX	7.94 (123.3)
LXVI	8.02 (118.5)		LVIII	7.94 (123.5)
LXXI	8.02 (118.5)			
LXVIII	7.97 (122)	A/B cis.	LVI	8.13 (112)
LXIX	8.02 (118.5)		LVII	8.14 (111.5)
LXXIV	7.98 (121)		L	8.13 (112)

Table 13. N.M.R. Data on the Acetate Methyl Protons of Various Hydrochrysene Derivatives.

The n.m.r. spectra of the hydrochrysene analogues studied also exhibited signals in the 7-8τ region, but before discussing these any further it is pertinent to mention the n.m.r. data for compound C. In the latter the three benzylic protons attached to C-6 and C-9 are evident as a broad band centered at 7.20τ(141). Similarly, the benzylic protons of the ethyl toluene and isopropyl toluene absorb at 7.38τ and 7.13τ, respectively (142). The low field position of these protons is attributed mainly to the anisotropy of the magnetic susceptibility of the π-system of the aromatic ring. If we now turn to examine the spectra of trans-anti-trans, trans-anti-cis, cis-syn-cis and syn-cis hydrochrysene compounds, two distinct splitting patterns are revealed in the above region. The latter two groups of compounds possess signals in this region which integrate for three protons, whereas the former



(C)

two groups show an integration for four protons. From previous work in the literature, a few examples of which are cited above, only three protons would be expected in this region. Initially it was thought that the extra proton resonating at low field may be the C-5β equatorial proton because of its close proximity to the aromatic ring. However, a comparison with molecular models of the C-5β proton with its counterpart, the C-11α equatorial proton, in compound C does not show any significant difference between the environments of these atoms. Clearly more work is needed to resolve unambiguously the assignments of protons resonating in this region of the n.m.r. spectrum, but the following observation may be of some importance. The trans-anti-trans-11,12-dehydro-8-acetate, LXXI (Figure 12), possesses signals in the region 7.0-7.9τ (Figure 35) which integrate for two hydrogen atoms, while the 12-keto-8-acetates, LXVIII (Figure 33) and LXIX (Figure 34), exhibit signals integrating for four protons. Since three of these latter protons can be readily assigned to the two C-11 and the C-4b protons, the remaining signal may be possibly due to the C-10b proton.

Table 14 lists the position of the benzylic proton resonances of the octahydrochrysene derivatives. It will be noted that all these compounds show values which are much lower than those for like protons in the ring D aromatic molecules. This extra deshielding is due to the fact that the benzylic protons are deshielded in the former substances by two aromatic rings, whereas these protons are only deshielded by one

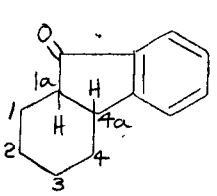
Compound		τ (c.p.s.)	
A/B bridged	LI	6.37	(218)
	LII	6.48	(211)
A/B cis	LIV	6.90	(186)
	LV	6.98	(181)
	LVI	6.95	(183)
A/B trans	LX	6.80	(192)

Table 14. N.M.R. Data on the Benzylic Protons of the Octahydrochrysene Analogues.

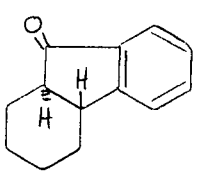
aromatic ring in the latter molecules. It is also apparent that the values given for the

bridged compounds, LI and LII, are significantly lower than for the other compounds listed in Table 14.

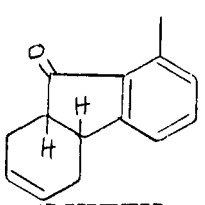
Now I would like to discuss the low field methylene and methine protons, which are not geminal to a hydroxyl group, and which are observed in the spectra of the C-nor-D-homo compounds. In the spectrum of the trans-anti-trans diketone, LXXXI, two protons (C-4b and C-10β) absorb in the region, 6.91-7.29τ (Figure 39), whereas in the spectrum of the trans-syn-cis isomer, LXXXII, a similar absorption is noted in the region, 6.31-6.83τ (Figure 41), for the C-4b and C-10α protons. The absorption at lower field in the latter compound also supports the assignment of stereochemistry made in the previous section. Molecular models immediately reveal that the C-4b proton in LXXXI is more out of the plane of the aromatic ring than in LXXXII. Therefore, the latter proton would be expected to resonate at lower field, and this is indeed the case. Furthermore, models similarly show that the C-10α proton in LXXXII is closer to the oxygen atom of the C-11 carbonyl group than is the corresponding C-10β proton in LXXXI. Hence, the C-10α proton would be predicted to resonate at lower field than the C-10β one. The following evidence will prove that the C-10b proton does <u>not</u> absorb at low field.



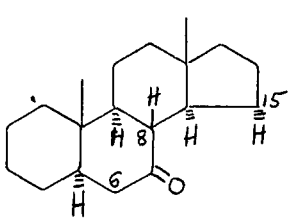
(LXXXVII)



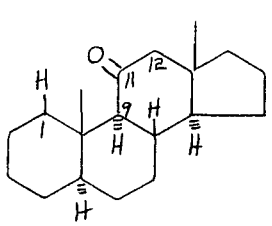
(LXXXVIII)



(LXXXIX)



(CI)



(CII)

Figure 51

It has been shown that in CI the C-8α (axial) and C-15α (pseudo equatorial) protons as well as those of C-6 resonate between 7.4-8.1τ. Moreover, it has been stated that in the spectrum of CII the C-1β proton has a peak at 7.55τ (doublet, J_{gem} = -12 c.p.s.) and a two proton singlet due to the C-12 protons at 7.73τ. Interestingly the C-9α (axial) hydrogen atom which might be also expected at low field does not in fact appear in this region (143). Also related to this discussion are the reported spectra of the compounds LXXXVII, LXXXVIII and LXXXIX (Figure 51). House and Carlson (99) have shown by deuteration studies on LXXXIX that the proton (C-1a) adjacent to the carbonyl group resonates at a higher field (7.0-7.3τ) than the benzylic proton (C-4b) (6.42τ). On the basis of the work of House and Carlson, Adamski and Cannon (144) in their n.m.r. data on LXXXVII assigned the quartets centered at 6.65τ ($J_{1a, 4a}$= 6-7 c.p.s., $J_{4, 4a}$ = 6-7 c.p.s.) and 7.35τ to the C-4a and C-1a protons, respectively. The same protons in the trans isomer LXXXVIII gave rise to very broad overlapping peaks centered at 7.0τ. It should be noted that the C-4a proton absorbs at higher field in the trans isomer than in the cis one. Recently, Johnson (52) reported some n.m.r. data on the diacetoxy aldehyde XXXVI (Figure 7). In this latter instance the C-4b proton gave a quartet at 6.33-6.67τ, while the formyl proton showed a singlet at 0.13τ.

With these results on hand it is possible to consider the n.m.r. spectra of the C-nor-D-homo compounds prepared in the present investigations. The n.m.r. spectrum of the diol aldehyde, LXXIX (Figure 38), shows a quartet centered at 6.50 τ(222.5, 216.5, 203.5 and 197.5 c.p.s.) which can be assigned to the C-4b proton which is spin-coupled to the two protons at C-5 . The diketo aldehyde, LXXX, however, has two low field protons —a doublet centered at 6.17τ (J=15 c.p.s.) and a complex multiplet in the region 6.49-6.92τ. One of these absorptions belongs to the C-4b hydrogen atom, while the other must be due to a C-10 proton in analogy with above work (143). The doublet is at a lower field than any corresponding

resonance observed in the spectra of the diketones LXXXI and LXXXII. This situation is quite reasonable when it is considered that in LXXX the formyl group can provide additional deshielding.

Now I would like to discuss the effect of solvents on the chemical shifts of the various protons studied in the n. m. r. investigations. It has been well established that certain solvents, particularly pyridine and benzene, can often exert sufficient influence on the chemical shifts and/or resolution of the spectrum to be of considerable aid in structural work. Slomp and MacKellar (145) demonstrated the effect of pyridine in the steroid series, and some previous work in our laboratory on hydrochrysene compounds (76) and steroidal sapogenins (146, 147) also showed similar results. More recently several groups have published their data on benzene-induced chemical shifts. For example, Connolly and McCrindle (148) studied n. m. r. solvent shifts of methyl groups in alicyclic ketones, and, on the basis of their results, they proposed the following generalization: if a reference plane "P" is drawn through the carbon atom of the carbonyl group as shown in Figure 52, then protons close to "P" show very small shifts ($\Delta\tau = \tau_{Benzene} - \tau_{Chloroform}$), whereas those on the side of the oxygen atom are deshielded and

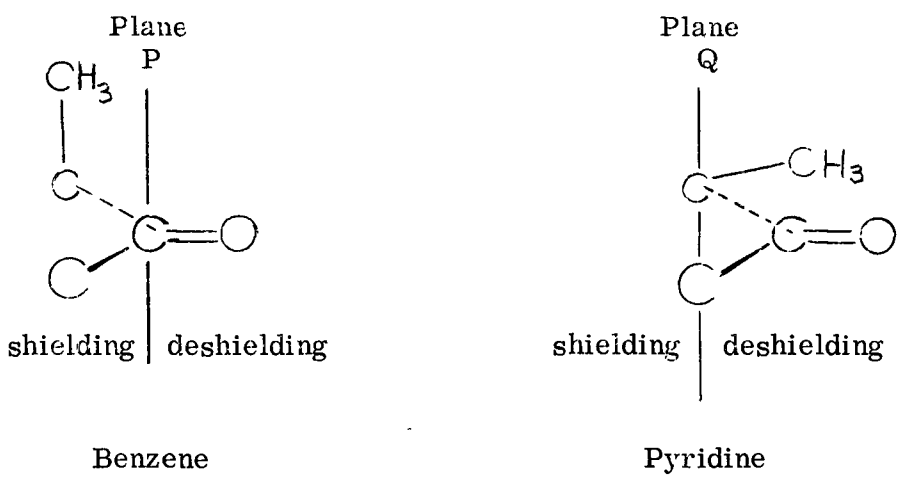


Figure 52

those on the other side are shielded. Moreover, the shifts appeared to be predictable. It was also reported that the shielding effect increased to a maximum and then decreased with distance behind the plane. Very recently, Williams (149) published his empirical "rule" for predicting the solvent shifts caused by pyridine. However, in his studies the reference solvent is carbon tetrachloride rather than the more commonly used deuteriochloroform. The corresponding correlation for $\Delta\tau_{\text{pyridine-}CCl_4}$ is illustrated pictorially in Figure 52. Protons in the plane "Q" are not affected by the solvent. However, this plane, unlike "P," is not through the carbonyl carbon atom but instead through the two carbon atoms α to the carbonyl function. As before, groups on the oxygen side of "Q" are deshielded, while those on the other side are shielded. It was found that the solvent effects of pyridine, in general, are not as large as those of benzene, although the effects of the former solvent were observed to complement those of the latter. For example, in a compound having a methyl group α to a carbonyl function, the axial methyl resonance is shifted more in benzene whereas the equatorial one is shifted more in pyridine. Of particular interest to us was the fact that these "rules" could be applied to aromatic conjugated ketones.

