[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., MEXICO, D. F., MEX.]

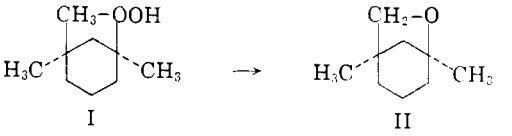
Steroids. CXLIII.[1] Transannular Reactions at Saturated Carbon Atoms. Part 1. C-3,9-Oxide Formation

BY A. BOWERS AND E. DENOT

RECEIVED NOVEMBER 30, 1959

The action of lead tetraacetate on a variety of steroid secondary alcohols has been investigated. Three different reaction pathways have been discerned, the nature of the product being dependent on the environment of the alcohol.

Two recent publications have demonstrated the controlled intramolecular attack by cationic oxygen on a suitably orientated methyl group. Corey and White[2] reported the conversion of 1,3,3-trimethyl cyclohexyl peroxide (I) into the bicyclic ether II by treatment with *p*-nitrobenzenesulfonyl



I II

chloride in pyridine. Shortly afterward Cainelli, Mihailovic, Arigoni and Jeger[3] showed that treatment of pregnane-3β,20β-diol 3-acetate (III) with lead tetraacetate in benzene solution under reflux led to oxygenation of the C-18 methyl group by formation of the C-18,20-oxide (IV).

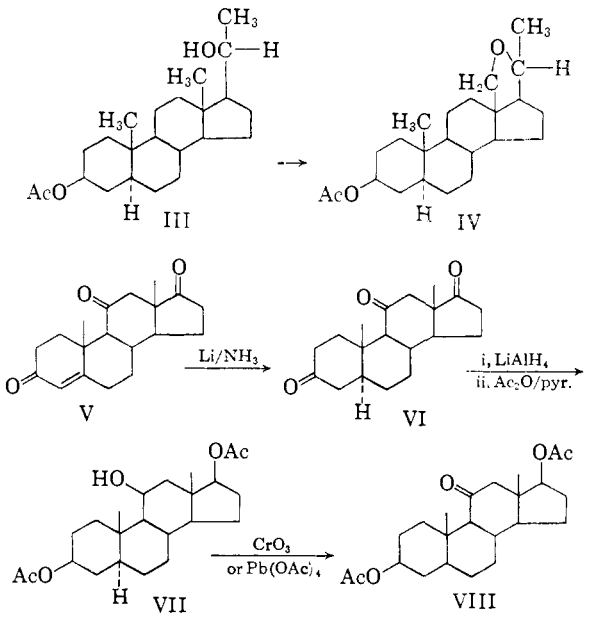


FIG. 1.

The Swiss work in particular indicated a potential use of this type of reaction for a partial synthesis of aldosterone[4] since it offered a solution to the most difficult phase of such a project, namely C-18 oxygenation.

Along these lines an investigation was initiated to examine the possibility that an 11β-hydroxyl group might enter into a reaction of this type. Although it is 1:3-diaxially oriented with respect to both the C-19 and C-18 angular methyl groups, molecular models show that the strain inherent in a *trans*-hydrindane system (rings C and D) is such that the C-18 methyl group is not perfectly perpendicular to the plane of ring C but is nearer to the axial 11β-hydroxyl group than is the C-19 methyl group. As such, C-18 might be expected to be the preferred site of attack by 11β-orientated cationic oxygen.

A suitable compound to study this reaction was 5α - androstane - 3β,11β,17β - triol 3,17 - diacetate (VII, Fig. 1), a product readily obtained by a three-step sequence from andrenosterone (V).[5] The first stage in the conversion of V into VII was the stereospecific reduction of the double bond with lithium in liquid ammonia using ammonium chloride as a proton source.[6] The crude reaction product was then treated with 8 *N* chromic acid in acetone solution[7] to oxidize back to the ketone any secondary alcohols which may have been formed by "over reduction." Alumina chromatography then furnished 5α-androstane-3,11,17-trione (VI).[8] Lithium aluminum hydride reduction of VI in tetrahydrofuran solution followed by a room temperature acetylation with acetic anhydride in pyridine afforded the triol diacetate VII. In the infrared VII had bands at 3450 cm.$^{-1}$ (-OH) and 1735 and 1250 cm.$^{-1}$ (acetate). Oxidation of VII with 8 *N* chromic acid[7] gave the known 11-keto 3,17-diacetate (VIII).[9]

A benzene solution of the 11β-hydroxy-3,17-diacetate VII was then treated with an excess of lead tetraacetate under reflux for 16 hours. Careful chromatography of the reaction mixture led only to the isolation of one product, 5α-androstane-3β,17β-diol-11-one diacetate (VIII) identical with the product obtained previously from the chromic acid oxidation of VII. No trace of an oxide was found.

