Anal. Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 74.32; H, 10.57.

Reduction of 4α,5-diacetoxycholestan-3β-ol with lithium aluminum hydride in the usual manner gave cholestan-3β,-4α,5-triol, m.p. 212–214°, undepressed by triol prepared by direct reduction of the α-diolone III.

Reduction of 4β,5-Diacetoxycoprostan-3-one with Sodium Borohydride.—In the manner described above 0.85 g. of this diacetoxy ketone was reduced with sodium borohydride to give **4β,5-diacetoxycoprostan-3α-ol** (tentative assignment[19] at 3), m.p. 163–166°.

Anal. Calcd. for $C_{31}H_{52}O_5$: C, 73.76; H, 10.38. Found: C, 73.56; H, 10.47.

Reduction of 4β,5-diacetoxycoprostan-3α-ol with lithium aluminum hydride in the usual manner gave coprostan-3α,-4β,5-triol, m.p. 81–82°, undepressed by triol prepared by direct reduction of the β-diolone II.

Reduction of 4β-Acetoxy-5-hydroxycholestan-3-one with Sodium Borohydride.—A suspension of 1.80 g. of this ketone in a solution of 0.5 g. of sodium borohydride in 45 ml. of methanol and 5 ml. of water was stirred for seven minutes and then diluted with dilute hydrochloric acid. After the evolution of hydrogen ceased the acidic mixture was extracted with ether, which was in turn washed with aqueous sodium bicarbonate, dried and evaporated. The residue was recrystallized from ethanol to give **4α-acetoxycholestan-3β,5-diol** (tentative assignment[19] at 3), m.p. 207–208°.

Anal. Calcd. for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.29; H, 10.82.

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KNOXVILLE, TENN.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. CXII.[1] Cycloethylene Ketal Formation of 19-Nor-Δ^4-3-keto Steroids

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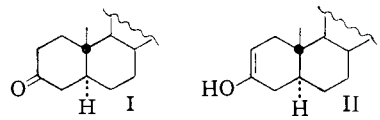
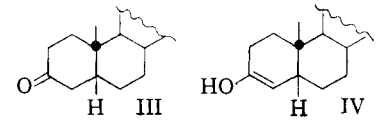
Cycloethylene ketal formation in the 19-nor-Δ^4-3-keto steroid series has been shown to produce a mixture of isomeric Δ^5 and $\Delta^{5(10)}$-3-cycloethylene ketals. The structure proofs for these double bond isomers were accomplished *via* epoxidation followed by fission of the epoxides with boron trifluoride. The resulting ketal fluorohydrins were then degraded to known or readily identified products. The results not only permit the unambiguous location of the double bonds but also provide a complete description for the stereochemistry of the intermediate epoxides.

In connection with another problem, we have had occasion to investigate the formation of 3-cycloethylene ketals in the 19-nor steroid series and now report some of our findings.

The fact that the formation of 3-cycloethylene ketal derivatives in the 10-methyl-Δ^4-3-ketone system results in rearrangement of the double bond to the Δ^5-position has been known[2] for some time. More recently the mechanism of the reaction has received attention[3] and the conclusion reached was that the isomerization resulted from the intermediate formation of a $\Delta^{3,5}$-enol ether type compound.

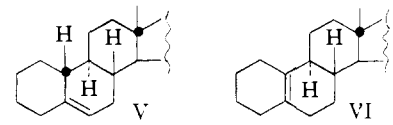
While the isomerization of the double bond was expected to occur in the 19-nor steroid series it was evident that such an isomerization could now lead to Δ^5- and/or $\Delta^{5(10)}$-cycloethylene ketal isomers. Several considerations must be taken into account in predicting the preferred position for the double bond in such cases. For example, it is known[4] that bromination of 3-keto allo steroids I leads to 2-bromo compounds, thus indicating that in the A/B *trans* series the enolic double bond is more stable in the Δ^2-position II. On the other hand, bromination and sulfonation evidence shows that in A/B *cis* steroids (III) the 3-4 position of the enolic double bond (IV) is favored.





It follows that the nature of the ring junction has an important bearing on the position for the double bond.

If these observations are now applied to the 19-nor steroid series and the B/C *trans* ring junction is equated to the A/B *trans* decalone type junction I, it might be expected that a double bond would be more stable in the Δ^5-position V rather than in the $\Delta^{5(10)}$-position VI.



