The collected solid was treated as in the 500-mmole run (see above); a yield of 475 g, 95%, of ethyl stearate, mp 29–32°, was obtained.

1,5,9-Cyclododecatriene.—One hundred and fifty mmoles (450 mequiv), 27.5 ml, 24.3 g) of 1,5,9-cyclododecatriene (Cities Service), $n^{20}D$ 1.5049, was hydrogenated externally in ethanol solvent at 55° using a steam-heated water bath to maintain the temperature. The reaction was complete in about 1 hr. The reaction mixture was heated to boiling, filtered hot, and evaporated until only a white solid remained. This was dissolved in ether to remove salts. The ether solution was dried and the ether was evaporated, a yield of 21.8 g, 87% of cyclododecane, mp 59–61°, being obtained.

Norbornene-5,6-dicarboxylic Acid Anhydride.—Five hundred mmoles (82.0 g) of norbornene-5,6-dicarboxylic acid anhydride (Eastman, White Label), mp 164°, was hydrogenated in dry tetrahydrofuran by the external procedure in just over 1 hr. The reaction mixture was filtered and most of the tetrahydrofuran removed by distillation. After recrystallization from the hexane, a yield of 74.4 g, 90%, of the saturated anhydride, mp 167°, was obtained. The infrared spectrum showed no bands at 5.9 μ indicating the absence of acid.

Benzalacetone.—Five hundred mmoles of benzalacetone (Eastman, White Label), recrystallized from pentane–ethyl acetate, mp 39°, was hydrogenated in ethanol solvent by the external procedure at 25°. The reaction, which required 1 hr, was run in the presence of acetic acid only, since strong acid greatly promotes hydrogenolysis of the carbonyl group. The reaction mixture was filtered and the ethanol was removed by distillation. The residue was dissolved in 300 ml of ether, then washed with water. The ether extract, dried over magnesium sulfate, was subjected to flash distillation to remove the ether. The residue was distilled through a 30-cm Vigreaux column. A yield of 69.2 g, 92%, of saturated phenyl ketone, bp 233–235°, $n^{20}D$ 1.5105, was obtained. The infrared spectrum showed a small band at 2.8 μ (OH); so the product was subjected to gas chromatographic analysis. This analysis showed 93% 1-phenyl-3-butanone, 6% 1-phenyl-3-butanol, and 1% *n*-butylbenzene. This ratio would indicate the uptake of 540 mmoles of hydrogen, the amount actually absorbed.

Cholesterol.—The hydrogenation of 8.3 g (21.5 mmoles) of cholesterol (Eastman, White Label), mp 150°, over 0.33 g of commercial PtO_2 (Adams catalyst) was carried out using the hydrogenator assembled for external hydrogenation. The substrate was dissolved in 110 ml of ethyl acetate containing 4 drops of 70% perchloric acid. This solution was placed in the reactor flask with the catalyst. The system was flushed with hydrogen and reaction was begun. Twenty minutes was required for complete hydrogenation. The reaction mixture was filtered to remove the catalyst, and about half of the solvent was removed. The remaining solution was allowed to stand at −10° for 2 days and the resulting solid was collected. A yield of 6.8 g, 81%, of cholestanol, mp 137–139°, was obtained. Hershberg, *et al.*,[9] report that about 1–2% each of coprostane, cholestane, and coprostanol are formed as side products.

Agitation.—Agitation for the rate runs was provided by a small LaPine magnetic stirrer. The stirrer's rheostat was set at 8.5 for internal hydrogenations and 10 for external hydrogenations. For the preparative runs, a large Precision Scientific Co. Senior Mag-Mix stirrer was employed.

Acknowledgment.—This study was assisted in part by a grant from Parke, Davis & Co.

Conformational Preference in Ring A of 5(10)-Unsaturated Steroids[1a]

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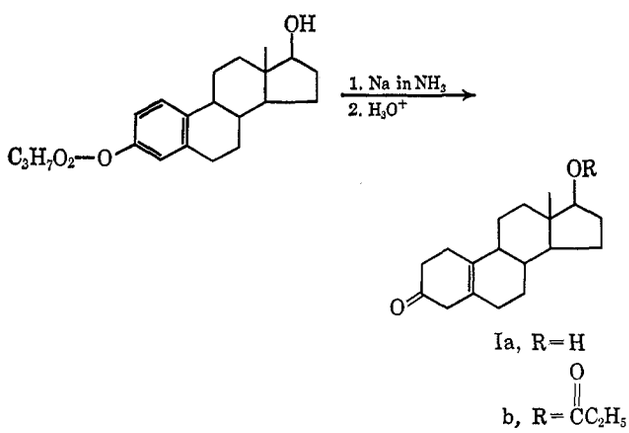
The hydride reduction of a $\Delta^{5(10)}$-3-keto steroid is found to be highly stereoselective, producing mostly the 3α-alcohol. This result is rationalized in terms of a preferred half-chair ring-A conformation (Xb) which is further supported by physical evidence.

A practical route to 5(10)-unsaturated steroids was not available until 1949 when Birch and Mukherji[2] reported the preparation of keto alcohol Ia *via* sodium in ammonia reduction of estradiol-3-glyceryl ether. Such



Ia, R = H

b, R = $\overset{O}{\overset{\|}{C}}C_2H_5$

β,γ-unsaturated ketones have since served as versatile intermediates for the preparation of nonaromatic 19-nor steroids of various structural types. Improvements of the original procedures are abundant and were spurred on, no doubt, by the great pharmacological importance of these end products. Recent developments have been reviewed both from the chemical[3,4] and biological[4] points of view.

Most of the above investigations have not been of such nature as to give insight into the *stereochemistry* of ring A in 5(10)-unsaturated steroids. A notable exception, however, is provided by Hartman's report[5] on the lithium aluminum hydride reduction of ketone Ia. We believe that the results of this experiment (described below) point to the operation of certain novel stereochemical effects in ring A of 5(10)-unsaturated steroids; our efforts toward elucidating these effects are described in this paper.[6]

The reduction of ketone Ia with ethereal lithium aluminum hydride was found[5] to produce a *single* 3,17β-diol in 77% yield; the purified product, mp 208–209°,

(1) (a) This work was supported by the National Institutes of Health, U. S. Public Health Service under Grant AM 09279 from the National Institute of Arthritis and Metabolic Diseases and Contract SA-43-ph-4351 from the Cancer Chemotherapy National Service Center; (b) Department of Chemistry, North Carolina State University, Raleigh, N. C.

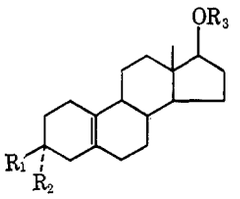
(2) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(3) F. J. Kakis in "Steroid Reactions—an Outline for Organic Chemists," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, Chapter 6.

(4) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 18.

(5) J. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955).

(6) A portion of these results has been reported in preliminary form: S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).