At the time that these papers appeared in print we had isolated the pure diketones, LXXXI and LXXXII, and it was important to consider the n.m.r. data in relation to the stereochemistry at C-10b in these two molecules. In order to attach some reliance to the solvent shifts in these instances we also considered the effects of solvent in a number of hydrochrysene compounds already available from our previous studies.

Tables 15-17 list the solvent shifts ($\Delta\tau$) of angular methyl and methoxyl protons when the standard solvent, deuteriochloroform, is replaced by benzene or pyridine. In a few instances, for example in XLIV and XLV, several methyl groups

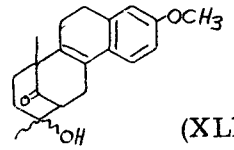
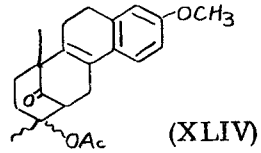
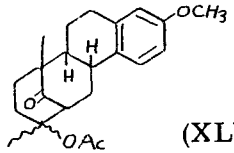
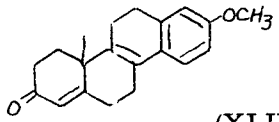
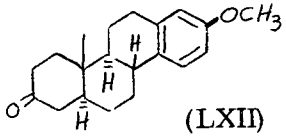
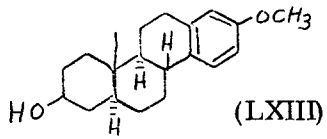
Compound	Methyl Proton Resonances				Methoxyl Proton Resonances			
	Benzene		Pyridine		Benzene		Pyridine	
	τ	Δτ	τ	Δτ	τ	Δτ	τ	Δτ
 (XLII)			8.73 8.58				6.28	
 (XLIV)			8.82 8.39	-0.03 +0.01			6.28	+0.06
 (XLV)			8.90 8.45	-0.05 -0.05			6.30	+0.03
 (XLIII)	8.95	+0.38	8.72	+0.15	6.55	+0.32	6.28	+0.05
 (LXII)	9.37	+0.38	9.13	+0.14	6.52	+0.26	6.29	+0.03
 (LXIII)	9.34	+0.17			6.56	+0.32		

Table 15. N. M. R. Data on the Solvent Shifts of the Angular Methyl and Methoxyl Protons

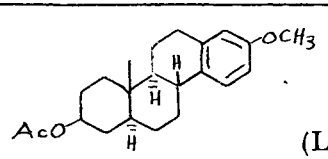
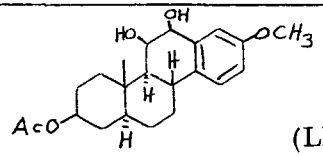
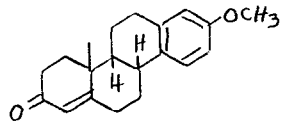
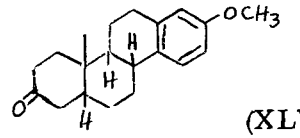
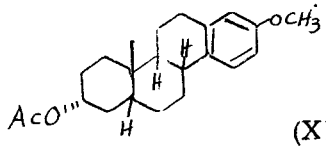
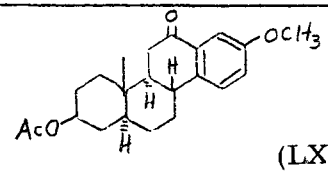
Compound	Methyl Proton Resonances				Methoxyl Proton Resonances			
	Benzene		Pyridine		Benzene		Pyridine	
	τ	Δτ	τ	Δτ	τ	Δτ	τ	Δτ
 (LXV)	9.35	+0.18	9.26	+0.09	6.54	+0.27	6.29	+0.02
 (LXXII)			9.13				6.32	
 (XLVI)	9.02	+0.44	8.77	+0.19	6.55	+0.28	6.32	+0.05
 (XLVII)	9.17	+0.37			6.56	+0.33		
 (XLIX)	9.08	+0.18	9.00	+0.10	6.57	+0.30	6.31	+0.04
 (LXVIII)	9.47	+0.42	9.22	+0.17	6.58	+0.43	6.27	+0.12

Table 16. N. M. R. Data on the Solvent Shifts of the Angular Methyl and Methoxyl Protons.

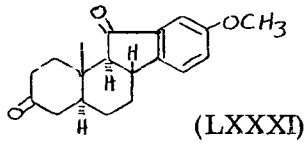
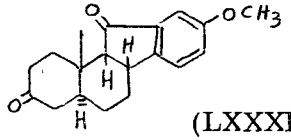
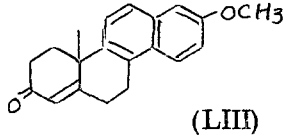
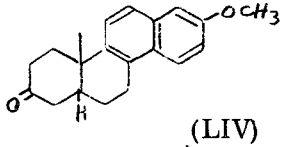
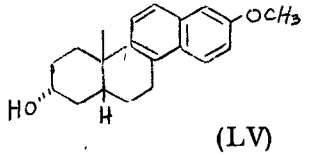
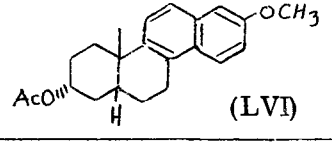
Compound	Methyl Proton Resonances				Methoxyl Proton Resonances			
	Benzene		Pyridine		Benzene		Pyridine	
	τ	Δτ	τ	Δτ	τ	Δτ	τ	Δτ
 (LXXXI)	9.20	+0.35			6.70	+0.47		
 (LXXXII)	9.24	+0.50			6.69	+0.51		
 (LIII)	8.73	+0.36	8.45	+0.08	6.52	+0.42	6.17	+0.07
 (LIV)	8.88	+0.25	8.67	+0.04	6.49	+0.34	6.17	+0.02
 (LV)	8.89	+0.06	8.77	-0.06	6.49	+0.32	6.17	0.00
 (LVI)	8.89	+0.11	8.82	+0.04	6.48	+0.31	6.18	+.01

Table 17. N.M.R. Data on the Solvent Shifts of the Angular Methyl and Methoxyl Protons.

are present in the molecule. In these cases it is obvious that the angular methyl protons resonate at higher field. It is immediately apparent that the solvent shifts of the methoxyl protons are not appreciably affected by changes in the molecule. For example, hydrochrysene derivatives in which ring D is aromatic and those in which both rings C and D are aromatic are shielded about 0.3τ in benzene and about 0.03τ in pyridine. However, these shifts are larger in compounds possessing a carbonyl group in conjugation with the aromatic systems (LXXXI, LXXXII, and LXVII). The latter observation is in agreement with that of Hatton and Richards (150) in their work on aromatic aldehydes. They reported that smaller solvent effects were seen when the aromatic substituents were electron-donating.

As expected, the angular methyl resonances are more susceptible to changes in structure of the compound than those of the methoxyl group, although no generalizations can be made in view of the results mentioned below. In the bridged compounds, XLIV and XLV, one would expect on the basis of the "rules" mentioned above that the angular methyl protons should be deshielded because they reside on the oxygen side of the plane. The experimental results do indeed agree with such a proposal. It is interesting to note that the trans-anti-trans compounds (LXII, LXIII and LXV) and the corresponding cis-syn-cis analogues (XLVI, XLVII and XLIX) gave the same shifts in magnitude as well as sign. In view of the large difference in the stereochemistry of these two series, it is somewhat surprising that the solvent effects are not appreciably different also. For example, the trans-anti-trans-8-keto compound, LXII, and the cis-syn-cis isomer XLVII, show little or no difference in spite of the fact that the 3-keto function in the 5α and 5β steroid series has a pronounced effect on the chemical shift of the C-19 methyl protons (137).

The effect of the other substituents at C-8 on the angular methyl group resonance appears to be small. For example, a β-hydroxyl group at C-8 (LXIII) has

a similar effect to the corresponding 8β-acetoxyl function (LXV).

On the basis of the above results, one can see that in the spectra of compounds possessing a C-8 keto function the angular methyl protons resonate at higher field. It has been suggested that benzene appears to form complexes with molecules containing centers of partial positive charge (151). Since polarization of the carbonyl double bond in ketones is generally more pronounced than in the corresponding acetates, one would expect greater solvent shifts in the former molecules. Clearly such complexing in the case of the alcohols would be even less likely.