Mediating against this conclusion are two factors, the first of which is that the nor steroid V does not accurately approximate the model I, since it is reasonable to expect that ring A will conformationally modify the double bond stability at Δ^5. Secondly, it is known that octalin-type double bonds are more stable when in the tetrasubstituted Δ^9-position, as may be witnessed by an interesting report[5] quantitatively describing the equilibria involved. As will be seen in the sequel, both of the possible positional isomers were obtained during the ketalization reaction.

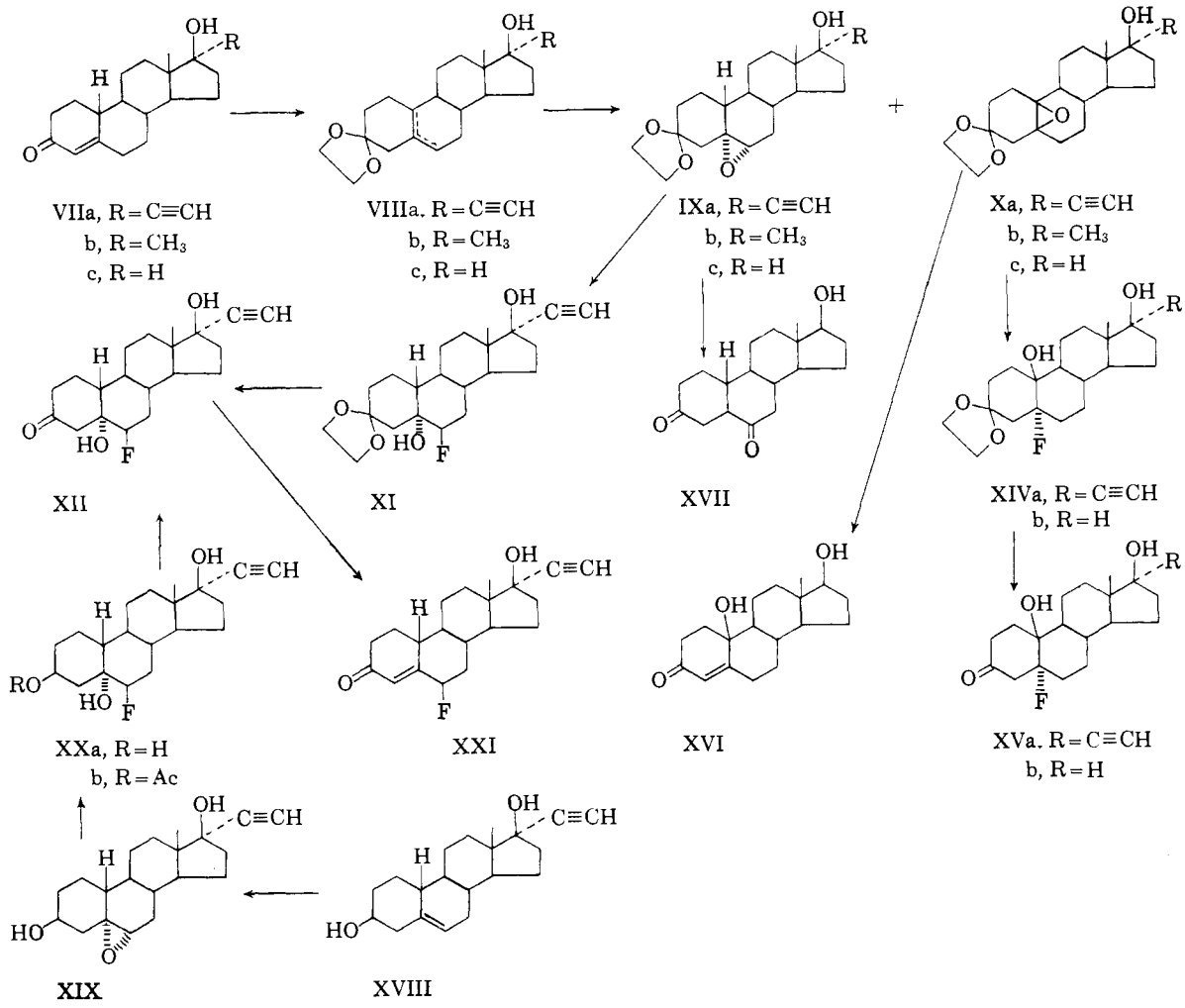
(1) Paper CXI, A. Bowers and H. J. Ringold, THIS JOURNAL, **81**, 1264 (1959).