(1) Steroids. CXLII. A. Bowers, E. Denot and R. Becerra, THIS JOURNAL, **82**, 4007 (1960).

(2) E. J. Corey and R. W. White, *ibid.*, **80**, 6686 (1958).

(3) G. Cainelli, M. Lj. Mihailovic, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959).

(4) A partial synthesis of aldosterone from a naturally occurring steroid has not yet been reported although several total syntheses are known; *cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 713-720. ADDED IN PROOF.—Two partial syntheses of aldosterone have been reported recently, *cf.* (a) K. Heusler, J. Kalvoda, C. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni and O. Jeger, *Experientia*, **16**, 21 (1960); (b) D. H. R. Barton and J. M. Beaton, THIS JOURNAL, **82**, 2641 (1960).

(5) Prepared by the oxidative degradation of cortisone; *cf.* T. Reichstein, *Helv. Chim. Acta*, **19**, 1107 (1936).

(6) For analogous reductions of C-19 nor-Δ^4-3-ketones, *cf.* A. Bowers, H. J. Ringold and E. Denot, THIS JOURNAL, **80**, 6115 (1958); see also F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2695 (1952).

(7) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *ibid.*, 2548 (1953).

(8) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942).

(9) H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger and O. Jeger, *ibid.*, **35**, 295 (1952).

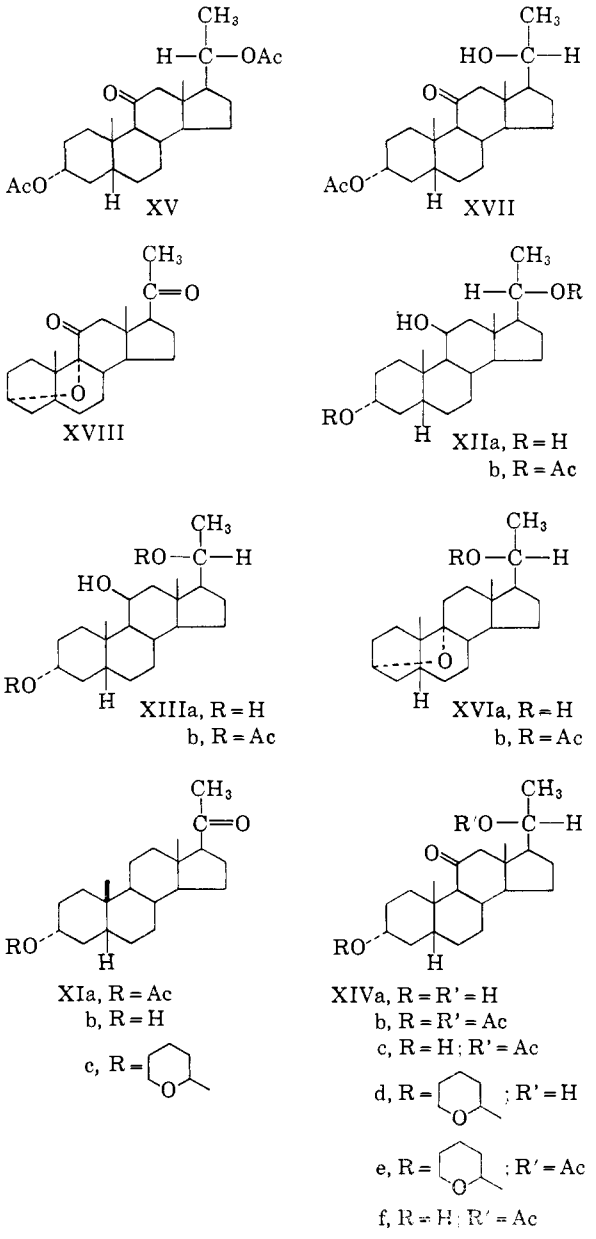
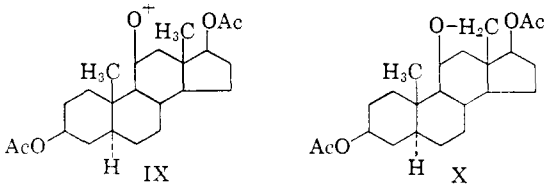


FIG. 2.

