THE SYNTHESIS AND STEREOCHEMISTRY OF C-NOR-D-HOMOPROGESTERONE ANALOGS

by

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TO MY PARENTS

whose love, encouragement
and perseverence made this
work possible.

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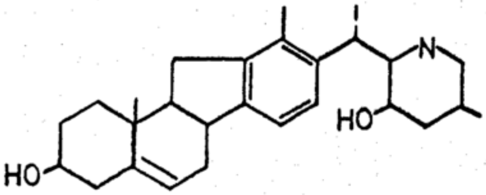
INTRODUCTION

Recently interest in the synthesis of C-nor-D-homosteroid analogs has been aroused due to the occurrence of the C-nor-D-homosteroidal ring system in several alkaloids, such as veratramine (I) and jervine (II) (1). On this account it was anticipated that C-nor-D-homosteroid hormone analogs might find natural receptor sites in order for them to exert their activity. Indeed the C-nor-D-homoepitestosterone acetate, which was synthesized by Kupchan and Levine (2), proved to be anti-androgenic (3).

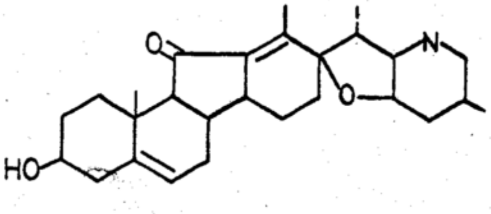
There are two major approaches to the synthesis of C-nor-D-homosteroids from readily available natural products. One of them utilizes the alkaloid, jervine (II), whose structure contains the C-nor-D-homosteroid skeleton, and the other makes use of the sapogenin, hecogenin (III). Both of these compounds are abundantly available natural products. There are three major research groups involved in the synthesis of C-nor-D-homosteroid hormone analogs. On the one hand, Kupchan *et al*. use jervine as starting material, and, on the other hand, Mitsuhashi in Japan and Johns at Searle use hecogenin.

Only a few C-nor-D-homosteroid hormone analogs have been reported. The first one reported was the C-nor-D-homotestosterone analog synthesized by Kupchan and

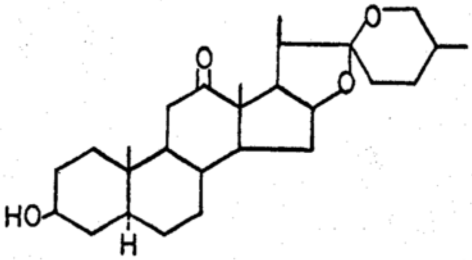
Chart 1



I



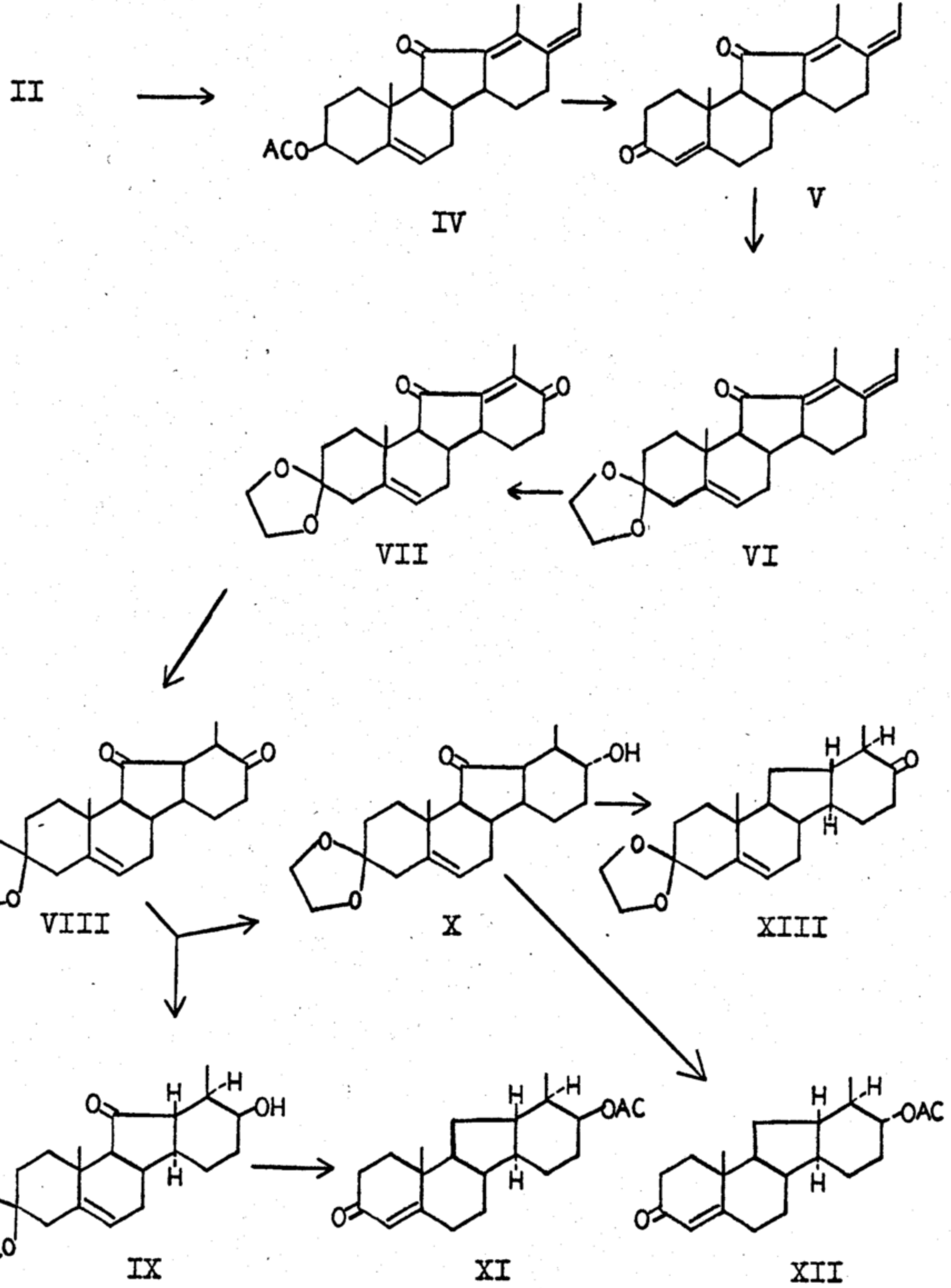
II



III

Levine (2). Their approach to the synthesis made use of the fragmentation reaction of jervine (II) developed in the course of the structure elucidations of the alkaloid (4). Further chemical transformations by the Squibb group (5) to synthesize analogs of this type afforded final proof for the β-orientation of the 3-hydroxyl group in jervine and veratramine, but did not result in the synthesis of any C-nor-D-homosteroid hormone analogs. The synthetic route suffered from the low yield of the degradation reaction of jervine (II) to $\Delta^{5,12,17(20)}$-17-ethyletiojervatriene-3β-ol-11-one acetate (IV), but the latter reaction was greatly improved by Levine. Two alternative routes led to the synthesis of the testosterone analog but only the most direct route will be discussed here. Compound IV was transformed to the trienedione V by hydrolysis with sodium hydroxide in dioxane and subsequent Oppenauer oxidation of the resulting trieneol. The 3-ketone in V was selectively ketalized to Δ^{5}-3-ethylene ketal derivative VI, suggesting considerable steric hindrance of the 11-ketone. The ethylidene side chain in VI was cleaved by selective osmylation of the $\Delta^{17(20)}$-double bond followed by periodate cleavage of the resulting 17,20-diol to yield the dienedione-3-ethylene ketal VII. The enedione grouping in VII was readily reduced by zinc in glacial acetic acid to the dihydrodione VIII. Sodium borohydride reduction of VIII gave only 4% of the desired

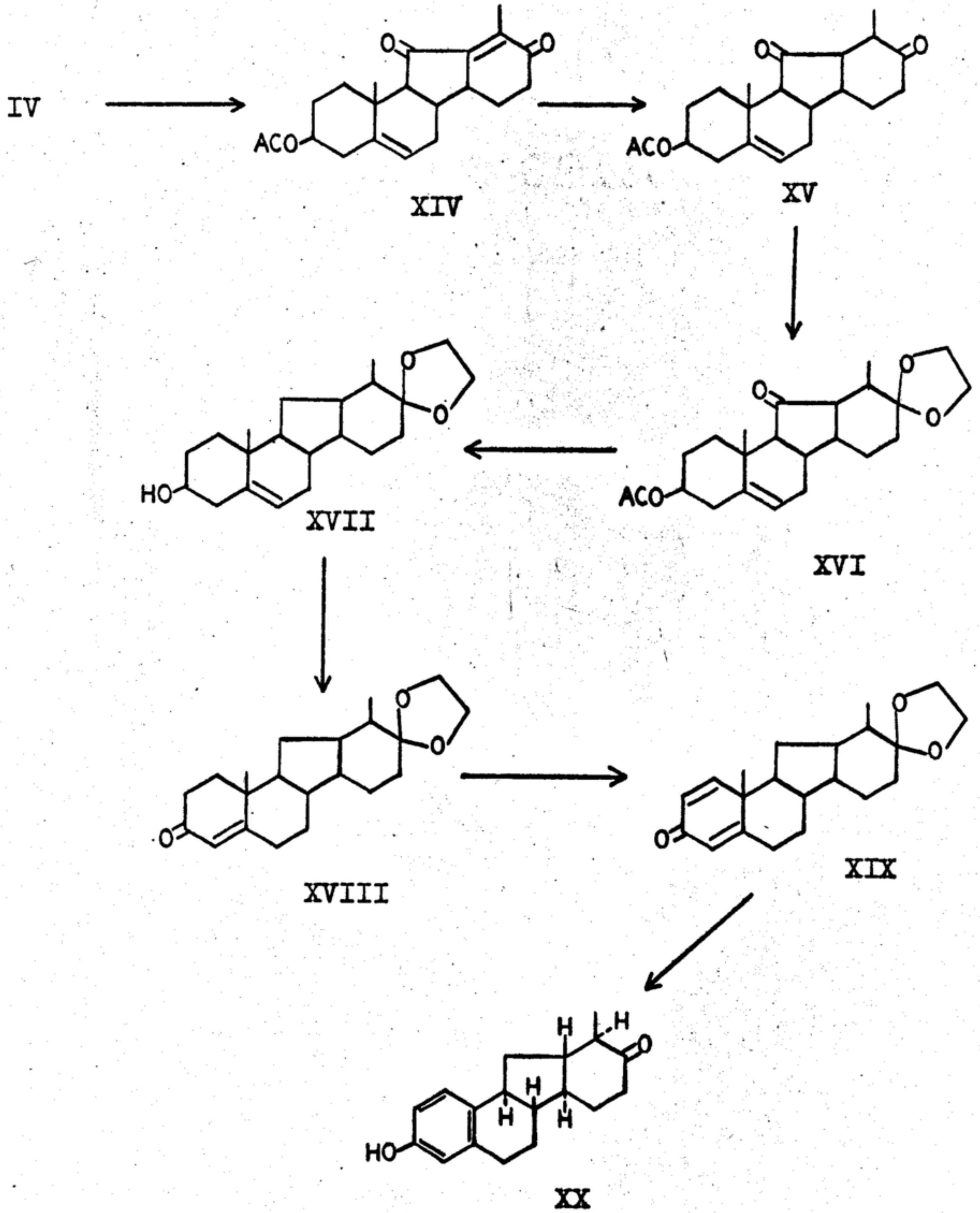
Chart 2



axial alcohol IX and 50-67% of the equatorial alcohol X. Assignment of configuration to the 17α- and 17β-alcohols was made on the basis of their rates of chromic acid oxidation, R_f values on tlc, and analogy to sodium borohydride reductions of unhindered ketones. A higher percentage of the axial alcohol was achieved when the reduction was carried out under Meerwein-Ponndorf conditions. Wolff-Kishner reduction of the 11-ketone in X, followed by hydrolysis of the 3-ethylene ketal and acetylation of the 17-alcohol afforded the C-nor-D-homoepitestosterone acetate XII. Under similar conditions the minor alcohol IX was transformed to the epimeric 17-acetate XI which is the C-nor-D-homotestosterone acetate. Optical rotatory dispersion studies on compound XIII, obtained by Wolff-Kishner reduction of X and subsequent oxidation of the crude product, revealed that the C/D ring juncture was <u>trans</u> since its Cotton curve was enantiomeric with B-nor-cholestane-3-one. Furthermore, the 18-methyl group was assigned the β-orientation (equatorial) due to its failure either to contribute to the amplitude of the Cotton curve or to isomerize in base.

Also starting from jervine, Kupchan, Flom and By (6) have recently completed the synthesis of the C-nor-D-homoestrone. The degradation product IV (Chart 2) from jervine was further degraded by chromic acid oxidation in acetic acid to the dienedione acetate XIV. Reduction of the 12,13-double bond was achieved by treatment

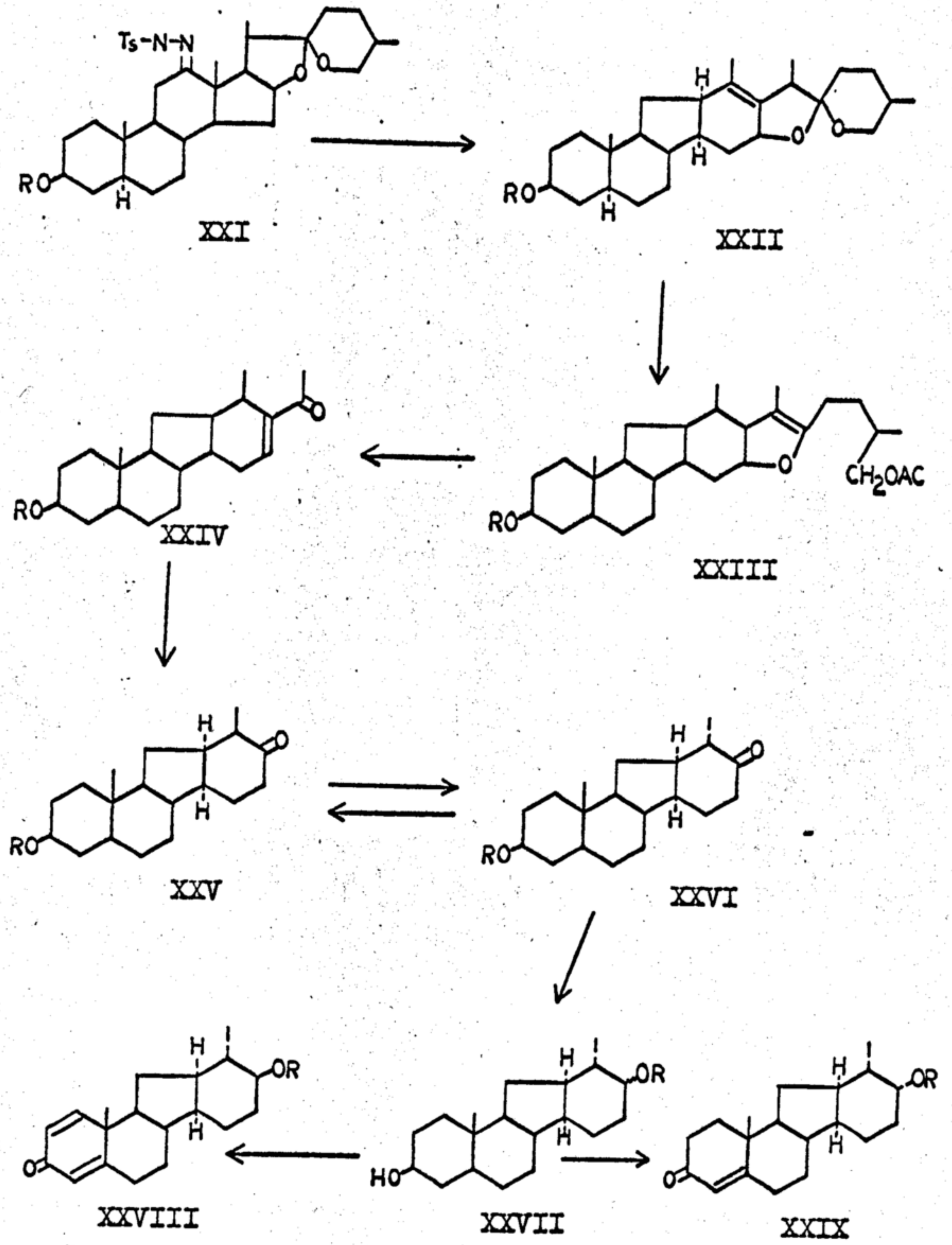
Chart 3



with zinc in acetic acid to provide XV whose 17-ketone was selectively ketalized to the 17-monoketal XVI. Wolff-Kishner reduction of the 11-ketone in XVI provided the 11-deoxo derivative XVII which was then oxidized under Oppenauer conditions to XVIII. Further oxidation of XVIII with DDQ yielded the dieneone XIX. Aromatization of ring A was achieved by the reductive aromatization method developed by Dryden (7); subsequent hydrolysis of the 17-ketal with hydrochloric acid in methanol provided XX, the C-nor-D-homoesterone.

The utilization of hecogenin or similar sapogenins for the synthesis of C-nor-D-homosteroid analogs is based on the rearrangement of their 12-tosylhydrazones or 12β-mesylates in base to the corresponding C-nor-D-homosteroid; a rearrangement known as the "Wendler" rearrangement, discovered by workers at Merck in 1954 during their investigation of the steroidal sapogenin, hecogenin (8). Starting from hecogenin (III) and employing a "Wendler" rearrangement, Johns and Laos reported the synthesis of an etiojervane analog of testosterone having the <u>cis</u> C/D ring fusion (i.e., 12-αH) (9). The 12-tosylhydrazone derivative of hecogenin (XXI) was rearranged in base to the C-nor-D-homosteroid XXII which was further transformed to XXIII by treatment with methyl ammonium chloride in acetic anhydride. Degradation of XXIII with chromic acid and dehydration in base afforded the α,β-unsaturated

Chart 4



XXI
XXII
XXIII
XXIV
XXV
XXVI
XXVIII
XXVII
XXIX

a, R = Benzoate
b, R = H

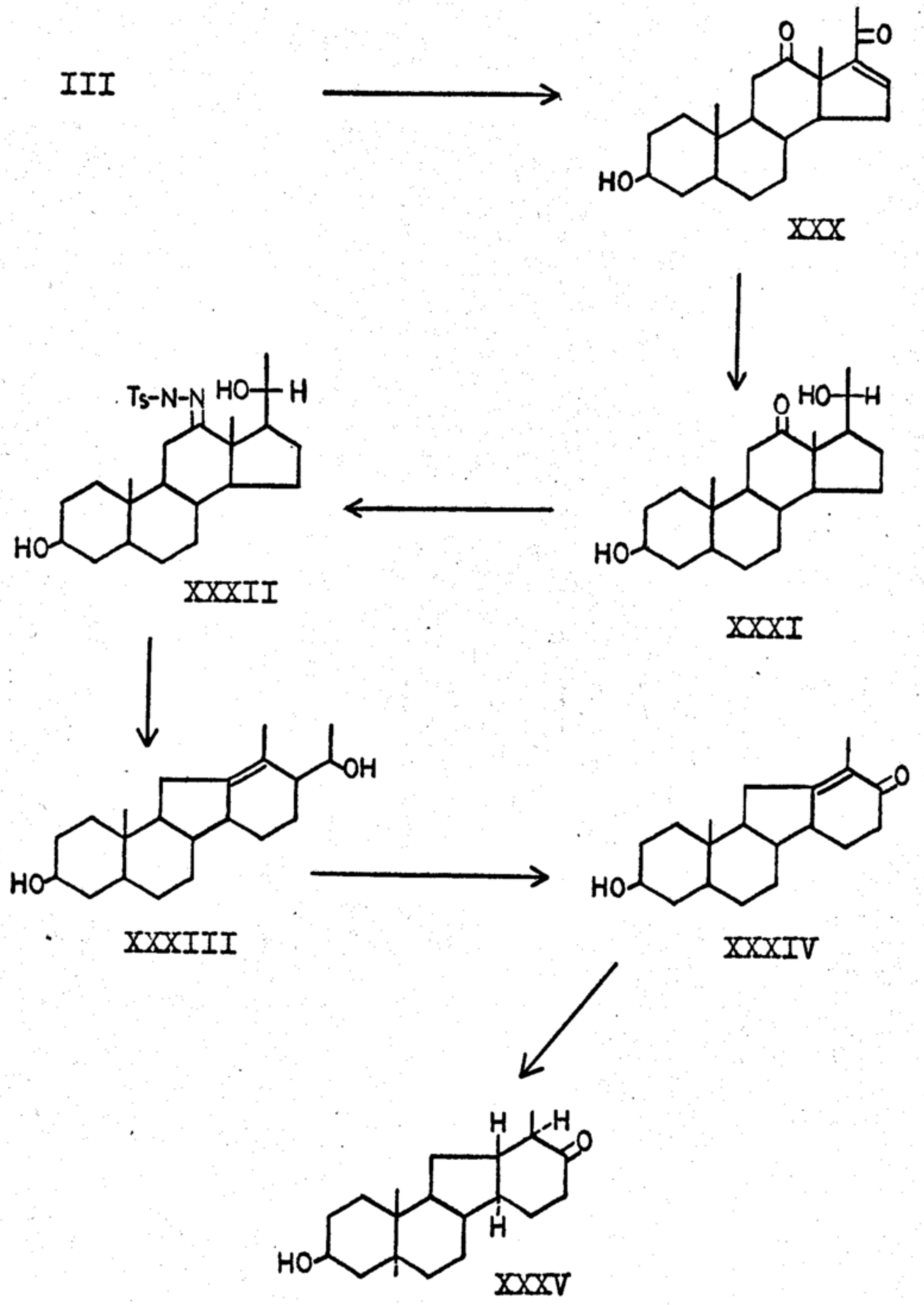
a, 17 = Benzoate
b, 17 = Benzoate

a, R=Benzoate
b, R=H

ketone XXIV. Further degradation of the side-chain in XXIV was accomplished by the Beckmann rearrangement and subsequent hydrolysis of the resulting amides to produce a mixture of epimeric ketones XXV and XXVI; the equilibrium favored XXVI (7:1). Stereochemical assignments at C-12 and C-17a were consistent with their ord and nmr studies. The major ketone XXVI was reduced to two isomeric alcohols XXVIIa and XXVIIb in equal amounts and the latter were separable only as their benzoate esters. The 17β-benzoate was converted by dibromination and dehydrobromination to the dieneone (XXVIII), which comprises the etiojervane analog of 1-dehydrotestosterone. The 17α-benzoate was monobrominated and dehydrobrominated to produce XXIXa as the major product; this was saponified to XXIXb, the desired etiojervane analog of testosterone.