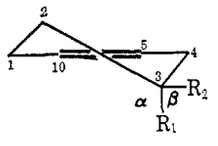


IIa, R_1 = OH; R_2 = H; R_3 = H

b, R_1 = H; R_2 = OH; R_3 = CC_2H_5 (=O)

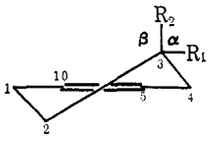
c, R_1 = OH; R_2 = H; R_3 = CC_2H_5 (=O)

was formulated as the 3β-alcohol IIa on grounds that would not now be considered sufficient. We were intrigued by the stereoselectivity of this reaction which seemed to elude explanation in any familiar terms. It is well established that hydride attack on an unhindered six-ring ketone ordinarily gives a single major product[7]—the equatorial alcohol. This generalization does not, however, suffice to explain the stereoselective reduction of a 5(10)-unsaturated 3-keto steroid. In such a case, ring A would be expected to alternate between the equivalent half-chair cyclohexene[8] forms, IIIa and IVa; these conformers should then provide equal



IIIa, R_1, R_2 = O

b, R_1 = H; R_2 = OH



IVa, R_1, R_2 = O

b, R_1 = OH; R_2 = H

amounts of the corresponding equatorial alcohols IIIb and IVb *which are seen to be opposite in C-3 configuration.*[9] The knowledge that one of these products is, in fact, favored, stimulated us to reinvestigate its C-3 configuration as a first step toward explaining the stereochemical selectivity of its formation.

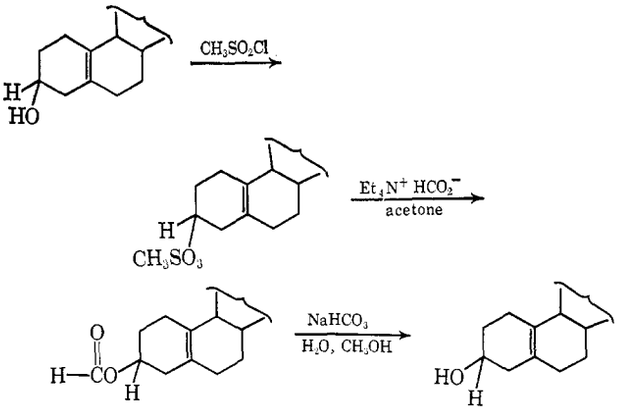
Preparation of the Epimeric 3-Alcohols.—Hartman's procedure[5] for lithium aluminum hydride reduction of the keto alcohol Ia was repeated and his results were generally confirmed. In addition, the expected presence of a minor product—presumably the opposite C-3 epimer—was substantiated by analytical thin layer chromatography (tlc). A pure sample of the minor epimer was not, however, obtainable by preparative chromatographic techniques. We anticipated that the chromatographic separability of ring-A alcohols would be enhanced by employing 17β-acyloxy steroids instead of the more polar 17β-alcohols. The resulting differentiation of ring-A and ring-D oxygenated functions was also to be of crucial importance in the management of later chemical steps. These objectives were pursued *via* the following synthetic route.

Treatment of 3-methoxyestra-2,5(10)-dien-17β-ol with propionic anhydride in pyridine gave the corresponding 17-propionate which was hydrolyzed under mild acidic conditions to give 17β-hydroxyestr-5(10)-en-3-one propionate (Ib). Reduction of this ketone was carried out at room temperature with lithium tri-*t*-butoxyaluminum hydride in order to preserve the 17-ester grouping. Analysis by tlc revealed only two products; these differed appreciably in mobility and the slower moving substance appeared to be by far the major component. The total products were separated by a combination of column chromatography (with continuous solvent gradient) and preparative tlc. This gave epimer A, 81–83% yield, mp 111–112°, $[\alpha]_D$ +134°; and epimer B, 13–15% yield, mp 115–117°, $[\alpha]_D$ +74°. Assay of the individual samples by tlc established that each substance was free of contamination by the other.

Saponification of epimer B gave a 3,17β-diol, mp 130–132°, $[\alpha]_D$ +112°. Similar treatment of the major epimer (A) produced an unsaturated diol, mp 205–207°, $[\alpha]_D$ +186°, identical in all respects with the purified product from lithium aluminum hydride reduction (Hartman's procedure) of 17β-hydroxyestr-5(10)-en-3-one (Ia). The major products of the two reduction reactions are thus shown to be identical in C-3 configuration.

We attempted to obtain larger amounts of the minor epimer (B) *via* C-3 inversion of epimer A. Some of the processes available for this purpose[11] were dismissed since they would lead initially to a 3,17-diacyloxy steroid incapable of selective saponification to a 17-monoacylate. The hydroxyl inversion procedure of Chang and Blickenstaff[12a] (heating an alcohol sulfonate in dimethylformamide) seemed promising though, since it provides an inverted *formate* which should be hydrolyzable in the presence of the 17-propionate ester. The mesylate ester derived from epimer A is, however, very labile toward elimination reactions and was largely converted to a mixture of ring-A dienes when heated in dimethylformamide. Treatment of epimer A mesylate with alumina[12b] led, likewise, to elimination products rather than the inverted alcohol. The desired conversion was finally achieved by means of the sequence shown in Chart I. In the key reaction, formate ion displacement of the mesyloxy group was

CHART I



(7) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962); O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1431 (1958).

(8) D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee, *Chem. Ind.* (London), 21 (1954).

(9) In the 3-ketone, ring A might also partake of the two quasi-boat forms[10] but this does not affect the argument.

(10) D. J. Baisted and J. S. Whitehurst, *J. Chem. Soc.*, 4089 (1961).

(11) *E.g.*, see P. A. Plattner and A. Furst, *Helv. Chim. Acta*, **26**, 2266 (1943).

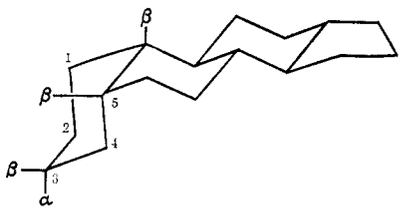
(12) (a) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958); (b) F. C. Chang and R. T. Blickenstaff, *Chem. Ind.* (London), 590 (1958).

performed with tetraethylammonium formate, prepared from tetraethylammonium hydroxide and formic acid. This formate salt is highly hygroscopic but has the virtue of being appreciably soluble in acetone which was used as the reaction solvent. Although elimination reactions again accompanied displacement, the over-all yield for conversion of epimer A to epimer B was approximately 50% and the product was comparable with the starting alcohol in purity.

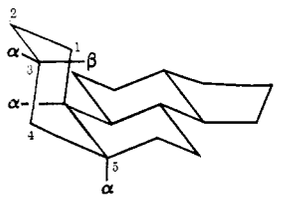
Determination of the 3-Alcohol Configurations.—The most usual methods[13] for assigning individual configurations to epimeric alicyclic alcohols apply only (a) when the ring system is of fixed and known conformation or (b) when a nearby asymmetric center is present and carries an appropriate functional group. Neither of these conditions obtains in the epimeric 3-hydroxy-5(10)-unsaturated steroids and these substances were, therefore, converted to products which would be more amenable to conformational analysis.