Assuming a heterolytic process,[21] two reaction courses are open to the transient cation IX. One



would be to behave in an analogous manner to the C-20β-hydroxyl group[3] and attack one of the angular methyl groups to form an oxide such as X. The alternate and preferred pathway is to lose the C-11α-hydrogen as a proton and form the C-11 ketone. Undoubtedly the gain in energy associated with ketone formation due to the release of steric compression is the governing factor. Parallel experiments in the pregnane series led to similar findings. Lithium aluminum hydride reduction of 5β-pregnane-3α-ol-11,20-dione acetate[10] (XIa, Fig. 2) led to a mixture of triols (XIIa and XIIIa), epimeric at C-20, from which 5β-pregnane-3α,11β,20β-triol (XIIIa)[11] was isolated in 72% yield. Acetylation of XIIIa under mild conditions led to 5β-pregnane-3α,11β,20β-triol 3,20-diacetate (XIIIb).[11,12] This compound was then treated with lead tetraacetate under reflux in benzene solution and the only product which could be identified was the C-11-ketone (XIVb)[11-13] identical with the product obtained by oxidation of XIIIb with 8 *N* chromic acid in acetone solution. Similar results were obtained when the lead tetraacetate reaction was carried out in tetrahydrofuran or methylene dichloride solution.

Mild acetylation of the mother liquors from the preparation of XIIIa (rich with the C-20α-epimer XIIa) and fractional crystallization of the product afforded 5β-pregnane-3α,11β,20α-triol 3,20-diacetate (XIIb).[14] Again, treatment with lead tetraacetate led only to oxidation of the hydroxyl group to furnish the C-11-ketone diacetate XV.[15]

The action of lead tetraacetate on 5β-pregnane-3α,20β-diol-11-one (XIVa)[16] and 5β-pregnane-3α,-11β,20β-triol (XIIIa)[11] was then investigated. Since it has already been established that 11β-alcohols are oxidized to the corresponding ketones, it was of interest to determine (a) whether C-20, 18-oxide formation[3] occurred in the presence of an oxygen function in ring C (11β-alcohol or 11-ketone) and (b) the effect of lead tetraacetate on a C-3α-hydroxyl group. The results were interesting and partly unexpected.

The keto-diol XIVa was readily obtained by alkaline hydrolysis of the diacetate XIVb and a suspension in benzene was heated under reflux with twice its weight of lead tetraacetate for 18 hours. Crystallization of the product led to the recovery of starting material in 20% yield and alumina chromatography of the mother liquors indicated that a complex mixture of products had been formed from which two pure products were isolated in low yield. The least polar product toward alumina (XVIa) exhibited strong bands in the infrared at 3650 (hydroxyl), 1705 (ketone) and 1000 cm.$^{-1}$ (ether linkage). Elemental analysis was in agreement with the formulation of XVIa as a monohydroxy-keto-oxide $C_{21}H_{32}O_3$ and it readily formed a *monoacetate* upon treatment with acetic anhydride in pyridine solution. In view of the Swiss workers results[3] this compound was originally considered to be 18,20β-oxidopregnane-3α-ol-11-one. However, treatment with chromium trioxide in acetic acid under conditions known[3] to oxidize

(10) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944).

(11) E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **75**, 488 (1953).

(12) L. H. Sarett, *ibid.*, **70**, 1690 (1948).

(13) L. H. Sarett, *ibid.*, **71**, 1169 (1949).

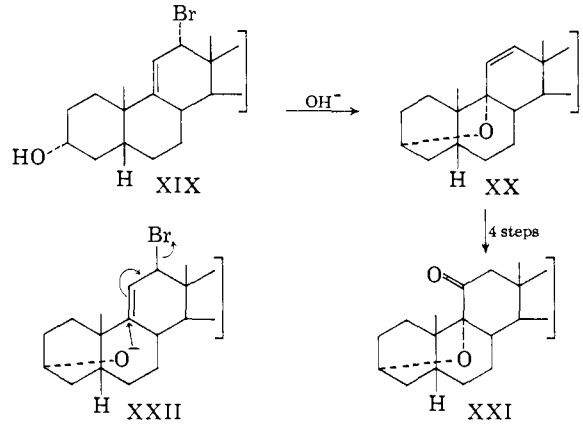
(14) D. K. Fukushima, A. D. Kemp, R. Schneider, M. B. Stokem and T. F. Gallagher, *J. Biol. Chem.*, **210**, 129 (1954).