Mitsuhashi _et_ _al_. (10,11,12) have also utilized hecogenin as the starting material for their studies on C-nor-D-homosteroids. Prior to the "Wendler" rearrangement to the C-nor-D-homoskeleton, hecogenin was first degraded in several steps to compound XXX, which was further transformed to the diol XXXI by hydrogenation of the 16-17 double bond, ketalization of the 12-ketone, sodium borohydride reduction of the 20-ketone and hydrolysis of the ketal back to the ketone. The tosylhydrazone derivative (XXXII) was made from XXXI, and was then rearranged in base to the C-nor-D-homosteroid XXXIII. The side-chain in XXXIII was degraded to yield

Chart 5

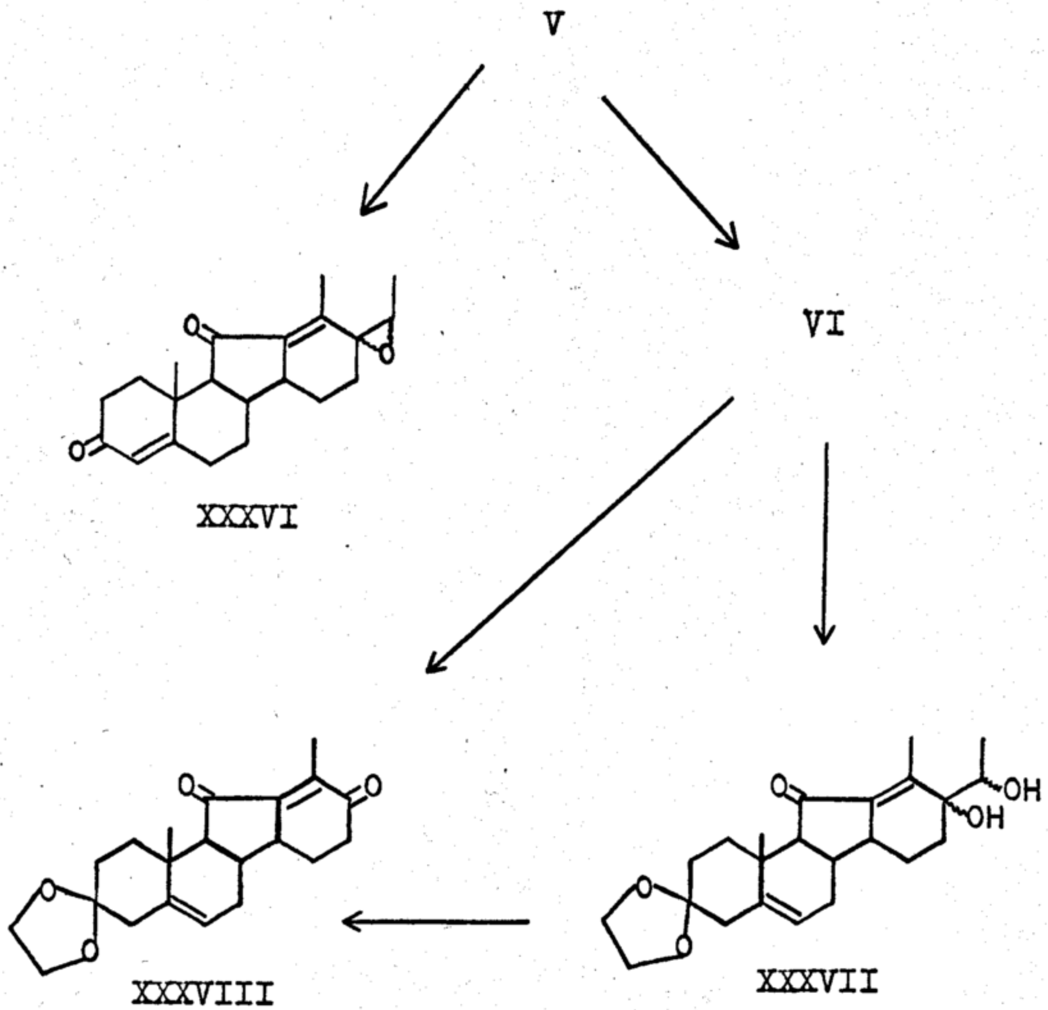

III
O
O
HO
XXX
Ts-N-N
HO
H
HO
XXXII
O
HO
H
HO
XXXI
OH
HO
XXXIII
O
HO
XXXIV
H
H
O
H
HO
XXXV

the 17-ketosteroid (XXXIV) by oxidation with manganese dioxide in chloroform, and in turn the latter compound was reduced with lithium in liquid ammonia to the dihydro derivative (XXXV), which constitutes the C-nor-D-homoepiandrosterone analog. The C/D ring fusion was assigned the <u>trans</u> configuration on the basis of some ord studies and the 18-methyl group was assigned the equatorial (β) configuration on the basis of its failure to epimerize in base.

This dissertation reports the synthesis of C-nor-D-homo analogs of 11-ketoprogesterone. It is apparent from the above literature survey that it would be disadvantageous to use hecogenin since the resulting C-nor-D-homosteroids obtained from a "Wendler" rearrangement invariably have the C/D ring fusion <u>cis</u> (C-12 α H), whereas in normal steroids the C/D ring fusion is <u>trans</u>. The introduction of a double bond into ring A would also be required. More seriously, hecogenin and its rearranged products lack the 11-oxygenated function whose presence is indispensable for the synthesis of 11-ketosteroids. The introduction of an oxygen function into the 11-position is extremely tedious. Hence, jervine was chosen as the starting material in this investigation.

The obvious approach to the synthesis of a C-nor-D-homo-11-ketoprogesterone analog starting from jervine would be to transform compound V (Chart 2), which already has all 21 carbon atoms, directly to the oxygenated analog, by suitable introduction of oxygen functions to the side-chain. This synthetic pathway was thoroughly investigated by Kupchan, Milne and Masamune (13), who showed that this approach suffered from several disadvantages. Compound V was selectively oxidized with monoperphthalic acid to the monoepoxide XXXVI, which did not prove to be of value in the proposed synthesis, because it could not be exclusively rearranged to the 20-ketone. Catalytic hydrogenation, and reductions with lithium aluminum hydride or lithium in liquid NH_3, gave rise to multi-component mixtures which could be only partially separated by chromatography. The 17,20-double bond in VI (Chart 2) was selectively oxidized with osmium tetroxide to the diol XXXVII. All attempts to oxidize the glycol XXXVII, with a variety of oxidizing agents, to the hydroxy ketone failed and only the diketone XXXVIII, resulting from cleavage of the glycol, was obtained. XXXVIII was also isolated after attempted reduction of XXXVII with lithium in liquid ammonia. Similarly, treatment of VI with hydrogen peroxide and osmium tetroxide, or with phenyliodosoacetate and osmium tetroxide, led to the formation of the diketone XXXVIII. Moreover, the 12,13-double bond in XXXVII resisted all attempts at hydrogenation under a variety of conditions. On this account it was deemed

Chart 6


V

VI

XXXVI

XXXVII

XXXVIII

necessary, first to cleave the side-chain to the 17-ketone, secondly, to reduce the 12,13-double bond, and thirdly, to reintroduce the side-chain by a suitable alkylation reaction on the 17-ketone.

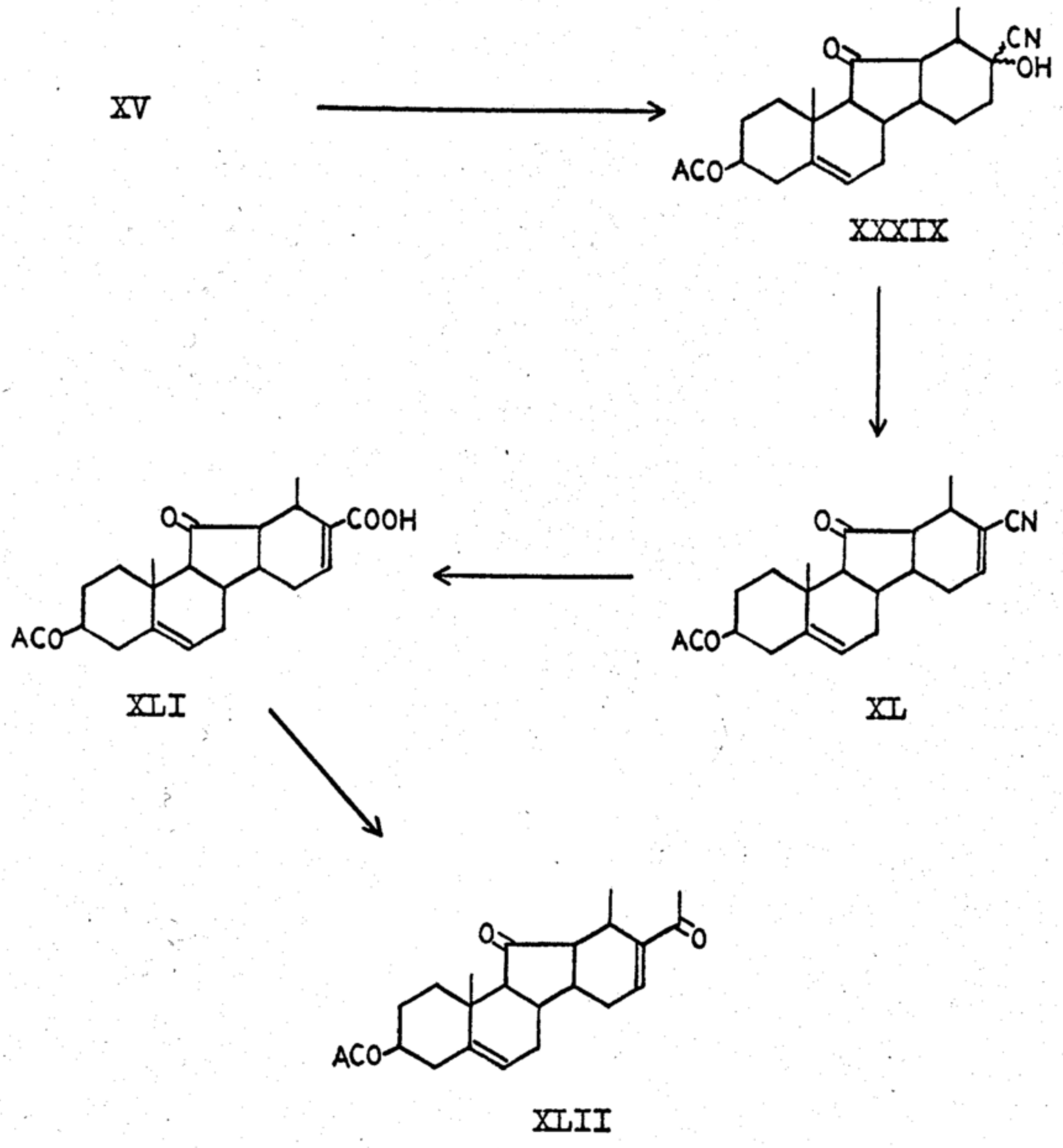
DISCUSSION

The degradation of the side-chain in IV (chart 2) was achieved by oxidation with chromic acid in acetic acid to produce compound XIV, whose 12,13-double bond was reduced with zinc in acetic acid to give the dihydroderivative XV, as shown in chart 3.

An important part of the partial synthesis of pregnane derivatives from 17-ketosteroids resides in the addition of a two-carbon fragment which will be transformed to the acetyl side-chain. Earlier, Kupchan and Levine have investigated some of the known condensation reactions on the 17-ketone in compound XV (15). Darzens condensation with α-chloropropionate, followed by treatment with alkali and decarboxylation of the resulting glycidic ester to the methyl ketone, proved to be unsuccessful.

The application of the Butenandt cyanohydration (16) procedure or its modified version which was developed by Italian workers (17), appeared to be promising. This approach was reinvestigated again in this thesis and only a brief account will be presented here. Exchange cyanohydration of compound XV with acetone cyanohydrin in the presence of base gave very high yield of a mixture of epimeric cyanohydrins (XXXIX). The infrared spectrum possessed peaks at 2.7 μ, 2.8 μ, 2.9 μ (broad) (17-OH)

Chart 7

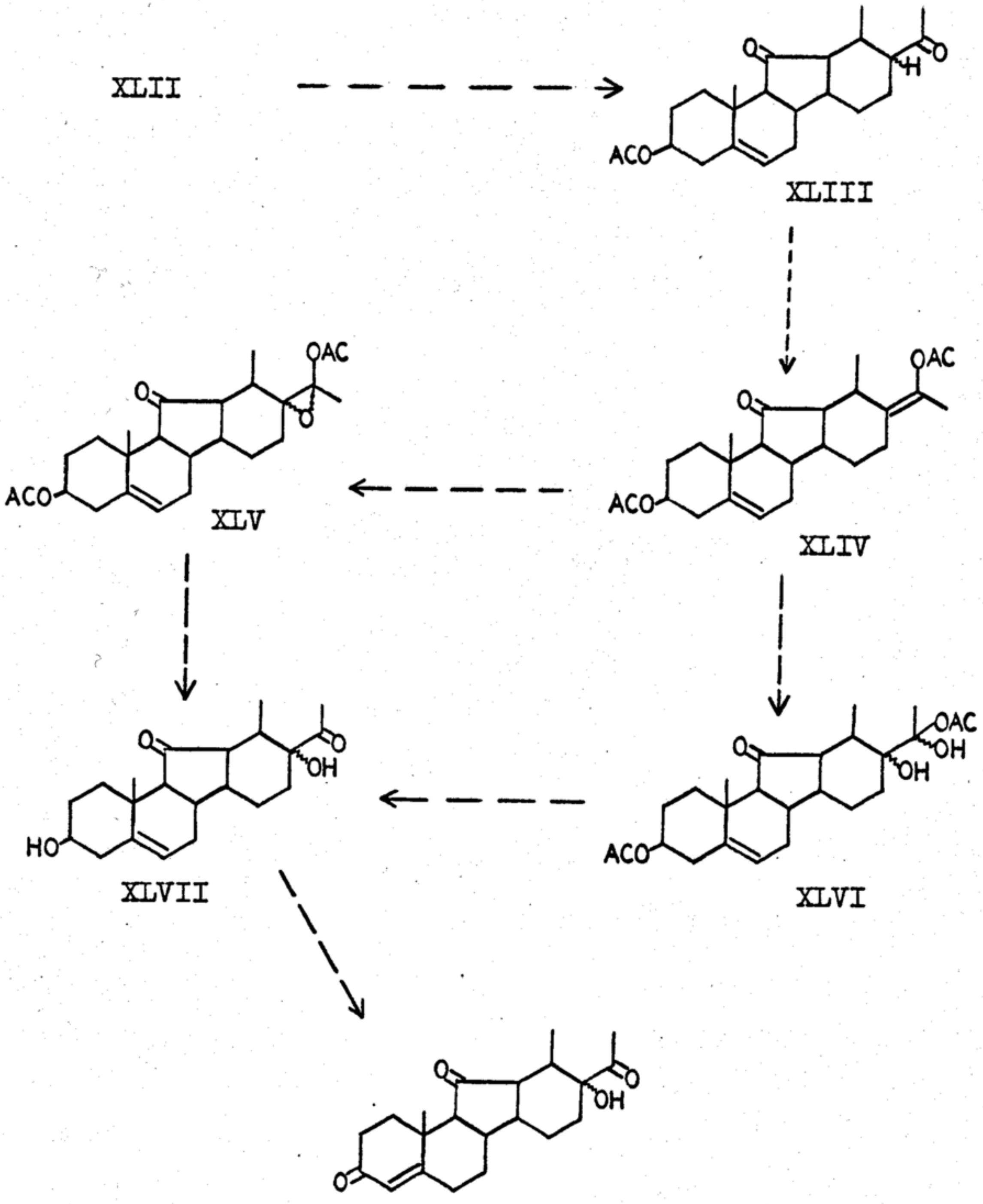


and 5.78 µ (ester carbonyl and 5-membered carbonyl). There was no peak assignable to the cyano group and this is precedented by some similar gem-cyanohydrins (18). The mixture of cyanohydrins was then dissolved in pyridine and dehydrated with phosphorous oxychloride to yield (25%) the α,β-unsaturated nitrile XL. The presence of the cyano group became evident by the presence of a peak at 4.5 µ (α,β-unsaturated nitrile) in its infrared spectrum. The mode of elimination of water was to produce a Δ^{16}-unsaturation and this was confirmed by the presence of a multiplet at 3.35 τ (C-16 vinyl hydrogen) in its nmr spectrum. Molecular models of the Δ^{16}-compound indicated much less strain in ring D than in its counterpart, the tetrasubstituted Δ^{13}-derivative.

The nitrile group in XL was then hydrolyzed to the corresponding carboxylic acid derivative by treatment with sodium hydroxide in ethylene glycol, and the crude acid was reacetylated with acetic anhydride and pyridine to afford XLI in an overall yield of 35%.

In order to convert the 17-carboxy function to the 17-acetyl side-chain, XLI was refluxed with thionyl chloride and the corresponding crude acid chloride was allowed to react directly with a suspension of dimethyl cadmium in benzene (19) to give a 40% overall yield of XLII. Its infrared spectrum exhibited peaks at 5.78 µ

Chart 8



(ester and 5-membered carbonyls), 6.0 μ (Δ^{16}-20-one) and 6.18 μ (conjugated double bond); and its ultraviolet spectrum exhibited λ_{max}^{EtOH} 228.5 mμ (ϵ 9650).

From here on the plan was to reduce the Δ^{16}-double bond in XLII (see chart 8), either by hydrogenation or by lithium in liquid ammonia, to yield the saturated ketone XLIII, and to convert the acetyl side-chain to the vinyl acetate as in XLIV. It was planned that the introduction of oxygen functions to $\Delta^{17(20)}$ could then be achieved either by epoxidation to yield the oxido-compound XLV, or osmium tetroxide oxidation to produce XLVI. Acid hydrolysis of either XLV or XLVI would then lead to the hydroxy ketone XLVII, which could be further oxidized by the Oppenauer method to afford the desired compound XLVIII. The difficulties, low yields and long synthetic route, made this pathway appear impractical and an alternate approach was undertaken.

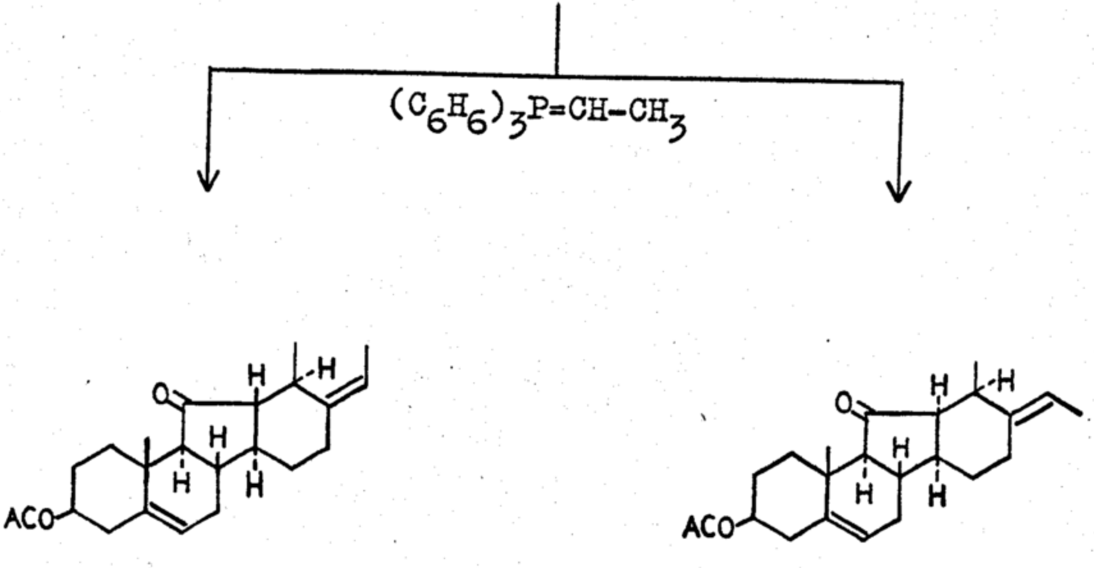
Our attention was then focused on the investigation of other alkylation reactions. The ideal alkylation reaction would be one that reinstalls the original side-chain (as in compound IV), since the exocyclic double bond ($\Delta^{17(20)}$), can easily be functionalized either by epoxidation or osmylation and the C-21 methyl group lacks any functionality that needs to be gotten rid of. Thus the applicability of the Wittig reaction seemed very attractive.

Depending on the bulkiness of the Wittig reagent and the steric hindrance of the 11-ketone in XV, it was hoped that reaction would only occur at the site of the C-17 ketone. Indeed reaction of XV with the ylide resulting from ethyl-triphenylphosphonium bromide and n-butyl lithium in ether and tetrahydrofuran, according to the procedure developed by Sondheimer (20), gave two isomeric compounds which were isolated in 40-50% yield after reacetylation of the crude reaction product and separation by column chromatography on acid-washed alumina. The major isomer (30-35% yield), Δ^5-17-cis-ethylidene-etiojervene-3β-ol-11-one acetate (XLIX), was slightly less polar than the minor isomer (10-15% yield), Δ^5-17-trans-ethylidene-etiojervene-3β-ol-11-one acetate (L). The reacetylation was necessary in order to overcome difficulties encountered during isolation of the corresponding alcohols, which seemed to overlap with the organophosphorous compounds during column chromatography. The separation of the two isomers was never complete and therefore rechromatography of the overlapping middle fractions was necessary.

The infrared spectra of both isomers were very similar even in the fingerprint region. Prominent peaks appeared at 5.80 μ (ester and 5-membered carbonyl) and 8.00 μ (C-O stretching of the ester). The peak at 5.80 μ was sharp in comparison with the broad multiple

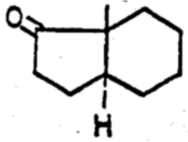
Chart 9

XV

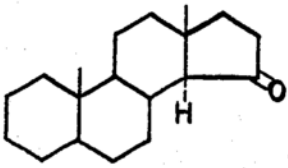

$(C_6H_6)_3P{=}CH{-}CH_3$

XLIX

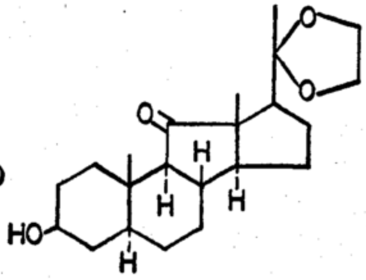
L



LI



LII



LIII

peak between 5.78 to 5.85 μ (ester carbonyl, 5-membered and 6-membered carbonyls) exhibited by the starting material (XV).

Of particular interest were the nmr spectra of XLIX and L, from which much information was gained about the structure and stereochemistry of the compounds (see Table 1). The presence of a doublet (at 8.40 τ (3H, J = 6.5 cps) and 8.41 τ (3H, J = 6.5 cps)) in the spectrum of each isomer assignable to the C-21 methyl group, and a quartet (at 4.75 τ (1H, J = 6.5 cps) in the spectrum of each isomer assignable to the C-20 vinyl proton, confirms the addition of an ethylidene group to the 17-ketone in XV. The C-19 methyl signals for compounds XV, XLIX and L appear as singlets at 8.91 τ (3H), 8.98 τ (3H), and 8.88 τ (3H), respectively; while the C-18 methyl signals appear as doublets at 8.66 τ (3H, J = 7 cps), 8.78 τ (3H, J = 6.5 cps) and 9.05 τ (3H, J = 7 cps), respectively. The C-18 methyl signal in XV has the lowest chemical shift (8.66 τ) due to double deshielding by both the C-11 and C-17 carbonyl groups. In XLIX the C-18 methyl is only deshielded by the C-11 carbonyl group and therefore is slightly shifted upfield (8.78 τ), while in the isomeric compound L there is a dramatic shielding of the C-18 methyl group to an upfield position. This can only happen if the C/D ring juncture in L is _cis_ and the C-18 methyl group is axial. This places the methyl group above the plane of the

Table 1

NMR DATA[a]

Compound	C-19 CH_3	C-18-Me	C-21 CH_3	$CH_3-\overset{O}{\overset{\|}{C}}-O-$	C-3 H	C-6 H	C-20 H
XV	8.91 (3H)s	8.66 (3H)d J=7 cps	—	7.97 (3H)s	5.38 (1H)m	4.56 (1H)m	—
XV*	9.01 (3H)s	8.47 (3H)d J=7 cps	---	8.22 (3H)s	5.28 (1H)m	4.76 (1H)m	---
XLIX	8.98 (3H)s	8.78 (3H)d J=6.5cps	8.40 (3H)d J=6.5cps	8.00 (3H)s	5.43 (1H)m	4.58 (1H)m	4.75 (1H)q J=6.5cps
XLIX*	9.02 (3H)s	8.46 (3H)d J=6 cps	8.39 (3H)d J=6.5cps	8.25 (3H)s	5.20 (1H)m	4.70 (1H)m	4.70 (1H)q J=undefined
L	8.88 (3H)s	9.05 (3H)d J=6.5cps	8.41 (3H)d J=6.5cps	7.98 (3H)s	5.43 (1H)m	4.58 (1H)m	4.75 (1H)q J=6.5cps
L*	8.89 (3H)s	9.03 (3H)d J=6.5cps	8.50 (3H)d J=7 cps	8.22 (3H)s	5.32 (1H)m	4.78 (1H)m	4.78 (1H)q J=undefined

[a] All chemical shifts are reported in τ values (ppm).
*Spectra determined in benzene.