According to the evidence which was discussed earlier, the C-nor-D-homo diketone LXXXI was assigned the trans-anti-trans configuration while the other isomeric diketone LXXXII was postulated with the trans-syn-cis stereochemistry. It is interesting to note at this point that the benzene solvent shifts were found to be +0.35τ and +0.50τ, respectively, for the angular methyl protons. These shifts are in agreement with the stereochemical assignments as indicated above and a brief comment on this point should be made presently. If one considers molecular models of LXXXI and LXXXII and bears in mind the "rules" quoted above, it is possible to evaluate the n.m.r. data in terms of stereochemistry. In the case of the trans-anti-trans diketone, LXXXI, the angular methyl group lies closer to the plane "P" which passes through C-11 (see Figure 52) than in the instance of the trans-syn-cis isomer, LXXXII. In 11-keto steroids this plane passes through C-10 and the C-19 methyl group resides on the negative (deshielding) side so that a small negative displacement of the signal may be expected. Actually Bhacca and Williams (152) found that shift to be -0.14τ in 5α-androstan-11-one. However, in our series where contraction of ring C to a 5-membered ring occurs, this plane is twisted so that the C-10 carbon atom is now on the side which is opposite to the oxygen atom. Hence the empirical "rule" would predict that <u>both</u> isomers will give positive solvent shifts

but that the trans-syn-cis isomer (LXXXII) will provide the larger shift. The experimental results clearly show a difference between these isomeric diketones, and it is interesting that the observed shifts are in agreement with the above predictions. Therefore we feel that this evidence, along with the data mentioned previously, supports the stereochemical assignment.

In contrast to the ring D aromatic compounds, the solvent shifts of the angular methyl protons of the octahydrochrysene molecules are far more erratic. It seems, however, that the aromatic rings in the latter substances contribute less to the solvent shifts than in the former series.

In their studies on steroidal molecules Bhacca and Williams (152) reported that benzene-induced shifts of acetoxyl protons were of the order, 0.23-0.31 τ, while the geminal proton was generally deshielded by about 0.1 τ. It is seen from the values in Table 18 that the solvent shifts of the acetoxyl protons in our hydrochrysene compounds are in close agreement with their findings. Pyridine, on the other hand, does not shift these protons very much.

To complete our discussion on solvent effects in this series, Tables 19 and 20 indicate the shifts of olefinic and benzylic protons in a few of the available compounds. In general the effects are rather small and no further discussion seems necessary at this time.

Finally, apart from the solvent shifts mentioned, the combined use of deuteriochloroform and benzene has provided strong n.m.r. evidence for the relative stereochemistry of LXXXI and LXXXI as presented in Figure 13, and for the assignments of the methylene and methine protons in the region, 6-7.5 τ, of the n.m.r. spectra of above compounds. The C-4b proton and one of the C-10 protons, but not the C-10b hydrogen atom, were found in this region.

It has already been mentioned in this section of the thesis that detailed deuteration experiments have shown that the counterpart of the C-10b proton in

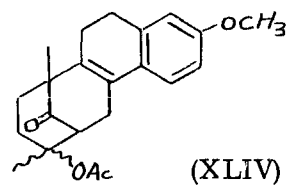
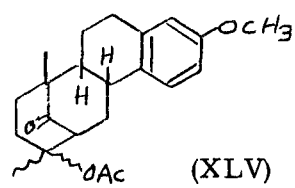
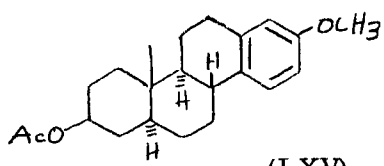
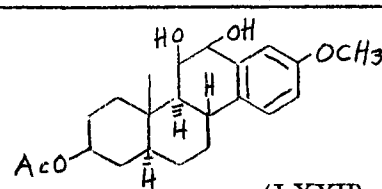
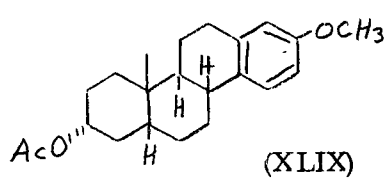
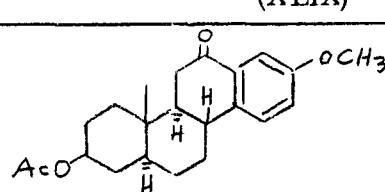
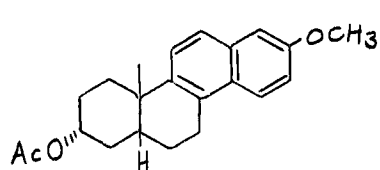
Compound	Benzene		Pyridine	
	τ	$\Delta\tau$	τ	$\Delta\tau$
 (XLIV)			8.10	+0.05
 (XLV)			8.10	+0.02
 (LXV)	8.21	+0.21	7.98	-0.02
 (LXXII)			7.99	
 (XLIX)	8.21	+0.21	7.96	-0.04
 (LXVIII)	8.22	+0.25	7.97	0.00
 (LVI)	8.31	+0.18	8.07	-0.06

Table 18. N.M.R. Data on the Solvent Shifts of the Acetate Methyl Protons.

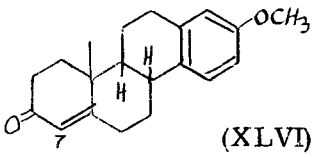
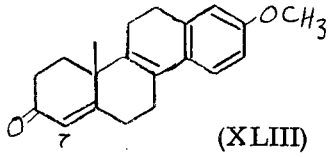
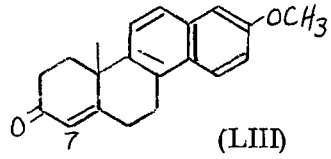
Compound	C-7 olefinic proton resonances				
	$CHCl_3$	C_6H_6		C_5H_5N	
	τ (c.p.s.)	τ (c.p.s.)	Δτ	τ (c.p.s.)	Δτ
 (XLVI)	4.21 (347.5)	4.17 (349.5)	-.04	4.16 (350.5)	-.05
 (XLIII)	4.17 (349.5)	4.14 (351.5)	-.03	4.12 (353)	-.05
 (LIII)	4.04 (357.5)	4.07 (356)	+.03		

Table 19. N. M. R. Data on the Solvent Shifts of the C-7 Proton.

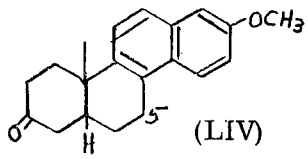
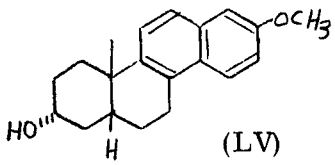
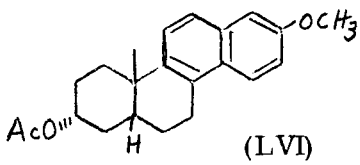
Compound	C-5 proton resonance			
	C_6H_6		C_5H_5N	
	τ (c.p.s.)	Δτ	τ (c.p.s.)	Δτ
 (LIV)	7.24 (165.5)	+.34	6.99 (180.5)	+.09
 (LV)	7.12 (173)	+.14	6.98 (181.)	.00
 (LVI)	7.15 (171)	+.20	6.98 (181)	+.03

Table 20. N. M. R. Data on the Solvent Shifts of the Benzylic Protons of the Octahydrochrysene Analogues.

LXXXI, namely the C-9 proton in 11-keto steroids (for example, CII, Figure 51), in fact absorbs at high field (143). Other workers have studied the n.m.r. spectra of cis-1,1a,2,3,4,4a-hexahydrofluoren-9-one (LXXXVII, Figure 51) and its derivatives and have observed that the proton, C-1a, which corresponds to the C-10bβ proton of LXXXII, adjacent to the carbonyl group resonates at higher field than the benzylic proton, C-4a, which is in a similar environment to the C-4b proton of the C-nor-D-homo diketones LXXXI and LXXXII (99,144). In the previous work (143) it was also established that the C-1β proton in 11-keto steroids, by virtue of its proximity to the 11-keto function, shows signals at low field in the n.m.r. spectra. This proton corresponds to the C-10β hydrogen atom in the trans-anti-trans diketone.

Molecular models clearly show that the C-10α (axial) proton in the trans-syn-cis diketone is very close to the carbonyl function in ring C. The corresponding model for the trans-anti-trans isomer reveals that the C-10β (equatorial) proton is also in close proximity to the carbonyl function. Furthermore, it is also evident that of these two protons, the C-10α one of the former diketone is much closer to the carbonyl function. Therefore, one would expect this proton to resonate at lowest field, and the multiplet observed for this proton should be broader than that for the corresponding C-10β (equatorial) proton of the trans-anti-trans diketone. In the former case, one must have axial-axial coupling with the adjacent methylene proton at C-9. Moreover, since the C-10b proton couples with only the C-4b proton, it should appear as a doublet and thus be easily distinquished from that of C-10 or C-4b which couples with three adjacent hydrogen atoms. On considering these molecular models and the empirical "rule" of Connolly and McCrindle (148), it appears that (a) the solvent effects for the C-10 (axial atom in trans-syn-cis model and equatorial atom in trans-anti-trans one) and C-4b protons

should be greater in the trans-syn-cis diketone than those in the trans-anti-trans isomer, because the protons in the former diketone are further removed from the plane "P" than those of the latter one, and (b) benzene should shield the C-4b whereas it should deshield the C-10 proton, because the former proton is on the side of "P" which is opposite to the C-11 carbonyl oxygen atom and the latter proton is on the other side.

An examination of the n.m.r. spectrum, in benzene, of the C-nor-D-homo diketone LXXXI reveals an unresolved complex two-proton multiplet in the region 6.83-7.48 τ (Figure 40), whereas the spectrum of isomer, LXXXII, in sharp contrast shows two well resolved quintets each integrating for one proton at 6.40 τ (203.5, 209.5, 215.5, 222.5, 228.5 c.p.s.) and at 7.08 τ (164, 169.5, 175, 180.5, 187 c.p.s.) (Figure 42). Although the multiplet in the region 6.83-7.48 τ was taken from a spectrum of LXXXI which was measured at 66° rather than at room temperature so as to increase the concentration of this compound in benzene, it was not expected that this increased temperature would significantly shift the resonance from that taken at room temperature. Indeed a subsequent spectrum taken at room temperature confirmed this expectation. It should be noted that even though the multiplet of LXXXI is not resolved, the greater resolution in benzene is sufficient to indicate, as the quintets of LXXXII do, that no low field methylene or methine proton resonates as a doublet. Thus, as expected the experimental results show that the C-10b proton of LXXXI and LXXXII does not absorb at low field. Hence, in analogy with the above cited literature, the C-4b proton and one of the C-10 protons must be absorbing at low field in the n.m.r. spectra.