(15) (a) L. H. Sarett, THIS JOURNAL, **71**, 1165 (1949); (b) S. Lieberman, D. K. Fukushima and K. Dobriner, *J. Biol. Chem.*, **182**, 299 (1950).

(16) L. H. Sarett, THIS JOURNAL, **71**, 1175 (1949).

an 18,20β-oxide to the corresponding γ-lactone gave a product which displayed only a single carbonyl band in the infrared at 1705 cm.$^{-1}$.

Alternate structures arising from oxide formation involving the C-3α-hydroxyl group were then considered. An attractive possibility was the C-3,-9-oxide XVIa. It was readily seen that this was the correct formulation when oxidation of XVIa with 8 *N* chromic acid afforded the previously described 3α,9α-oxidopregnane-11,20-dione XVIII.[17] The C-3α,9α-oxide system had originally been obtained by base treatment of a $\Delta^{9(11)}$-3α-hydroxy-12α-bromide system (XIX → XX). The $\Delta^{9(11)}$-oxide was then converted by a four-step sequence to the C-11-ketone XXI.[18] Although an alternate mechanism has been suggested[19] it would seem most likely that oxide formation from the allylic bromide proceeds in a concerted manner as depicted in XXII.



The structure of the second new product from the action of lead tetraacetate on the keto-diol XIVa was then considered. Infrared and analytical data were in agreement with the compound being a keto-diol monoacetate. The two most likely structures were 5β-pregnane-3α,20β-diol-11-one 20-acetate (XIVe) or 5β-pregnane-3α,20β-diol-11-one 3-acetate (XVII). The former structure was shown to be correct by an unambiguous synthesis. 5β-Pregnane-3α-ol-11,20-dione (XIb) smoothly formed the corresponding tetrahydropyranyl ether (XIc) upon treatment of a benzene solution with dihydropyran in the presence of *p*-toluenesulfonic acid. Sodium borohydride reduction of XIc gave the C-20β-alcohol XIVc which readily furnished the monoacetate XIVd. Finally, removal of the tetrahydropyranyl ether protecting group with aqueous hydrochloric acid in acetic acid afforded 5β-pregnane-3α,20β-diol-11-one 20-acetate (XIVe) identical in every respect with the product from the lead tetraacetate reaction.

The recovery of 20% of starting material and the isolation of XVIa and XIVe in yields of 2.5 and 2.4%, respectively, clearly did not account for all the products of this reaction. However, oxidation of aliquots of the non-crystalline fractions with chromium trioxide in acetic acid under reflux[3] in no instance led to a product which exhibited the characteristic band of a γ-lactone in the infrared. It was concluded therefore that the presence of a C-11-keto group reduces the possibility of C-18,20β-oxide formation. Presumably this is due to the changes in bond angles brought about by the trigonal carbon atom in ring C.

Finally, the effect of lead tetraacetate on 5β-pregnane-3α,11β,20β-triol (XIIIa) was investigated. The major product from this reaction was 5β-pregnane-3α,20β-diol-11-one (XIVa) (24% yield) indicating that an 11β-alcohol is attacked by lead tetraacetate at a much faster rate than either a C-3α- or a C-20β-alcohol. This is an expected result and conforms to the general oxidation pattern of steroid alcohols. The release of steric compression with a consequent energy gain provides a strong driving force for the oxidation of 11β-alcohols.[20]

Two additional products were isolated in low yield. One was the C-3,9-oxide XVIa identical in every respect with the product obtained from the action of lead tetraacetate on the keto-diol XIVa and the second was 5β-pregnane-3α,20β-diol-11-one 3-acetate (XVII) identical with a compound described previously by Sarett.[12] Oxidation of XVII smoothly afforded 5β-pregnane-3α-ol-11,20-dione acetate (XIa).

It is clear that the balance between the various products is dependent on the environment of the alcohol. Ketone formation will be the dominant reaction when steric compression of the hydroxyl group is an important energy consideration and oxide formation will only take place when the participating groups are geometrically favorably disposed. It was noted above, for example, that introduction of a trigonal carbon atom into ring C appears to inhibit C-18,20β-oxide formation.