(2) (a) F. Fernholz and H. E. Stavely, abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, N. J., 1941, p. 39 M; see also E. Fernholz, U. S. Patents 2,356,154 and 2,378,918; (b) R. Antonucci, S. Bernstein, R. Littell, K. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952); (c) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(3) C. Djerassi and M. Gorman, *ibid.*, **75**, 3704 (1953).

(4) A. Butenandt and A. Wolff, *Ber.*, **68B**, 2091 (1935).

(5) W. G. Dauben, E. C. Martin and G. J. Fonken, *J. Org. Chem.*, **23**, 1205 (1958).



Thus when the 19-nor-Δ^4-3-ketones, VIIa,[6a] b,[6a] c,[6b] were treated under the usual conditions for ethylene ketal formation, the total crude reaction products were always obtained noncrystalline and on the basis of their low ultraviolet absorption maxima appeared to be 90–95% converted to the 3-cycloethylene ketals. From these gums by careful chromatography in each of the three cases, only a single pure compound VIII could be isolated and it has been necessary to express its formula either as a Δ^5- or $\Delta^{5(10)}$-isomer since the small amounts of the pure compounds available precluded the possibility of structure proofs. It was, however, readily apparent that either of the structural forms was possible, since on epoxidation of the total crude ketalization products there always resulted two isomeric epoxides IX and X.

At this point it may be pertinent to mention that the formation of the 3-cycloethylene ketal of 17α-methyl-19-nortestosterone (VIIb) proceeded without dehydration at C-17, since the epoxides IXb and Xb were obtained in fair over-all yields based on the starting ketone VIIb. This point becomes of interest in view of the report[7] that attempts to form the 3-cycloethylene ketal of 17α-methyltestosterone resulted in dehydration of the 17β-hydroxy group.

In order to prove the structures of the epoxides IX and X the main effort was concentrated on the 19-nortestosterone VIIc[6b] and 17α-ethynyl-19-nortestosterone (VIIa)[6a] cases, since in these series most of the final products of the proposed structure proofs were already known. Thus in the 19-nortestosterone case it was found that the epoxide IXc on treatment first with perchloric acid to effect epoxide fission, followed by strong alkaline dehydration and rearrangement,[8] led to a product whose analytical data and infrared spectrum indicated the structure of 3,6-diketo-19-norandrostane-17β-ol (XVII). Indeed, the agreement of the physical constants with those in the literature[9] leaves little doubt that structure XVII is correctly assigned. It now logically followed that XVII could only arise from a 5,6-epoxide although the stereochemistry of the epoxide had not yet been established.

With regard to the isomeric epoxide Xc, it was allowed to react with boron trifluoride under condi-

(6) (a) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954); (b) A. J. Birch, *J. Chem. Soc.*, 367 (1950); A. L. Wilds and N. A. Nelson, THIS JOURNAL, **75**, 5366 (1953).

(7) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957); however, J. A. Campbell, J. C. Babcock and J. A. Hogg, THIS JOURNAL, **80**, 4717 (1958), report a 75% yield of the ketal of 17α-methyltestosterone.

(8) B. Ellis and V. A. Petrow, *J. Chem. Soc.*, 1078 (1939).

(9) R. L. Pederson, J. A. Campbell, J. C. Babcock, S. H. Eppstein, H. C. Murray, A. Weintraub, R. C. Meeks, P. D. Meister, L. M. Reineke and D. H. Peterson, THIS JOURNAL, **78**, 1512 (1956).

tions which are already known[10] to give the fluorohydrins of 5,6- and 5(10)-epoxides. By this means there was obtained the fluorohydrin XIVb which upon treatment with perchloric acid in tetrahydrofuran[2c] was smoothly converted to the 5α-fluoro-10β-hydroxy-3-ketone (XVb). This same compound was recently prepared in this Laboratory[10c] by an unambiguous route and a comparison of the samples showed them to be completely identical. Furthermore, since the structure of XVb was proved[10c] by base-catalyzed dehydrofluorination to 10β-hydroxy-19-nortestosterone (XVI), and since this same 10β-hydroxy compound has now been obtained directly from the 5,10-epoxy-3-ketal Xc by treatment with perchloric acid followed by dilute alkali, there can be no question that the epoxide Xc is correctly formulated as 5β,10β-oxido-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal.

There still remained the problem of stereochemical assignment to the 5,6-epoxides and this was accomplished by studying the isomeric epoxides IXa and Xa in the 17α-ethynyl series.

When the epoxide Xa was treated with boron trifluoride it provided the ketal fluorohydrin XIVa which was then hydrolyzed at C-3 to yield the known[10c] 5α-fluoro-17α-ethynyl-19-norandrostane-10β,17β,diol-3-one (XVa). The isolation of this compound characterized the epoxide Xa as 5β,10β-oxido-17α-ethynyl-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal.