Now that it is established that the C-4b proton and one of the C-10 protons resonates at low field, it remains to consider the assignment of multiplets to these protons. It has already been mentioned previously in this section that the C-10α proton in the diketone, LXXXII, and the C-10β proton in the isomer, LXXXI,

resonate at low field. It is now interesting to discuss the solvent effects of these protons. The observed solvent effects of the C-10 and C-4b protons are in agreement with predictions from the empirical "rule" of Connolly and McCrindle. That is, the C-10α proton of LXXXII, which gives rise to quintet at 6.40τ and is on the 11-carbonyl oxygen side of "P", has been deshielded in benzene, whereas the C-4b proton of the same compound, which resonates as a quintet at 7.08τ and is on the opposite side of "P", has been shielded. Similarly, the C-4b proton of LXXXI is shielded in benzene and thus its resonance is shifted to higher field. Also, as predicted the solvent effects were smaller for the compound LXXXI than for its isomer LXXXII, since the C-10β and C-4b protons of the former molecule are closer to the plane "P", than the corresponding protons (C-4b and C-10α) of the latter one. Thus, the solvent effects support the previous assignments of the low field C-10 protons.

Hence, the n. m. r. data indicated above confirms the trans-anti-trans and trans-syn-cis stereochemistry assigned to the isomers LXXXI and LXXXII, respectively.

Conclusion

These studies have provided the successful synthesis of trans-anti-trans- and trans-syn-cis-C-nor-2-methoxy-8, 11-diketo-10a-methyl-4b, 5, 6, 6a, 7, 8, 9, 10, 10a, 10b, 11-undecahydrochrysene. It is hoped that these compounds will prove to be excellent intermediates for the synthesis of alkaloids such as jervine and veratramine.

The nuclear magnetic resonance data was very useful for the characterization of the various hydrochrysene compounds and also provided evidence for interesting solvent, stereochemical and substituent effects.

Experimental

The melting points were determined on a Kofler block unless otherwise stated and are uncorrected. The ultraviolet spectra were recorded in 95% ethanol on a Cary 11 or 14 recording spectrometer, and the infrared spectra were taken on a Perkin-Elmer Model 21 spectrometer as potassium bromide pellets unless otherwise stated. The nuclear magnetic resonance (n.m.r.) spectra were measured at 60 megacycles per second on a Varian A60 instrument. The centers of gravity of multiplets, or their centers (c. of m.) are given in the Tiers τ scale (153) with reference to tetramethylsilane as the internal standard set at 10.0 τ units. The type of protons, integrated area, multiplicity, half-height width ($W_{1/2}$) in cycles per second (c.p.s.), the spin-spin coupling constant (J) in c.p.s., and peak positions in c.p.s. are indicated in parenthesis. Deuteriochloroform was used as the solvent unless otherwise stated. The analyses were performed by Dr. A. Bernhardt and his associates, Mulheim (Ruhr) Germany, and by Mrs. Aldridge, Mrs. C. Jenkins and Mr. P. Borda, University of British Columbia. Every molecular weight (M.W.) quoted was determined on either the Associated Electrical Industries MS 9 (A.E.I. MS 9) or the Atlas CH-4 mass spectrometer.

Synthesis of cis-2-Methoxy-8-keto-10a-methyl-5,6,6a,7,8,9,10,10a,11,12-decahydrochrysene (LXI).

The tetracyclic ketone, XLIII (134 mg.), was dissolved in benzene (5 ml.)

and to this solution one small drop of 48% hydrobromic acid and 10% palladium on charcoal (28 mg.) were added. The solution was stirred under hydrogen at room temperature and under atmospheric pressure for 2 1/4 hours. The catalyst was filtered off and washed with benzene. The benzene extract was concentrated in vacuo to yield a colorless gum (140 mg.). Chromatography on alumina (7 g., activity grade II-III) using petroleum ether (30-60°)-benzene (3:1) as the eluant gave the desired 6a,7-dihydro tetracyclic ketone (LXI, 104 mg.). After several recrystallizations from benzene and petroleum ether (65-100°), pure LXI (60 mg.), m. pt. 81.0-82.5° (literature: reference (83), m. pt. 82-85°), was obtained. Ultraviolet: λ_{max} (logϵ) 273 (4.22) mμ; λ_{min} (logϵ) 236 (3.47) mμ. Infrared: 5.83, 5.85, 6.24, 5.38, 6.67μ; (Nujol) 5.83, 5.85, 6.23, 6.66μ. N.m.r. signals: 8.75 (angular methyl, 3H, singlet, 75), 6.22 (CH_3O- , 3H, singlet, 227), 2.86 (c. of m., C-4H, 1H, triplet, 433, 427.5, 423.5), 3.58 (c. of m., C-1H and C-3H, 2H, quintet). Found: C, 80.74; H, 8.28; O, 11.13. Calc. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; O, 10.80.

Further elution with ethyl ether provided unreacted tetracyclic ketone, XLIII (21 mg.).

Birch Reduction of 2-Methoxy-8-keto-10a-methyl-5,6,8,9,10,10a,11,12-octahydrochrysene (XLIII).

To a stirred mixture of anhydrous liquid ammonia (210 ml., dried by passing through sodium hydroxide pellets) and dry aniline (35 ml., freshly distilled and and dried over sodium hydroxide pellets), sodium (3.5 g.) was added in small pieces. A solution of tetracyclic ketone, XLIII, (3.5 g.) (74,75,76) in anhydrous tetrahydrofuran (70 ml.) was added to the blue ammonia solution over a period of 7 minutes with dry nitrogen being passed through the apparatus during the addition. The mixture was stirred for a further 14 minutes, after which time ammonium chloride (8.4 g.) was added in portions to destroy the blue color. The ammonia was allowed to evaporate, and then the resulting residue was treated with water and extracted with ethyl ether.

The ether layer was washed successively with dilute hydrochloric acid (until the aqueous layer was essentially colorless), aqueous sodium carbonate, and finally with water. After the solution was dried over anhydrous magnesium sulfate and filtered,the solvent was removed to yield a yellow solid (3.24 g.). This solid was purified by chromatography on alumina (175 g., activity grade III). Elution with benzene-ethyl ether (2:1) provided trans-anti-trans-2-methoxy-8-keto-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXII, 773 mg.). Several recrystallizations from ethanol provided the pure product (600 mg.), m. pt. 142.7-145.5°. Ultraviolet: λ_{max} (log ϵ) 277 (3.20), 286 (3.17) mμ. Infrared: 5.87, 6.21, 6.35, 6.67μ. N.m.r. signals: 8.99 (angular methyl, 3H, singlet, 60.5), 6.26 (CH_3O- , 3H, singlet, 224.5), 2.81 (C-4H, 1H, doublet, 428.2, 436.1, $J_{4,3}$ = 7.9), 3.28 (C-3H, 1H, partly hidden quartet, 407.8, 405.0, $J_{3,1}$= 2.8), 3.37 (C-1H, 1H, singlet, 397.3); (C_5H_5N) 9.13 (angular methyl, 3H, singlet, 52), 6.29 (CH_3O-, 3H, singlet, 222.5); (C_6H_6) 9.37 (angular methyl, 3H, singlet, 38), 6.52 (CH_3O- , 3H, singlet, 208.5). Found: C, 80.77; H, 8.56; O, 10.93; M. W. (Atlas CH-4) 298; Calc. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72; M.W. 298.

Further elution with benzene-ethyl ether (1:2) provided trans-anti-trans-2-methoxy-8β-hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXIII, 2.193 g.). This solid, on recrystallization from either ethyl ether or a mixture of benzene and methyl cyclohexane, proved a pure sample of the alcohol (1.9 g.), m. pt. 157.5-160°. Ultraviolet: λ_{max}(log ϵ) 277 (3.20), 286 (3.17) mμ. Infrared: 2.89, 6.22, 6.36, 6.67μ. N.m.r. signals: 9.17 (angular methyl, 3H, singlet 49.5), 6.24 (CH_3O- , 3H, singlet, 225.5), 7.63 (HO—, 1H, singlet, disappears with D_2O, 142), about 6.37 (C-8αH, 1H, broad multiplet, about 218), 2.80 (C-4H, 1H, doublet, 429.5, 437.3, $J_{4,3}$=7.8), 3.26 (C-3H, 1H, partly hidden quartet, 408.8, 406.2, $J_{3,1}$= 2.6), 3.36 (C-1H, 1H,

singlet, 398.5), 7.05-7.8 (C-12H, C-4bH, HO- plus one other proton, 5H); (C_6H_6) 9.34 (angular methyl, 3H, singlet, 39.5), 6.56 (CH_3O-, 3H, singlet, 206.5), 7.15-7.95 (C-12H, C-4bH plus one other proton, 4H). Found: C, 80.32; H, 9.08. Calc. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39.

The relative quantities of ketone and alcohol were sometimes difficult to reproduce, especially if high percentages of ketone were desired. In general, long reaction periods (a reaction time of about 30 minutes after addition) gave rise to almost pure alcohol, whereas short periods yielded the former compound.

Sodium Borohydride Reduction of trans-anti-trans-2-Methoxy-8-keto-10a-methyl-4b, 5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXII).

A solution of the saturated ketone LXII (2.66 g.) in methanol (105 ml.) was treated with a solution of sodium borohydride (1.37 g.) in methanol (105 ml.) and water (26 ml.), and the mixture was refluxed for 3 hours. The mixture was treated with concentrated hydrochloric acid (26 ml.) and refluxed for a further hour. The solution was concentrated in vacuo to a volume of 30 ml., water and ethyl ether were added, and the ether layer was separated. The organic layer was washed with water, and then dried over anhydrous magnesium sulfate. Removal of the solvent provided a crystalline product (2.57 g.). This compound was identical with the 8β alcohol, LXIII, obtained from the above Birch reduction.

Acetylation of trans-anti-trans-2-Methoxy-8β-hydroxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXIII).