A further competing reaction is acetate formation which could arise by either a direct esterification process or an SNi reaction of the lead complex >CH–O–Pb $(OAc)_3$[21] *via* a six-membered cyclic transition state.

Experimental[22]

5α-Androstane-3,11,17-trione (VI).—A solution of Δ^4-androstene-3,11,17-trione (V) (25 g.) in dioxane (800 cc.) was added to a solution of lithium (10 g.) in anhydrous liquid ammonia (2.5 l.) during 15 min. with good stirring. At the end of the addition the blue color was discharged by the addition of solid ammonium chloride and the ammonia allowed to evaporate. The product was extracted with methylene dichloride and washed successively with water, 2 *N* hydrochloric acid and water. After drying over anhydrous sodium sulfate the solvent was removed *in vacuo*

(17) V. R. Mattox, R. B. Turner, W. F. McGuckin, E. J. H. Chu and E. C. Kendall, THIS JOURNAL, **74**, 5818 (1952).

(18) R. B. Turner, V. R. Mattox, W. F. McGuckin and E. C. Kendall, *ibid.*, **74**, 5814 (1952).

(19) *Cf.* ref. 4, p. 643.

(20) *Cf.* J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955).

(21) *Cf.* R. Criegee, *Angew. Chem.*, **70**, 173 (1958).

(22) Melting points were determined on a Fisher–Johns hot-stage and are uncorrected. Rotations were measured in chloroform solution unless stated otherwise and the ultraviolet light absorption spectra in 95% ethanol. We are grateful to Dr. J. Matthews and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer with a sodium chloride prism. The alumina used for chromatography had been suspended in ethyl acetate for 24 hours and then dried at 80–100° for 48 hours. The lead tetraacetate was crystallized prior to use from acetic acid and dried *in vacuo*. The elemental analysis were carried out by Dr. A. Bernhardt, Mulheim (Ruhr), Germany.

and the product was suspended in acetone (600 cc.) and treated with an excess of 8 *N* chromic acid[7] for 10 min. at 5–10° with good stirring. Addition of ice-water and extraction with methylene dichloride afforded a product which was adsorbed from benzene onto alumina (500 g.). Elution with benzene-ether (80:20, 5 l.) and one crystallization from acetone–hexane afforded 5α-androstan-3,11,17-trione (VI) (9.9 g.), m.p. 174–176°, $[\alpha]_D$ +165°; lit.[8] m.p. 182–183°, $[\alpha]_D$ +152° (acetone).

5α-Androstane-3β,11β,17B-triol 3,17-Diacetate (VII).—A solution of the trione VI (3.3 g.) in tetrahydrofuran (100 cc.) was added dropwise during 30 min. to a refluxing suspension of lithium aluminum hydride (5.0 g.) in tetrahydrofuran (200 cc.). After heating under reflux for a further 18 hours the excess of reagent was destroyed by the careful addition of ethyl acetate. A saturated solution of sodium sulfate (10–20 cc.) was then added, followed by solid sodium sulfate until the tetrahydrofuran formed a clear supernatant solution. The inorganic salts were removed by filtration over Celite and then washed with ethyl acetate. The filtrates were combined and the solvent removed *in vacuo*. The residue was dissolved in pyridine (50 cc.) containing acetic anhydride (5 cc.) and heated at 90° for 1 hour. The reaction mixture was then poured onto ice-water and isolated by extraction with ethyl acetate. The product was adsorbed from benzene–hexane (50:50) onto alumina (120 g.). Elution with benzene (2.5 l.) and one crystallization from methylene dichloride–hexane afforded 5α-androstane-3β,17β-triol 3,11β,17-diacetate (VII) (1.22 g.), m.p. 158–161°. After several crystallizations from methylene dichloride–hexane the analytical sample had m.p. 163–164°, $[\alpha]_D$ +5°; λ_{max}^{KBr} 3600, 1745, 1730 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25; O, 20.38. Found: C, 70.56; H, 9.09; O, 20.35.