Table 2

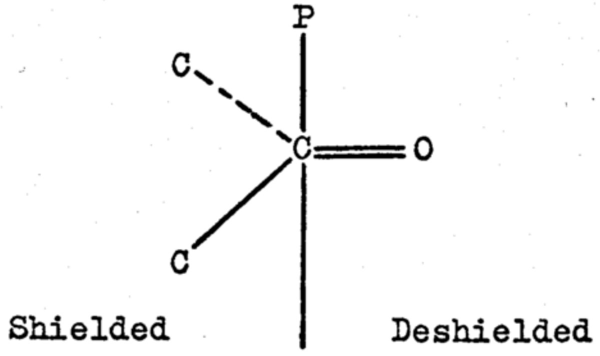
Effect of Benzene on the C-19 and C-18 Methyl Resonances (τ values in ppm)

Compound		$\Delta\tau = \tau^{CDCl_3} - \tau^{C_6H_6}$
XV	C-19	0.1
	C-18	-0.19
XLIX	C-19	0.04
	C-18	-0.32
L	C-19	0.01
	C-18	0.02

carbonyl group and results in shielding.

The formation of the minor isomer L could then be explained by assuming that XV, which originally had the C/D ring fused in a trans fashion must have equilibrated at C-12 under the basic Wittig reaction conditions to provide a C/D cis-fused product before reacting with the Wittig reagent.

It is well established that aromatic solvents, such as benzene, can exert appreciable influence on the chemical shifts of various protons adjacent to a carbonyl, especially the angular methyl groups in steroids (21). This is attributed to a complex that forms between the carbonyl group and benzene ring. The shift may be positive or negative depending on the position of the proton relative to the plane of the carbonyl. If a reference plane "P" is drawn through the carbon atom bearing the carbonyl group, as shown in the figure below, then the protons close to "P" show very small



shifts ($\Delta\tau = \tau_{CDCl_3} - \tau_{C_6H_6}$), whereas those on the side of the oxygen are deshielded and those on the other side are shielded. The shifts appear to be predictable from molecular model examinations; therefore from the magnitude and sign of the chemical shift stereochemical assignments become possible.

The nmr spectra of XV, XLIX and L were determined in benzene and compared with those determined in deuterochloroform, and the chemical shifts for the C-19 and C-18 methyl groups were determined (see Table 1). The $\Delta\tau$ values for the C-19 and C-18 methyl groups are listed in Table 2. In 11-ketosteroids the shift reported for the C-19 methyl is -0.14 ppm. Examination of the molecular models of the C-nor-D-homosteroids (XV, XLIX and L) show that the C-19 methyl groups fall in the shielded sector and therefore one predicts a positive shift for them. This is in agreement with the experimental values (see Table 2) and constitutes the first example reported for the C-19 methyl group in 11-ketosteroids to have an upfield shift.

The C-18 methyl group in XV is equatorial and one predicts a strong negative deshielding effect in benzene. The experimental value ($\Delta\tau$ = 0.1 ppm) was found to be in accord with the prediction. In compound XLIX the C-18 methyl group occupies the same position (equatorial) as in compound XV and one expects strong deshielding for it. If it occupies the axial position no shift is predicted for it, since it falls in the "P" plane. The fact that it is deshielded ($\Delta\tau$ = -0.32 ppm) by benzene indicates that it is indeed equatorial. In compound L where the C/D juncture is <u>cis</u>, one predicts a slight positive shift for the C-18 methyl group in the axial position since it falls in the "P" plane, and a strong negative shift in the equatorial position. The value of $\Delta\tau$ (0.02 ppm) supports the assignment of the axial position for the C-18 methyl group in L.

Confirmatory evidence for the stereochemistry of XLIX and L comes from ord studies. Klyne (22) applied the octant rule to hexahydroindanones. Of particular interest to us are some studies on <u>trans</u>-hexahydroindanones (22,23,24). They led to the conclusion that the cyclopentanone ring is skewed (half-chair), and in such compounds the large amplitude of the rotatory dispersion curve is due to the presence of two out-of-plane, or skewed, ring atoms; hence the large negative amplitude which characterizes the <u>trans</u>-hexahydroindan-2-ones. In contrast with symmetrical cyclohexanones in the chair conformation, in such indanones, the five-membered ring is not symmetrical and it is this asymmetry of the ring itself which gives rise to high amplitudes in such compounds. However, precise knowledge about the exact conformation of five-membered rings is still lacking, and therefore no accurate quantitative treatment can be made.

All examples cited in the literature for cyclopentanones of similar nature fused in a trans fashion with five-, or six-membered rings indicate that the above explanation is justifiable. Examples from various classes of compounds are indicated below: (-)-trans-8-methylhydroindan-1-one (LI) (23) has a "min" $[\alpha]^{322.5}$ $- 3100^\circ$; "max" $[\alpha]^{280}$ $+ 2700^\circ$ in dioxane (a = -88°); androstane-16-one (LII) is enantiomeric in nature to LI, "min" $[\alpha]^{297}$ $- 2390^\circ$; and "max" $[\alpha]^{318}$ $+ 2740^\circ$ (a = $+ 140^\circ$). The closest compounds reported in the literature resembling our system are a series of C-nor-steroids reported by Ourisson (25). For example, the C-nor-steroid LIII exhibited a "min" $[\alpha]^{295}$ $+ 1161^\circ$ and "max" $[\alpha]^{332.5}$ -953° (a = $- 106^\circ$).

Djerassi (26) studied the ord of a series of bicyclic ketones in which the carbonyl-containing ring is five- or six-membered, and came to the conclusion that the sign of the Cotton effect is not affected by the size of the adjacent, non-oxygenated ring. However, the amplitude of the Cotton effect may be affected. Therefore, for purposes of absolute configurational assignments, the optical rotatory dispersion approach may be employed between substances in which the size of the ring not bearing the carbonyl group is different.

The ord curves (see figure 1) of XLIX [$[\Phi]^{pk.}_{280}$ $+ 5729^\circ$; $[\Phi]^{tr.}_{330}$ $- 10442^\circ$; a = -161°] and L [$[\Phi]^{pk.}_{287}$ $+ 2194^\circ$; $[\Phi]^{tr.}_{330}$ $- 6546^\circ$; a = -87°] were both negative, and this is

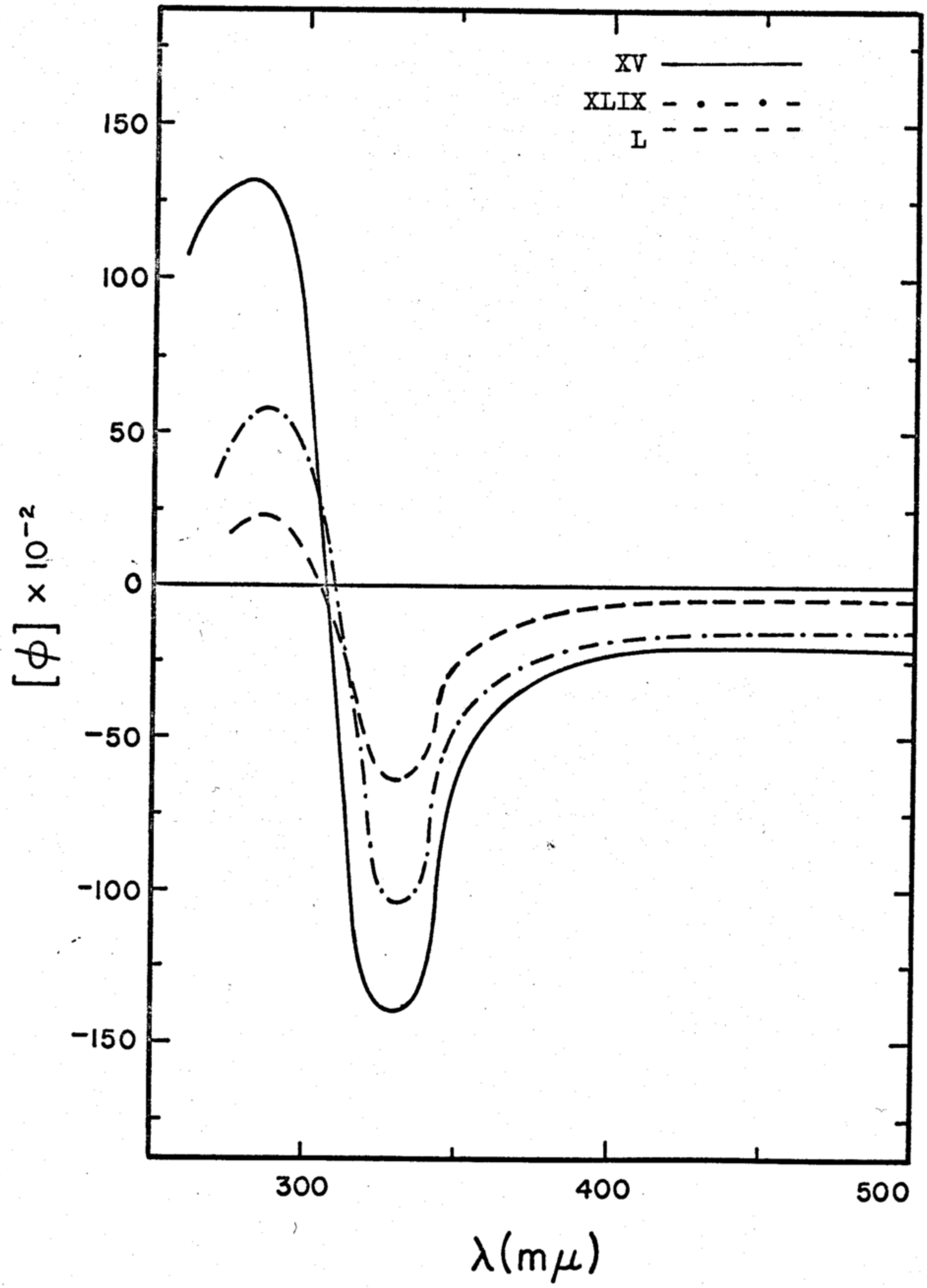
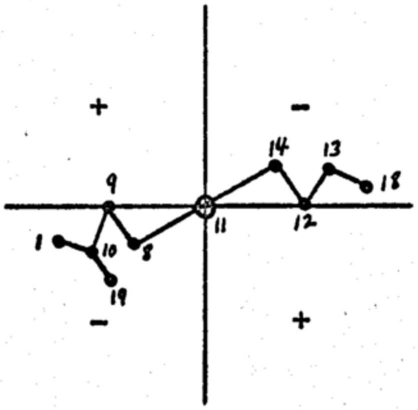
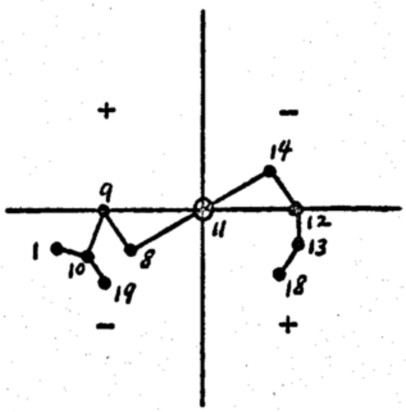


Figure 1

in agreement with all trans-fused 5-membered ring compounds reported above. However, the amplitudes for XLIX and L varied drastically. Examination of molecular models in the light of the octant rule for cyclopentanones (as suggested by Klyne (22)) explain these differences very nicely. As shown in the projection diagrams below, the cyclopentanone ring is severely skewed in both XLIX and L and both C-8 and C-14 appear in negative quadrants. The strong negative amplitude for XLIX is attributable to additional carbons falling in negative quadrants, while the diminished amplitude in L is attributable to C-13 and C-18 falling in a positive quadrant due to the C/D cis fusion. Thus XLIX possesses the C/D trans, while L possesses the C/D cis ring junctures.



XLIX



L

The orientation of the C-21 methyl groups in both XLIX and L remained undefined at this stage and will be discussed later in conjunction with spectroscopic studies on the corresponding alcohols LIV and LV.

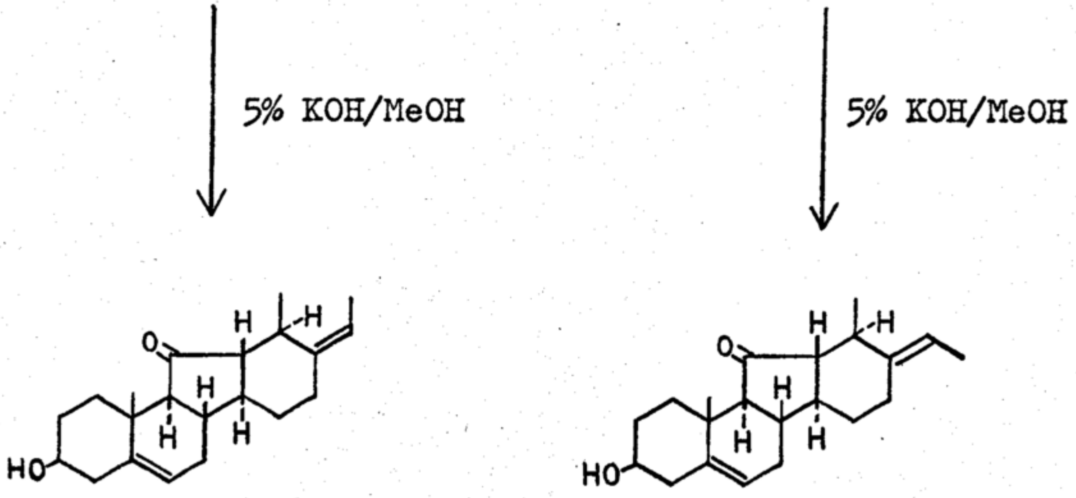
Hydrolysis of the C-3 acetates in XLIX and L with 5% potassium hydroxide in methanol at room temperature for 24 hr gave, after crystallization from ether, high yields of the corresponding alcohols, Δ^5-17-cis-ethylidene-etiojervene-3β-ol-11-one (LIV), and Δ^5-17-trans-ethylidene-etiojervene-3β-ol-11-one (LV). The hydrolysis of the esters was confirmed by the appearance of absorption peaks at 2.80 µ (OH) and the disappearance of the band at 8.00 µ (C-O stretching of the ester), in their infrared spectra.

The nmr spectrum of LIV when compared with that of XLIX indicated the absence of the methyl signal for the C-3 acetate and an appropriate shift to higher field of the C-3 H (6.59τ (1H)m). The hydroxyl signal appears at 8.12 τ and disappears upon exchange with deuterium after shaking with D_2O. The C-18 methyl protons resonate at 8.68 τ (3H,d,J=6cps) indicating no change in configuration at C-12.

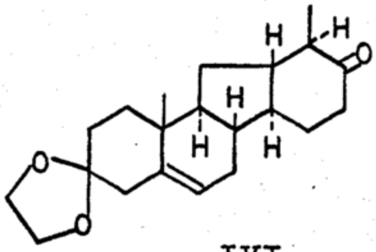
The nmr spectrum of LV was different in several respects from that of its parent compound L. The C-18 methyl signal of LV appears at 8.81τ (3H,d,J=6.5cps), suggesting isomerization in base of L at C-12α to C-12β-(axial)H during ester hydrolysis. This

Chart 10

XLIX L



LIV LV



LVI

isomerization puts the C-18 methyl group back in the C-18β(equatorial) position and therefore subject to the deshielding influence of the C-11 ketone. The C-19 methyl protons now resonate in a normal position at 8.95τ, whereas in L they were slightly deshielded due to the close proximity of the C-18β(axial) methyl. The peak for the C-3 acetate was absent and the C-3 H shifted to a higher field (6.52τ,1H,m). As in LIV the OH signal appears at 8.13τ (1H)s, which disappears when exchanged with deuterium by shaking with D_2O.

Further comparison of the nmr spectra of LIV and LV indicated differences in the chemical shifts for the C-18 as well as the C-21 methyl groups. The C-18 methyl doublet in LIV appears at 8.68τ while in LV the doublet appears at 8.81τ. This downfield shift of the C-18 methyl in LIV (-0.13 ppm) is attributed to the proximity of the C-21 methyl group which due to electronic repulsion of the hydrogens deshields the C-18 methyl (27,28). The C-21 methyl in LIV resonates at 8.40τ while in LV it resonates at 8.45τ. The deshielding effect of the C-18 methyl on the C-21 methyl is less pronounced since the C-21 methyl is already strongly deshielded by the 17,20-double bond. Therefore the C-21 methyl was assigned the <u>cis</u>-configuration in LIV and the <u>trans</u>-configuration in LV. Hence the <u>cis</u>- and <u>trans</u>-configurations for the C-21 methyl were assigned to the parent compounds XLIX and L respectively.

Further support for the retention of configuration in LIV and inversion of configuration at C-12 in LV was obtained by ord studies. The ord curves (see figure 2) of LIV $[[\Phi]^{pk.}_{290} + 8252°; [\Phi]^{tr.}_{332.5} -8886°; a = -171°]$ and LV $[[\Phi]^{pk.}_{285} + 5924°; [\Phi]^{tr.}_{322} - 11336°; a = -172°]$ were in good agreement with that of XLIX, indicating a C/D trans juncture in both LIV and L.

Since it is dangerous to make quantitative correlations between ord curves of compounds containing cyclopentanones, the magnitude of the Cotton effect due to ring C was extrapolated according to the "additivity rule" (30,31,32) as follows.

The ord of the known 11,17-diketo XV was determined (see Figure 1) $[[\Phi]^{pk.}_{280} + 13261°; [\Phi]^{tr.}_{330} - 14294°; a = -275°]$, and the ord of the known 17-keto compound LVI (see Chart 10) was studied by Kupchan and Levine (2) ($a = -97°$). Therefore the contribution from the 5-membered 11-ketone in XV is theoretically -178° and this is in close agreement with the experimental values obtained for XLIX, LIV and LV (a = -161°, -171°, -172° respectively) confirming the all-trans juncture for ring C.

The stability of the C/D trans system with C-18β (equatorial) methyl in XLIX, LIV, and LV and the instability of the C/D cis system with C-18β (axial) methyl in L is very nicely precedented by studies on the

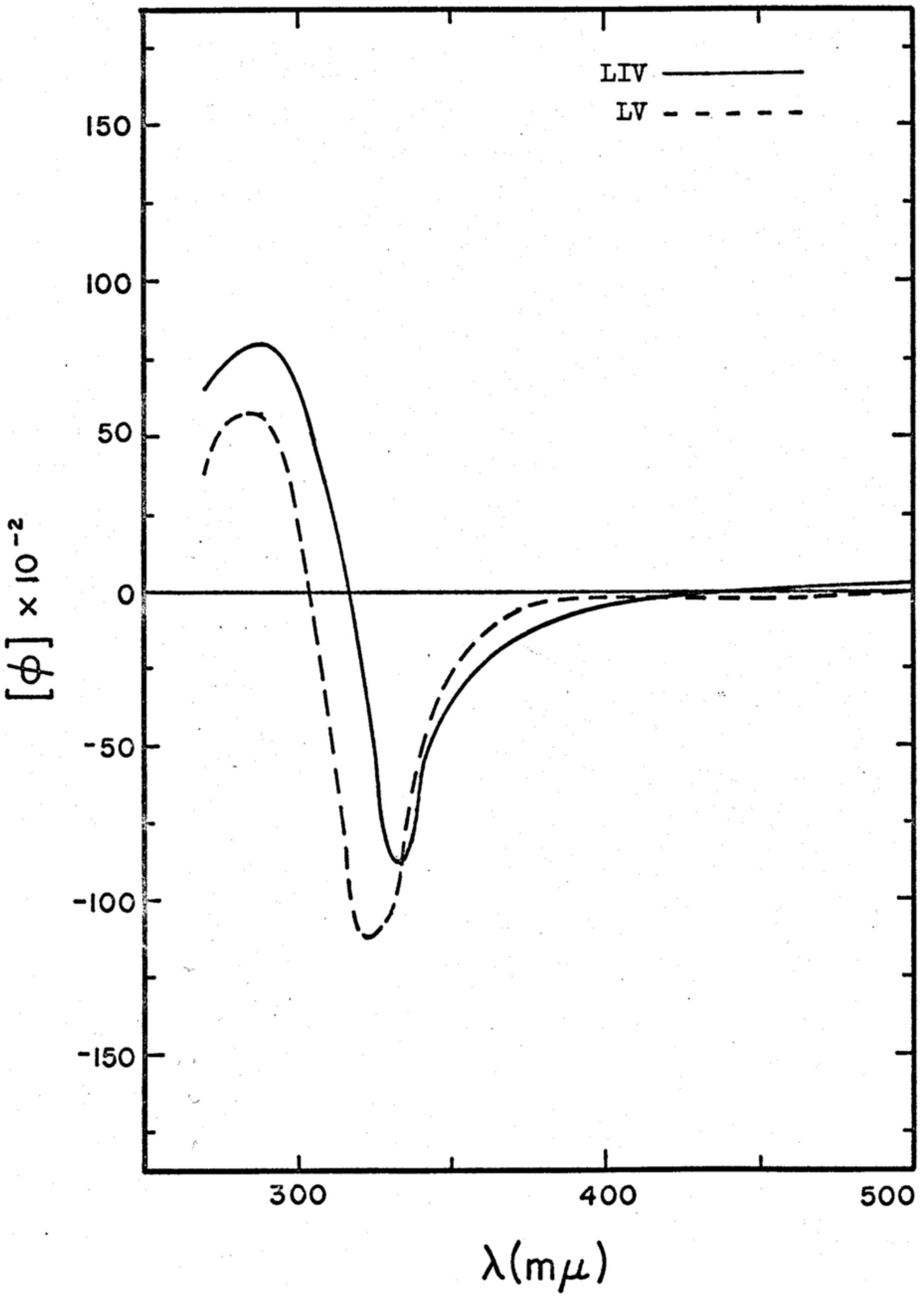
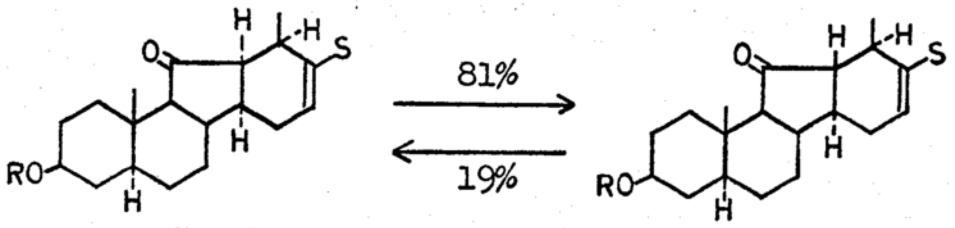


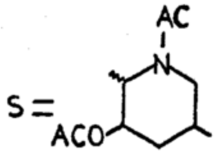
Figure 2

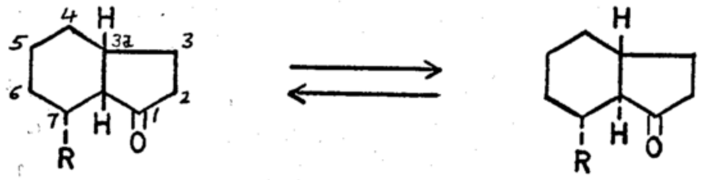
Chart 11



LVII

LVIII





LIX, R = H

LXI, R = CH_3

LX, R = H

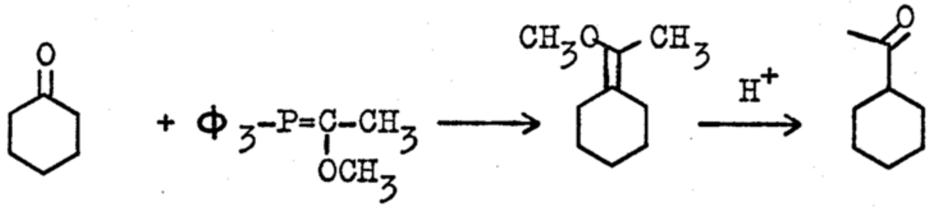
LXII, R = CH_3

C/D cis-trans equilibria in tetrahydrojervine derivatives with open ring E by Wintersteiner and Moore (33). They showed that compound LVII, having the C/D cis system with C-18β(axial) methyl, equilibrated to the more stable isomer having the C/D trans system with C-18β(equatorial) methyl (LVIII) (see Chart 11). At equilibrium under basic conditions, 81% of LVIII and only 19% of LVII were found. The C-18β(axial) methyl in LVIII was said to be the factor contributing to the instability of the C/D cis system.