The crude alcohol LXIII (95 g.) was dissolved in a mixture of pyridine (60 ml.) and acetic anhydride (300 ml.), and this mixture was allowed to stand at room temperature for 22 1/2 hours. After this period most of the acetic anhydride was distilled off in vacuo using a steam bath, and the cooled residue was treated with ice water. The mixture was then allowed to stand for about 30 minutes after which

time it was extracted with benzene. The combined organic layer was washed thoroughly with dilute hydrochloric acid, then once with water, once with a saturated sodium bicarbonate solution, and finally with water. After drying the benzene solution over anhydrous sodium sulfate, the solvent was removed to yield the crude acetate LXV (100 g.). This product was chromatographed on alumina (500 g., activity grade II-III). Elution with petroleum ether-benzene (2:1) provided a semi-pure acetate LXV (91 g.) while elution with chloroform-methanol (1:1) provided a polar material (8 g.). Rechromatography of semi-pure LXV and subsequent recrystallization from ethyl ether and petroleum ether of the early fractions yielded trans-anti-cis acetate LXVI (2.5 g.) as needles, m. pt. 138-140.5°. Further recrystallization from benzene and petroleum ether (65-110°) gave analytically pure trans-anti-cis-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXVI, 2.0 g.), m. pt. 142-142.5° (Fisher-Johns). Infrared: 5.78, 8.0μ. Ultraviolet: λ_{max}(log ϵ) 280 (3.27), 286 (3.24)mμ; λ_{min}(log ϵ) 247 (2.26), 284.5 (3.21) mμ. N.m.r. signals: 9.76 (angular methyl, 3H, singlet, 14.5), 6.24 (CH_3O- , 3H, singlet, 225.5), 8.02 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 118.5), 5.30 (C-8αH, 1H, broad multiplet, 282, $W_{1/2}$=23), 7.0-7.75 (C-12H, C-4bH plus one other proton, 4H), 3.34 (C-1H, 1H, singlet, 399.6), 2.87 (C-4H, 1H, doublet, 424.7, 433.9, $J_{4,3}$= 9.2), 3.27 (C-3H, 1H, partly hidden quartet, 402.0, 406.1, 408.6, $J_{3,1}$= 2.5). Found: C, 77.06; H, 8.55; O, 14.15; M.W. (A.E.I. MS 9) 342. Calc. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83; O, 14.02; M.W. 342.

The later chromatography fractions (84 g.) were recrystallized from ethanol or methyl cyclohexane to provide pure trans-anti-trans-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXV, 80 g.), m. pt. 96.5-99°. Infrared: 5.80, 6.24, 6.35, 6.68, 8.03μ. Ultraviolet: λ_{max} (logϵ) 278 (3.18), 287 (3.14) mμ. N.m.r. signals: 9.17 (angular methyl, 3H,

singlet, 50), 6.27 (CH_3O- , 3H, singlet, 224), 8.00 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 120), 5.27 (C-8αH, 1H, broad multiplet, 284, $W_{1/2}$= 21), 3.39 (C-1H, 1H, singlet, 396.5), 2.83 (C-4H, 1H, doublet, 427, 435.5, $J_{4,3}$ = 8.5), 3.30 (C-3H, 1H, partly hidden quartet, 404.2, 407, $J_{3,1}$= 2.8), 7.05-7.8 (C-12H, C-4b H plus one other proton, 4H); (C_6H_6) 9.35 (angular methyl, 3H, singlet, 39), 6.54 (CH_3O- , 3H, singlet, 207.5), 8.21 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 107.5), 5.25 (C-8αH, 1H, broad multiplet, 285, $W_{1/2}$=21), 7.2-7.95 (C-12H, C-4bH plus one other proton, 4H); (C_5H_5N) 9.26 (angular methyl, 3H, singlet, 44.5). 6.29 (CH_3O- , 3H, singlet, 222.5), about 5.18 (C-8αH, 1H, broad multiplet, about 289), 7.22-7.8 (C-12H, C-4bH plus one other proton, 4H). Found: C, 80.77; H, 8.56; O, 10.93; M.W. (Atlas CH-4) 342. Calc. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72; M.W. 342.

Oxidation of trans-anti-trans-2-Methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXV).

A solution of t - butyl chromate in carbon tetrachloride was prepared according to the procedure of Heusler and Wettstein (154) except the final solution was concentrated to 600 ml. instead of 100 ml. Aliquots of this solution were used for the various experiments.

The acetate LXV (6.70 g.) was dissolved in carbon tetrachloride (180 ml.), and the t-butyl chromate solution (90 ml.) which was initially mixed with acetic anhydride (15 ml.) was then added. The mixture was stirred under reflux for 4 hours, and the excess oxidant was then destroyed by stirring with a solution of oxalic acid (75 g.) in water (500 ml.) for 2 hours with occasional cooling with ice water to control the frothing. More water was added to the solution, and then the red carbon tetrachloride layer was separated off. The purple aqueous layer was extracted three more times with chloroform, and this extract was combined with the carbon tetrachloride layer. It was noted that if all the t-butyl chromate was not reduced the latter chloroform extracts would be yellow instead of colorless. It

was found that this rather detailed work-up procedure is best to minimize formation of emulsions.

The organic layer was now washed once with water to remove the chromium salts, with aqueous sodium bicarbonate to remove most of the residual acetic acid, and then with a 1:1 mixture of a saturated aqueous sodium bicarbonate and a 1N sodium carbonate solution to remove the acidic reaction products. The basic washings, which were initially slightly pink in color, were combined and extracted once with chloroform. The combined organic layer was finally washed with water and dried over anhydrous magnesium sulfate. After removal of the drying agent and evaporation of the solvent, a crude neutral product (6.25 g.) was obtained. The organic material in the basic aqueous solution was negligible. The neutral material was purified by chromatography on alumina (300 g., activity grade III). Elution with benzene-petroleum ether (7:3) provided starting material (3.74 g., 56% recovery) and further elution with benzene-ethyl ether (9:1) yielded the desired crude keto-acetate LXVIII (77) (1.16 g., 16% yield). A more careful chromatography was then carried out on the crude keto-acetate. After several recrystallizations of the middle fractions from benzene and petroleum ether, colorless needles of the desired trans-anti-trans-2-methoxy-8β-acetoxy-12-keto-10a-methyl-4b,5,6,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXVIII, 0.73 g.), m. pt. 142-145.5°, were obtained. Infrared: 5.80, 5.99, 6.26, 6.39, 6.71μ. Ultraviolet: λ_{max}(logϵ) 222 (4.08), 254 (3.68), 322 (3.14) mμ. N.m.r. signals: 9.05 (angular methyl, 3H, singlet, 56.7), 6.15 (CH_3O- , 3H, singlet, 231), 7.97 ($CH_3\overset{O}{\overset{\|}{C}}O$— , 3H, singlet, 122), 5.20 (C-8α H, 1H, broad multiplet, 288, $W_{1/2}$ = 21), 2.42 (C-1H, 1H, doublet, 453.3, 455.9, $J_{1,3}$ = 2.6), 2.64 (C-4H, 1H, doublet, 439.4, 447.6, $J_{4,3}$ = 8.6), 2.86 (C-3H, 1H, quartet, 419.5, 423.3, 429.4, 432.4, $J_{3,1}$ = 2.7 and 3.0, $J_{3,4}$ = 8.7), 6.9-7.7, (C-11H, C-4bH plus one other proton, 4H); (C_6H_6) 9.47 (angular methyl, 3H,

singlet, 31.5), 6.58 (CH_3O- , 3H, singlet, 205), 8.22 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 107), about 5.27 (C-8αH, 1H, broad multiplet, about 284, $W_{1/2}$ = 17.5); (C_5H_5N) 9.22 (angular methyl, 3H, singlet, 47), 6.27 (CH_3O- , 3H, singlet, 223.5), 7.97 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 122), about 5.2 (C-8αH, 1H, broad multiplet, about 288), 7.0-7.85 (C-11H, C-4bH plus one other proton, 4H). Found: C. 74.10; H, 7.76. Calc. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92.

If a crude sample of the trans-anti-trans acetate LXV was oxidized instead of pure LXV, the 12-keto-8-acetoxy isomer, LXIX, m.pt. 162.5-165^{o}(benzene-methyl cyclohexane), could also be isolated in a very small quantity. Infrared: 5.80, 5.94, 6.21, 6.67μ. Ultraviolet: λ_{max}(logϵ) 222 (4.32), 253.5 (3.88), 320 (3.43)mμ; λ_{min}(logϵ) 237 (3.67), 253.5 (2.59) mμ. N.m.r. signals: 8.88 (angular methyl, 3H, singlet, 67), 6.27 (CH_3O- , 3H, singlet, 224), 8.02 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H singlet, 118.5), 5.12 (C-8H (axial), 1H, 293, $W_{1/2}$= 22), 7.0-7.8 (C-11H, C-4bH plus one other proton, 4H), 2.67 (C-1H, doublet, 438.5, 441.4, $J_{1,3}$ = 2.9), 2.85 (C-4H, 1H, doublet, 426.7, 435.5, $J_{4,3}$ = 8.8), 3.08 (C-3H, 1H, quartet, 407.2, 410.3, 416.1, 418.7, $J_{3,1}$= 2.6 and 3.1). Found: C, 74.11; H, 7.87; O, 17.94. Calc. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; O, 17.96.

Synthesis of trans-anti-trans-2-Methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (LXXI).

The C-12 ketone LXVIII (3.2 g.) was dissolved in methanol (400 ml.), and a solution of sodium borohydride (1.0 g.) in methanol (200 ml.) and the water (20 ml.) was added. The mixture was stirred at room temperature for 3.5 hours. Then acetic acid (15 ml.) was added and the solution was stirred for 30 minutes. After concentrating the methanol in vacuo to a volume of 35 ml., water and ethyl ether were added. The aqueous solution was extracted three times with ethyl ether, and the combined ethereal solution was washed with water, aqueous sodium bicarbonate

and finally with water. The ether extract was dried over magnesium sulfate, and the solvent removed in vacuo to yield the gummy alcohol LXX (3.2 g.). The ultraviolet and infrared spectra showed no sign of a conjugated carbonyl group at C-12. The n.m.r. spectrum showed three intense singlets at 9.16 (angular methyl), 7.99 ($CH_3C\overset{O}{\overset{\|}{O}}-$), and 6.23 ($CH_3O-$). This alcohol was used for the dehydration reaction without further purification.