Epimer A was transformed by osmium tetroxide in benzene to a mixture of two triols (3ξ,5α,10α and 3ξ,5β,10β) which were easily distinguished by tlc. Column chromatography on silica gel gave pure saturated products A_1, mp 201–202°, and A_2, mp 191–193°, each having the composition $C_{21}H_{34}O_5$, corresponding to addition of two hydroxyl groups to the starting olefin. From epimer B, similar steps led to isomeric triols B_1, mp 150–152°, and B_2, mp 149–150°.

Models of the two possible A/B *cis*-steroid ring system (V and VI) having elsewhere the normal ring junc-



V



VI

ture configurations reveal a simple relationship between the orientation and configuration of ring A substituents. In the all-chair form of *either* system (5α,10α or 5β,10β) a 3α substituent is equatorial and a 3β substituent is axial. This property of A/B *cis* steroids enabled us in the following spectral study to determine the C-3 configurations of the four osmium tetroxide addition products.

The nmr spectra of the four osmium tetroxide products were examined with particular attention to the region τ 5.0–7.0 in which protons of type $-\overset{|}{C}(H)-O-$ are observed. Each of these spectra included a rough triplet centered close to τ 5.40 which is associated with the 17α proton of a 17β-acyloxy steroid.[14] A second signal, occurring within this region in each case, must be assigned to the C-3 proton. Recorded in Table I are the chemical shift and half-height width[15] ($W^{1/2}$) of this signal as found in the four isomeric triols.

TABLE I
C-3 PROTON RESONANCE SIGNALS

Compd	Structure	C-3–H	Chemical shift, τ	$W^{1/2}$, cps
A_1	VIIa[a]	Axial	5.92	20
A_2	VIIIa[a]	Axial	6.30	22
B_1	VIIb[a]	Equatorial	5.99	8
B_2	VIIIb[a]	Equatorial	5.88	8
A	IIb[b]	Axial	6.23	19
B	IIc[b]	Equatorial	6.00	11
	XIb[b]	Axial	6.56	20
	XIIb[b]	Equatorial	6.24	12

[a] Measured in $CDCl_3$ at 60 Mc/sec. [b] Measured in $CDCl_3$ at 100 Mc/sec.

It will be noted that isomers A_1 and A_2 each give rise to a broad band ($W^{1/2}$ approximately 21 cps) characteristic of axial protons whereas the relatively narrower ($W^{1/2}$ 8 cps) C-3 proton signal found for isomers B_1 and B_2 must arise from equatorial (weakly coupled) protons. It follows that the osmium tetroxide products A_1 and A_2 both possess a 3β proton (3α-OH) *and that the predominant hydride reduction product (A) is 5(10)-estrene-3α,-17β-diol 17-propionate (IIb).*[16] Similarly, the isomeric triols B_1 and B_2 must be in the 3β-hydroxy series, consistent with their origin from the minor reduction product (B), 5(10)-estrene-3β,17β-diol 17-propionate (IIc).

The C-3 configurations assigned to the four 3,5,10-trihydroxy-17-propionates on the basis of half-height line width are also in accord with the corresponding chemical-shift values. The C-3 proton resonances of triols B_1 and B_2 appear at τ 5.99 and 5.88, respectively, as expected for equatorial C-3 protons of steroidal 3-alcohols.[17] The osmium tetroxide product A_2 exhibits its axial C-3 proton signal at τ 6.30—also in agreement with earlier literature values. Although the C-3 hydrogen of triol A_1 must also be axial, its resonance appears at τ 5.92, approximately 0.4 unit downfield from the expected location. We suggest that this deshielding results from the presence of a hydroxyl group located 1,3-*cis*, diaxial with respect to the proton in question. This effect is manifested in cholestane-3β,5α-diol in which the 3α-proton (axial) resonance appears at τ 5.9. The deshielding of protons by a nearby hydroxyl group is now recognized as a general effect.[18]

The configurations of these four triols at C-5 and C-10 were also determined. A 1,3-*cis*, diaxial relationship between the 3β hydrogen and C-5 hydroxyl of triol A_1 would identify it as the 3α,5β,10β-triol VIIa. This

(13) "Technique of Organic Chemistry," K. W. Bentley, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapters III, IV, and XIX.

(14) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 353.

(15) The use of bandwidth at half-height ($W^{1/2}$) in determining the axial or equatorial orientation of an alicyclic methine proton has been discussed and exemplified by H. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964). More recent refinements of this method (and their range of applicability) are discussed by H. Feltkamp, N. C. Franklin, K. D. Thomas, and W. Brugel, *Ann. Chem.*, **683**, 64 (1965).

(16) A 3α-alcohol is also the major product from sodium borohydride reduction of a $\Delta^{5(10)}$-3-ketone: A. D. Cross, E. Denot, R. Acevedo, R. Urquiza, and A. Bowers, *J. Org. Chem.*, **29**, 2195 (1964). We thank Dr. Bowers for giving us this information prior to its publication.

(17) R. E. Counsell, *Tetrahedron*, **18**, 202 (1961).

(18) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 8; T. Okamoto and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **11**, 643 (1963).

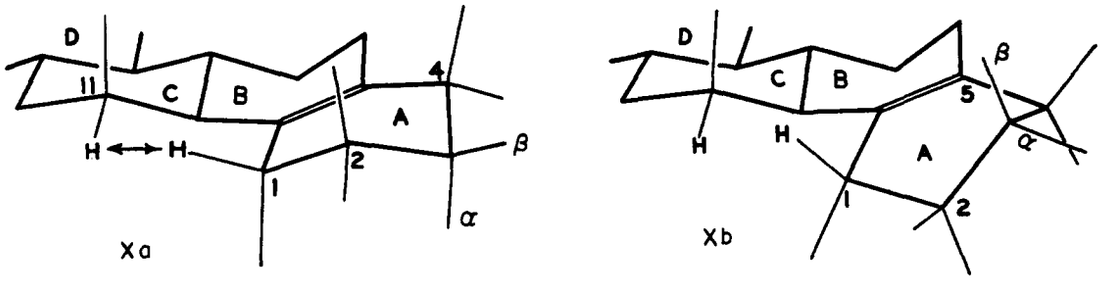
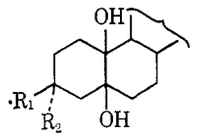
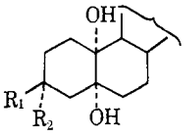


Figure 1.—The 5(10)-unsaturated steroid skeleton in the alternative half-chair ring-A conformations.