5α-Androstane 3β,17β-diol-11-one Diacetate (VIII).—An excess of 8 *N* chromic acid[7] was added to a solution of the 11β-hydroxy diacetate VII (200 mg.) in acetone (20 cc.) at 0–5°. After 2 min. addition of water, extraction with ether and crystallization of the product from acetone–hexane afforded 5α-androstane 3β,17β-diol-11-one diacetate (VIII) (110 mg.), m.p. 157–159°, $[\alpha]_D$ +9°; λ_{max}^{KBr} 1738, 1705 and 1250 cm.$^{-1}$; lit.[9] m.p. 153–154°, $[\alpha]_D$ +14°.

Treatment of 5α-Androstane-3β,11β,17β-triol 3,17-Diacetate (VII) with Lead Tetraacetate.—Lead tetraacetate[23] (500 mg.) was added to a solution of the triol diacetate VII (250 mg.) in dry benzene (30 cc.) and heated under reflux for 18 hours. Addition of water and isolation with benzene afforded a product which was adsorbed from hexane onto alumina (15 g.). Elution with hexane–benzene (70:30, 500 cc.) and one crystallization from acetone–hexane afforded 5α-androstane-3β,17β-diol-11-one diacetate (VIII) (90 mg.), m.p. 154–156°, undepressed on admixture with an authentic sample, $[\alpha]_D$ +7°.

5β-Pregnane-3α,11β,20β-triol (XIIIa).—A solution of 5β-pregnane-3α-ol-11,20-dione acetate (XIa) (50 g.) in anhydrous tetrahydrofuran (1 l.) was added dropwise over 45 min. to a stirred suspension of lithium aluminum hydride (30 g.) in tetrahydrofuran (2 l.) under reflux. After heating under reflux for a further 18 hours, ethyl acetate was added cautiously to the cooled reaction mixture to destroy the excess of reagent. A saturated solution of sodium sulfate (approx. 50 cc.) was added and then an excess of anhydrous sodium sulfate. The inorganic salts were removed by filtration over Celite and washed well with hot acetone. The filtrates were combined and the solvent removed *in vacuo*. Two crystallizations of the product from acetone and ethyl acetate afforded 5β-pregnane-3α,11β,-20β-triol (XIIIa) (33.1 g.), m.p. 236–238°, $[\alpha]_D$ +39° (dioxane); lit.[11] m.p. 233–235°, $[\alpha]_D$ + 39° (dioxane).

5β-Pregnane-3α,11β,20β-triol 3,17-Diacetate (XIIIb).—Acetic anhydride (25 cc.) was added to a solution of 5β-pregnane-3α,11β,20β-triol (XIIIa) (10 g.) in pyridine (200 cc.) at 20°. After 16 hours at 20°, addition of water and isolation with ether followed by one crystallization of the product from methanol led to the diacetate XIIIb (8.95 g.), m.p. 165–167°. The analytical sample had m.p. 170–172°, $[\alpha]_D$ +71°;[24] λ_{max}^{KBr} 3400, 1720 (broad) and 1250 cm.$^{-1}$ (broad).

(23) Prepared according to the procedure described by L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p. 325.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.46; H, 9.47; O, 18.79.

Alkaline hydrolysis of XIIIb readily afforded XIIIa.

5β-Pregnane-3α,20β-diol-11-one Diacetate (XIVb).—An excess of 8 *N* chromic acid[7] was added to a solution of the triol diacetate XIIIb (400 mg.) in acetone (10 cc.) at 0–5°. After 1–2. min. addition of ice-water and filtration followed by one crystallization from acetone–hexane afforded 5β-pregnane-3α,20β-diol-11-one diacetate (XIVb) (250 mg.), m.p. 157–159°, $[\alpha]_D$ +65°; λ_{max}^{KBr} 1735, 1705 and 1250 cm.$^{-1}$. The m.p. was undepressed with an authentic sample kindly supplied by Dr. E. P. Oliveto; lit.[11] m.p. 156–157°, $[\alpha]_D$ +69° (acetone).

Lead Tetraacetate Treatment of 5β-Pregnane-3α,11β,-20β-triol 3,20-Diacetate (XIIIb).—Lead tetraacetate (8.0 g.) was added to a solution of the triol diacetate XIIIb (4.0 g.) in benzene (100 cc.) and heated under reflux for 18 hours. The reaction mixture was then diluted with 250 cc. of benzene and added to 1 liter of water. The dark brown inorganic salts were removed by filtration over Celite and washed with benzene. The combined benzene solutions were washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo*. Crystallization of the solid product from methanol afforded 5β-pregnane-3α,20β-diol-11-one diacetate (XIVb) (2.76 g.), m.p. 153–155°, $[\alpha]_D$ +68°, identical in every respect with an authentic sample. A second crop (650 mg.), m.p. 148–157°, of slightly less pure material was obtained from the mother liquors. Removal of the remaining solvent from the mother liquors and chromatography of the residue over alumina (30 g.) led only to the isolation of a further 170 mg. of XIVb. Total yield of XIVb was 89.5%.