The positionally isomeric epoxide IXa, when similarly treated, led to the fluorohydrin XI and upon hydrolysis of its ethylene ketal group it provided the fluorohydrin-3-one XII, whose constitution was demonstrated as follows:

Starting with 17α-ethynyl-Δ^5-19-norandrostene-3β,17β-diol (XVIII)[11] and treating with monoperphthalic acid, there was isolated in 70–80% yield a single epoxide (XIX) which upon treatment with boron trifluoride was converted to 6β-fluoro-17α-ethynyl-19-norandrostane-3β,5α,17β-triol (XXa). The stereochemistry of XXa and hence of XIX, was clearly indicated by the fact that upon acetylation XXa provided only a 3-monoacetate (XXb) as shown by elemental analysis and acetyl determination. Had XXa been a 5β,6β-epoxide, it would have led to a 5α-fluoro-3β,6β-diol and it has already been shown[10a] that compounds of this type readily form diacetates.

Additional confirmation for the 5α-hydroxy-6β-fluoro structure was obtained by oxidation of the fluorohydrin XXa to the 3-keto-fluorohydrin XII which could then be dehydrated to provide 6β-fluoro-17α-ethynyl-19-nortestosterone (XXI). The structure of this latter compound was indicated by its elemental analysis, ultraviolet spectrum and characteristic[12] rotatory dispersion curve.

Since XII has been obtained both from the authentic 5α,6α-epoxide XIX as well as from the ketal epoxide IXa, it follows that IXa is correctly represented as 5α,6α-oxido-17α-ethynyl-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal.

While the stereochemistry of the 5α,6α-oxido-19-nortestosterone 3-cycloethylene ketal (IXc) was not proved rigorously as in the preceding case IXa, there appears to be no reason to assume that the epoxidation of its precursor would differ from that of the corresponding 17α-ethynyl analog IXa.

As shown in the Experimental section, the 5β,10β-epoxides X were less polar than the 5α,6α-epoxides IX in both the 19-nortestosterone and 17α-ethynyl-19-nortestosterone series. Applying this observation to the 17α-methyl-19-nortestosterone derivatives, one may assign to the less polar epoxide the structure 5β,10β-oxido-17α-methyl-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal (Xb) and to the more polar epoxide that of 5α,6α-oxido-17α-methyl-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal (IXb).

It is interesting to note that in the 5,6-position, the epoxide appears to be almost completely in the α-configuration whereas, in contrast, at the 5,10-position the β-epoxide is the sole product isolated.[10c] Considering that in the 19-nor steroids the relatively bulky 10β-angular methyl group has been replaced by hydrogen, it is perhaps surprising that a considerable quantity of the 5β,6β-epoxide is not formed. The possibility that a small amount of the 5β,6β-epoxide is contained in the epoxides mother liquors cannot be completely discounted since our recovery of the two pure epoxides IXa and Xa was only 67%. A suitable rationale for the predominant formation of the 5β,10β-epoxides rather than the epimeric 5α,10α-epoxides has already been presented in an earlier paper[10c] from these laboratories.

On the basis of the yields encountered for the isomeric epoxides IX and X, and assuming no 5β,6β-epoxide formation, it can be concluded that the ratio of $\Delta^{5(10)}$ and $\Delta^{5,6}$-3-cycloethylene ketals is in excess of two to one. This in turn suggests that the governing factor in the stability relationship is the higher degree of substitution as found in the $\Delta^{5(10)}$-isomer.

Experimental[13]

3-Cycloethylene Ketal of 17α-Ethynyl-19-nortestosterone (VIIIa).—To 150 ml. of benzene, 15 ml. of ethylene glycol and 2.00 g. of 17α-ethynyl-19-nortestosterone (VIIa),[6a] was added 0.10 g. of *p*-toluenesulfonic acid. The resulting mixture was then stirred under reflux for 14 hours using a water separator. After this time the solution was washed first with dilute aqueous sodium bicarbonate, then water and finally dried over sodium sulfate and evaporated. There remained 1.8 g. of gum, λ_{max}^{EtOH} 244 mμ, log ε 2.77, which was chromatographed on 35 g. of neutral alumina. Elution with benzene–ether provided 0.3 g. of crystals (m.p. 140–150°) which were repeatedly recrystallized from ether–hexane to furnish the analytical sample, m.p. 163–165°, $[\alpha]_D$ −27°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.50; H, 8.85.