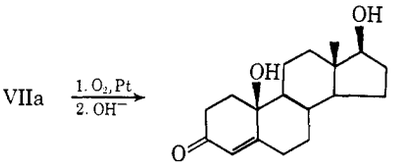


VIIa, $R_1 = H$, $R_2 = OH$
b, $R_1 = OH$; $R_2 = H$



VIIIa, $R_1 = H$; $R_2 = OH$
b, $R_1 = OH$; $R_2 = H$

structure was confirmed by the following transformation. Catalytic oxidation of triol A_1 with platinum and oxygen in acetic acid led to a mixture of saturated and unsaturated ketones. The total product, after heating under reflux with potassium hydroxide in methanol, yielded 10β-hydroxy-19-nortestosterone (IX), mp 213–



IX

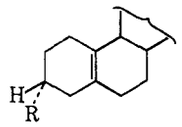
217°, identical by mixture melting point and infrared comparison with an authentic sample.[19] The assignment of structure VIIa to triol A_1 requires that the accompanying osmium tetroxide product A_2 be formulated as the 3α,5α,10α-triol VIIIa.

Complete structures were assigned to the 3β,5,10-triols B_1 and B_2 based on infrared spectral data. All four triols reacted with acetic anhydride in pyridine to give the corresponding 3-monoacetates.[20] In three cases, the 3- and 17β-ester functions gave rise to a combined carbonyl absorption maximum at 1738 cm^{-1}. The 3-acetate of triol B_1, however, exhibited maxima at 1738 and 1752 cm^{-1}. The latter high-frequency position is readily explained by hydrogen bonding between a 5β-hydroxyl group and the ether oxygen of the 3β-acetate.[22] This requires formulations VIIb and VIIIb for the triols B_1 and B_2, respectively.

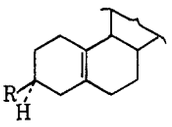
Conformation of Ring A.—Having established that hydride reduction of a $\Delta^{5(10)}$-3-ketone is indeed selective and that it leads predominantly to the 3α-alcohol, we may now inquire into the origin of this unexpected effect. Inspection of Dreiding models reveals that one of the two expected half-chair conformations of ring A involves a particularly severe, nonbonded interaction between the equatorial 11α-H and the quasi-equatorial 1β-H. This compression effect is indicated by the double-headed arrow in the perspective drawing Xa (Figure 1). The distance between nuclear centers (derived from measurements[23] on the Dreiding model) can be estimated at 1.80 A, comparable to the separation of the axial "bow and stern" hydrogens in the *classical* boat form of cyclohexane.[24] The alternative half-chair form (Xb) appears to be free of any serious repulsion effects. In the latter (presumably preferred) conformation of the molecule, a 3α substituent is equatorial and a 3β substituent is axial. The preferential reduction of a $\Delta^{5(10)}$-3-ketone to the 3α-alcohol then follows from the amply demonstrated[7] property of hydride reducing agents to produce a preponderance of the equatorial alcohol from an unhindered ketone.[25]

Direct evidence for conformational preference in ring A was provided by the nmr spectra (Figure 2) of the epimeric alcohols IIb and IIc. The C-3 proton of the 3β-alcohol (IIc) exhibits a half-height band width (12 cps) which is only slightly larger than those values found for equatorial C-3 protons in the saturated axial alcohols VIIa and VIIIa. Similarly, $W^{1/2}$ for the 3α-alcohol IIb is 19 cps, approaching the large bandwidth values found for C-3 protons in the saturated equatorial alcohols VIIb and VIIIb. The C-3 protons of epimers IIa and IIb show a chemical-shift difference ($\Delta\tau$ 0.23) in such direction as to be in agreement with the above linewidth data.

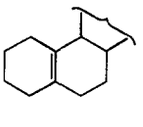
Further evidence for a preferred conformation of ring A in 5(10)-unsaturated steroids was obtained by synthesis of the 3α- and 3β-azides and examination of their nmr spectra (Figure 3). The 3α-alcohol IIb reacted with methanesulfonyl chloride to give the mesylate ester XIa which underwent displacement with sodium



XIa, $R = O_3SCH_3$
b, $R = N_3$



XIIa, $R = O_3SCH_3$
b, $R = N_3$



XIIIa (17-propionate)
b (17-alcohol)

(19) This sample was kindly supplied by Dr. A. D. Cross, Syntex, S. A., Mexico City.

(20) The preparation of these substances was anticipated at the outset of this work and at that point we had expected that the monoacetyl derivatives would serve as the major source of information regarding the orientation (hence, configuration) of the C-3 oxygen substituents. The usefulness of infrared data (on acetate esters) in the 1250-cm^{-1} region for determinations of this type has been reviewed[21] and certain anomalous results have been noted. In this series of monoacetates, the method did not lead to clear-cut conclusions. Our use of 17-propionate rather than the more usual acetate esters had the intended purpose of leaving clear the 1250-cm^{-1} region.

(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 189.

(22) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(23) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(24) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Friesch, L. H. Dreger, and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(25) The nmr data do not rigorously exclude the possibility of a preferred half-boat conformation for ring A. Such a form should, however, be intrinsically less favorable by approximately 2.7 kcal/mole.[26] The half-chair form has, moreover, been directly verified in part of our current work which will be reported at a later time.

(26) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Am. Chem. Soc.*, **70**, 4227 (1948).

azide in dimethylformamide furnishing the $\Delta^{5(10)}$-3β-azide XIIb. A similar sequence starting with the 3β-alcohol yielded the 3α-azide XIb. The nmr spectra of these substances provided chemical-shift and bandwidth data (Table I) which are in line with those obtained for the corresponding alcohols.

The above nmr data clearly indicate a significant degree of conformational preference in ring A. The data are not, however, amenable to quantitative interpretation. Relative conformer populations are ordinarily calculated[27] by comparing the magnitude of some physical (or chemical) property of a compound with the corresponding value for a conformationally pure species. The latter quantity is most often derived from similar measurements on a conformationally stabilized model compound. Such a reference substance does not appear to be available in the cyclohexene series. To circumvent the need for model compounds, we tried to employ the low-temperature nmr method[28] previously used successfully with the cyclohexyl halides. Measurements were conducted at $-40°$[29] on the 3α-alcohol IIb but no change in 3β-proton signal was observed.

Some conclusions regarding the percent of conformational preference in ring A may be reached by considering again the hydride reduction reaction leading from the $\Delta^{5(10)}$-3-ketone to the epimeric 3-alcohols. The ratio of epimers formed at 25° was approximately 6:1. It is reasonable to assume that this result is due largely to local rather than long-range directing effects. A conformational bias to at least this extent must then be operating at the transition state of the reduction reaction.

Optical Rotation Differences.—If stereostructure Xb is accepted as representing the preferred conformation of ring A in 3-substituted 5(10)-unsaturated steroids, then certain predictions can be made regarding optical rotation differences within this series. A semiempirical method has been developed by Brewster[30] for estimating rotation differences in substituted cycloalkanes and cyclo olefins. In this method, the cyclic structure is analyzed by means of a set of Newman projections taken along each of the ring bonds. For each such member, note is made of the skew interaction (ordinarily axial–equatorial or equatorial–equatorial) between adjacent substituents. The direction of skew determines whether a unit will make a positive or negative contribution to the rotation of the molecule. The magnitude of this contribution is determined by the identity of the substituent groups. Replacing a hydrogen atom by a new substituent will result in the loss of certain interactions and the gain of new interactions involving that substituent. Brewster has compiled numerical tables by means of which this net change can be evaluated in terms of an expected increase (or decrease) in molecular rotation.