The crude alcohol, LXX, was dissolved in benzene (150 ml., dried over sodium) and phosphorus pentoxide (3.2 g.) was added. After refluxing for 2 hours, the reaction mixture was cooled in ice water, and then the solution was decanted into another flask. A small amount of ice was added to this yellowish-green fluorescent solution. The dark brown residue which remained in the original reaction flask was cooled to about 0°, and ice water was then quickly poured into the flask. After most of the residue had dissolved, ethyl ether and sodium chloride were added and finally sodium bicarbonate, in small portions, was added until the solution became slightly basic. It was found difficult to dissolve the residue completely and to destroy the emulsions which formed at this point. The aqueous layer was extracted three times with ethyl ether. The latter was combined with the benzene solution, and then the combined organic layer was washed with aqueous sodium bicarbonate and finally with water. After drying over anhydrous magnesium sulfate and removing the solvent, a crude material (2.7 g.) was obtained. This product was purified by alumina chromatography (100 g., activity grade III). Elution with petroleum ether ($30-60^{\circ}$) -benzene (1:1) gave the desired olefinic product (2.2 g.). Recrystallization from ethanol gave pure trans-anti-trans-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b-decahydrochrysene (LXXI, 2.0 g.), m. pt. $105-106.5^{\circ}$. Infrared: 5.81, 6.15, 6.25, 6.40, 6.73μ. Ultraviolet: λ_{max}(logϵ) 221 (4.44), 262.5 (3.94), 270 (shoulder) (3.88), 302 (3.51), 312 (shoulder) (3.40) mμ; λ_{min}(logϵ) 247 (3.83), 284 (3.48) mμ. N.m.r. signals: 9.15 (angular methyl, 3H, singlet, 51),

6.29 (CH_3O- , 3H, singlet, 222.5), 8.02 ($CH_3\overset{O}{\overset{\|}{C}}O$—. 3H, singlet, 118.5), 5.30 (C-8αH, 1H, broad multiplet, 282, $W_{1/2}$= 23), 7.0-7.85 (C-4bH plus one other proton, 2H), 4.08 (C-11H or C-12H, 1H, doublet, 358.5, 348.5, $J_{11,12}$= 10, $W_{1/2}$ = 4), 3.66 (C-11H or C-12 H, 1H, quartet, 375.8, 378.3, 385.8, 388.3, $J_{11,12}$=10, J=2.5), 3.44 (C-1H, 1H, singlet, 393.5), 2.99 (C-4H, 1H, doublet, 418, 426.1, $J_{4,3}$= 8.1), 3.34 (C-3H, 1H, partly hidden quartet, 401, 403.6, $J_{3,1}$= 2.6). Found: C, 77.48; H, 8.23; O, 14.44. Calc. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29; O, 14.10.

Synthesis of trans-anti-trans-2-Methoxy-11β,12β-dihydroxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene (LXXII).

The olefin LXXI (600 mg.) was dissolved in dry ethyl ether (20 ml.). Osmium tetroxide (500 mg., 12% excess) was dissolved in dry ethyl ether (10 ml.), and the latter solution was quickly added to the former solution. The flask, which had contained the osmium tetroxide solution, was rinsed with dry ethyl ether (10 ml.), and this was also added to the reaction mixture. The solution was allowed to stand at room temperature in the dark for 57 hours. The black or dark brown precipitate which separated after this standing period was treated with methanol (6 ml.) and water (1 ml.). Hydrogen sulfide gas was passed into the mixture for 5 minutes, the solution was stirred for a further 5 minutes, and then the precipitate was filtered off using a sintered glass funnel. The precipitate was first washed with methanol, then removed from the funnel and treated again with a mixture of chloroform and methanol. The solution was saturated with hydrogen sulfide (3-5 minutes), stirred for 5 minutes and subsequently filtered again. The latter operations were repeated once more to ensure complete hydrolysis of the osmate ester. Finally the solvent was rapidly evaporated in vacuo to yield the crude solid product (0.688 g.). This substance was kept in the refrigerator until immediately prior to its purification by chromatography. The osmate ester appears to be more soluble in chloroform than either methanol or ethyl ether.

The product was chromatographed on Woelm neutral silica gel. Elution with benzene-chloroform (1:1) provided a non-polar fraction (101 mg.) while elution with 5% methanol in chloroform gave the desired diol isomers (590 mg.), LXXII and LXXIII. The polar fractions showed two spots on silica gel G thin-layer chromatography . The R_f values were 0.17 for the minor isomer LXXIIIand 0.13 for the major isomer LXXII when chloroform was used as the eluant and the absorbent thickness was 0.25 mm. The spots appeared yellow initially and then changed to an olive green color when the chromatoplate was sprayed with antimony trichloride-acetic acid (1:1) and then heated a few minutes at about 110°. Recrystallization of the polar fraction from chloroform and petroleum ether produced an analytical sample of LXXII (310 mg.), m. pt. 225-226° (Fisher-Johns). Infrared: 2.90, 5.87, 6.21, 6.31, 6.67μ; ($CHCl_3$) 2.83, 5.82, 6.22, 6.34, 6.70μ. Ultraviolet: λ_{max}(logϵ) 276 (3.21), 282 (3.19) mμ; λ_{min}(logϵ) 280 (3.16), 244.5 (2.13) mμ. N.m.r. signals: (C_5H_5N) 9.13 (angular methyl, 3H, singlet, 52), 6.32 (CH_3O- , 3H, singlet, 220.5), 7.99 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 120.5), 5.24 (C-12αH, 1H, doublet, 284, 288, $J_{12\alpha,11}$= 4), 5.61 (C-11αH, 1H, triplet, 260, 263.5, 267.5, $W_{1/2}$=9), about 5.2 (C-8αH, 1H, broad multiplet). Found: C, 70.18; H, 7.99; 0, 21.57. Calc. for $C_{22}H_{23}O_5$: O, 70.56; H, 8.08; O, 21.36.

Since the osmium tetroxide tends to give a black precipitate when dissolved in ethyl ether, the success of this reaction was dependent for the most part on the amount of ethyl ether used and on the time required for the work-up of the reaction mixture. Both should be kept to a minimum. The isomers LXXII and LXXIII were not separated for the subsequent cleavage reaction as mentioned below.

Synthesis of trans-anti-trans-11,12-Seco-11,12-dioxo-2-methoxy-8β-acetoxy-10a-methyl-4b,5,6,6a,7,8,9,10,10a,10b,11,12-dodecahydrochrysene(LXXIV).

The diol mixture (166.7 mg.) was dissolved in methanol (77.5 ml.) and a

solution of periodic acid in water (24 ml., 0.0219 molar) was added to the above mixture. Immediately upon addition of the periodic acid solution, the temperature of the reaction mixture increased from 19° to 28°. The extent of conversion was followed by withdrawing aliquots of the reaction mixture and measuring the ultraviolet spectrum. These spectra indicated that the reaction was quite rapid. The reaction mixture was allowed to stand at room temperature in the dark for a period of 2 hours after which time the solution had attained a slightly yellow color. Ethylene glycol (0.39 ml.) was added, and the reaction was allowed to react for a further 55 minutes to destroy the excess periodic acid. Most of the methanol was removed in vacuo, and then water and benzene were added. The aqueous layer was extracted three times with benzene. The organic layer was washed successively with water, saturated sodium bicarbonate solution, and finally with water again. After drying over anhydrous magnesium sulfate and removing the solvent, the expected product (173.4 mg.) was obtained. Thin-layer chromatography showed only one spot (chloroform-ethyl acetate (1:1), silica gel G). Crystallization from benzene and petroleum ether produced an analytical sample of LXXIV, m. pt. 130-133.5°. Infrared: 3.63, 5.79, 5.86, 5.97, 6.24, 6.67μ; ($CHCl_3$) 3.66, 5.84, 5.92, 6.23, 6.37, 6.67μ. Ultraviolet: λ_{max} (logϵ) 225 (4.33), 255.5 (3.86), 321 (3.50) mμ; λ_{min} (logϵ) 242.5 (3.75), 281 (2.70) mμ. N.m.r. signals: 8.85 (angular methyl, 3H, singlet, 69), 6.19 (CH_3O- , 3H, singlet, 228.5), 7.98 ($CH_3\overset{O}{\overset{\|}{C}}O$- , 3H, singlet, 121), 5.35 (c. of m., C-8αH plus one other proton, 2H), 7.58 (C-10bH, 1H, quartet, 136.5, 141, 148.8, 152.5, $J_{10b,4}$=11.6, $J_{10b,11}$= 4.2 and 4.5), -0.30 (C-12H, 1H, singlet, 618), 0.46 (C-11H, 1H, doublet, 570.5, 574.5, $J_{11,10b}$=4), 2.93 (C-3H, 1H, quartet, 416, 418.5, 424.8, 427.2, $J_{3,4}$= 8.8, $J_{3,1}$= 2.4 and 2.5), 2.74 (C-4H, 1H, doublet, 433 (shoulder), 441.8), 2.74 (C-1H, 1H, doublet, about 434, 436.8). Found: C, 70.96; H, 7.46; O, 21.84. Calc. for $C_{22}H_{28}O_5$: C, 70.94;

H, 7.58; O, 21.48.

Attempts at chromatographic purification of the product on alumina gave discouraging results, since poor recovery from the column was sometimes obtained. Since the dialdehyde was not particularly stable, it was used directly from the reaction mixture for the intramolecular aldol condensation reaction. In general both reactions were done on the same day.

Synthesis of C-Nor-2-methoxy-8β, 11ξ, -dihydroxy-10bξ -formyl-10a-methyl-4bβ, 5, 6, 6aα, 7, 8, 9, 10, 10a, 10b, 11-undecahydrochrysene (LXXIX).