Similarly prepared were: **3-cycloethylene ketal of 17α-methyl-19-nortestosterone** (VIIIb), m.p. 124–126°, $[\alpha]_D$ +61°, recrystallized from ether–hexane.

(10) (a) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957); (b) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958); (c) J. Perez Ruelas, J. Iriarte, F. Kincl and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(11) J. Iriarte, C. Djerassi and H. J. Ringold, THIS JOURNAL, **81**, 436 (1959).

(12) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958), record the optical rotatory dispersion curves of 6α- and 6β-fluorotestosterone.

(13) All melting points are uncorrected and the rotations have been determined in chloroform unless otherwise stated. The infrared spectra of all compounds have been recorded and are in accord with the proposed structures. We are indebted to Dr. Lewis J. Throop and staff for all rotations and spectral determinations.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.46; H, 9.72.

3-Cycloethylene ketal of 19-nortestosterone (VIIIc), m.p. 133–136°, $[\alpha]D$ +19°, recrystallized from ether–acetone.

Anal. Calcd. for $C_{20}H_{30}O_3.2.5C_3H_6O$: C, 71.24; H, 9.78. Found: C, 71.26; H, 9.65.

5β,10β- and 5α,6α-Oxides of 17α-Ethynyl-19-nortestosterone 3-Cycloethylene Ketal (Xa and IXa).—The total crude product from a ketalization of 15 g. of 17α-ethynyl-19-nortestosterone was dissolved in 400 ml. of chloroform and chilled to 0°. An ethereal solution of monoperphthalic acid (400 ml. of 0.9 *N*) was then added and after the mixture had been kept at 0° overnight it was made alkaline with 5% aqueous sodium carbonate. The resulting solution was then washed with water, dried over sodium sulfate and evaporated to leave 17 g. of gum. Upon fractional crystallization from acetone there was obtained in three crops 3.05 g. of crystals, m.p. 275–285°, which following further recrystallization from the same solvent provided 2.85 g. of the pure 5α,6α-epoxy-3-cycloethylene ketal (IXa), m.p. 290–293°, $[\alpha]D$ −52°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.29; H, 8.42.

By further fractional crystallization from acetone, 4.70 g., m.p. 205–208°, of almost pure 5β,10β-epoxy-3-cycloethylene ketal (Xa) was obtained. Following recrystallization from acetone, the analytical sample was obtained, m.p. 209–211°, $[\alpha]D$ ±0°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; O, 17.85. Found: C, 73.78; H, 8.31; O, 18.00.

When the total mother liquors from the above samples were combined and adsorbed on 250 g. of silica, elution with benzene–ether (4:1) produced 6.5 g. of gum which was easily crystallized from acetone to provide an additional 2.00 g., m.p. 204–208°, of the 5β,10β-epoxide Xa, for a total yield of 6.70 g., 43%. Further elution with the same solvent pair then provided 0.83 g. of crystals which after recrystallization from acetone gave 0.73 g. of pure 5α,6α-epoxide IXa. The total yield for this isomer was then 3.68 g., 24%.

By identical procedures the following epoxides were also prepared:

5β,10β-Oxido-17α-methyl-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal (Xb): eluted from silica with benzene–ether (4:1) and recrystallized from ether, m.p. 169–171°, $[\alpha]D$ ±0°. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.46; H, 9.16.

5α,6α-Oxido-17α-methyl-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal (IXb): eluted from silica with benzene–ether (4:1, 3:2) and recrystallized from ether, m.p. 205–207°, $[\alpha]D$ −38°. *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.57; H, 9.20; O, 18.34.

5β,10β-Oxido-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal (Xc): eluted from silica with benzene–ether (3:2) and recrystallized from ether, m.p. 167–169°, $[\alpha]D$ +21°. *Anal.* Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; O, 19.14. Found: C, 71.98; H, 9.10; O, 19.22.

5α,6α-Oxido-19-norandrostane-17β-ol-3-one 3-cycloethylene ketal (IXc): eluted from silica with benzene–ether (3:2, 1:1) and recrystallized from ether, m.p. 81–83°, $[\alpha]D$ −4°. *Anal.* Calcd. for $C_{20}H_{30}O_4.{}^1/_2H_2O$: C, 69.94; H, 9.10; O, 20.96. Found: C, 69.43; H, 9.00; O, 21.44.