It follows from Brewster's method of analysis that an *equatorial* homoallylic substituent will make little or no contribution to the rotation of a cyclohexene derivative. The effect of an *axial* homoallylic substituent should,

(27) For an excellent review on conformational analysis by nmr, see N. C. Franklin and H. Feltkamp, *Angew. Chem.*, **77**, 798 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 774 (1965).

(28) A discussion of this method and its limitations is given in the preceding reference; examples of application are cited in ref 16–18 in that paper.

(29) This was the lower limit of our measurement capability.

(30) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959), and preceding papers.

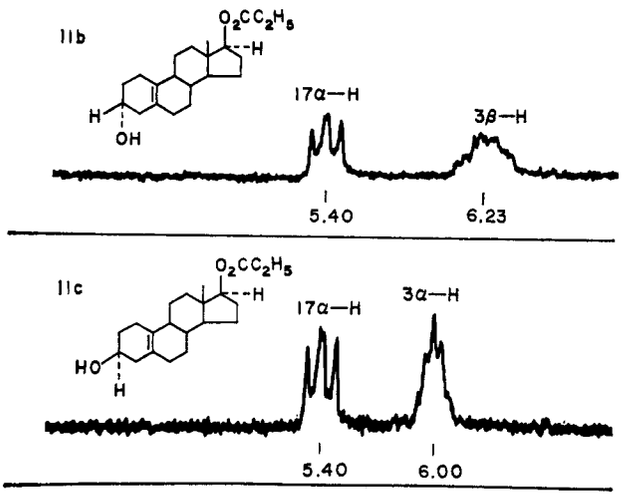


Figure 2.—Partial nmr spectra of 3-hydroxy-5(10)-unsaturated steroids IIb and IIc.

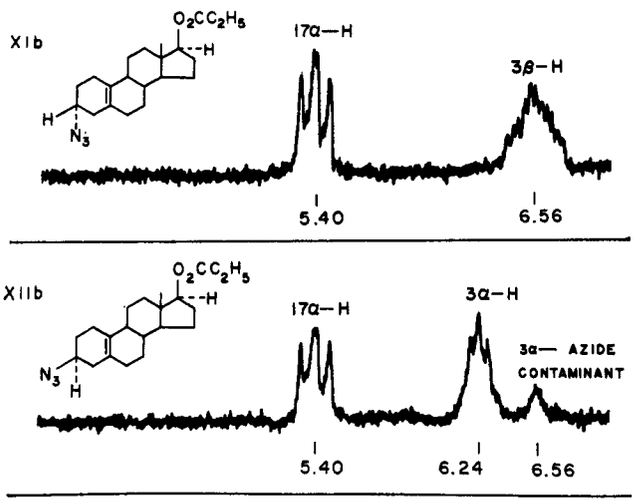


Figure 3.—Partial nmr spectra of 3-azido-5(10)-unsaturated steroids XIb and XIIb.

however, be significant and the magnitude of this contribution can be estimated. Using Brewster's methods and parameters, we have calculated[31] that the 3β-alcohol IIc, in conformation Xb, should be more levorotatory than the parent 3-deoxy steroid XII by approximately 75°. The latter substance was synthesized in order to test this prediction.

The reaction of lithium aluminum hydride with the 5(10)-unsaturated 3α-mesylate XIa led to reductive loss of the sulfonate ester substituent. The 3-deoxy steroid product (XIII) obtained as the 17β-alcohol, was

(31) Using Brewster's notation, the increment in molecular rotation on introduction of the 3β-hydroxyl group is given by

$$\Delta[M] = k(O - H)(C - H) - k(O - H)(C^*{=}C^* - H) \quad (1)$$

This expression can now be evaluated using the following empirical parameters

$$k(C - H)(C^*{=}C^* - H) = 140° \quad (2)$$

$$k(C - H)(O - H) = 50° \quad (3)$$

$$k(O - H)(O - H) = 45° \quad (4)$$

from which it may be derived that

$$k(C^*{=}C^* - H)(O - H) = 126° \quad (5)$$

Substitution of eq 3 and 5 in eq 1 gives

$$\Delta[M] = 50 - 126 = -76°$$

contaminated (approximately 20%) with a mixture of ring-A dienes formed by elimination of the mesyloxy group. The total products were subjected to chromatographic and crystallization procedures both before and after conversion to the 17-propionate ester; in none of these cases was a satisfactory separation achieved. It was finally found that osmium tetroxide, added in limited amount, reacted preferentially with the diene contaminants which were then easily removed as the osmate esters. The resulting 3-deoxy steroid XIIIa was sharp melting and completely devoid of vinyl proton absorption in the nmr. The molecular rotation of this substance and of its 17-alcohol analog are given in Table II along with corresponding values for the 3α- and 3β-alcohol derivatives. The rotations of other 3-substituted steroids, obtained only as the 17-propionates, are also included. The increment in molecular rotation Δ[M] corresponding to the introduction of each C-3-substituent is given in the last two columns.

TABLE II
MOLECULAR ROTATIONS [M] OF 5(10)-UNSATURATED STEROIDS AND ROTATION INCREMENTS Δ[M] FOR INTRODUCTION OF C-3 SUBSTITUENT

C-3 substituent	[M] 17-OH	[M] 17-$O_2CC_2H_5$	Δ[M] 17-OH	Δ[M] 17-$O_2CC_2H_5$
3-H	+475	+420	...	...
3α-OH	+514	+445	+39	+25
3β-OH	+310	+246	−165	−174
3α-N_3		+421		+1
3β-N_3		+242		−178
3α-O_3SCH_3		+485		+65
3β-O_3SCH_3		+283		−137

It is apparent that these rotation results are at least in qualitative agreement with predictions based on conformation Xb for ring A. Thus, within each epimeric pair it is the 3α-substitution (equatorial) product whose molecular rotation more closely approximates that of the 3-deoxy steroid XIII. The expected levorotatory contributions of the 3β substituents (axial) are also apparent. However, the magnitude of this effect in the 3β-alcohol is seen to be more than double the calculated value of 76°. Such a discrepancy may not be surprising in view of the approximations and assumptions involved in making these estimates.[32]

Our further work involves the synthesis and conformational study of 2,3-disubstituted, 5(10)-unsaturated steroids and will be reported at a later time.

Experimental Section

Optical rotations, unless otherwise specified, were taken as solutions (*ca.* 1%) in chloroform at 25°. Melting points were determined with a Kofler micro melting point apparatus and are uncorrected. Analytical thin layer chromatography plate coatings were of 0.25-mm thickness and prepared using Brinkmann silica gel G; preparative plates, except where noted, were coated to a 1.0-mm thickness using Brinkmann silica gel H. The developed preparative plates, after evaporation of solvent were sprayed lightly with water. In most cases this allowed delineation of product zones which appeared opaque (white) on a translucent background.