Another example where conformational effects alter the usual order of stability is cited by House and Rasmussen (34) on their study of perhydroindanone derivatives. They showed that the presence of a methyl group at position 7 and trans to the C-3aH as in LXI (see Chart 11) reverses the usual stability order of the perhydroindan-1-one (LIX) where the cis isomer is known to be more stable (35). Hence compound LIX is much more stable than LX, while LXI is much less stable than LXII, due to the 1-3 diaxial interactions caused by the axial methyl group at position 7.

Application of the modified Wittig reaction in dimethyl sulfoxide to this system according to Corey et al. (36), led to a variety of isomeric products that could not be separated by column chromatography. Crystalline isolates from column chromatography, each thought to be composed of one single entity on the basis of melting point and purity according to tlc, proved to be mixtures of isomeric products as evidenced by the multiplicity of the C-18 methyl signals in the region between 8.8τ to 9.3τ. Failure of this reaction was attributed to the enhancement of isomerization of XV in dimethylsulfoxide and base. While our studies were in progress, the applicability of this procedure to C-17 oxosteroids was demonstrated (37); and Oliveto (38) reported this method as a means to convert androstanes to pregnanes in good yield.

Coulson (39) modified the Wittig aldehyde synthesis (40) for the synthesis of methyl ketones as shown in the scheme below.



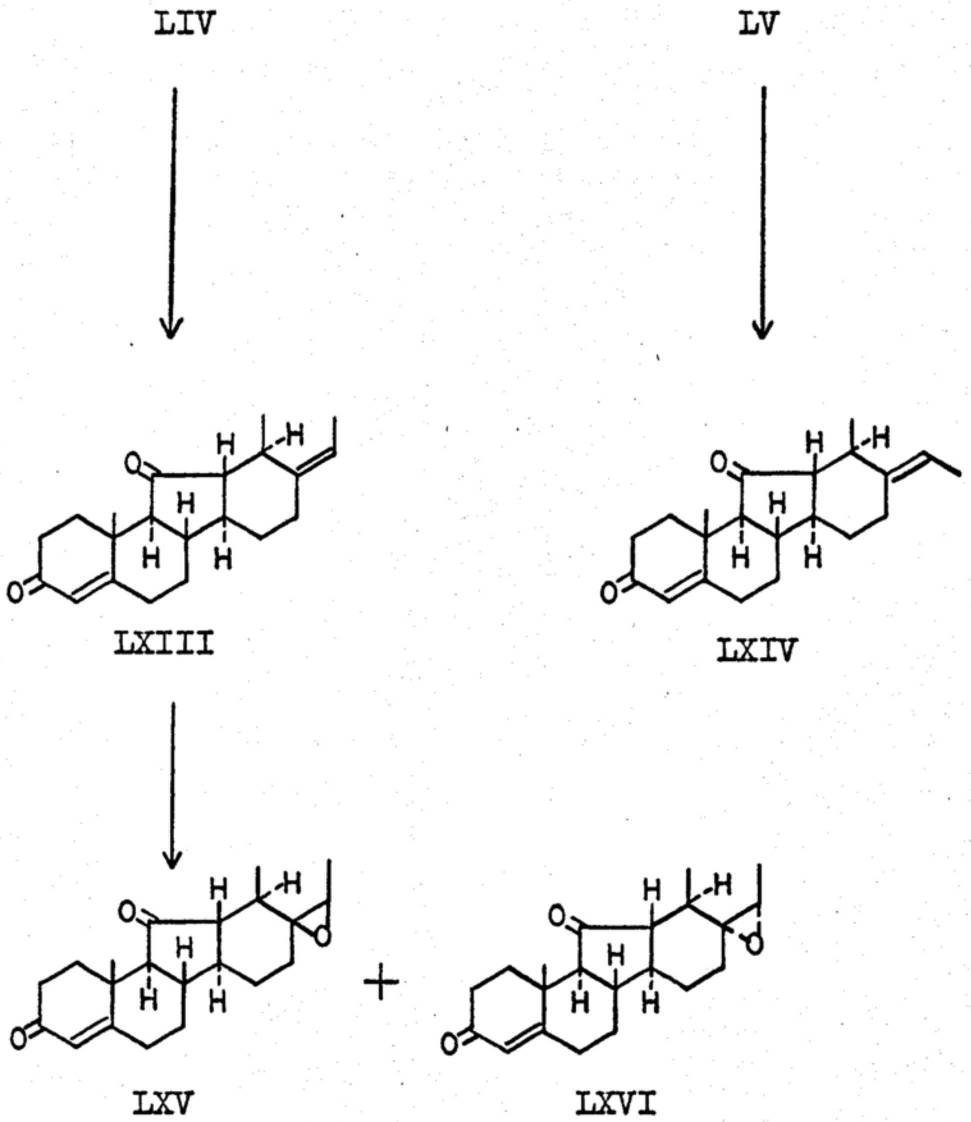
Unfortunately, only low yields of the vinyl ether were observed when XV was reacted with the modified reagent.

The first study on the kinetics of the Wittig reaction (41) indicated that the inclusion of 1.1 equivalents of a 1:1 complex mixture of potassium t-butoxide and t-butanol to a Wittig reaction increased the yields of the olefinic products appreciably. Indeed the application of this procedure to XV increased the total yield of XLIX and L up to 70-80% of crude product. However, the column chromatography and crystallization of the fractions become more tedious, due to overlapping of a brown coloring matter; also the ratio of isomers XLIX:L was increased. This was expected since the potassium *t*-butoxide is a strong base and therefore enhances the isomerization of XV at C-12.

The next step in the synthesis was the introduction of oxygen functions to the $\Delta^{17(20)}$-double bond. It is known that exocyclic double bonds are more vulnerable to addition reactions than endocyclic double bonds. However, the selective oxidation of the $\Delta^{17(20)}$-double bond in LIV, either by epoxidation with *m*-perphthalic acid to yield the 17,20-oxido derivative, or by osmylation to produce the 17,20-diol, could not be achieved without simultaneous oxidation of the Δ^5-double bond, as evidenced by tlc analysis.

In order to reduce the nucleophilicity of the Δ^5-double bond, compound LIV was oxidized by the Oppenauer procedure (aluminum isopropoxide, cyclohexanone, toluene) according to the method of Kupchan, Milne and Masamune (13), to afford the oxidation product, Δ^4-17-*cis*-ethylidene-etiojervene-3,11-dione (LXIII), in 65-70% yield. The infrared spectrum indicated the absence of the OH absorption at 2.80 μ, and the appearance of new bands at 6.02 μ (Δ^4-3-one) and 6.20 μ

Chart 12



(conjugated double bond) in addition to the band at 5.80 μ (5-membered carbonyl). The ultraviolet spectrum possessed λ_{max}^{EtOH} 236 mμ (ϵ 17,000) and this is in good agreement with the presence of a Δ^4-3-one system.

The nmr spectrum indicated a downfield shift of the vinyl proton to 4.24 τ (C-4 vinyl proton) and, for the first time, a clear quartet for the C-20 vinyl proton appears at 4.74 τ (J = 7 cps). The C-19 methyl protons now resonate at 8.77 τ and those of the C-18 methyl at 8.80 τ (doublet, J = 7 cps).

Likewise compound LV was oxidized by the Oppenauer method to give Δ^4-17-trans-ethylidene-etiojervene-3,11-dione (LXIV), also in 65-70% yield. The infrared spectrum of LXIV was similar to that of LXIII and likewise possessed absorption bands at 5.78 μ (5-membered carbonyl), 6.00 μ (Δ^4-3-one), 6.20 μ (conjugated double bond); there was no alcohol absorption at 2.80 μ. Compound LXIV showed one single absorption in the ultraviolet, λ_{max}^{EtOH} 236 mμ (ϵ 17,000).

In order to prove that oxidation of LIV and LV to LXIII and LXIV respectively under Oppenauer conditions does not involve isomerization at any center, the ord curves of LXIII and LXIV were determined and compared with those of their parent compounds (see Figure 3). Both compounds show equal negative Cotton effects, LXIII [$[\Phi]_{286}^{pk.}$ + 5467°; $[\Phi]_{329}^{tr.}$ - 10935°; a = -164°]

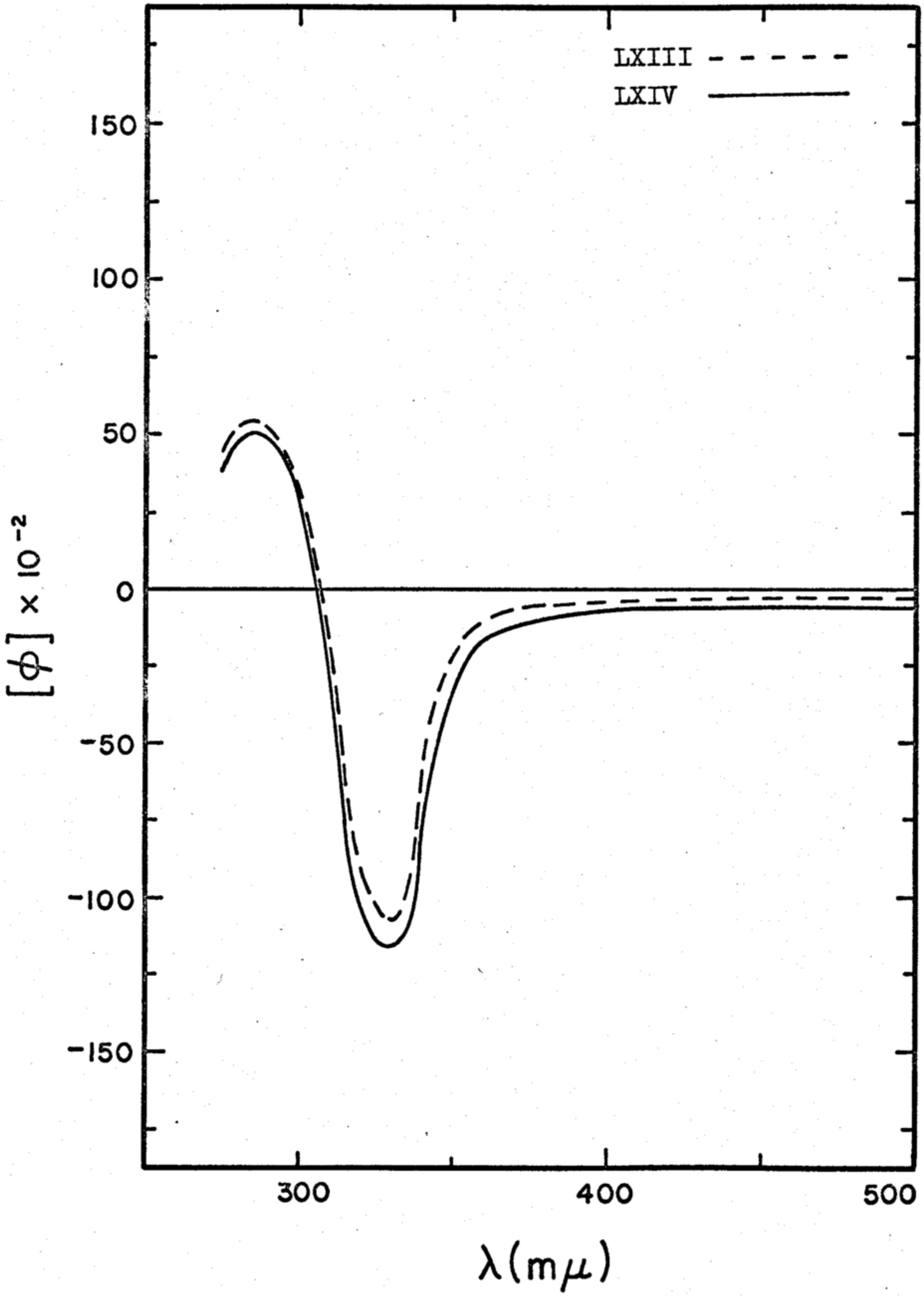

LXIII
LXIV
150
100
50
0
-50
-100
-150
$[\phi] \times 10^{-2}$
300
400
500
$\lambda(m\mu)$

Figure 3

and LXIV $[[\Phi]^{pk.}_{286} + 4999°; [\Phi]^{tr.}_{329} - 11663°; a = -166°]$ and these are in excellent agreement with those for LIV and LV, confirming that no isomerization had occurred at any of the centers.

Now that the nucleophilicity of the Δ^4-double bond had been lessened by conjugation with the C-3 ketone, it was expected that the selective oxidation of $\Delta^{17(20)}$-double bond should present no complications. Indeed, incubation of LXIII with about 10 equivalents of m-perphthalic acid in an ether solution at room temperature for 24 hr led to exclusive attack on the $\Delta^{17(20)}$-double bond to produce high yields of two isomeric epoxides which were separated by fractional crystallization from ether. The major isomer, Δ^4-17-ethyletiojervene-3,11-dione-17β,20β-oxide (LXV) was obtained in 65% yield; while the minor isomer, Δ^4-17-ethyletiojervene-3,11-dione-17α,20α-oxide (LXVI), was obtained in 20% yield and had a lower R_f value than LXV.

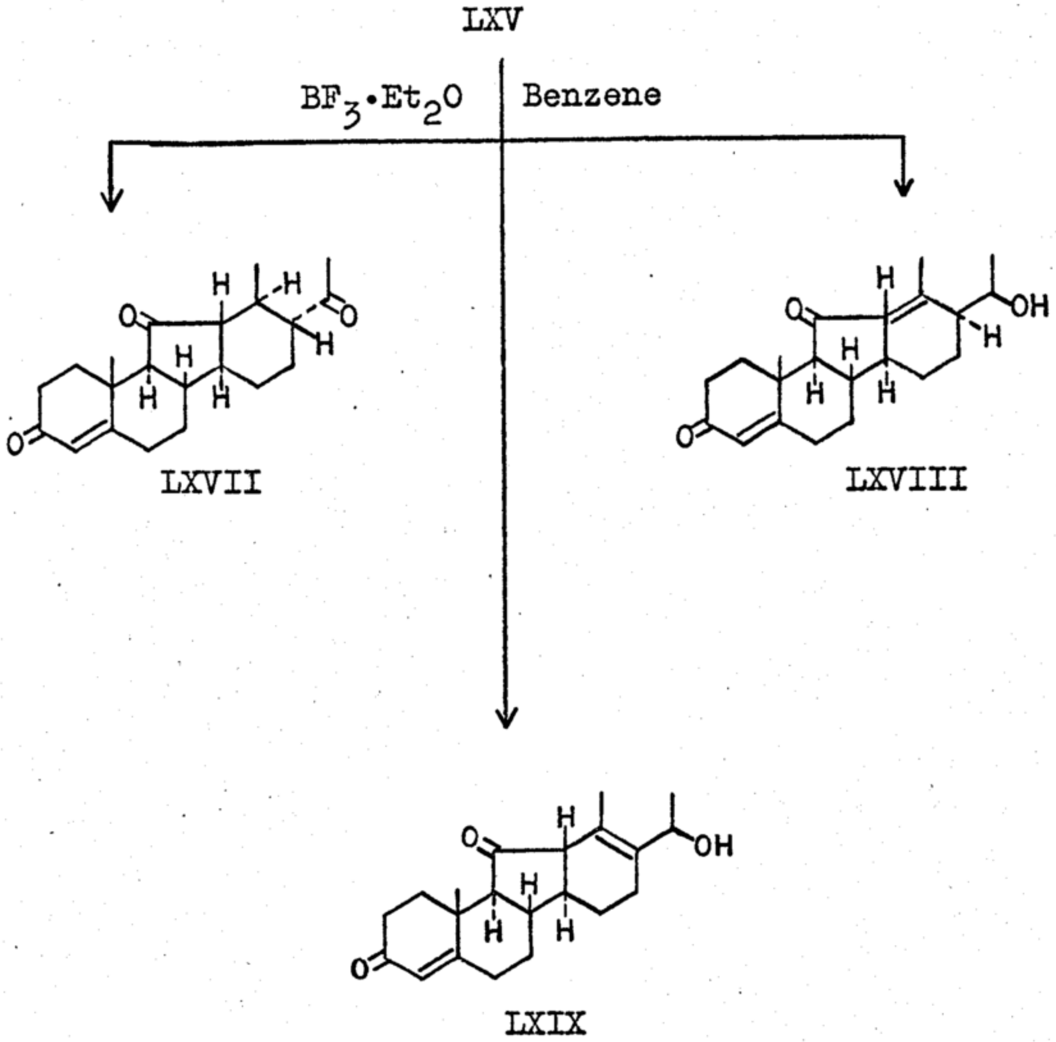
The infrared spectra of both isomers were very similar and possessed absorption bands at 5.79 µ (5-membered carbonyl), 6.00 µ (Δ^4-3-one), 6.20 µ (conjugated double bond), 9.70 µ, 10.50 µ and 11.02 µ (due to the epoxide). Their ultraviolet spectra were analogous to those of the parent compounds and possessed maximum absorptions at 236 mµ.

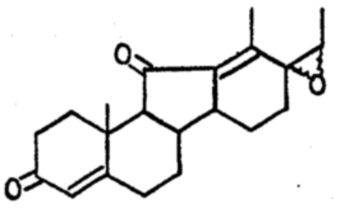
The nmr spectrum of LXV (see Table 3) is completely compatible with its structure. The C-20 proton now appears as a well-resolved quartet centered at 7.18 τ (J = 6 cps), and the C-21 methyl appears as a doublet at 8.75 τ (J = 6 cps). A doublet assigned for the C-18 methyl appears at 8.85 τ (J = 6 cps), overlapping the singlet due to the C-19 methyl group.

The assignment of the β-configuration for the epoxide in LXV follows from its behavior toward boron trifluoride in benzene, as discussed later. Hence, the α-configuration was assigned for the epoxide in LXVI, and this was not studied any further due to the scarcity of material.

In order to prepare a C-nor-D-homoprogesterone analog, it was necessary to transform the epoxide in LXV to the C-20 ketone. It is known that epoxides rearrange to ketones by a 1-2 hydride shift by reaction with various Lewis acids in appropriate solvents (42). Treatment of LXV with boron trifluoride etherate in dry benzene at room temperature for 5 min gave three different products, as identified by tlc, in addition to some unconverted material. Separation of the crude reaction mixture by preparative tlc, and extraction of the bands afforded several compounds. The compound of highest R_f was Δ^4-17α-ethyletiojervene-3,11,20-trione (LXVII) (see Chart 13). The structure assigned to this

Chart 13





LXX

compound was supported by its infrared spectrum, which possessed a new carbonyl absorption at 5.84 μ (C-20 carbonyl), in addition to the bands at 5.78 μ (5-membered carbonyl), 6.00 μ (Δ^4-3-one) and 6.20 μ (conjugated double bond), and its ultraviolet spectrum with $\lambda_{\max}^{\mathrm{EtOH}}$ 237 mμ (ε 18,000). Compound LXVII did not isomerize in base and therefore exists in its most stable form. This suggests that the acetyl side-chain is α (equatorial). From the β-epoxide LXV one expects to obtain the β-acetyl configuration (see mechanism later); however under the acidic reaction conditions isomerization at C-17 can easily take place. The ord curve of LXVII (see Figure 4) [$[\Phi]_{305}^{\mathrm{pk.}}$ + 7593°; $[\Phi]_{332.5}^{\mathrm{tr.}}$ - 1708°; a = -93°], a moderate negative curve compared to that of LXIII, also supports the α-position for the acetyl side-chain on the basis of an earlier observation (12).