5α-Fluoro-17α-ethynyl-19-norandrostane-10β,17β-diol-3-one 3-Cycloethylene Ketal (XIVa).—A solution (300 ml.) of anhydrous ether–benzene (1:1) containing 2.00 g. of the 5β,10β-epoxide Xa and 2.0 ml. of freshly distilled boron trifluoride etherate was allowed to stir for 3.5 hours at room temperature. After this time the mixture was filtered from a crystalline residue, 0.45 g., m.p. 160–165° dec., and the filtrate was washed neutral with water, dried over sodium sulfate and concentrated to provide a second crop of crystals, 0.49 g., m.p. 178–181°. These crystalline fractions were combined and after repeated recrystallization from benzene provided the analytical sample, m.p. 214–215°, $[\alpha]D$ −26°.

Anal. Calcd. for $C_{22}H_{31}O_4F.{}^1/_4C_6H_6$: C, 70.74; H, 8.21; F, 4.76. Found: C, 70.59; H, 8.33; F, 4.67.

5α-Fluoro-17α-ethynyl-19-norandrostane-10β,17β-diol-3-one (XVa).—Five ml. of tetrahydrofuran containing 0.23 g. of the 5α-fluoro-10β-hydroxy compound XIVa was treated with 3 ml. of 3 *N* perchloric acid and allowed to stand at room temperature for 3 hours. It was then diluted with 15 ml. of water and the resulting crystals (0.2 g., m.p. 263–267°) were collected. After recrystallization from methanol–benzene the crystals exhibited, m.p. 250–255°, $[\alpha]D$ −22° (methanol), and while the melting point was not easily reproducible, the compound was shown to be completely identical with an authentic sample[10c] of XVa on the basis of mixture melting points and infrared spectra comparisons.

5α-Fluoro-19-norandrostane-10β,17β-diol-3-one 3-Cycloethylene Ketal (XIVb).—Under the fluorinating conditions described above, 0.80 g. of the 5β,10β-epoxide Xc was converted to its fluorohydrin XIVb. The crystalline product, 0.29 g. which was obtained by chromatography was purified by recrystallization from benzene, m.p. 157–158°, $[\alpha]D$ +9°.

Anal. Calcd. for $C_{20}H_{31}O_4F$: C, 67.76; H, 8.81; F, 5.36. Found: C, 67.99; H, 8.84; F, 5.77.

5α-Fluoro-19-norandrostane-10β,17β-diol-3-one (XVb).—The hydrolysis of the 5α-fluoro-10β-hydroxy-3-cycloethylene ketal (XIVb) was carrried out by the previously described method to yield the 5α-fluoro-10β-hydroxy-3-onc XVb, m.p. 217–220°. The identity of this compound was confirmed by mixture melting point and infrared spectral comparison with an authentic sample[10c] (m.p. 215–217°).

10β-Hydroxy-19-nortestosterone (XVI).—Approximately 0.10 g. of the 5β,10β-epoxy-3-cycloethylene ketal (Xc) was dissolved in 2 ml. of tetrahydrofuran and treated with 2 ml. of 3 *N* perchloric acid. After 3 hours at room temperature, the mixture was diluted with water, extracted with chloroform and the extracts washed neutral with water. After evaporation, the residue was heated at reflux temperature for 45 minutes in 10 ml. of 5% methonolic potassium hydroxide. The solution was then diluted with water, chloroform extracted and the extracts washed neutral. After drying and evaporation, the residue was recrystallized from acetone to yield 0.02 g. of crystals, m.p. 216–218°, which were identical with authentic[10c] 10β-hydroxy-19-nortestosterone by mixture melting point and infrared spectral comparison.

19-Norandrostane-17β-ol-3,6-dione (XVII).—Employing the conditions described in the preceding experiment, 200 mg. of crude 5α,6α-oxido-19-norandrostane-17β-ol-3-one cycloethylene ketal (IXc) contaminated with some of the 5β,10β-epoxide Xc provided, after the alkaline hydrolysis stage, 150 mg. of gum which was chromatographed on 3 g. of neutral alumina. By elution with benzene–ether (4:1) there was obtained 50 mg. of gummy crystals which after crystallization from acetone–hexane gave 28 mg., m.p. 80–85°. Upon further recrystallization the final sample was obtained, m.p. 82–87°, then resolidifying with m.p. 141–143°, $[\alpha]D$ −22° (methanol); λ_{max}^{KBr} 2.89, 5.88 μ; lit.[9] m.p. 145–146°, $[\alpha]D$ −14° (methanol).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 74.44; H, 9.03. Found: C, 74.35; H, 8.69.