(32) Professor Brewster has kindly informed us that further refinements in this method of estimating rotation differences will include the consideration of "long range" effects. The interaction between an axial 3β substituent and the 5(10) double bond should give rise to a rotatory contribution in such direction as to diminish the above discrepancies. We are grateful to Professor Brewster for this information.

3-Methoxyestra-2,5(10)-dien-17β-ol Propionate.—A solution of 3-methoxyestra-2,5(10)-dien-17β-ol (20.0 g) in pyridine (200 ml) and propionic anhydride (67.0 ml) was left at 25° for 16 hr, then added slowly to 1500 ml of water and ice with rapid stirring. The crystalline precipitate was collected, washed with cold water in a Waring Blendor, and recollected; this washing procedure was repeated twice. The final filter cake (slightly moist) was taken up in benzene, washed with saturated brine, dried over magnesium sulfate, and freed of solvent at reduced pressure. The solid residue was recrystallized from methanol (*ca.* 220 ml) giving 19.5 g (82%) of the 17-propionate, mp 98–101°. Further recrystallization from methanol gave an analytical sample: mp 103.5–104.5°, $[\alpha]_D$ +90° (acetone), ν^{CS_2} 1730 (propionate) and 1663 and 1691 cm^{-1} (3-alkoxy-$\Delta^{2,5(10)}$-diene).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.41; H, 9.32.

17β-Hydroxyestr-5(10)-en-3-one Propionate (Ib).—A solution of oxalic acid (16.70 g) in water (167 ml) was added over 15 min to a stirred solution of 3-methoxyestra-2,5(10)-dien-17β-ol propionate (9.76 g) in methanol (1100 ml) while maintaining a reaction temperature of 24–26° by outside cooling. An aqueous slurry of sodium bicarbonate (23.5 g) was cautiously added to the reaction solution which was then freed of methanol at reduced pressure. The residue was taken up in benzene and water and the organic layer was washed neutral with water, dried over $MgSO_4$, and evaporated. The resulting solid, after recrystallization from hexane, gave 7.42 g (79%) of the keto ester Ib, mp 128–132°, showing no ultraviolet absorption near 240 mμ. This product, once more crystallized from hexane, had mp 129–130°, $[\alpha]_D$ +125° (acetone), ν^{CS_2} 1720–1740 cm^{-1} (ketone and propionate).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.49; H, 9.24.

Estr-5-ene-3α,17β-diol 17-Propionate (IIb) and Estr-5-ene-3β,-17β-diol 17-Propionate (IIc).—A solution of the $\Delta^{5(10)}$-3-ketone (Ib, 1.000 g) in tetrahydrofuran (8.0 ml) was added slowly with stirring to a cold (−70°) solution of lithium tri-*t*-butoxyaluminum hydride (4.0 g) in the same solvent. After 16 hr at −70°, the reaction mixture was poured into 180 ml of cold water containing glacial acetic acid (6.0 ml). After removal of the organic solvent at reduced pressure, the reaction products were extracted into benzene, washed with water, dried, and concentrated leaving 1.001 g of residue. Examination by tlc using 20% ethyl acetate in chloroform as eluent showed the presence of two components, R_f 0.6 (minor) and 0.5 (major).

A portion (0.482 g) of this residue was chromatographed on a column of Woelm alumina, activity III (60 g, 1.8 × 22 cm). The eluting solvent (500 ml total) was supplied in a continuous concentration gradient from benzene to 7% ether in benzene and the individual fractions (10 ml) were automatically collected.

Fractions 16–18 yielded 0.017 g of the less polar component. Fractions 19–22 gave 0.085 g of a two-component mixture which was resolved by preparative tlc giving 0.015 g of the less polar and 0.057 g of the more polar component. Fractions 23–50 contained 0.384 g of the more polar compound which was combined with the smaller sample above, giving a total of 0.441 g (91%) of the 3α-alcohol, mp 112.5–115°, showing only one spot on a thin layer chromatogram. An analytical sample of the 3α-alcohol IIb, prepared by recrystallization from hexane, had mp 111–112.5°, $[\alpha]_D$ +134°, ν^{CS_2} 3605 (OH) and 1735 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.70; H, 9.44.

The two fractions containing the less polar product were combined, giving 0.032 g (7%) of the 3β-alcohol, mp 117–119°, showing only one spot in a thin layer chromatogram. Additional material was obtained by repetition of the hydride reduction at 25°, in this case giving the 3β-alcohol IIc, 16% yield. An analytical sample, recrystallized from petroleum ether (bp 30–60°), had mp 115–117°, $[\alpha]_D$ +74°, ν^{CS_2} 3605 (OH) and 1735 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.65; H, 9.90.

Estr-5-ene-3α,17β-diol (IIa).—The diol monoester IIb was heated under reflux for 90 min in 5% methanolic potassium hydroxide. The product, after crystallization from methanol, had mp 205–207°, $[\alpha]_D$ +186°.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.75; H, 10.12.

The melting point of this compound was not depressed on admixture with a similar sample obtained by Hartman's procedure from the keto alcohol Ia.

Estr-5(10)-ene-3β,17β-diol.—Saponification of the diol monoester IIc was carried out as above. The product, after recrystallization from methylene chloride–hexane and then from ether–hexane, had mp 130–132°, $[\alpha]_D$ +112°.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.36; H, 10.34.

5α,10α-Estrane-3α,5,10,17β-tetrol 17-Propionate (VIIIa) and 5β,10β-Estrane-3α,5,10,17β-tetrol 17-Propionate (VIIa).—A solution of the unsaturated 3α-alcohol IIb (5.000 g) and OsO_4 (5.00 g) in benzene (140 ml) and pyridine (4.0 ml) was allowed to remain at *ca.* 25° for 96 hr, then cooled to 0°, and saturated with hydrogen sulfide. The resulting black residue was removed by centrifuge and washed well with ethyl acetate. The combined organic solutions were filtered through Celite and freed of solvent to leave 6 g of crystalline residue.

This product was assayed by tlc (40% acetone in hexane as eluent) and found to consist entirely of two components, R_f 0.23 and 0.33, respectively. The total material was chromatographed on a column of Woelm alumina activity III (330 g) and eluted by continuous solvent gradient from chloroform to 10% ethanol in chloroform in eighty fractions (5000 ml total). Fractions 19–35, after removal of solvent and crystallization of the residue from hexane containing a small amount of ether, gave the 3α,5β,10β-triol VIIa: 3.330 g, 60.5%, R_f 0.33, mp 200–201°. An analytical sample had mp 201–202.5°, $[\alpha]_D$ +14°, $\nu_{max}^{CHCl_3}$ 3400–3600 (free and H-bonded OH) and 1730 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.90; H, 9.30.

Treatment of triol VIIa with acetic anhydride in pyridine at room temperature for 16 hr and crystallization of the product from ether gave the corresponding 3-acetate: mp 167.5–168.5°, $[\alpha]_D$ + 24°, $\nu_{max}^{CS_2}$ 3600–3560 (H-bonded OH) and 1740 cm^{-1} (3-acetate and 17-propionate).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.35; H, 8.83.