$\Delta^{4,12(13)}$-17β-ethyletiojervene-20β-ol-3,11-dione (LXVIII) was isolated from the second band. The assignment of structure LXVIII was supported by its infrared and ultraviolet spectra. The infrared spectrum shows absorption bands at 2.80 μ (C-20 OH), a new carbonyl band at 5.85 μ and the absence of the original band at 5.78 μ, indicating conjugation of the 5-membered carbonyl. The peaks at 6.00 μ and 6.12 μ remained unchanged. The ultraviolet spectrum shows no absorption

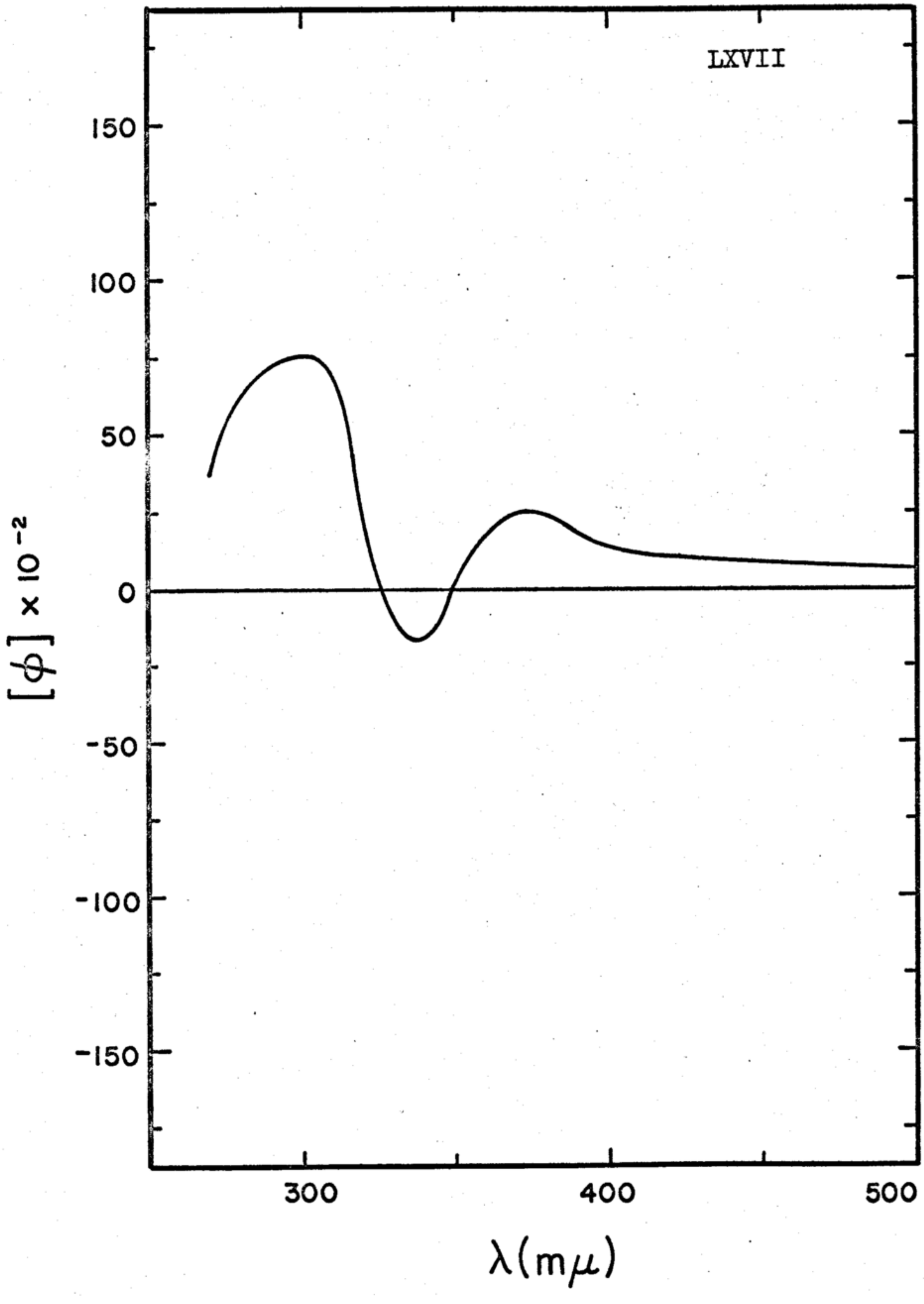


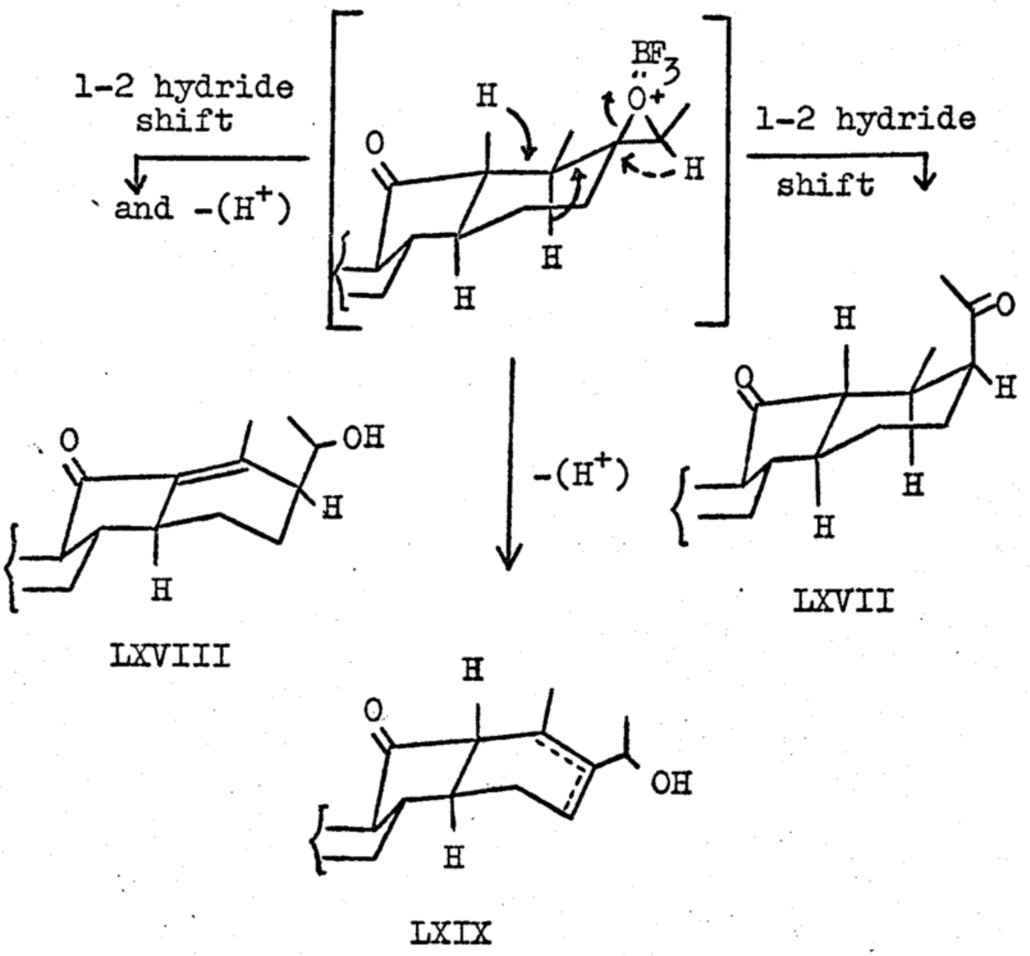
Figure 4

at 236 mμ for the chromophore in ring A; instead, there is a more intense absorption at higher wavelength, [λ_{max}^{EtOH} 247 mμ (ϵ 24,480)]. This is in good agreement with similar compounds, e.g. compound LXX [λ_{max}^{EtOH} 252 mμ (ϵ 24,400)] (13).

From the most polar band was isolated a yellowish oil which failed to crystallize. The compound shows absorption bands in the infrared at 2.90 μ (OH), 5.77 μ (5-membered carbonyl), 6.00 μ (Δ^4-3-one), 6.19 μ (conjugated double bond), and no absorption at 5.85 μ. Its ultraviolet spectrum possesses the usual absorption at 236 mμ. From the above data and mechanistic considerations (see below) the compound was tentatively assigned the $\Delta^{4,13(or16)}$-17 -ethyletiojervadiene-20β-ol-3,11-dione (LXIX) structure.

The formation of compounds LXVII, LXVIII and LXIX from LV can be rationalized from the mechanism of opening of steroidal epoxides in Lewis acids (42). The strongly electrophilic boron trifluoride promotes considerable ionization of the bond from oxygen to the most alkylated carbon center by coupling with the epoxide (see the scheme below).

The complex intermediate shown in this scheme either rearranges to the ketone (LXVII) <u>via</u> a 1-2 hydride shift of the C-20 H to C-17 as represented by the dotted arrow, or loses the adjacent C-13 or C-16



antiparallel (axial) proton to produce the elimination product LXIX. A combination of both mechanisms, i.e. a 1-2 hydride shift of the C-13 antiparallel (axial) proton to C-17α position with concomitant opening of the epoxide to the C-20 OH leaves a tertiary carbonium ion at C-13 which is then compensated by loss of the C-12β-(axial)-H to produce the other elimination product, LXVIII. The mechanism for the formation of LXVIII can also be a concerted one.

The formation of the elimination products is only possible if the 17,20-epoxide in LXV occupies the antiparallel configuration to C-13α-(axial)-H, which in turn is antiparallel to the C-12β-(axial)-H. On this account the epoxide in LXV was assigned the β-configuration and from this follows the assignment of the α-epoxide to the other isomer (LXVI).

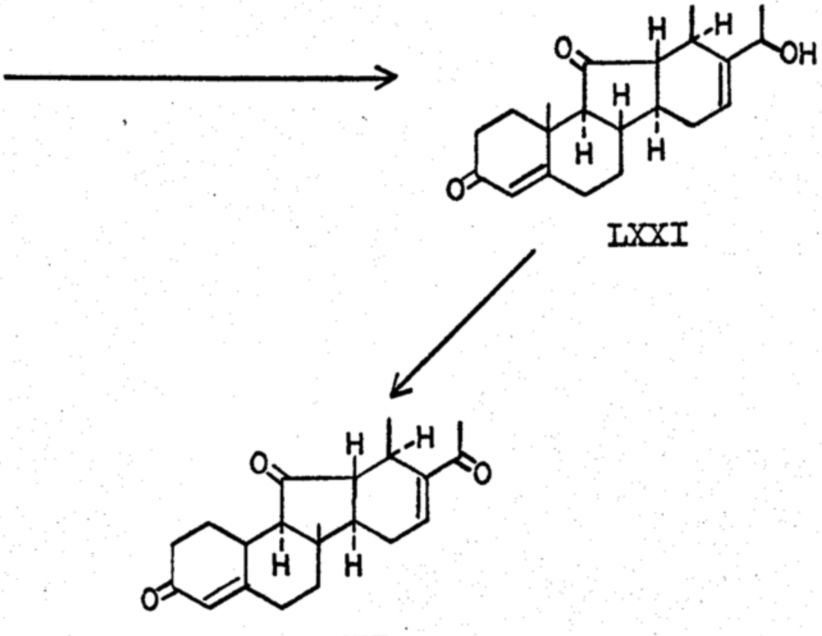
The rearrangement of the epoxide in LXV with various other Lewis acids, such as magnesium bromide in ether (43) had no advantage over the use of boron trifluoride, although it had been reported that magnesium bromide gives higher yields of rearrangement products than elimination products.

To obtain 17,20-oxygenated C-nor-D-homoprogesterone derivatives, attempts were made to make use of the epoxy compound LXV. Fieser (44) reported the oxidation of the 5,6β-epoxide in the cholesterol series with potassium dichromate in acetic acid at room temperature to give a high yield of the corresponding 5α-hydroxy-6-ketone. Oxidation of LXV under the same reaction conditions yielded an intractable mixture from which no pure crystalline product could be isolated.

Cohen and Tsuji (45) have shown that epoxides may be oxidized to hydroxy ketones with dimethyl sulfoxide in the presence of catalytic amounts of boron trifluoride at steam bath temperature. Other products such as the diol may also be formed. Treatment of LXV on a steam bath in dimethyl sulfoxide with boron trifluoride gave almost a quantitative yield of $\Delta^{4,16}$-17-ethyletio-

Chart 14

LXV



LXXI

LXXII

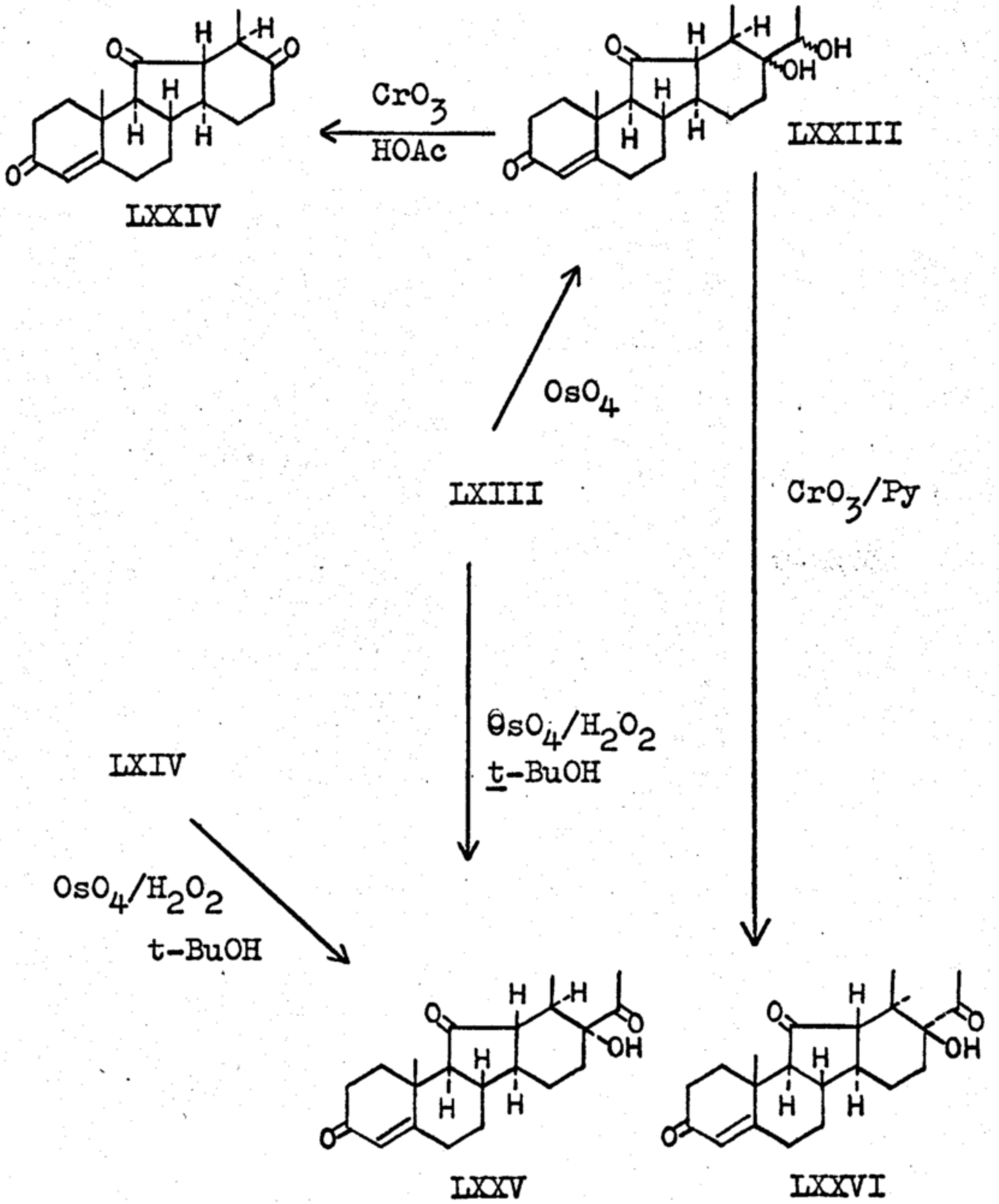
jervadiene-20β-ol-3,11-dione (LXXI). Its infrared spectrum in Nujol showed absorption bands at 2.80 μ, 3.00 μ (C-20 OH), 5.78 μ (5-membered carbonyl), 6.00 μ (Δ^4-3-one) and 6.20 μ (conjugated double bond). As expected, its ultraviolet spectrum possessed one peak, λ_{max}^{EtOH} 236 mμ (ϵ 15,500). Studies were pursued on its oxidation product which led to its structural elucidation. (It is interesting to note that the minor isomer LXVI under the same reaction conditions gave high yields of LXXI.)

Oxidation of LXXI with Sarett's reagent (chromic acid in pyridine) gave a high yield of $\Delta^{4,16}$-17-ethyletiojervadiene-3,11,20-trione (LXXII). The ultraviolet spectrum of LXXII indicated the presence of two overlapping chromophores since it possesses an unusually intense absorption, λ_{max}^{EtOH} 232.5 mμ (ϵ 24,500). Also, strong absorption bands at 6.00 μ (Δ^4-3-one and Δ^{16}-20-one) and 6.20 μ (Δ^4, and Δ^{16}-conjugated) appear in its infrared spectrum. The direction of elimination of water to produce the trisubstituted double bond (Δ^{16}) instead of the more stable tetrasubstituted double bond (Δ^{13}) became evident from its nmr spectrum, which possesses two vinyl absorptions, a singlet at 4.22 τ (C-4 H) and a multiplet at 3.25 τ (C-16 H), in good agreement for the position of a proton on the β-carbon of an α,β-unsaturated ketone. Furthermore, a singlet at 7.70 τ (3H, C-21 CH_3) is in agreement with the position for a methyl ketone. The signal for the C-18 methyl doublet overlaps with the signal for the C-19 singlet and both appear at 8.80τ (6H). The position of the C-18 methyl signal suggests that no isomerization at C-12 occurred.

The mode of elimination of water to produce the trisubstituted double bond (Δ^{16}) instead of the tetrasubstituted (Δ^{13}) becomes evident from examination of molecular models. The 16,17-double bond seems to cause much less strain in ring D than the 13,17-double bond. An analogous situation is that of the dehydration of the cyanohydrin XLIX to produce the α,β-unsaturated nitrile XL (see Chart 7). The opening of the epoxide in LXV to the trans diol with 1.5 N perchloric acid in acetone (46) gave a mixture of products and this approach did not meet with success.

The conclusion was that the utilization of the epoxide LXV did not look too promising and therefore attention was turned to the possibility of selectively oxidizing the 17,20-double bond in LXIII with the hydroxylating agent osmium tetroxide. Incubation of LXIII with 1 equivalent of osmium tetroxide in ether at room temperature for 58 hr gave a grey precipitate of the osmate esters which was collected and decomposed into the diols either with sodium bisulfite in pyridine (47), or with 7% mannitol in 1% potassium hydroxide solution (48). The mixture of α- and β-cis glycols (LXXIII),

Chart 15


LXXIV
CrO_3
HOAc
LXXIII
OsO_4
LXIII
CrO_3/Py
OsO_4/H_2O_2
t-BuOH
LXIV
OsO_4/H_2O_2
t-BuOH
LXXV
LXXVI

which was obtained in over 80% yield as a crude greyish solid, could not be separated by column chromatography.

The infrared spectrum of LXXIII confirmed the exclusive oxidation of the 17,20-double bond since there were absorption bands at 2.80 μ and 2.90 μ (broad and intense due to H-bonding) and the carbonyl region remained unchanged and the bands persisted at 5.78 μ (5-membered carbonyl), 6.00 μ (Δ^4-3-one) and 6.20 μ (conjugated double bond). Moreover, there was an absorption band at 236 mμ in the ultraviolet.

The separation of the two isomeric glycols (LXXIII) was not necessary at this stage since the next step requires the oxidation of the C-20 hydroxyl group to the corresponding ketone. Therefore, the separation of the two isomers was left until after the oxidation of the C-20 hydroxyl group.

The oxidation of the glycols LXXIII to the hydroxyketones, as compared to similar oxidations of 17,20-cis-glycols in normal steroids, has taken a different course and presented unexpected difficulties (see Chart 15). The oxidation of LXXIII with chromic acid in acetic acid at room temperature gave, in about 80% yield, the known cleavage product, Δ^4-etiojervene-3,11,17-trione (LXXIV).

An alternative procedure to prepare the diol (LXXIII) is by oxidation of the 17,20-double bond with catalytic amounts of osmium tetroxide in the presence of potassium chlorate in tetrahydrofuran and water at 48° for a period of 24 hr. Thin layer chromatography of the isolated crude product indicated a high yield of the glycols (LXXIII) and minute amounts of the hydroxyketones. The crude reaction mixture was then oxidized with Sarett's reagent (chromic acid in pyridine) and the reaction product was chromatographed on acid-washed alumina. A fraction eluted with 30% ether in benzene failed to crystallize but all examinations (tlc, ir and uv analysis) indicated it to be the dehydrated product LXXII. Further elution with 40% ether in benzene gave low yields of the desired product, Δ^4-17-ethyletiojervene-17α-ol-3,11,20-trione (LXXV). Further elution with ether also gave low yields of the isomeric product, Δ^4-17-ethyletiojervene-3,11,20-trione-17β-ol (LXXVI).

Oxidation of the <u>cis</u>-glycols (LXXIII) with Jones' reagent (8 N chromic acid in dilute sulfuric acid) in acetone at 0° for a short period showed only little improvement over the other procedures. Unlike similar models in normal steroids, the diol (LXXIII) or the products from its oxidation seem to be very sensitive to acidic or basic media. This is attributed to the D-homo character of these steroids where dehydration is much more facile than in normal steroids.

Finally, the synthesis of the hydroxyketones LXXV and LXXVI was achieved by a one step oxidation of the 17,20-double bond in LXIII under neutral conditions according to the procedure of Miescher and Schmiden (49). Treatment of LXIII with catalytic amounts of osmium tetroxide and hydrogen peroxide in t-butanol and water under a nitrogen atmosphere gave good yields of LXXV and LXXVI after chromatography on silica gel. In an analagous manner compound LXIV was also converted to LXXV and LXXVI, to confirm the argument presented earlier to prove that compounds XLIX and L differed only in the orientation of the C-21 methyl group around $\Delta^{17(20)}$-double bond. Consequently, the derivatives obtained from them (LXIII and LXIV) bear the same relationship.

The characteristics of the infrared spectra of LXXV differ from that of LXXVI. The spectrum of LXXV possesses a weak absorption band for the OH at 2.90 μ and three distinct carbonyl bands at 5.78 μ (5-membered carbonyl), 5.86 μ (C-20 carbonyl) and 6.00 μ (Δ^4-3-one); while the spectrum of LXXVI possesses two absorption bands for the OH at 2.80 μ (sharp but weak) and 2.90 μ (broad and intense) indicating strong H-bonding. Examination of the carbonyl region suggested that the C-17 hydroxyl is chelated with the C-20 ketone since the band at 5.86 μ is less intense than the other two bands at 5.78 μ (5-membered carbonyl) and 6.00 μ (Δ^4-3-one). In order to have H-bonding between the C-17 hydroxyl and the C-20 ketone both groups must be in the same plane.

Examination of molecular models showed that in the case of the equatorial alcohol, when the C-20 ketone is in the same plane as the alcohol, there is a steric interaction between the C-21 methyl group and the C-12β-(axial)-H. For this reason the β-acetyl side-chain is forced out of the plane of the hydroxyl group and therefore chelation is not possible. In the axial alcohol the α-acetyl side-chain has no steric interactions when the C-20 ketone is in the same plane with the 17-hydroxyl, hence chelation is possible. On this account a tentative assignment was made based on the infrared spectral observations, and LXXV was assigned the 17α-hydroxy configuration (no H-bonding) and LXXVI the 17β-hydroxy configuration (strongly H-bonded). The ultraviolet spectra of LXXV and LXXVI were very similar, with λ_{max}^{EtOH} 236 mμ (ϵ 17,000) and λ_{max}^{EtOH} 236 mμ (ϵ 18,000), respectively.

Examination of Table 3 shows that the nmr spectra of LXXV and LXXVI are similar and no stereochemical conclusions can be deduced from them. The C-21 methyl protons in LXXV resonate at 7.62τ while the resonance of those of LXXVI is shifted upfield by 0.14 ppm (7.76τ), most probably due to chelation with the C-17 hydroxyl group. In compound LXXV the hydroxyl signal appears as a complex multiplet between 6τ and 6.5τ (1H) while in LXXVI it appears as a single peak at 7.20τ. Both signals disappeared upon exchange with deuterium when the compounds were shaken with D_2O. The positions of the C-18 methyl doublet in both compounds LXXV and LXXVI (8.69 and 8.74τ respectively) were in good agreement with other C/D trans compounds containing the C-18β-(equatorial)-CH_3. This suggests that no isomerization took place at C-12.

The fact that compound LXII shows one intense absorption maximum in the ultraviolet [λ_{max}^{EtOH} 232.5 mμ (ϵ 24,500)] for both chromophores in ring A and ring D made it possible to determine the rate of elimination of water in compounds LXXV and LXXVI using ultraviolet analysis. Indeed when the ultraviolet spectra of

$$\text{LXXV} \xrightarrow[\text{Slow}]{-H_2O} \text{LXII} \xleftarrow[\text{Fast}]{-H_2O} \text{LXXVI}$$

alcohols LXXV and LXXVI were observed in a solution of methylene dichloride containing 0.3% phosphorous oxychloride and the increase in absorptions were observed at appropriate time intervals (equal concentrations of LXXV and LXXVI were used), the rate of incremental increase in absorption observed for LXXVI was much faster than for LXXV, suggesting a more facile dehydration in LXXVI. It is known that axial alcohols eliminate water many times faster than the equatorial ones, hence LXXVI was assigned the 17β-(axial)-hydroxyl and LXXV was assigned the 17α-(equatorial)-hydroxyl. This is in agreement with the tentative assignment based on the infrared spectral observations.