Further elution of the column with the same solvent afforded 60 mg. of a gum. Several recrystallizations then led to 10β-hydroxy-19-nortestosterone (XVI), m.p. 213–216°, which arose from the 5β,10β-epoxide Xc.

6β-Fluoro-17α-ethynyl-19-norandrostane-5α,17β-diol-3-one 3-Cycloethylene Ketal (XI).—From 1.5 g. of the 5α,6α-epoxy-3-cycloethylene ketal IXa under the previously described reaction conditions there was obtained 0.45 g. of XI which was recrystallized from ether; m.p. 210–212°, $[\alpha]D$ −84°.

Anal. Calcd. for $C_{22}H_{31}O_4F$: C, 69.85; H, 8.25; F, 5.00. Found: C, 69.93; H, 8.40; F, 5.03.

6β-Fluoro-17α-ethynyl-19-norandrostane-5α,17β-diol-3-one XII. (a) From the Ketal XI.—By the perchloric acid–tetrahydrofuran hydrolysis method previously described, 0.38 g. of the above ketal XI led to 0.30 g. of crystals, which after six recrystallizations from ether–acetone yielded the analytical sample of XII, m.p. 265–267°, $[\alpha]D$ −22°.

Anal. Calcd. for $C_{20}H_{27}O_3F$: C, 71.82; H, 8.13; F, 5.68. Found: C, 71.24; H, 8.12; F, 5.66.

(b) **From 3β-Hydroxyfluorohydrin XXa.**—To 20 ml. of pure acetone containing 0.75 g. of 6β-fluoro-17α-ethynyl-19-norandrostane-3β,5α,17β-triol (XXa) was added 1.3 ml. of

chromium trioxide–sulfuric acid reagent.[14] The mixture was kept at 0° for 7 minutes, then diluted with 30 ml. of salt water. Chloroform extraction followed by washing until neutral, drying and evaporation provided 0.65 g. of gummy crystals which after recrystallization from ethyl acetate gave 0.36 g., m.p. 240–245°. Several further recrystallizations from ether–acetone led to the pure sample, m.p. 265–267°, $[\alpha]_D$ −21°. Mixture melting points and infrared comparison established identity of this compound with a specimen prepared according to (a).

5α,6α-Oxido-17α-ethynyl-19-norandrostane-3β,17β-diol (XIX).—To one liter of chloroform containing 13.8 g. of 17α-ethynyl-Δ⁵-19-norandrostene-3β,17β-diol (XVIII)[11] was added one liter of a 0.5 *N* ether monoperphthalic acid solution. After being kept in a refrigerator for 20 hours the mixture was washed with cold aqueous sodium bicarbonate followed by water. After drying and evaporation there remained 13 g. of a white froth which was crystallized from ether–acetone to provide 8.70 g., m.p. 198–200°. By chromatography of the mother liquors on 100 g. of neutral alumina an additional 0.85 g. was obtained. Recrystallization from ether–acetone yielded the analytical sample, m.p. 202–205°, $[\alpha]_D$ −63°.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.95; H, 8.93; O, 15.45.

6β-Fluoro-17α-ethynyl-19-norandrostane-3β,5α,17β-triol (XXa).—By the method previously described 1.3 g. of the 5α,6α-epoxy-3β-ol (XIX) was treated with boron trifluoride to yield 0.76 g., m.p. 225–230°. Recrystallization from ether–acetone provided the pure sample m.p. 244–246°, $[\alpha]_D$ −54°.

Anal. Calcd. for $C_{20}H_{29}O_3F$: C, 71.39; H, 8.69; F, 5.64. Found: C, 70.89; H, 8.62; F, 5.49.

6β-Fluoro-17α-ethynyl-19-norandrostane-3β,5α,17β-triol 3-acetate (XXb) was prepared from XXa under the usual acetylating conditions of pyridine and acetic anhydride at room temperature for 15 hours. The resulting product obtained in 95% yield was recrystallized several times from acetone, m.p. 250–252°, $[\alpha]_D$ −52°.

Anal. Calcd. for $C_{22}H_{31}O_4F$: C, 69.81; H, 8.25; O-acetyl, 11.38. Found: C, 69.27; H, 7.99; O-acetyl, 11.57.