Fractions 40–70, after removal of solvent and crystallization of the residue from hexane containing a small amount of ether, gave the 3α,5α,10α-triol VIIIa: 1.426 g, 26%, R_f 0.23, mp 191–193.5°, $[\alpha]_D$ +30°, $\nu_{max}^{CHCl_3}$ 3605 and 3400–3550 (free and H-bonded OH) and 1723 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.92; H, 9.57.

Acetylation of this compound with acetic anhydride in pyridine and crystallization of the product from ether gave the corresponding 3-acetate: mp 161.5–162°, $[\alpha]_D$ +23°, $\nu_{max}^{CS_2}$ 3550 (H-bonded OH) and 1740 cm^{-1} (3-acetate and 17-propionate).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.79; H, 8.81.

5β,10β-Estrane-3β,5,10,17β-tetrol 17-Propionate (VIIb) and 5α,10α-Estrane-3β,5,10,17β-tetrol 17-Propionate (VIIIb).—A solution of the unsaturated 3β-alcohol IIc (0.551 g) and OsO_4 (0.50 g) in benzene (20 ml) and pyridine (0.5 ml) was allowed to remain at 26° for 96 hr, then worked up as for the corresponding 3α-alcohol (see above). An accident occurred at one stage which resulted in the mechanical loss of 23% of the crude reaction product; yields reported below are based on the amount of material remaining.

The product, as assayed by tlc (40% acetone in hexane as eluent), consisted entirely of two components, R_f 0.38 and 0.58, respectively. This material was chromatographed on a column of Woelm neutral alumina, activity III (44 g), and eluted by a continuous solvent gradient from chloroform to 5% ethanol in chloroform (2000-ml total volume). The early eluates provided 0.158 g (28%) of a crystalline triol fraction which was pure by tlc (R_f 0.58). This material, combined with a similar fraction (0.090 g) from an earlier column, was recrystallized from ether–hexane to give 0.208 g of the 3β,5β,10β-triol as blades: mp 150.5–152°, $[\alpha]_D$ +19°, $\nu_{max}^{CHCl_3}$ 3600 (OH), 3470 (broad, H-bonded OH), and 1721 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.57; H, 9.21.

Treatment of this compound with acetic anhydride in pyridine at room temperature for 16 hr and crystallization of the product from ether–hexane gave the corresponding 3-acetate: mp 154–155°; $[\alpha]_D$ +35°; $\nu_{max}^{CS_2}$ 3550 and 3570 (H-bonded OH), 1752 (3-acetate), and 1740 cm^{-1} (17-propionate).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.62; H, 8.91.

The later column eluates (2–3% ethanol in chloroform) provided 0.215 g (38%) of a more polar triol which was pure by tlc (R_f 0.38). This material, combined with a similar fraction (0.072 g) from an earlier preparation, was recrystallized from ether–hexane to give 0.220 g of the 3β,5α,10α-triol VIIIb as blades: mp 149.5–150.5°; $[\alpha]_D$ +23°; $\nu_{max}^{CHCl_3}$ 3605 (OH), 3550 (broad, H-bonded OH), and 1720 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.91; H, 9.31.

The corresponding 3-acetate, obtained as above, had mp 149.5–152°; $[\alpha]_D$ +21.5°; $\nu_{max}^{CS_2}$ 3610 (OH), 3560 (H-bonded OH), and 1735 cm^{-1} (3-acetate and 17-propionate).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.57; H, 8.93.

10β-Hydroxy-19-nortestosterone (IX).—A 0.050-g sample (mp 201–202.5°, pure by tlc) of the triol VIIa was dissolved in 15 ml of glacial acetic acid containing suspended platinum (from 0.200 g of platinum oxide) and stirred in an atmosphere of oxygen for 96 hr at 42°. Platinum black was then removed by filtration and the solvent was evaporated at reduced pressure. The residue was chromatographed by use of two tlc plates (20 × 20 cm) coated with silica gel G (0.5 mm). Development with ethyl acetate gave rise to three zones which were individually removed and eluted with ethyl acetate. The slowest moving zone was found to contain traces of residual starting triol. The middle component (0.013 g) appeared to be a hydroxy ketone, ν^{CHCl_3} 1720 cm^{-1} (broad, ketone and propionate). The least polar fraction (0.022 g) provided a conjugated ketone, ν^{CHCl_3} 1670 cm^{-1}. The latter two fractions were combined, sealed in a glass tube (under N_2) with potassium hydroxide (0.026 g) in methanol (0.5 ml), and heated at 65° for 45 min. The reaction mixture was then cooled, neutralized with glacial acetic acid (0.030 ml), and freed of solvent at reduced pressure. The resulting solid was recrystallized from acetone in benzene to give 0.013 g (35%) of 10β-hydroxy-19-nortestosterone (IX), mp 213–217°. A mixture with an authentic sample[19] (mp 215–218°) had mp 212–216°. The infrared spectra of these two samples were rich in fine structure and virtually identical.

Estr-5(10)-ene-3α,17β-diol 3-Methanesulfonate, 17-Propionate (XIa).—A cooled (0°) solution of the 3α-alcohol IIb (5.00 g) in pyridine (50.0 ml) was treated with methanesulfonyl chloride (5.00 ml) and allowed to remain at 0° for 16 hr. The reaction solution was then slowly added to a rapidly stirred mixture of ice and water. Stirring was continued during gradual warming of the mixture to near room temperature and for 1 hr at 20–25°. Cold 2 *N* H_2SO_4 (316 ml) was added and the crystalline product was collected. This material, in benzene, was washed with aqueous sodium bicarbonate and water. The dried (magnesium sulfate) solution was evaporated at reduced pressure and the residue was crystallized from ether–hexane giving 5.518 g (84%) of the 3α-mesylate XIa, mp 113–116°. One additional crystallization gave an analytical sample: mp 115–116°, $[\alpha]_D$ +118°.

Anal. Calcd for $C_{22}H_{34}O_5S$: C, 64.37; H, 8.35. Found: C, 64.12; H, 8.33.

Estr-5(10)-ene-3β,17β-diol 3-Methanesulfonate, 17-Propionate (XIIa).—The 3β-alcohol IIc (2.020 g) was treated with methanesulfonyl chloride (4.00 ml) and pyridine (20.0 ml) in the manner described above. Successful crystallization of crude product from the aqueous pyridine was in this case particularly dependent on rapid agitation (*e.g.*, by means of a Waring Blendor) during the mixing process. Crystallization from ether–hexane yielded 2.049 g (80%) of product, mp 82–86°. One further recrystallization gave the 3β-mesylate XIIa: mp 83.5–85.5°, $[\alpha]_D$ +69°.

Anal. Calcd for $C_{22}H_{34}O_5S$: C, 64.37; H, 8.35. Found: C, 64.22; H, 8.31.