Confirmatory evidence for the assignment of stereochemistry comes from ord studies (see Figure 5) on LXXV $[[\Phi]^{pk.}_{270}$ + 17411°; $[\Phi]^{tr.}_{322}$ -17360°; a = -347°] and LXXVI $[[\Phi]^{pk.}_{280}$ + 7021°; $[\Phi]^{tr.}_{328}$ -12287°; a = -193°]. The contribution due to the C-3 and C-11 ketones are expected to be the same as in the parent compound LXIII (a = -164°). In LXXV, the β-acetyl side-chain has been suggested to be out of the plane of the 17α-hydroxyl due to steric interaction with the C-12β-(axial)-hydrogen. Examination of molecular models indicates that a strong negative Cotton effect is predicted for the 17β-acetyl group, since when the β-acetyl group is fitted into the octant diagram, the rest of the molecule falls in a negative quadrant (see diagram below). This is in good agreement with the experimental amplitude obtained for LXXV (a = -374°). In the other isomer, LXXVI, it has been shown that there is chelation between the 17β-hydroxyl and the C-20 ketone and therefore the α-acetyl side-chain is fixed in the plane of the 17β-hydroxyl. Examination of molecular models indicates a slight contribution to the Cotton effect for the 17-ketone according to the octant diagram since part of the molecule falls in a positive quadrant and the other part of it falls in a negative quadrant and these seem to counter-balance each other (see diagram below). This

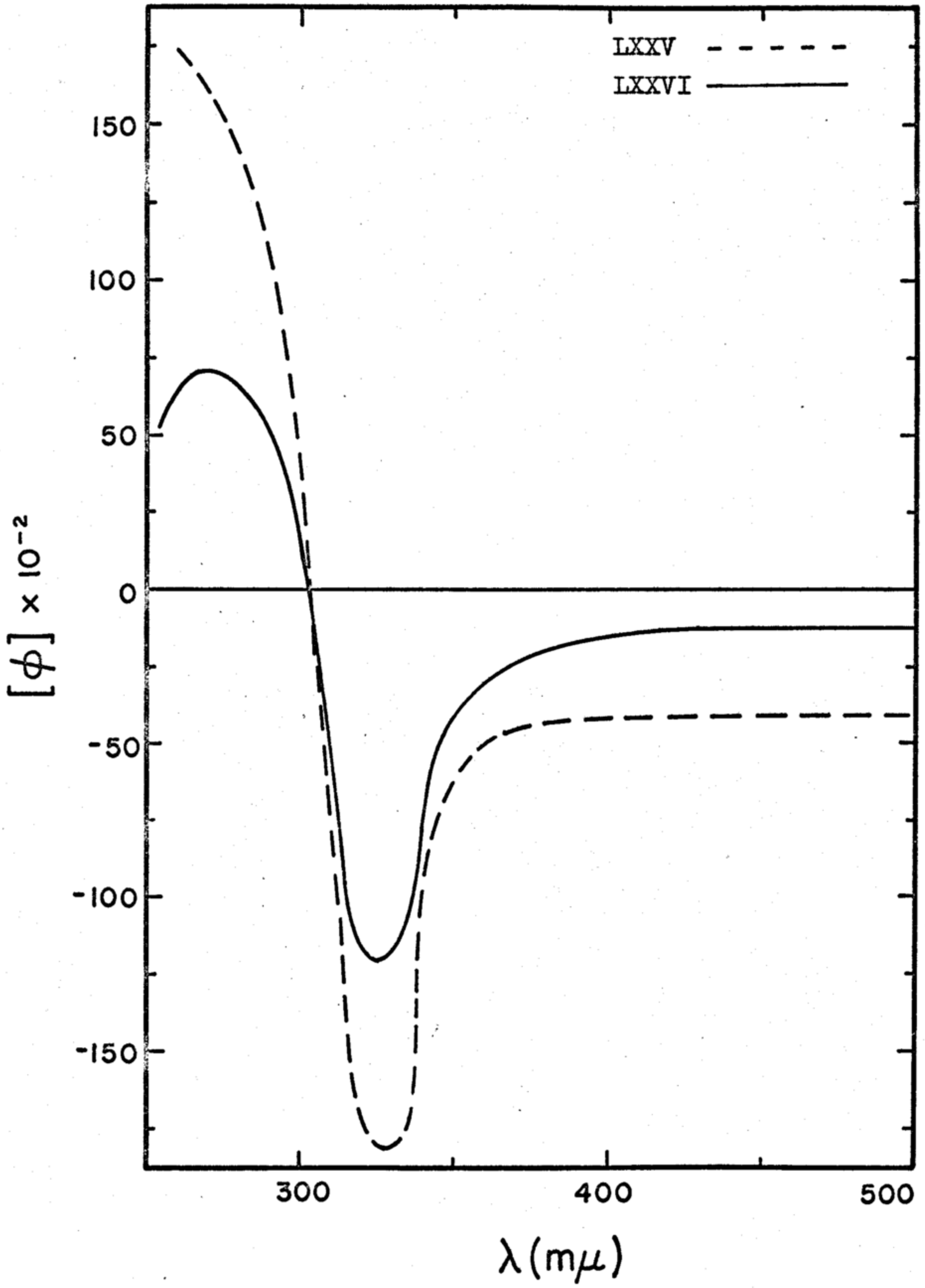
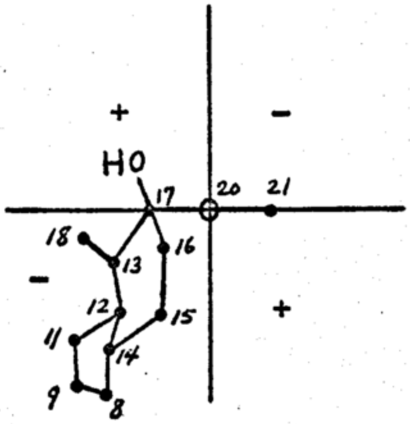
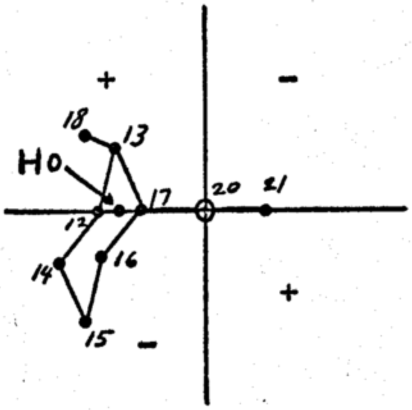

LXXV
LXXVI
150
100
50
0
-50
-100
-150
$[\phi] \times 10^{-2}$
300
400
500
$\lambda (m\mu)$

Figure 5

is also in good agreement with the experimental value obtained for LXXVI (a = -193°).



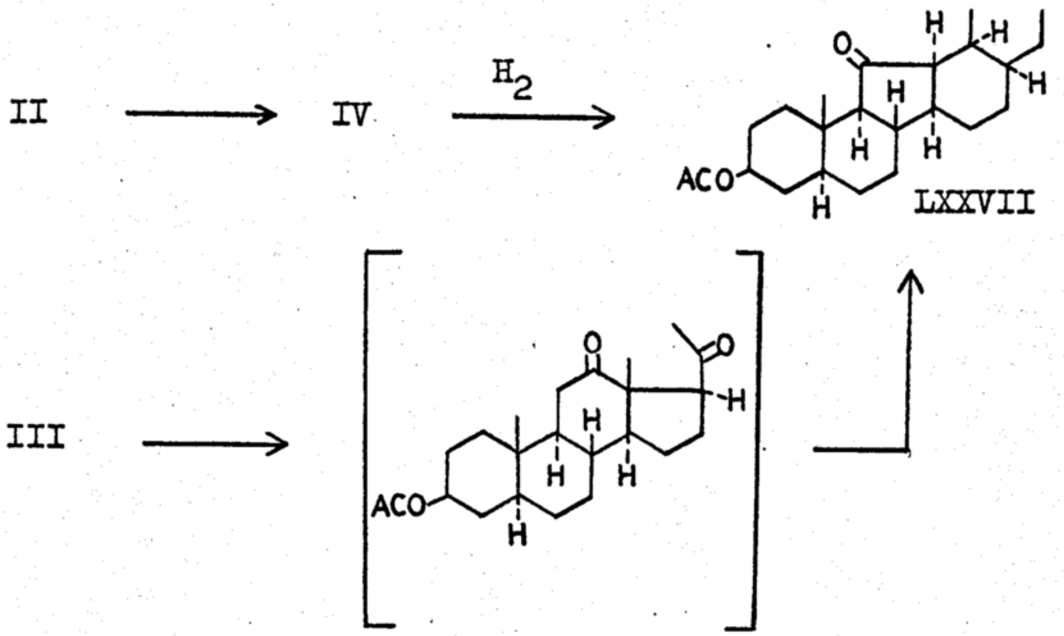
LXXV

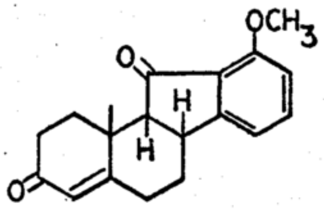


LXXVI

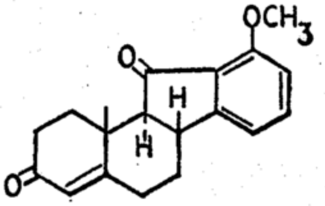
So far the spectral data of all the intermediates discussed have presented enough evidence for the stereochemistry at C-12, C-13 and C-17. The configurations around the other four asymmetric centers, C-8, C-9, C-10 and C-14 were established by the interrelation of hecogenin (III) with a jervine degradation product (LXXVII) by Mitsuhashi and Shimizu (50,51) as shown in Chart 16. Hence jervine was assigned the same configurations as those of normal steroids: C-8β, C-9α, C-10β and C-14α. Assuming that no isomerization took place at C-9, then all intermediates originating from

Chart 16





LXXVIII



LXXIX

jervine have the same configurations. Recently, further evidence for the C-9 α configuration of the veratrum alkaloids was presented (52,53).

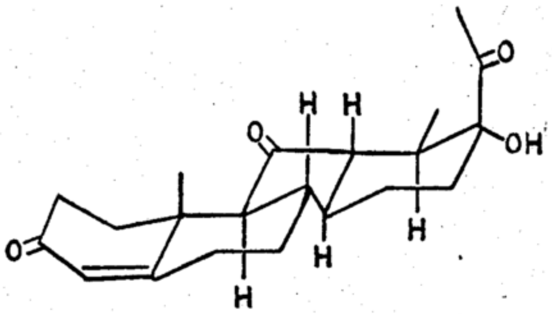
One might still question the stability at C-9(α) in base; however, all indications support stability at this position. In their studies of C-nor-steroids, Ourisson *et al*. (25) showed that the configuration at C-9 remains α and that contraction of ring C of normal steroids through the benzilic rearrangement of C-11, C-12-diketones does not result in a change of configuration at C-9. They also showed by ord studies that the stability of the 11-keto-C-nor-steroids towards epimerization is independent of the configuration at C-5.

In the C-nor-steroids where the C/D ring juncture is *trans*, ring C is much more strained than in C-nor-D-homosteroids. Since C-9 is stable in the C-nor-steroid series, it is most unlikely that isomerization at C-9 in the C-nor-D-homo series takes place.

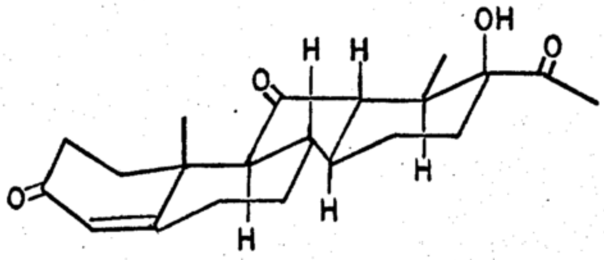
W. S. Johnson (54,55) synthesized several C-nor-D-homosteroids, some having B/C *cis* and some B/C *trans* ring junctures, in which ring D was aromatic, as in LXXVIII and LXXIX respectively (see Chart 16). He showed that whenever the B/C juncture was *trans*, the C-19 methyl protons resonate at about 8.8 τ (LXXIX, C-19 Me, 8.81 τ), whereas when the B/C juncture was *cis* the C-19 methyl protons are deshielded and therefore resonate at about 8.4τ (LXXVIII, C-19 Me, 8.45τ). Examination of the nmr data for all the intermediates synthesized in the present work (Tables 1 and 3) indicate that the signals for the C-19 methyl group appear in the same region as for the normal B/C trans steroids. Therefore, it is safe to assume that no isomerization occurred during the synthesis of all the intermediates.

This concludes the synthesis and stereochemistry of two epimeric C-nor-D-homoprogesterone analogs, LXXV and LXXVI. The equatorial alcohol (LXXV) is C-nor-D-homo-11-keto-17α-hydroxyprogesterone, since it possesses the progesterone configuration at each of the ring junctions and the planarity of this molecule (LXXX, as represented in Chart 17) resembles the planarity of naturally-occurring 11-keto-17α-hydroxyprogesterone (LXXXI) itself. The axial alcohol (LXXVI), C-nor-D-homo-11-keto-17β-hydroxyprogesterone, is as represented in LXXXII (see Chart 17).

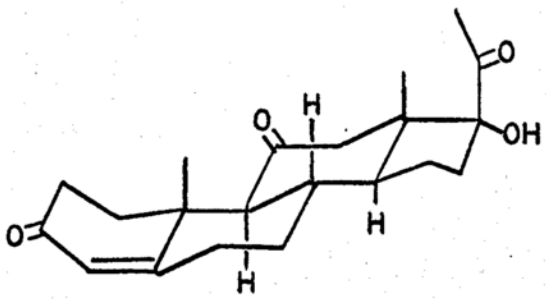
Chart 17



LXXX



LXXXII



LXXXI

Table 3

NMR DATA[a]

Compound	C-19 CH_3	C-18 CH_3	C-21 CH_3	C-6 H	C-3 H	OH	C-20 H	C-4 H	C-16 H
LIV	9.00 (3H)s	8.68 (3H)d J=6cps	8.40 (3H)d J=6cps	4.60 (1H)m	6.59 (1H)m	8.12 (1H)s	4.75 (1H)q J=6cps	---	---
LV	8.95 (3H)s	8.81 (3H)d J=6.5cps	8.45 (3H)d J=6.5cps	4.62 (1H)m	6.52 (1H)m	8.13 (1H)s	4.77 (1H)q J=6.5cps	---	---
LXIII	8.77 (3H)s	8.80 (3H)d J=7cps	8.42 (3H)d J=7cps	---	---	---	4.74 (1H)q J=7cps	4.24 (1H)s	---
LXV	8.85 (3H)s	8.85 (3H)d J=6cps	8.75 (3H)d J=6cps	---	---	---	7.18 (1H)q J=6cps	4.22 (1H)s	---
LXXII	8.70 (3H)s	8.70 (3H)d J=7cps	7.71 (3H)s	---	---	---	---	4.23 (1H)s	3.25 (1H)m
LXXV	8.79 (3H)s	8.69 (3H)d J=6.5cps	7.62 (3H)s	---	---	6-6.5 (1H) broad m	---	4.23 (1H)s	---
LXXVI	8.79 (3H)s	8.74 (3H)d J=6cps	7.76 (3H)s	---	---	7.20 (1H)s	---	4.22 (1H)s	---

[a] All chemical shifts are reported in τ values (ppm).

PHARMACOLOGY

Compounds LXXV and LXXVI are under pharmacological evaluation by Dr. Leonard L. Lerner at the Squibb Institute for Medical Research (56). Preliminary tests have shown that both LXXV and LXXVI show anti-androgenic activity but no uterotrophic activity. The results are summarized below:

C-nor-D-homo-11-keto-17α-hydroxyprogesterone (LXXV):--Anti-androgenic activity in the cockerel: active at 500 mcg (37% inhibition of testosterone-induced comb growth). Uterotrophic-antiestrogenic activity in the mouse: inactive as uterotrophic at 400 mcg total dose, weak inhibition of estrogen-induced uterine hypertrophy (14%) at 400 mcg total dose.

C-nor-D-homo-11-keto-17β-hydroxyprogesterone (LXXVI):--Anti-androgenic activity in the cockerel: active at 500 mcg (32% inhibition of testosterone-induced comb growth). Uterotrophic-antiestrogenic activity in the mouse: inactive uterotrophic at 500 mcg total dose, not antiestrogenic at the same dose but added to the uterotrophic effect of 0.1 mcg of estradiol benzoate (19%).

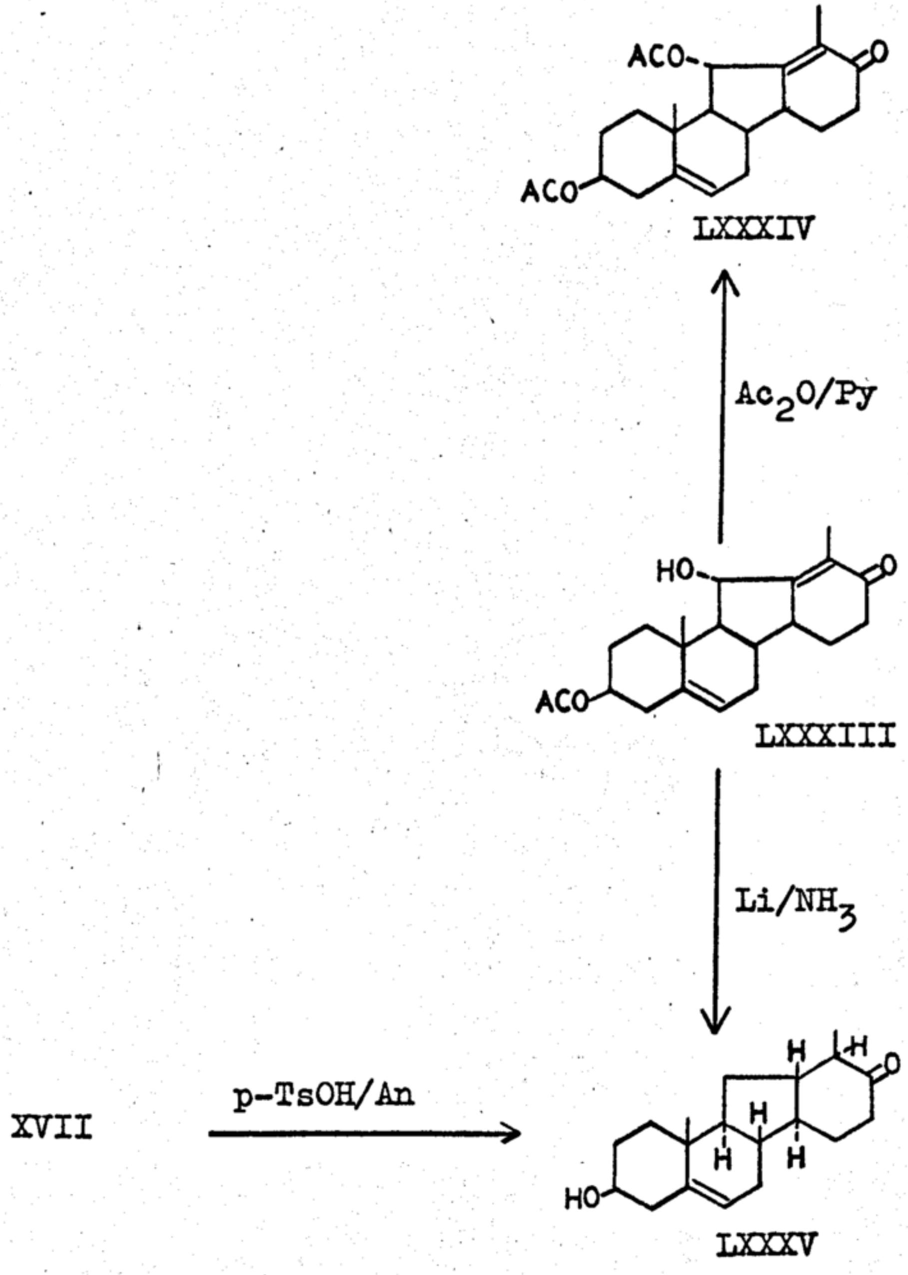
Both compounds LXXV and LXXVI exhibit weak progesterone-like activity. Further evaluation of the endocrine spectrum of these compounds is in progress.

ADDENDUM

During the preparation of the intermediate XV from XIV by reduction with zinc in acetic acid another much more polar compound was isolated. The compound had a much higher melting point, mp 230-235° d; $[\alpha]_D^{26°}$ -66° (c 0.10, $CHCl_3$) and still showed an ultraviolet absorption [λ_{max}^{EtOH} 248 mμ (ε 14,500)]. Examination of its infrared spectrum showed bands at 2.78 μ, 2.88 μ and 2.90 μ (broad) suggesting the presence of a hydroxyl group. There were bands at 5.78 μ and 8.00 μ (acetate) and 6.00 μ and 6.15 μ (suggesting the presence of a 6-membered α,β-unsaturated ketone).

The nmr spectrum showed the usual signal for the C-19 methyl at 8.87 τ, and indicated the presence of a downfield signal for a methyl group on the α-carbon of an α,β-unsaturated ketone (C-18 CH_3; 8.10 τ (s)). There were three downfield protons, corresponding to the C-6 H, at 4.53 τ (m), the C-3 H, at 5.40 τ (m), and to an allylic hydrogen of a secondary alcohol, an unresolved doublet at 5.23 τ (J = 7 cps) integrating for one proton. From the above spectral data the compound was assigned the structure LXXXIII. The C-11-hydrogen signal at 5.23 τ was split into a doublet with a coupling constant (J = 7 cps) indicating it to be antiparallel to the C-9α-(axial)-H. Furthermore compound LXXXIII was

Chart 18


ACO
ACO
LXXXIV
Ac$_2$O/Py
HO
ACO
LXXXIII
Li/NH$_3$
XVII
p-TsOH/An
H
H
H
H
H
HO
LXXXV

easily acylable with acetic anhydride in pyridine at room temperature for 2 hr, hence the 11-hydroxy group is not in a hindered position, and therefore occupies the 11α-position.

The acetylation of LXXXIII produced the diacetate LXXXIV, λ_{max}^{EtOH} 248 mμ (ε 14,000). Its infrared spectrum showed no hydroxyl peaks and showed prominent peaks at 5.78 μ, 8.00 μ (C-3 and C-11 acetates), 6.00 μ (Δ^{12}-17-one), 6.10 μ (shoulder) and 6.18 μ (conjugated double bond). The nmr spectrum indicated a downfield shift of the C-11β-H from 5.23 τ to 3.90 τ . The latter signal appeared as a poorly-resolved doublet (J = 7 cps) probably attributable to long range homoallylic coupling with the C-18 methyl group, which, in turn, was shifted upfield to 8.30 τ , probably due to shielding by the carbonyl of the C-11α acetate. The signal for the acetates appeared at 7.91 τ (s, 6H).