6β-Fluoro-17α-ethynyl-19-nortestosterone (XXI).—To 25 ml. of acetic acid containing 1.0 g. of the ketofluorohydrin XII was added 2.0 ml. of concentrated hydrochloric acid. After 65 min. at room temperature, the mixture was diluted with 60 ml. of ice-water and the resulting crystals were collected and washed almost to neutrality with water. Drying in air then provided 0.65 g. of tan crystals which were adsorbed on 20 g. of neutral alumina. By benzene elution there was obtained 0.24 g. of crystals which were repeatedly recrystallized from methanol to provide the analytical sample, m.p. 184–187°; λ_{max}^{EtOH} 234 mμ, log ε 4.10; R.D., *c* 0.059 (dioxane): $[\alpha]_{700}$ −54.7°, $[\alpha]_{589}$ −113°, $[\alpha]_{365}$ −1285°, $[\alpha]_{310}$ +556°, $[\alpha]_{305}$ +25.7°.

Anal. Calcd. for $C_{20}H_{25}O_2F$: C, 75.92; H, 7.96. Found: C, 75.58; H, 8.00.

APARTADO POSTAL 2679. MEXICO, D. F.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Stereospecific Syntheses of 11-Deuterated Steroids

BY E. J. COREY AND G. A. GREGORIOU[1]

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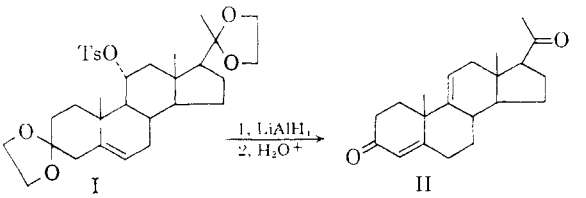
The synthesis of pregnane-3,20-dione-11β-*d* has been accomplished by the sequence: pregnane-3,11,20-trione → pregnane-3,11,20-trione-3,20-bis-ethylene ketal → pregnane-3,20-dione-11β-ol-11α-*d*-3,20-bis-ethylene ketal ($LiAlD_4$) → $\Delta^{9:11}$-pregnene-3,20-dione-11-*d* ($POCl_3$–C_5H_5N, followed by HOAc) → pregnane-3,20-diol-11β-*d* (Pt, H_2, HOAc followed by deacetylation with $LiAlH_4$) → pregnane-3,20-dione-11β-*d* (CrO_3–HOAc). Pregnane-3,20-dione-9α,11α,12α-$d_{2.8}$ has been prepared by the route: $\Delta^{9:11}$-pregnene-3,20-diol ($LiAlH_4$) → pregnane-3,20-diol-9α,11α,12α-$d_{2.80}$ (D_2, DOAc, Pt) → pregnane-3,20-dione-9α,11α,12α-$d_{2.80}$ (CrO_3).

Recently we have determined the stereochemical course of the enzyme-catalyzed hydroxylation of steroids at C_7 or C_{11} through the use of compounds labeled stereospecifically with deuterium or tritium at those positions,[2,3] and in the preceding paper the methods employed for the synthesis of 7-labeled steroids have been described. This article is concerned with another part of this work, the synthesis of epimeric 11-deuterated pregnane-3,20-diones.

At the outset two methods seemed worthy of consideration for the stereospecific introduction of hydrogen isotope at C_{11}—nucleophilic displacement by hydride and addition of hydrogen to a $\Delta^{9:11}$- or $\Delta^{11:12}$-olefin. It was anticipated that application of the former approach to 11β-substituted steroids would result in the occurrence of elimination, either during attempts to prepare reactive derivatives for displacement, or during the reaction with nucleophile. Consequently, displacement was first studied with a reactive 11α-substituted compound, progesterone bisethylene ketal 11α-toluenesulfonate (I). Attempts to replace toluenesulfonate in I by hydrogen using lithium aluminum hydride in ether were unsuccessful, however, due to rapid elimination, and $\Delta^{9:11}$-dehydroprogesterone (II) was isolated in 60% yield after acid hydrolysis. Because elimination proceeded so readily and because it was clear that displacement of an 11α-toluenesulfonate from the backside would be retarded enormously by the angular methyl groups (C_{18} and C_{19}), no further studies were made of the displacement approach.



I II

The strong shielding of the β-side of C_{11} by the angular methyl groups is a highly desirable effect in the introduction of hydrogen isotope at C_{11} by an addition process and this was exploited in the successful syntheses of 11α- and 11β-labeled preg-

(1) Alfred P. Sloan Foundation Fellow 1956–1958.

(2) S. Bergstrom, S. Lindstedt, B. Samuelsson, E. J. Corey and G. Gregoriou, THIS JOURNAL, **80**, 2337 (1958).

(3) E. J. Corey, G. A. Gregoriou and D. H. Peterson, *ibid.*, **80**, 2338 (1958).