A solution of crude dialdehyde LXXIV (480 mg.) in methanol (110 ml.) was added to a solution of sodium hydroxide (100 mg.) in water (1.4 ml.). The reaction mixture was refluxed for a period of 3 hours, and the solvent was removed in vacuo on a steam bath. Chloroform (90 ml.) and water (5 ml.) were added to the residue remaining, and the layers were separated. The chloroform extract was washed with water (5 ml.), and the combined aqueous layer was extracted with a small amount of chloroform. The chloroform extract was then dried over anhydrous magnesium sulfate, the drying agent filtered off and the solvent removed to give an orange neutral reaction product (397 mg.). A small amount of the dialdehyde which bears a C-8 hydroxyl function was shown to be present in the reaction product — the ultraviolet spectrum showed weak absorption at 320 mμ and the thin-layer chromatography showed a small spot having a larger R_f value than that of the desired LXXIX. The spot due to LXXIX gave rise to an intense pinkish-orange color and showed fluorescence in the ultraviolet after the thin-layer chromatography plate was sprayed with a solution of acetic acid and antimony trichloride (1:1) followed by heating at 110°. The first recrystallization from benzene and methyl cyclohexane gave slightly grayish crystals (263 mg.), m. pt. 174-181°. Two further recrystallizations from benzene produced an analytical sample of LXXIX, m. pt. 175-182°. Infrared: 2.96, 3.65, 5.84, 5.89, 6.19, 6.30, 6.75μ;

($CHCl_3$) 2.81, 3.64, 5.90, 6.22, 6.30, 6.72 μ. Ultraviolet: λ_{max}(logϵ) 284 (3.36), 289 (shoulder) (3.32) mμ; λ_{min}(logϵ) 257 (2.74) mμ. N.m.r. signals: 8.90 (angular methyl, 3H, singlet, 66), 6.23 (CH_3O- , 3H, singlet, 226), 4.56 (C-11H, 1H, broad singlet, 326.5), 3.05 (C-1H, 1H, singlet, 417), 3.00 (C-4H, 1H, doublet, 425, about 417), 3.28 (C-3H, 1H, quartet, 396.5, 399, 404, 407, $J_{3,4}\sim 8$, $J_{3,1}\sim 2.5$-3.0), about 6.4 (C-8αH, 1H, broad multiplet), 6.50 (C-4bH, 1H, quartet, 197.5, 203.5, 216.5, 225.5), 0.30 (-CHO, 1H, doublet, 580.5, 583.5, J = 3). Found: C, 72.66; H, 7.85; O, 19.58. Calc, for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93; O, 19.37. Thin-layer chromatography (chloroform-ethyl acetate (1:1) on silica gel G or ethanol-benzene (1:19) on silica gel G or neutral Woelm alumina) showed only one spot, indicating only one compound or an inseparable mixture.

The desired material is much more insoluble than the alcohol derivative of LXXIV. A chromatographic purification of the mother liquors can be conveniently carried out on Woelm neutral alumina (deactivated with water, 7% v/w). The dialdehyde impurity was eluted with a mixture of chloroform and benzene (3:7), while LXXIX was eluted with chloroform. The recovery was satisfactory and the compound was also stable to this technique.

Synthesis of C-Nor-2-methoxy-8,11-diketo-10bξ,-formyl-10a-methyl-4bβ,5,6,6aα,7,8,9,10,10a,10b,11-undecahydrochrysene (LXXX).

Jones reagent (155) (0.6 ml., 3 atoms O per molecule) was added rapidly with stirring to a solution of diol aldehyde (260 mg., m. pt. 175-182°) in acetone (20 ml.). After stirring at room temperature for 30 minutes, the excess chromic acid was decomposed with a small amount of methanol. The solvent was removed in vacuo on a steam bath, and to the residue water and benzene were added. The aqueous solution was extracted three times with benzene, and the combined benzene extract was washed with water and then dried over anhydrous magnesium sulfate.

Evaporation of the solvent yielded a pale yellow gummy product (260 mg.) which had the desired ultraviolet spectrum (λ_{max} 220, 255, 326 mμ; λ_{min} 244, 282 mμ) and infrared spectrum (CCl_4 film, 5.82, 5.91μ). Two recrystallizations from benzene and cyclohexane gave crystals melting at 140-152°. N.m.r. signals: 0.32 (-CHO, 1H, singlet, 580.5), 8.78 (angular methyl), 3H, singlet, 73), 6.19 (CH_3O- , 3H, singlet, 228.3), 6.17 (C-10H, 1H, doublet, 222, 237), 6.71 (c. of m., C-4bH, 1H, multiplet). This crystalline material was chromatographed on a plate in a manner somewhat different from conventional thin-layer chromatography. In this instance Woelm neutral alumina suitable for column chromatography was placed in dry powder form on a flat plate of glass which was held in an almost horizontal position. This chromatoplate was then developed with chloroform as eluant. The solvent was allowed to run to the top of the plate, the latter was removed from the chromatography tank and allowed to dry after which time it was placed back into the tank and redeveloped with chloroform. This operation was repeated twice and at this time four distinct bands were noted on the chromatoplate. The bands were cut out and eluted with methanol to yield four fractions (order of decreasing R_f; 69, 17, 44, 21 mg.). The largest fraction gave a n.m.r. spectrum identical to that of a 1:1 mixture of the diketo isomers LXXXI and LXXXII obtained by deformylation of LXXX with potassium hydroxide as mentioned below. This isomeric mixture on recrystallization form benzene and cyclohexane provided a crystalline material which was obviously still a mixture (m. pt. 150-205°). The other major fraction (44 mg.) also showed no aldehyde proton absorption in the n.m.r. spectrum (angular methyl protons at 8.74) as well as only one carbonyl peak in the infrared spectrum. The most polar fraction (21 mg.) had a R_f = O and therefore was not examined. Since the second fraction (17 mg.) was a mixture of compounds and in small quantity, it was not investigated.

The amount of acidic material(extractable with sodium bicarbonate solution) obtained from this oxidation was always very low (less than 10% of total reaction

mixture).

Potassium Hydroxide Deformylation of C-Nor-2-methoxy-8,11-diketo-10bξ,-formyl-10a-methyl-4bβ,5,6,6aα,7,8,9,10,10a,10b,11-undecahydrochrysene (LXXX).

The crude diketo aldehyde LXXX (147 mg.) was taken up in dioxane (37 ml.) and water (3.7 ml.) and to this solution potassium hydroxide (214 mg.) was then added. The mixture was refluxed for 100 minutes after which time most of the dioxane was removed in vacuo. The residue was treated with water and benzene, and dilute hydrochloric acid was added until the mixture was acidic. The aqueous solution was extracted three times with benzene. Thereafter the combined benzene extract was washed twice with water, three times with saturated sodium bicarbonate solution and again twice with water. After drying over anhydrous magnesium sulfate and evaporating off the solvent, a neutral product (94 mg.) was obtained. The yellow basic aqueous solution from the sodium bicarbonate washings was acidified with hydrochloric acid and then extracted three times with benzene. The benzene solution was washed with water until neutral, dried over anhydrous magnesium sulfate, and then evaporated to give the acidic material (24 mg.). The acidic product had λ_{max} 308 mμ and λ_{min} 273 mμ in its ultraviolet spectrum.

The n.m.r. spectrum on the neutral product showed no low field protons due to a formyl group but two angular methyl peaks in an intensity ratio of about 1:1 were evident at high field. It was therefore obvious that two compounds were in fact present. All attempts to separate these compounds (shown later to be the isomers LXXXI and LXXXII) on silica gel or alumina chromatography met with failure. These substances possess a slightly larger R_f value than the starting material LXXX, but all three compounds show the same behaviour towards 20% antimony pentachloride in carbon tetrachloride on thin-layer chromatoplates. Prior to heating the spots slowly turn from yellow to tan color, but when heated to 110° they become pink in color. From thin-layer chromatography on the neutral product

it was possible to exclude the presence of any unreacted starting material. Ultraviolet spectra on the reaction mixture showed that the reaction was essentially completed in 30 minutes — a change in the maxima from 329 to 318 mμ occurred in this time. Fortunately the trans-anti-trans isomer, LXXXI, was less soluble than the trans-syn-cis isomer, LXXXII, and thus these two compounds could be separated by careful fractional crystallization. Since these compounds crystallized in different crystal types, hand separation of these crystals greatly facilitated purification on a small scale. To remove trace impurities which hampered crystallization, the crude reaction product was first chromatographed on neutral Woelm alumina, and the fractions (60 mg.) containing LXXXI and LXXXII were combined. Recrystallization from benzene and petroleum ether (65-110°) or cyclohexane gave orange needles and colorless plates. A mixture of these crystals, m. pt. 137-150° and 175-195°, was used for microanalysis. Found: C, 76.30; H, 7.35; O, 16.48. Calc. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43; O, 16.09. After several more recrystallizations the pure trans-anti-trans diketone, LXXXI, was obtained as orange needles, m. pt. 188.5-201.5° (decomposition). Infrared: 5.85, 6.22, 6.32, 6.71 μ. Ultraviolet: λ_{max}(logϵ) 219 (4.44), 249 (3.92), 319 (3.59) mμ ; λ_{min}(log ϵ) 237 (3.83), 273 (2.98) mμ. N.m.r. signals: 8.85 (angular methyl, 3H, singlet, 69), 6.23 (CH_3O- , 3H, singlet, 226), 7.06 (c. of m., C-10βH and C-4bH, 2H, multiplet), 2.74 (c. of m., aromatic, 1H, sextet, 431, 431.9, 434.5, 435.4, 439.6, 440.5, J = 0.9), 2.96 (c. of m., aromatic, 2H, sextet, 416.3, 418.6, 422.1, 424.5, 425.5, 427.8); (C_6H_6) 9.20 (angular methyl, 3H, singlet, 48), 6.70 (CH_3O- , 3H, singlet, 198), 7.16 (c. of m., taken at 66°, C-10βH and C-4bH, 2H, broad multiplet). Found: M.W. (A.E.I. MS 9) 298. Calc. for $C_{19}H_{22}O_3$: M.W. 298.