Confirmatory evidence for structure LXXXIII was adduced by correlating it with the known compound XVII. Lithium in liquid ammonia reduction of LXXXIII gave low yields of the hydrogenolysis product LXXXV. The latter compound could also be obtained in high yield from XVII by hydrolysis of the 17-ketal to the corresponding ketone with p-toluenesulfonic acid in acetone and water.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus. Values of $[\alpha]_D$ have been approximated to the nearest degree. Ultraviolet absorption spectra were determined in 95% ethanol on a Beckman (Model DK2A) recording spectrophotometer. Infrared absorption spectra were recorded in chloroform (unless otherwise specified) on a Beckman (Model 5A) double beam infrared recording spectrophotometer. Optical rotatory dispersions were determined in dioxane on a Cary (Model 60) spectropolarimeter. Nuclear magnetic resonance spectra were recorded on a Varian Associates recording spectrometer (A60A) at 60 mc/sec in deuterated chloroform (unless otherwise specified) using tetramethyl silane as an internal standard. Chemical shifts were recorded in τ values (ppm). Microanalyses were carried out by J. F. Alicino, P.O. Box 267, Metuchen, N.J. and Spang Microanalytical Laboratory, P.O. Box 1111, Ann Arbor, Michigan. Thin layer chromatography (tlc) was carried out with silica gel G and silica gel $F_{254+366}$ (Brinkmann instruments). Alumina refers to Merck acid-washed alumina. Pyridine was dried over potassium hydroxide. Boron trifluoride etherate was freshly distilled before use. Benzene was distilled and dried over sodium. Dioxane was purified as described in

Vogel (57). Aluminum isopropoxide refers to Eastman practical grade. Petroleum ether refers to the fraction of bp 60-80°.

$\Delta^{5,12(13),17(20)}$-17-Ethyletiojervatriene-3β-ol-11-one Acetate (IV).--A solution of jervine (II, 222 g, mp 248-250°dec) in acetic anhydride (2000 ml) and boron trifluoride etherate (21 ml, freshly distilled, bp 126°) was refluxed for 5 hr. The reaction mixture was concentrated *in vacuo* to one-third the volume. After cooling at room temperature overnight, a crystalline solid precipitated out. This was filtered, washed with water, and dried (mp 180-185°). Crystallization from benzene yielded pure IV (47 g, mp 187-189°, 26%). Mixture mp with authentic sample was undepressed and the ir was superimposable upon that of the authentic sample.

$\Delta^{5,12(13)}$-Etiojervadiene-3β-ol-11,17-dione Acetate (XIV).--To a solution of IV (30 g, mp 187-189°) in glacial acetic acid (2.5 l.) was added dropwise, while stirring at room temperature over a period of 1 hr, a solution of chromic acid in 95% acetic acid (350 ml). The reaction mixture was stirred for 1 hr more, and ethanol (25 ml) was added to decompose the excess chromic acid. The acetic acid was evaporated *in vacuo* to a sirupy consistency and the residual acetic acid was carefully neutralized with a saturated sodium bicarbonate solution while the organic material was taken up in

ether. The ethereal extract (2.5 l.) was washed once more with sodium bicarbonate solution, twice with water and dried over anhydrous sodium sulfate. Evaporation of the ether to dryness yielded a brown residue (27.5 g) which was chromatographed on silica gel (700 g) packed in benzene. The fractions eluted with benzene and benzene-chloroform (up to 50% $CHCl_3$) were combined and evaporated to dryness. The residue was crystallized from benzene-petroleum ether to provide pure XIV (13 g, mp 176-177.5°). Mixture mp with an authentic sample was undepressed.

Δ^5-Etiojervene-3β-ol-11,17-dione Acetate (XV); $\Delta^{5,12(13)}$-Etiojervadiene-3β,11α-diol-17-one-3-Acetate (LXXXIII).--$\Delta^{5,12(13)}$-etiojervadiene-3β-ol-11,17-dione acetate (14 g, mp 178-179°) was dissolved in glacial acetic acid (1.5 l.) while warming briefly on a steam bath. Zinc dust (20 g, Fisher--technical grade) was added in small portions while swirling the solution until the disappearance of the yellow color (20 min). The solution was then filtered and the residue washed with chloroform. The filtrate was concentrated to dryness under reduced pressure and the residue was taken up in chloroform (2 l.) and water (1 l.). The chloroform layer was washed twice with a saturated solution of sodium bicarbonate, twice with water, and then dried over anhydrous sodium sulfate. The residue (14.4 g) obtained

after evaporation of the chloroform was chromatographed on acid-washed alumina (420 g) packed in petroleum ether. Fractions eluted with benzene and benzene-ether mixtures (up to 20% ether in benzene) were combined and evaporated to dryness. Crystallization of the residue from chloroform-isopropyl ether gave pure XV (7.8 g, mp 171-172°). The mother liquor failed to crystallize any further and the residue obtained upon evaporation was rechromatographed on acid-washed alumina (200 g) in the same manner as above to yield more of compound XV (1.9 g, mp 170-172°). The melting point was not depressed by admixtures of an authentic sample (4). The product showed λ_{max} 5.78 μ, 5.80 μ, 5.82 μ, 8.00 μ; nmr, 8.91 (3H, singlet), 8.66 (3H, doublet, J = 7 cps), 7.97 (3H, singlet), 5.38 (1H, multiplet), 4.56 τ (1H, multiplet); nmr in C_6H_6, 9.01 (3H, singlet), 8.47 (3H, doublet, J = 7 cps), 8.22 (3H, singlet), 5.28 (1H, multiplet), 4.76 τ (1H, multiplet); ord $[\Phi]_{280}^{pk.}$ + 13261°; $[\Phi]_{330}^{tr.}$ - 14294°; a = -275°.

The column was eluted further with ether to yield a fraction which failed to crystallize. Further elution with methanol-ether mixtures (up to 5% methanol in ether) yielded a crystalline solid which was crystallized from benzene-petroleum ether to give LXXXIII (0.8 g, mp 230-235° dec). Further crystallization from benzene-petroleum ether provided the analytical sample, mp 230-235° dec; $[\alpha]_D^{26°}$ -66° (c 0.10 $CHCl_3$); λ_{max} 2.80 μ, 2.90 μ, 5.81 μ, 6.05 μ, 6.20 μ, 8.00 μ; λ_{max}^{EtOH} 248 mμ (ε 14,500); nmr, 8.87 (3H, singlet), 8.10 (3H, singlet), 5.40 (1H, multiplet), 5.23 (1H, unresolved doublet, J = 7 cps), 4.53 τ (1H, multiplet).

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.19; H, 8.18.

$\Delta^{5,16}$-17-Cyanoetiojervadiene-3β-ol-11-one Acetate (XL).--Δ^5-etiojervene-3β-ol-11,17-dione acetate (XV, 3.0 g, mp 171-172°) was dissolved in acetone cyanohydrin (15 ml, Aldrich Chemicals) and 10% sodium hydroxide (0.25 ml) was added. The reaction mixture was allowed to stand at room temperature for 2 hr and poured into ice-water (200 ml) containing glacial acetic acid (1 ml). The mixture was vigorously stirred whereupon the oil which separated solidified. This was extracted with ether (500 ml), and the ethereal layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue solidified upon the addition of ethanol to afford an epimeric mixture of 17-cyanohydrins XXXIX (3.1 g, mp 139-143°, λ_{max} 2.70 μ, 2.78 μ, 2.90 μ, 5.78 μ).

A portion of the above cyanohydrin mixture (500 mg) was dissolved in pyridine (20 ml, dried over potassium hydroxide) and phosphorous oxychloride (0.5 ml) was added. The reaction mixture was warmed on a steam bath for 13 hr, cooled, and poured into an ice-water mixture and concentrated hydrochloric acid (50 ml). The dehydration product was extracted into ether, and the ether layer was washed with 5% hydrochloric acid and water, and dried over anhydrous sodium sulfate. The ether residue (471 mg) was chromatographed on acid-washed alumina (15 g). Elution with benzene-petroleum ether (1:1), benzene, and benzene-10% ether gave a residue after the evaporation of the solvent which was crystallized from ether-petroleum ether to afford XL (161 mg, mp 190-192°). A sample was recrystallized for analysis from ether-petroleum ether, mp 193-195°, $[\alpha]_D^{24^\circ}$ -222° (c 0.32, $CHCl_3$); λ_{max} 4.50 µ, 5.78 µ, 8.00 µ; nmr, 3.35 (1H, multiplet), 4.60 τ (1H, multiplet).

<u>Anal</u>. Calcd. for $C_{22}H_{27}NO_3$: C, 74.57; H, 7.70; N, 3.69. Found: C, 74.48; H, 7.85; N, 4.09.

<u>$\Delta^{5,16}$-17-Carboxyetiojervadiene-3β-ol-11-one Acetate (XLI)</u>.---A solution of XL (3.5 g, mp 191-193°) was dissolved in ethylene glycol (50 ml) and water (5 ml) containing sodium hydroxide (4 g). The reaction mixture was refluxed for 3 hr, cooled, and diluted with water. The aqueous solution was neutralized with 5% hydrochloric acid to precipitate the free acid. The precipitate was collected and dried over phosphorous pentoxide to afford the crude $\Delta^{5,16}$-17-carboxyetiojervadiene-3β-ol-11-one (2.7 g).

The acid was warmed for 4 hr on a steam bath with acetic anhydride (10 ml) and pyridine (2 ml). The reaction mixture was then diluted with water and extracted with chloroform. The chloroform extract was washed with water and dried over sodium sulfate. The chloroform residue (2.8 g) was chromatographed on acid-washed alumina (70 g). Elution with benzene-5% ether, benzene-10% ether, and benzene-33% ether and evaporation of the combined fractions yielded a solid residue which was crystallized from chloroform-isopropyl ether to afford starting material (XL, 150 mg, mp 188-190°). Further elution with ether-10% benzene and ether-methanol mixtures (up to 75% methanol) and evaporation of the solvents gave a residue which was crystallized from chloroform-acetone to afford XLI (1.22 g, mp 237-239°). A sample was recrystallized for analysis, mp 238-239°, $[\alpha]_D^{28^\circ}$ -316° (c 0.45, $CHCl_3$); λ_{max} 3.20 μ (broad), 5.78 μ, 5.92 μ, 6.15 μ, 8.00 μ.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.06; H, 7.62.

$\Delta^{5,16}$-17-Ethyletiojervadiene-3β-ol-11,20-dione Acetate (XLII).--A solution of XLI (1.22 g, mp 238-240°) in thionylchloride (10 ml) was refluxed for 80 min and the excess reagent was removed *in vacuo*. Benzene was added and portion of it was removed *in vacuo*. The acid chloride in benzene was then added to a suspension of dimethyl cadmium in benzene prepared as follows: The Grignard reagent was prepared from magnesium (395 mg) and iodomethane (1.2 ml), treated with cadmium chloride (1.5 g, dried at 130° for 2 hr), refluxed, and stirred for 90 min until a negative Gilman test was obtained. The reaction mixture was refluxed and stirred for 2 1/4 hr, then ice, 5% hydrochloric acid, and ether were added. The organic layer was washed with a saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. Removal of the solvents left a residue (1.02 g) which was chromatographed on acid-washed alumina (30 g). Elution with benzene-ether mixtures (15-90% ether) and crystallization of the residue after evaporation of the solvents afforded XLII (515 mg, mp 169-171°). A sample was recrystallized from ether and gave the analytical sample, mp 178-180°, $[\alpha]_D^{27^\circ} -312^\circ$ (c 0.17, $CHCl_3$); λ_{max} 5.78 μ, 6.00 μ, 6.18 μ, 8.00 μ; λ_{max}^{EtOH} 228.5 mμ (ε 9,650).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.45; H, 8.22.

Δ^5-17-*cis*-Ethylidene-etiojervene-3β-ol-11-one Acetate (XLIX); Δ^5-17-*trans*-Ethylidene-etiojervene-3β-ol-11-one Acetate (L).--Method A: To a suspension of ethyl-triphenylphosphonium bromide (6.5 g, mp 206-208°) in anhydrous ether (50 ml) was added a solution of 15% *n*-butyllithium in *n*-hexane (7.7 ml) at room temperature, while stirring under a nitrogen atmosphere. The mixture was stirred for 2 hr. A solution of XV (3.0 g, mp 171-172°) in dried tetrahydrofuran (10 ml) was then added dropwise during a period of 15 min. The reaction mixture was stirred for 4 hr more and allowed to stand at room temperature overnight. Tetrahydrofuran (50 ml) was then added at the same time the ether was distilled off until most of the latter was displaced. The mixture was refluxed for 6 hr while stirring. After cooling, ether (100 ml) and water (100 ml) were added. The organic layer was washed successively with 5% hydrochloric acid solution, a saturated sodium bicarbonate solution, and water. The ether was evaporated to dryness, after being dried over anhydrous magnesium sulfate, to provide a residue (4.25 g) which was reacetylated by allowing it to stand at room temperature for 15 hr in acetic anhydride (20 ml) and pyridine (20 ml). The reaction mixture was poured over cracked ice and more water was added. The yellow gum which separated out was extracted three times with ether (50 ml each time), and the combined ether extracts were washed with a saturated sodium bicarbonate, 5% hydrochloric acid, and finally with water. The ether solution was then dried over anhydrous sodium sulfate and evaporated to dryness to give a brownish semi-solid (3.5 g) which was chromatographed on acid-washed alumina (100 g) packed in petroleum ether. Elution with petroleum ether in benzene (1:1, 1.5 l.) and 1:4, 1 l.) gave, upon evaporation, a white solid (XLIX, 1.1 g) which crystallized from methanol (1.0 g, mp 144-146°). A sample was recrystallized from methanol for analysis, mp 146-147°, $[\alpha]_D^{28°}$ -181.0° (c 0.16, $CHCl_3$); λ_{max} 5.80 μ, 8.00 μ; nmr, 8.89 (3H, singlet), 8.78 (3H, doublet, J = 6.5 cps), 8.40 (3H, doublet, J = 6.5 cps), 8.00 (3H, singlet), 5.43 (1H, multiplet), 4.75 (1H, quartet, J = 6.5 cps), 4.58 τ (1H, multiplet); nmr in C_6H_6, 9.02 (3H, singlet), 8.46 (3H, doublet, J = 6 cps), 8.39 (3H, doublet, J = 6.5 cps), 8.25 (3H, singlet), 5.20 (1H, multiplet), 4.70 τ (2H, multiplet); ord $[\Phi]_{280}^{pk.}$ + 5729°; $[\Phi]_{331}^{tr.}$ - 10442°; a = -161°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.41; H, 8.97.

Continued elution with benzene (1 l.) yielded a mixture of XLIX and L (0.2 g). Further elution with benzene (1 l.) yielded a solid which crystallized from methanol to afford L (0.15 g, mp 152-154°). A sample was recrystallized from methanol to yield the analytical sample, mp 153-154°, $[\alpha]_D^{29°}$ -79.0° (c 0.57, $CHCl_3$); λ_{max} 5.80 μ, 8.00 μ; nmr, 8.88 (3H, singlet), 9.05 (3H, doublet, J = 6.5 cps), 8.41 (3H, doublet, J = 6.5 cps), 7.98 (3H, singlet), 5.43 (1H, multiplet), 4.75 (1H, quartet, J = 6.5 cps), 4.58 (1H, multiplet), 6.72 τ (2H, quintet, J = 7 cps); nmr in C_6H_6, 8.89 (3H, singlet), 9.03 (3H, doublet, J = 6.5 cps), 8.50 (3H, doublet, J = 7 cps), 8.22 (3H, singlet), 5.32 (1H, multiplet), 4.78

(2H, multiplet), 6.72 τ (2H, multiplet); ord $[\Phi]^{pk.}_{287}$ + 2194°; $[\Phi]^{tr.}_{330}$ - 6546°; a = -87°.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.44; H, 9.14.

Method B: To a suspension of ethyl-triphenylphosphonium bromide (9.0 g, mp 206-208°) in anhydrous ether (75 ml) was added a solution of 15% n-butyllithium in n-hexane (7.8 ml) at room temperature while stirring under an atmosphere of nitrogen. The mixture was stirred for 2 hr, after which a solution of XV (3.0 g, mp 171-172°) in dry tetrahydrofuran (10 ml) was added dropwise during a period of 15 min. The mixture was stirred for another 3 hr at room temperature. A slurry of potassium t-butoxide (4.2 g) and t-butanol (3.0 g) in tetrahydrofuran (10 ml) was poured into the reaction vessel, and stirring was continued for 1 hr more. Dry tetrahydrofuran (100 ml) was then added at the same time the ether was being distilled off, until most of the latter was displaced. The mixture was then refluxed for 3 hr, cooled, decomposed with water (150 ml), and ether (150 ml) was added. The ethereal layer was washed successively with a saturated solution of sodium bicarbonate, 5% hydrochloric acid, and water. The ether solution was then dried over anhydrous magnesium sulfate and evaporated to dryness to give a residue (5.9 g) which was reacetylated as described under Method A.

Chromatography of the acetylation product (6.1 g) on acid-washed alumina (180 g) packed in petroleum ether and elution with petroleum ether (4:1, 1 l.) gave an oil which crystallized when triturated with methanol (0.5 g) and this was characterized to be an organophosphorous compound. Elution with petroleum ether:benzene (1:1, 2.5 l.) gave a brownish residue which crystallized from methanol with difficulty to afford XLIX (0.8 g, mp 142-147°). Further elution with petroleum ether: benzene (1:2, 2 l.) yielded a brownish residue, which failed to crystallize (0.53 g) and consisted of a mixture of XLIX and L. Continued elution of the column provided a fraction rich in L and this was crystallized from methanol to give pure L (0.15 g, mp 153-154°).

Rechromatography of the mother liquors on acid-washed alumina (30 g) and repeating this process twice provided more of XLIX (0.28 g, mp 144-146°) and L (0.22 g, mp 152-154°). The combined mother liquors (0.8 g) were still rich in both isomers but further chromatography or preparative tlc failed to yield additional pure materials.

Δ^5-17-*cis*-Ethylidene-etiojervene-3β-ol-11-one (LIV).--A solution of XLIX (360 mg, mp 146-147°) in 5% potassium hydroxide in methanol (20 ml) was allowed to stand at room temperature for 24 hr. Water was added and part of the methanol was evaporated under vacuum. A fine, white solid separated out and this was extracted with ether (150 ml). The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. Crystallization of the residue (310 mg) from a mixture of ether and petroleum ether gave prisms of LIV (290 mg, mp 172-174°). Two further crystallizations from ether gave the analytical sample as fine needles, mp 174.5-175.5°, $[\alpha]_D^{20^\circ}$ + 27° (c 0.15, dioxane from ord), λ_{max} 2.80 µ, 5.78 µ, 6.10 µ (weak); nmr, 9.00 (3H, singlet), 8.68 (3H, doublet, J = 6 cps), 8.40 (3H, doublet, J = 6 cps), 8.12 (1H, singlet), 6.59 (1H, multiplet), 4.75 (1H, quartet, J = 6 cps), 4.60 τ (1H, multiplet); ord $[\Phi]_{290}^{pk.}$ + 8252°; $[\Phi]_{332.5}^{tr.}$ - 8886°; a = -171°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.43; H, 9.55.

Δ^5-17-trans-Ethylidene-etiojervene-3β-ol-11-one (LV).---A solution of L (460 mg, mp 153-154°) in 5% potassium hydroxide in methanol (20 ml) was allowed to stand at room temperature for 24 hr. Water was added and a fraction of the methanol was distilled off under vacuum whereby a fine solid precipitated out which was extracted with ether (200 ml). The ethanol extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to leave a white residue (420 mg). The solid was crystallized from a mixture of ether and petroleum ether to afford white needles of LV (380 mg, mp 204-205°). The analytical sample was prepared by recrystallization from ether to yield needles, mp 205-206°, $[\alpha]_D^{20^\circ} + 21.0^\circ$ (c 0.117 dioxane, obtained from ord); λ_{max} 2.80 µ, 5.78 µ, 6.10 µ (weak); nmr, 8.95 (3H, singlet), 8.81 (3H, doublet, J = 6.5 cps), 8.45 (3H, doublet, J = 6.5 cps), 8.13 (1H, singlet), 6.52 (1H, multiplet), 4.77 (1H, quartet, J = 6.5 cps), 4.62 τ (1H, multiplet); ord $[\Phi]_{285}^{pk.}$ + 5924°; $[\Phi]_{322}^{tr.}$ - 11336°; a = -172°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.11; H, 9.65.

Δ^4-17-cis-Ethylidene-etiojervene-3,11-dione (LXIII).--To a mixture of dry toluene (250 ml) and cyclohexanone (20 ml) was added compound LIV (1.23 g) and some toluene (80 ml) was distilled off. Aluminum isopropoxide (1.5 g) in toluene (15-20 ml) was added to the hot reaction mixture and refluxing was continued for 2.5 hr. To the cooled reaction mixture was added a saturated solution of Rochelle's salt (50 ml) and the mixture was steam distilled until the distillate became clear. The aqueous layer was then extracted with chloroform (300 ml) and the chloroform solution was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from ether to provide prisms of LXIII (0.5 g, mp 163-165.5°). The mother liquor was chromatographed on 20 g of acid-washed alumina packed in benzene. The fraction eluted with benzene (1.5 l.) was evaporated to dryness and the residue was crystallized from ether to yield more of the product (0.4 g, mp 163-165°). Recrystallization from ether gave the pure analytical sample, mp 164.5-165.5°, $[\alpha]_D^{27°} - 185.0°$ (c 0.54, $CHCl_3$); λ_{max} 5.80 μ, 6.02 μ, 6.20 μ; λ_{max}^{EtOH} 236 mμ (ε 17,000); nmr, 8.77 (3H, singlet), 8.80 (3H, doublet, J = 7 cps), 8.42 (3H, doublet, J = 7 cps), 4.74 (1H, quartet, J = 7 cps), 4.24τ (1H, singlet); ord $[\Phi]_{286}^{pk.}$ + 5467°; $[\Phi]_{329}^{tr.}$ - 10935°; a = -164°.

<u>Anal</u>. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.79; H, 9.05.

<u>Δ^4-17-trans-Ethylidene-etiojervene-3,11-dione (LXIV)</u>.--To a mixture of dry toluene (50 ml) and cyclohexanone (8 ml) was added compound LV (0.35 g, mp 204-206°) and toluene (20 ml) was distilled off. A solution of aluminum isopropoxide (0.3 g) in toluene (10 ml) was added and the refluxing was continued for 2.5 hr. A saturated solution of Rochelle's salt (15 ml) was added after cooling and the mixture was steam distilled until the distillate became clear. The aqueous layer was extracted with chloroform (75 ml) and the chloroform was evaporated to dryness after being washed with water and dried over sodium sulfate. The residue (0.41 g) was chromatographed on acid-washed alumina (10 g) packed in petroleum ether. The fractions eluted with mixtures

of benzene:petroleum ether (1:3, 250 ml), (1:1, 500 ml), (3:1, 500 ml) and benzene (500 ml) were combined and evaporated to dryness to yield a residue which was crystallized from ether to afford needles of LXIV (0.22 g, mp 173-175°). Recrystallization from ether yielded the pure analytical sample, mp 175-176°; $[\alpha]_D^{27°}$ -132.0° (c 0.85, $CHCl_3$); λ_{max} 5.78 µ, 6.00 µ, 6.20 µ; λ_{max}^{EtOH} 236 mµ (ε 16,900); ord $[\Phi]_{286}^{pk.}$ + 4999°; $[\Phi]_{329}^{tr.}$ - 11663°; a = -166°.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.63; H, 8.89.