Estr-5(10)-en-17β-ol (XIIIb).—A solution of the 3α-mesylate XIa (2.681 g, 6.5 mmoles) in dry ether (125 ml) was added dropwise at approximately 25° to a stirred suspension of lithium aluminum hydride (2.14 g) in 275 ml of dry ether. After 16 hr, the reaction mixture was cooled in an ice bath and excess reagent was decomposed by cautious addition of ethyl acetate (10 ml) followed by 2 *N* H_2SO_4 (150 ml). The organic layer was washed neutral with water, shaken with saturated brine, dried over $MgSO_4$, and freed of solvent. An infrared spectrum on this residue showed a small amount of olefinic hydrogen absorption. A benzene solution of the residue was treated with OsO_4 (0.24 g, 1.0 mmole). After 3 hr, the reaction solution was freed of black osmate esters by filtering through a very short column of Woelm

alumina, activity III. The filtrate and benzene washings were combined and evaporated leaving 1.029 g (61%) of crystalline 3-deoxy product (XIIIb) which was homogeneous by tlc and displayed no olefinic hydrogen absorption in the infrared or nmr spectra. An analytical sample, prepared from a small portion of this material by recrystallization from petroleum ether, had mp 104–106°, $[\alpha]_D$ +180°.

Anal. Calcd for $C_{18}H_{28}O$: C, 83.03; H, 10.84. Found: C, 82.84; H, 10.62.

The remaining 17-alcohol (0.998 g) was treated at room temperature with propionic anhydride in pyridine for 16 hr. Solvents were removed at reduced pressure and the residue, in benzene, was filtered through a small amount of alumina. The product was crystallized twice from acetonitrile, giving 0.544 g of estr-5(10)-en-17β-ol propionate (XIIIa): mp 96.5–97.5°, $[\alpha]_D$ +133°, ν^{CS_2} 1735 cm^{-1} (propionate).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.81; H, 10.23.

Tetraethylammonium Formate.—A 25% aqueous solution of tetraethylammonium hydroxide (61.0 ml) was treated with 90% formic acid (4.36 ml). An aliquot (1.0 ml) of this solution, after dilution with distilled water (15 ml) had pH 7.6. The remaining neutralized solution was concentrated at reduced pressure to approximately 25 ml. The viscous syrup was efficiently stirred with benzene (125 ml) while heating under reflux for at least 16 hr employing a Dean–Stark trap for removal of water. The resulting crystalline precipitate was pulverized while still under benzene, collected on a sintered glass funnel, and washed with dry benzene while maintaining a nitrogen atmosphere. The product (dried *in vacuo*) was transferred to a tared, nitrogen-flushed bottle and amounted to 15.6 g. A sample of this salt was transformed to an aqueous syrup within 20 sec after exposure to air. Weighing and transfer operations with this reagent should be performed in a drybox, if possible.

Owing to its hygroscopic nature, the compound was not quantitatively characterized.

Estr-5(10)-ene-3β,17β-diol 3-Formate, 17-Propionate.—A solution of the 3α-mesylate XIa (1.557 g) and tetraethylammonium formate (2.5 g) in dry acetone (60 ml) was heated under reflux for 17 hr. The reaction mixture was cooled, freed of acetone, and partitioned between water and benzene. The organic solution was dried and concentrated, and the residue (1.301 g) was separated by chromatography on a column (32 × 3.7 cm) of 50% silica gel–Celite (120 g). Elution with benzene containing continuously increasing amounts of ethanol provided two well-separated fractions. The early eluates contained a crystalline elimination product mixture (0.524 g) which showed vinyl hydrogen absorption (infrared and nmr) but was not further characterized. Later eluates (>2% ethanol) provided 0.758 g (55%) of a pure (tlc) crystalline product which was recrystallized from 50% ethanol–water giving 0.566 g of estr-5(10)-ene-3β,17β-diol-3-formate, 17-propionate: mp 93–94°, $[\alpha]_D$ +80°, τ 1.97 (formate proton).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.18; H, 8.97.

Estr-5(10)-ene-3β,17β-diol 17-Propionate (IIc) by Formate Displacement.—The 3α-mesylate (1.503 g) was again treated with tetraethylammonium formate as above. The crude product was boiled for 30 min with methanol (110 ml) containing 11 ml of saturated aqueous sodium bicarbonate. Removal of solvent and extraction with benzene gave a hydrolysis product mixture which was chromatographed on 60 g of Woelm alumina, activity III. Elution with benzene gave 0.514 g of a ring-A diene mixture. Later eluates (2–3% ether) gave 0.664 g (55%) of pure (tlc) 3β-alcohol IIc, mp 117–119° alone or admixed with an authentic sample.

3α-Azido-5(10)-estren-17β-ol Propionate (XIb).—To a solution of the 3β-mesylate XIIa (0.200 g) in dry dimethylformamide (5.0 ml) was added sodium azide (0.200 g) and the reaction mixture was heated at 100° for 3 hr. Removal of solvent at reduced pressure left a residue which was taken up in water and benzene. The organic layer was washed with water, dried over magnesium sulfate, and freed of solvent leaving 0.170 g of an oil. Analysis by tlc revealed the presence of two components which were widely separated in mobility.

A portion (0.041 g) of the above mixture was applied to a large (40 × 20 cm) tlc plate coated with silica gel H. The plate was eluted using 50% benzene in hexane and, after drying, was eluted a second time in the same solvent mixture. The less polar zone was found to contain a mixture of ring-A dienes and was discarded. The more polar zone provided 0.026 g of 3α-azide, mp 38–54°, which showed only one spot on tlc. Additional material (0.053 g) having these characteristics was obtained by chromatographing the remaining reaction mixture on a column of alumina. The two azide fractions were combined and crystallized from methanol at −20°, giving 0.040 g of the 3α-azide XIb: mp 54–55°, $[\alpha]_D$ +118°, ν^{CS_2} 2090 cm^{-1} (azide).

Anal. Calcd for $C_{21}H_{31}O_2N_3$: C, 70.55; H, 8.74; N, 11.76. Found: C, 70.72; H, 8.56; N, 12.03.

3β-Azido-5(10)-estren-17β-ol Propionate (XIIb).—To a solution of the 3α-mesylate XIa (1.07 g) in dry dimethyl formamide (32 ml) was added sodium azide (1.07 g) and the reaction mixture was heated at 100° for 4 hr. Solvent was then removed at reduced pressure. The residue was extracted into benzene–ether (50%), washed with water, dried, and concentrated. This left a solid which was crystallized from methanol, giving the α-azide XIIb (0.574 g), mp 70–74°. An additional recrystallization from methanol gave the analytical sample: mp 75–76°, $[\alpha]_D$ +68°, ν^{CS_2} 2090 cm^{-1} (azide).

Anal. Calcd for $C_{21}H_{31}O_2N_3$: C, 70.55; H, 8.74; N, 11.76. Found: C, 70.75; H, 8.95; N, 11.63.

An nmr spectrum of this material (Figure 3) indicated that it was contaminated to a small extent with the 3β epimer. A further recrystallization from methanol did not alter the product composition. Chromatographic separation did not seem feasible since the epimeric azides have identical tlc mobilities.

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