Three crystallizations from benzene and cyclohexane produced an analytical sample of the trans-syn-cis diketone, LXXXII, as colorless plates, m. pt. 140-142°

(no decomposition). Infrared: 5.87, 6.20, 6.70 μ. Ultraviolet: λ_{max} (log ϵ) 218 (4.47), 249 (3.98), 318 (3.58) mμ; λ_{min} (log ϵ) 236 (2.88), 272 (2.09) mμ. N.m.r. signals: 8.74 (angular methyl, 3H, singlet, 75.5), 6.18 (CH_3O- , 3H, singlet, 229), 6.57 (c. of m., C-10αH and C-4bH, 2H, broad multiplet), 2.81 (c. of m., aromatic, 3H, singlet, 45.5); (C_6H_6) 9.24 (angular methyl, 3H, singlet, 45.5), 6.69 (CH_3O- , 3H singlet, 198.5), 6.40 (c. of m., C-10αH, 1H, quintet, 203.5, 215.5, 222.5, 228.5), 7.08 (c. of m., C-4bH, 1H, quintet, 164, 169.5, 175, 180.5, 187). Found: M.W. (A.E.I. MS 9) 298. Calc. for $C_{19}H_{22}O_3$: M.W. 298.

Both isomers decompose at about 200° to give rise to new maxima at about 234, 270 and 281 mμ in the ultraviolet spectra in addition to the other three maxima already mentioned. This accounts for the poor melting point which was obtained for the trans-anti-trans diketone LXXXI.

Synthesis of trans-anti-trans-2-Methoxy-8β-hydroxy-10-methyl-1,4,4b,5,6,6a,7,8,9,10,10a,10b,11,12-tetradecahydrochrysene (XC).

The trans-anti-trans acetate, LXV, (1 g.) was dissolved in anhydrous tetrahydrofuran (60 ml.). Liquid ammonia (125 ml., passed through sodium hydroxide pellets) was condensed into a 500 ml. 3-necked flask through which dry nitrogen was slowly passing. The above acetate solution was then carefully poured into the liquid ammonia, and lithium (2 g.), in small pieces, was immediately added to this mixture. The reaction mixture was then stirred for 13 minutes, and after this time anhydrous ethanol (18 ml.) was slowly added over a period of 38 minutes to the blue solution. At the end of the addition the reaction mixture was colorless. The ammonia was carefully evaporated with the aid of a warm water bath, and then cold water was cautiously added. The solution was extracted four times with benzene, and the benzene extract was washed with water until it was neutral to pH paper. After drying over anhydrous magnesium sulfate, the solvent was evaporated to provide a viscous gum (1.14 g.). Three recrystallizations from

benzene and cyclohexane gave an analytical sample (0.40 g.) of XC as fine white needles, m. pt. 124.5-127°. Infrared: 3.09, 5.89, 6.00. 8.15μ. N.m.r. signals: 9.22 (angular methyl, 3H, singlet, 47), 6.47 (CH_3O- , 3H, singlet, 212), 5.37 (C-3H, 1H, singlet, 278), 8.07 (HO-, disappeared when D_2O was added, 116), 7.34 (C-1H and C-4H, 4H, broad singlet, 159.5), about 6.3 (C-8αH, 1H, broad multiplet). Found: C, 79.54; H, 9.80. Calc. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. This compound had an R_f value of 0.34 on Woelm neutral alumina chromatoplate when chloroform was used as the eluant. This value was found to be the same for the trans-anti-trans alcohol LXIII, but the latter was more insoluble that XC.

The yields of XC, which were best determined by integration of the methoxyl peaks in the n.m.r. spectrum of the crude product, were found to be between 60 and 80%. Since purification was difficult at this stage, it was decided to proceed with the conversion of the crude XC to the conjugated ketone XCII.

Synthesis of trans-anti-trans-anti-2-Keto-8β-hydroxy-10a-methyl-2,3,4,4a,5,6,7,8,9,10,10a,10b,11,12-hexadecahydrochrysene (XCII).

The crude enol ether XC (730 mg.) was refluxed in a solution containing methanol (50 ml.) and sulfuric acid (5 ml. of 3.6 N) for one hour. Most of the methanol was removed in vacuo on a steam bath, and the residue was treated with water and chloroform. The layers were separated, and the aqueous solution was extracted three times with chloroform. The combined chloroform extract was first washed three times with water, then dried over anhydrous sodium sulfate, and finally evaporated to dryness to give a crystalline product (706 mg.). Thin-layer chromatography and the infrared spectrum showed that a very small amount of saturated ketone (having a 4a, 12a-double bond) was still present. The saturated ketone shows an R_f value intermediate between that for the trans-anti-trans alcohol LXIII, and the conjugated ketone, XCII. Chromatography was carried out on alumina

which was deactivated 4% with 10% aqueous acetic acid. The alcohol LXIII was eluted first with a mixture of benzene and chloroform (5:1), while the desired conjugated ketone was removed subsequently with a 1:1 mixture of the same solvents. The recovery of the material from the column was very good. The last fraction contained a small amount of a phenolic component. The desired conjugate ketone was less soluble than the alcohol LXIII, and several recrystallizations from benzene and cyclohexane gave an analytical sample (390 mg.) of XCII, m. pt. 182-185.5°. Infrared: (nujol) 2.91, 2.98, 5.99, 6.06, 6.16, 6.19 μ. Ultraviolet: λ_{max} (log ϵ) 239.5 (4.23), 308 (1.91) mμ; λ_{min} (log ϵ) 284.5 (1.81) mμ. N.m.r. signals: 9.24 (angular methyl, 3H, singlet, 45.5), 7.65 (HO-, disappeared when D_2O was added, 141), 6.38 (C-8αH, 1H, broad multiplet, 217, $W_{1/2}$ = 22), 4.19 (C-1H, singlet, 348.5), no absorption between 6.7 and 7.3. Found: C, 79.21; H, 10.01; M.W. (Atlas CH-4) 288. Calc. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79; M.W. 288.

Synthesis of trans-anti-trans-anti-2-Keto-8β-hydroxy-1,10a-dimethyl-2,3,4,4a,5,6,6a,7,8,9,10,10a,10b,11,12-hexadecahydrochrysene (XCIV).

The conjugated ketone XCII (251 mg.) was dissolved in a mixture of benzene (10 ml.) and pyrrolidine (0.4 ml.). The reaction mixture was refluxed over a period of 190 minutes during which time water was gradually removed from the reaction by azeotropic distillation with benzene with the help of a Dean-Stark apparatus. After this time all the solvent was evaporated in vacuo, and the residual product showed in its ultraviolet spectra a strong maxima at 276 mμ in methanol and at 274.5 mμ in a mixture of hydrochloric acid and methanol. The dienamine was refluxed under a dry nitrogen atmosphere with anhydrous methanol (6 ml.) and methyl iodide (0.9 ml.) for 47 hours (115). On addition of methyl iodide to the methanolic solution of the dienamine a white precipitate formed immediately, but it dissolved when the solution was heated. After this reflux period, the solvent was evaporated in vacuo on a steam bath. The reaction product was then refluxed under

nitrogen with methanol (4 ml.), water (1 ml.), acetic acid (0.4 ml.) and sodium acetate (500 mg., anhydrous) for 250 minutes. Most of the methanol was removed in vacuo on a steam bath, and, after cooling, the residue was treated with water and chloroform. The layers were separated, and the aqueous layer was extracted three times with chloroform. The combined chloroform solution was washed three times with water, dried over anhydrous sodium sulfate, filtered, and then evaporated to dryness to yield an orangish-brown solid glassy product (272 mg.). This material showed a maxima at 242 mμ(methanol) in the ultraviolet spectrum as well as a small band due to a saturated carbonyl group in its infrared spectrum. The product was then dissolved in methanol (15 ml.) and refluxed for 1 1/2 hours with dilute hydrochloric acid (2 ml. of concentrated acid in 3 ml. water.) After this period, the methanol was removed in vacuo on a steam bath. After having cooled the residue to room temperature, water and chloroform were added to it. The layers were separated, and the aqueous layer was extracted several times with chloroform. The combined organic solution was then washed with water until neutral to pH paper, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to give 245 mg. of crude product. The infrared spectrum of the latter showed that this product contained less unconjugated ketonic material than from the previous work-up. Chromatography on alumina (20 g., activity grade II-III) with a mixture of chloroform and benzene (1:4) gave four fractions (62 mg.) which contained the desired XCIV (about 40 mg., 15% yield). The earlier fractions of the chromatography yielded 29 mg. of a substance, while the later fractions contained 143 mg. The latter fractions possessed mostly conjugated ketone XCII. The desired material could be easily identified on thin-layer chromatography, since it behaved differently from the starting ketone, XCII. The methylated compound, XCIV, formed an orange spot on silica gel G chromatoplates when sprayed with a mixture of antimony trichloride and acetic acid (1:1) followed by heating to 110°. Its R_f

value of about 0.25 (ethyl acetate-chloroform (1:10) as eluant) was slightly greater than that of XCII which gave a red spot with this spray reagent. Further purification of the fractions (62 mg.) on preparative silica gel (0.5 mm. thick, 50 g.) thin-layer chromatography plates (eluant was ethyl acetate-chloroform (1.5:10), run 3 times) gave 25 mg. of XCIV (10% yield). Recrystallization from benzene and cyclohexane gave crystals, m. pt. 170-183°. Infrared: (CCl_4 film) 6.05μ. Ultraviolet: λ_{max} 250, 309 mμ; λ_{min} 287 mμ. N.m.r. signals: 9.25 (angular methyl, 3H, singlet, 45), 8.22 (C-1 methyl, singlet, 107), 6.38 (C-8αH, 1H, broad multiplet, 217), 8.11 (HO- , singlet, 113.5), 7.10 (c. of m., C-12βH, 1H, doublet, 168($W_{1/2}$ = 7-8), 180 ($W_{1/2}$ = 5-6), J_{gem} about -12). Found: M.W. (Atlas CH-4) 302. Calc. for $C_{20}H_{30}O_2$: M.W. 302.

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