Δ4-17-Ethyletiojervene-3,11-dione-17ξ,20ξ-oxides (LXV and LXVI).--To a solution of LXIII (0.41 g, mp 164-165°) in dry ether (125 ml) was added a solution of monoperphthalic acid in ether (15 ml, 75 mg/ml) and the mixture was allowed to stand in the dark at room temperature for 24 hr. After washing the reaction mixture first with a saturated solution of sodium bicarbonate and then with water, it was dried over anhydrous sodium sulfate and concentrated to about 20 ml. Upon standing, the major product, Δ4-17-ethyletiojervene-3,11-dione-17β, 20β-oxide (LXV, 0.17 g, mp 193-194°) crystallized in the form of needles. Further concentration of the mother liquor and cooling provided more of LXV (0.07 g, mp 192-194°). One more crystallization from ether gave the analytical sample, mp 193-194°; $[\alpha]_D^{26°}$ -76° (c 0.51,

$CHCl_3$); λ_{max} 5.79 μ, 6.00 μ, 6.20 μ, 9.70 μ, 10.50 μ, 11.02 μ; λ_{max}^{EtOH} 236 mμ (ε 18,000); nmr, 8.85 (3H, singlet), 8.85 (3H, doublet, J = 6 cps), 8.75 (3H, doublet, J = 6 cps), 7.18 (1H, quartet, J = 6 cps), 4.22 τ (1H, singlet).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.03; H, 8.83.

The mother liquor was further concentrated and a few drops of petroleum ether were added. Upon standing for a long time the minor isomer, Δ^4-17-ethyletiojervene-3,11-dione-17α,20α-oxide (LXVI, 0.06 g, mp 185-186°) crystallized out as large prisms; $[\alpha]_D^{26°}$ + 84.0° (c 0.39, $CHCl_3$); λ_{max} 5.79 μ, 6.00 μ, 6.20 μ, 9.70 μ, 10.50 μ, 11.02 μ; λ_{max}^{EtOH} 236 mμ (ε 18,100).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.88; H, 8.69.

Δ^4-17-Ethyletiojervene-3,11,20-trione (LXVII).--A solution of the β-epoxide LXV (0.1 g, mp 194-195°) in dry benzene (5 ml, distilled over sodium metal) was treated with 3-4 drops of freshly distilled boron trifluoride etherate (bp 126°) for 7 min at room temperature. The reaction was stopped by shaking the benzene solution with sodium bicarbonate solution (10 ml) and ether (30 ml). The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness to give a yellowish gum (0.103 g) which failed to crystallize from a variety of solvents.

Preparative tlc on silica gel F (1 mm thick), separation of the fluorescing bands, and elution of the bands with chloroform gave three compounds. From the band of highest R_f was isolated starting material (30 mg, mp 192-195°). The residue from the second band was crystallized from ether to give pure needles of Δ^4-17-ethyletiojervene-3,11,20-trione (20 mg, mp 188-190°). The analytical sample was prepared by recrystallization from ether to yield needles, mp 189-190°; $[\alpha]_D^{20°}$ + 115° (c 0.17, dioxane, from ord curve); λ_{max} 5.78 μ, 5.84 μ, 6.00 μ, 6.20 μ; λ_{max}^{EtOH} 237 mμ (ε 18,000); ord, $[\Phi]_{305}^{pk.}$ + 7593°; $[\Phi]_{332.5}^{tr.}$ - 1708°; a = -93°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.85; H, 8.64.

The material obtained from the third band crystallized also from ether to yield a pure sample of $\Delta^{4,12(13)}$-17β-ethyletiojervadiene-20β-ol-3,11-dione (LXVIII, 20 mg, mp 205-206°); λ_{max} 2.80 μ, 5.85 μ, 6.00 μ, 6.10 μ; λ_{max}^{EtOH} 247 mμ (ε 24,400).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.59; H, 8.50.

The fourth band yielded a yellow gum (LXIX, 13 mg) which failed to crystallize; λ_{max} 2.90 μ, 5.75 μ, 6.00 μ, 6.15 μ; λ_{max}^{EtOH} 236 mμ.

$\Delta^{4,16}$-17-Ethyletiojervadiene-3,11,20-trione (LXXII).---A solution of LXV (65 mg, mp 194-195°) in purified tetrahydrofuran (5 ml) and purified dimethyl sulfoxide (5 ml) was refluxed for 5 hr in the presence of catalytic amounts of boron trifluoride etherate (bp 126°, 1 drop). White fine needles precipitated out upon addition of water (30 ml). The solid was filtered, washed with water, taken up in chloroform (20 ml) and the chloroform solution was dried over anhydrous sodium sulfate. Evaporation of the chloroform gave a white solid which crystallized from a mixture of chloroform and ether to provide $\Delta^{4,16}$-17-ethyletiojervadiene-20β-ol-3,11-dione (LXXI, 60 mg, mp 197-198°); λ_{max}^{Nujol} 2.80 μ, 3.00 μ (broad), 5.78 μ, 6.00 μ, 6.20 μ; λ_{max}^{EtOH} 236 mμ (ϵ 15,500).

A solution of compound LXXI (50 mg) in pyridine (5 ml) was treated slowly with a solution of chromic acid (20 mg) in pyridine (15 ml) and the mixture was allowed to stand at room temperature for 15 hr. The reaction mixture was poured over cracked ice and was extracted with ether (150 ml). The ethereal layer was washed with 5% hydrochloric acid, sodium bicarbonate solution and then water. The ether solution was dried over anhydrous sodium sulfate and was then evaporated to dryness to yield a white solid (LXXII, 42 mg, mp 196-200°). Two recrystallizations from ether-petroleum ether gave pure needles of $\Delta^{4,16}$-17-ethyletiojervadiene-3,11,20-trione, mp 198.5-200°; $[\alpha]_D^{28°}$ -70° (c 0.49, $CHCl_3$); λ_{max} 5.75 μ, 6.00 μ (v. intense), 6.20 μ (intense); λ_{max}^{EtOH} 232.5 mμ (ε 24,500); nmr, 8.70 (3H, singlet), 8.70 (3H, doublet, J = 7 cps), 7.71 (3H, singlet), 4.23 (1H, singlet), 3.25 τ (1H, multiplet).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.44; H, 8.18.

Δ^4-17-Ethyletiojervene-17ξ,20ξ-diol-3,11-dione (LXXIII).--A solution of compound LXIII (40 mg, mp 175.5-176.5°) in anhydrous ether (5 ml) was treated dropwise with a solution of osmium tetroxide (31 mg) in anhydrous ether (2 ml) over a period of 15 min at room temperature. The reaction mixture was allowed to stand in the dark for 58 hr. The precipitated osmate esters were collected and decomposed to the diols by either of two methods.

Method 1. A solution of the osmate esters in chloroform was shaken with 7% mannitol in 1% potassium hydroxide solution (15 ml) for a period of 12 hr. The organic layer was washed with water, dried over anhydrous sodium sulfate, and was evaporated to dryness to provide a purplish-gum (44 mg).

Method 2. The osmate esters (600 mg) were dissolved in pyridine (7 ml) and the solution was treated while stirring for 30 min with sodium bisulfite (0.9 g) in water (15 ml) and pyridine (10 ml). The reaction mixture was then extracted with chloroform (150 ml) and the chloroform layer was washed three times with 5% hydrochloric acid solution, two times with water and dried over anhydrous sodium sulfate. The chloroform solution was filtered through Celite and evaporated to dryness to yield a crude gummy mixture of the diols (485 mg).

The crude reaction product was chromatographed on acid-washed alumina (15 g) packed in benzene. Elution with 1% methanol in ether (2 l.) and 5% methanol in ether (0.5 l.) provided, after evaporation to dryness, a greyish-gum which solidified upon trituration with ether (LXXIII, 387 mg). The solid product showed $\lambda_{\max}$ 2.80 μ, 2.90 μ (broad and intense), 5.78 μ, 6.00 μ, 6.20 μ; $\lambda_{\max}^{\mathrm{EtOH}}$ 236 mμ.

The mixture of diols was then utilized as such.

<u>Δ^4-Etiojervene-3,11,17-trione (LXXIV)</u>.--A mixture of the epimeric diols (LXXIII, 25 mg) was oxidized with chromic acid (20 mg) in glacial acetic acid (10 ml) and water (1 ml) at room temperature for a period of 4 hr. The reaction mixture was poured over cracked ice and was extracted with chloroform (30 ml). The chloroform layer was washed with a saturated sodium bicarbonate solution, water and was then dried over anhydrous sodium sulfate. Evaporation of the chloroform gave a brownish-solid which was crystallized from acetone-petroleum ether to provide needles of LXXIV, mp 214-216°;

λ_{max} 5.78 μ, 5.85 μ, 6.00 μ, 6.20 μ (superimposable upon that of the authentic sample); λ_{max}^{EtOH} 236 mμ (ε 15,500); mixture melting point with the authentic sample was undepressed.

<u>Δ^4-17-Ethyletiojervene-17α-ol-3,11,20-trione (C-Nor-D-Homo-11-Keto-17α-Hydroxyprogesteretone (LXXV); Δ^4-17-Ethyletiojervene-17β-ol-3,11,20-trione (C-Nor-D-Homo-11-Keto-17β-Hydroxyprogesterone) (LXXVI)</u>.--Method A. To a solution of LXIII (700 mg, mp 164-165°) in _t_-butyl alcohol was added a solution of 1.5 M H_2O_2 (4 ml) in _t_-butyl alcohol (5 ml), followed by a solution of osmium tetroxide (25 mg) in _t_-butyl alcohol (10 ml) which was added slowly over a period of 1 hr while the solution was stirred under a nitrogen atmosphere. Stirring was continued for 48 hr after which was added a solution of sodium sulfite (0.7 g) in water (5 ml) and the stirring was continued for 15 min more. Water was added and the reaction mixture was extracted with ether (0.5 l.). The ethereal extract was washed with water, and dried over anhydrous sodium sulfate. Evaporation of the ether to dryness gave a solid (0.95 g).

Column chromatography of the residue on silica gel (30 g) packed in benzene and elution with chloroform-benzene mixtures (up to 50% $CHCl_3$, 2 l.) gave starting material (300 mg). Further elution with chloroform-benzene (1:1, 1 l.) provided, after evaporation to dryness, a white solid (280 mg, mp 208-212°) composed of LXXV. Crystallization from chloroform-petroleum ether gave white needles, mp 215-216°; $[\alpha]_D^{26°}$ + 54.0° (c 0.52, $CHCl_3$); λ_{max} 2.85 μ (weak), 5.78 μ, 5.84 μ, 6.00 μ, 6.20 μ; λ_{max}^{EtOH} 236 mμ (ε 17,100); nmr, 8.79 (3H, singlet), 8.69 (3H, doublet, J = 6.5 cps), 7.62 (3H, singlet), 6-6.5 (1H, v. broad), 4.23 τ (1H, singlet); ord, $[\Phi]_{270}^{pk.}$ + 17411°; $[\Phi]_{332}^{tr.}$ - 17360°; a = -347°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.28; H, 8.45.

Continued elution with chloroform (1 l.) yielded a white solid (250 mg, mp 225-232°) composed mainly of LXXVI. Crystallization from chloroform-petroleum ether afforded colorless plates, mp 230-235° dec; $[\alpha]_D^{27°}$ + 56.0° (c 0.43, $CHCl_3$); λ_{max} 2.80 μ, 2.90 μ (broad and intense), 5.78 μ, 5.84 μ (moderate), 6.00 μ, 6.20 μ; λ_{max}^{EtOH} 236 mμ (ε 18,000); nmr, 8.79 (3H, singlet), 8.74 (3H, doublet, J = 6 cps), 7.76 (3H, singlet), 7.20 (1H, singlet), 4.22 τ (1H, singlet); ord, $[\Phi]_{280}^{pk.}$ + 7021°; $[\Phi]_{328}^{tr.}$ - 12287°; a = -193°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.48; H, 8.39.

Oxidation of LXIV (60 mg) according to the above procedure yielded three major bands when chromatographed on preparative tlc on silica gel F. The bands were extracted with 1% methanol in chloroform. Band I yielded starting material (20 mg). Band II yielded pure LXXV (18 mg, mp 215-216°) after crystallization from chloroform-petroleum ether. Band III yielded pure LXXVI (25 mg) after crystallization from chloroform-petroleum ether.

Method B. To a solution of potassium chlorate (100 mg) and a catalytic amount of osmium tetroxide (5-10 mg) in tetrahydrofuran (10 ml) and water (5 ml) was added a solution of LXIII (150 mg, mp 164-165°) in tetrahydrofuran (5 ml). The solution was maintained at 48-50° for a period of 24 hr (or until the disappearance of LXIII, followed by tlc). Water was added and the resulting precipitate was extracted with ether (200 ml) and the ethereal extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave a greyish-gum of LXXIII (155 mg), which was dissolved in pyridine (10 ml) and treated with a solution of chromic acid (80 mg) in pyridine (10 ml). The reaction mixture was allowed to stand at room temperature for 30 min and refrigerated for 18 hr more. This was poured over cracked ice and water was added before extraction with chloroform (100 ml). The chloroform layer was washed successively with 5% hydrochloric acid solution, 5% sodium bicarbonate solution, water and was then dried over anhydrous sodium sulfate. The chloroform was evaporated to dryness to leave a brown residue (120 mg), which was chromatographed on acid-washed alumina (4 g) packed in benzene. Elution with 30% ether in benzene (200 ml) gave an oil (40 mg, λ_{max} 5.78 μ, 6.00 μ, 6.20 μ; λ_{max}^{EtOH} 249 mμ), which failed to crystallize. This was believed to be the dehydrated product, $\Delta^{4,16}$-17-ethyletiojervadiene-3,11,20-trione (LXXII). Further elution with 40% ether in benzene gave a solid (25 mg) which crystallized from chloroform-petroleum ether as white needles (LXXV, mp 215-216°).

Continued elution with ether (400 ml) gave a solid (27 mg) which also crystallized from chloroform-petroleum ether to provide colorless plates of LXXVI, mp 230-234° dec.

$\Delta^{5,12(13)}$-Etiojervadiene-3β,11α-diol-17-one Diacetate (LXXXIV).--A solution of compound LXXXIII (30 mg, mp 230-235° dec) in acetic anhydride (2 ml) and pyridine (2 ml) was allowed to stand at room temperature for 3 hr. The reaction mixture was worked up in the usual manner to provide a white solid (25 mg, mp 150-160°). Two recrystallizations from petroleum ether yielded prisms of LXXXIV, mp 163.5-164.5°; $[\alpha]_D^{26°}$ -102° (c 0.5, $CHCl_3$); λ_{max} 5.78 μ, 6.00 μ, 6.10 μ (shoulder), 6.20 μ, 8.00 μ;λ_{max}^{EtOH} 248 mμ (ϵ 14,000); nmr, 8.81 (3H, singlet), 8.30 (3H, broad singlet), 7.91 (6H, singlet), 5.40 (1H, multiplet), 4.53 (1H, multiplet), 3.90 τ (1H, unresolved doublet, J = 7-8 cps).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.43; H, 7.91.

Δ^5-Etiojervene-3β-ol-17-one (LXXXV).--Anhydrous liquid ammonia was collected in a 100 ml three-necked round-bottomed flask provided with a mechanical stirrer, a dropping funnel and a cooling finger. Lithium (200 mg) was added, and after a short while the solution turned blue. Tetrahydrofuran (10 ml) was added, followed by a solution of LXXXIII (100 mg, mp 230-235° dec) in tetrahydrofuran (20 ml). Stirring was continued for 2 hr and the reaction mixture was decomposed with solid ammonium chloride (3 g). The ammonia was allowed to evaporate spontaneously, after which water was added and the mixture was extracted with ether (100 ml). The ethereal extract was washed with water and dried over anhydrous sodium sulfate. The residue (120 mg) obtained after evaporation of the ether was chromatographed on acid-washed alumina (5 g). The desired product (LXXXV, 15.6 mg) was eluted with 5% chloroform in benzene. The product was crystallized from acetone-petroleum ether to yield prisms, mp 164-165°; $[\alpha]_D^{26°}$ -106° (c 0.49, $CHCl_3$); λ_{max} 2.80 µ, 5.90 µ.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.98; H, 9.86.

To a solution of XVII (30 mg, mp 172-173°) in acetone (10 ml) and water (2 ml) was added a catalytic amounts of p-toluenesulfonic acid (4 mg). The reaction mixture was refluxed on a steam bath for 5 hr, after which the acetone was evaporated and water was added. The resulting precipitate was extracted with ether (50 ml) and the ethereal layer was washed with water and was dried over anhydrous sodium sulfate. The residue after evaporation of the ether was crystallized from acetone-petroleum ether to afford Δ^5-etiojervene-3β-ol-17-one (20 mg); mp 164-165°. Mixture melting point with the authentic sample was undepressed and the respective infrared spectra were superimposable.

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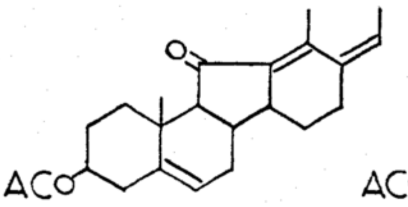
THE SYNTHESIS AND CONFIGURATION OF C-nor-D-HOMOPROGESTERONE ANALOGS

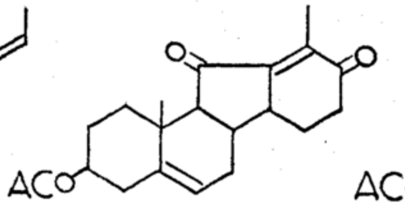
by Marwan J. Abu El-Haj

Under the supervision of Professor S. Morris Kupchan

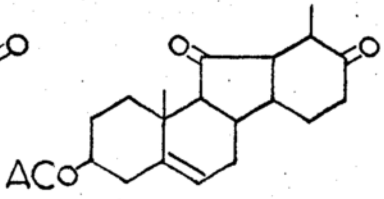
Jervine was degraded to I which in turn was oxidized with chromic acid in acetic acid to afford II.



I



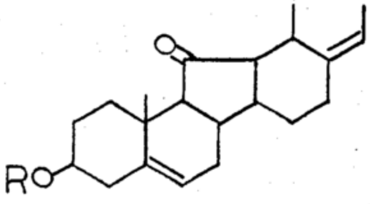
II



III

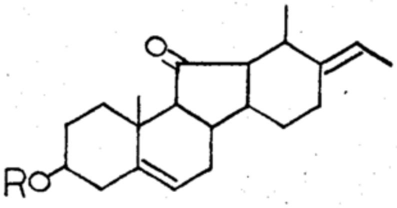
Reduction of II with zinc in acetic acid gave III.

Treatment of III with ethylidene triphenylphosphorane in ether and tetrahydrofuran yielded, after chromatographic separation, two isomeric products IV (major isomer) and V (minor isomer).



IV R = Ac

VI R = H

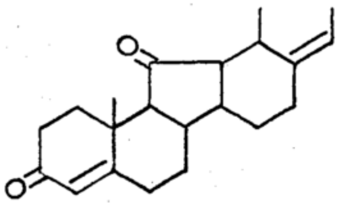


V R = Ac

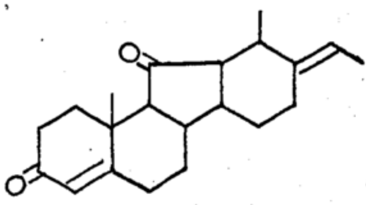
VII R = H

Ester hydrolysis of IV and V with 5% potassium hydroxide in methanol provided the corresponding alcohols VI and VII, respectively. NMR and ORD studies showed that IV and VI possess the C/D <u>trans</u> juncture, the C-18β-(equatorial)-CH_3, and the C-21-<u>cis</u>-CH_3. The studies also showed that V possesses the unstable C/D <u>cis</u> juncture, and the C-18β-(axial)-CH_3. V was isomerized at C-12 during ester hydrolysis as shown by the NMR and ORD studies which revealed VII to possess the stable C/D <u>trans</u> juncture, and the C-18β-(equatorial)-CH_3. Moreover, C-21-CH_3 in VII was assigned the configuration <u>trans</u> to the methyl group at C-13.

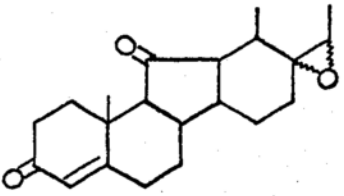
Oppenauer oxidation of VI and VII afforded VIII and IX, respectively. No isomerization took place during the oxidation, as evidenced by both NMR and ORD studies.



VIII

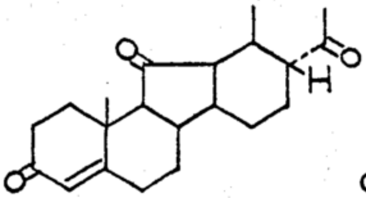


IX

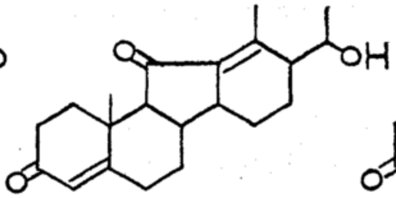


X = α-epoxide
XI = β-epoxide

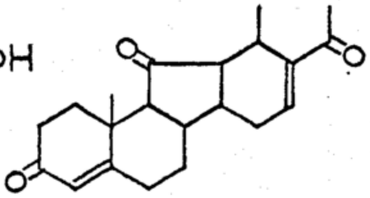
Epoxidation of VIII with monoperphthalic acid in ether gave two epimeric epoxides (separated by fractional crystallization from ether); the minor epimer X, and the major epimer XI. XI was formulated as the β-epoxide on the basis of its behavior toward boron trifluoride etherate in benzene during its attempted rearrangement to the triketone XII. In addition to XII, the elimination



XII



XIII

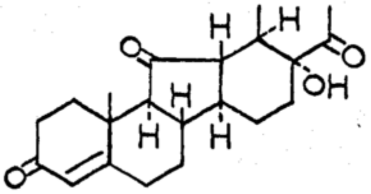


XIV

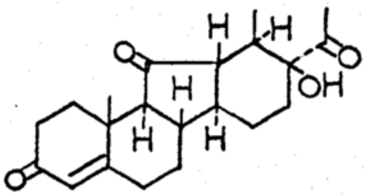
product XIII was isolated and this could only form, if the epoxide in XI were β. Therefore, the epoxide in XI was assigned the β-configuration. The rearrangement product XII was assigned the α-acetyl configuration on the basis of its ORD, and resistance to isomerization in base. Since the β-acetyl configuration is expected to be formed from the β-epoxide in XI, it was assumed that epimerization at C-17 took place under the reaction conditions.

Attempted oxidation of XI to the hydroxyketone with dimethyl sulfoxide and boron trifluoride etherate gave an alcohol which was oxidized to the ketone with chromic acid in pyridine. This was assigned the structure XIV on the basis of its IR, UV and NMR spectra.

Oxidation of either VIII or IX with osmium tetroxide and hydrogen peroxide under neutral conditions provided two epimeric hydroxyketones (separated by chromatography on silica gel) in almost equal yields.



XV



XVI

Assignment of configuration was made by comparison of their IR, NMR and ORD spectra, as well as their rates of elimination of water (using UV analysis). The alcohol of higher R_f was assigned the 17α-configuration, leading to the C-nor-D-homo-11-keto-17α-hydroxyprogesterone representation XV, and the other alcohol was assigned the 17β-configuration, leading to the C-nor-D-homo-11-keto-17β-hydroxyprogesterone representation XVI.

The configuration at four centers (C-8, C-9, C-10 and C-14) could be assigned to be the same as in normal steroids on the basis of earlier studies; while the configuration at the other three centers (C-12, C-13 and C-17) was determined, for all intermediates, by spectroscopic studies. The compounds were found to possess the C-12β-H and the C-13α-H.

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