5β-Pregnane-3α,11β,20α-triol 3,20-Diacetate (XIIb).—The mother liquors from the preparation of 5β-pregnane-3α,11β,20β-triol (XIa→XIII) afforded 10.4 g. of a product which was kept for 18 hours at room temperature in a mixture of pyridine (125 cc.) and acetic anhydride (25 cc.). Addition of ice-water and isolation with ethyl acetate afforded a product which after two crystallizations from acetone–hexane gave 5β-pregnane-3α,11β,20α-triol 3,20-diacetate (XIIb), m.p. 185–187°, $[\alpha]_D$ +54°. The m.p. was raised to a constant value of 189–191° after further crystallizations; λ_{max}^{KBr} 3560, 1725, 1740, 1255 and 1245 cm.$^{-1}$; lit.[14] m.p. 192–192.5°, $[\alpha]_D$ +56°.

Lead Tetraacetate Treatment of 5β-Pregnane-3α,11β,20α-triol 3,20-Diacetate (XIIb).—Lead tetraacetate (2.0 g.) was added to a solution of the 11β-hydroxy diacetate XIIb (1.0 g.) in benzene (25 cc.) and heated under reflux for 18 hr. Addition of water, extraction with benzene (after filtering off the insoluble lead dioxide) and one crystallization of the product from methylene dichloride–hexane gave 5β-pregnane-3α,20α-diol-11-one diacetate (XV) (570 mg.), m.p. 208–215°, raised by one crystallization from methylene dichloride–hexane to 229–231° (390 mg.), $[\alpha]_D$ +61°; λ_{max}^{KBr} 1725, 1700 and 1238 cm.$^{-1}$. This product was identical in every respect with the product obtained by oxidation of XIIb with 8 *N* chromic acid in the usual way; lit.[15] reports m.p. 230–231°, $[\alpha]_D$ +62.5° for XV.

Lead Tetraacetate Treatment of 5β-Pregnane-3α,20β-diol-11-one (XIVb) with Lead Tetraacetate.—Lead tetraacetate (7.6 g.) was added to a supension of 5β-pregnane-3α,20β-diol 11-one (XIVb) (3.8 g.) in benzene (100 cc.) and heated under reflux for 16 hours. The reaction mixture was then diluted with ethyl acetate (300 cc.) and heated to boiling point. Filtration removed inorganic salts which were then washed well with hot ethyl acetate. The combined filtrates were then washed several times with water and then dried over anhydrous sodium sulfate. Removal of the solvent and crystallization of the product from ethyl acetate–hexane gave recovered starting material (XIVb) (1.49 g.), m.p. 236–238°, $[\alpha]_D$ +46° (EtOH). The m.p. was undepressed upon admixture with starting material and the infrared spectra were identical. After removal of the solvent from the mother liquors the residue was adsorbed from benzene onto alumina (200 g.). Elution with benzene–ether (80:20, 750 cc.) and one crystallization from

(24) Lit.[11] reports m.p. 119–120°, $[\alpha]_D$ +67.8° (acetone); Dr. E. P. Oliveto has kindly informed us, however, that subsequent preparations of XIIIb in his laboratory have afforded the higher melting (170°) form. A mixture m.p. determination and infrared comparison of our sample with that of the higher melting product from the Schering Laboratories showed their identity.

methylene chloride–hexane afforded 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) (190 mg.), m.p. 203–206°, raised by crystallizations from methylene dichloride–hexane to 208–209°, $[\alpha]_D$ +71°; λ_{max}^{KBr} 3650, 1705 and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.40. Found: C, 75.59; H, 9.50; O, 14.63.

Further elution with benzene–ether (70:30, 1 l.) and one crystallization from acetone–hexane gave 5β-pregnane-3α,20β-diol-11-one 20-acetate (XIVc) (170 mg.), m.p. 191–201°, raised by crystallizations from acetone–hexane to 228–229°, $[\alpha]_D$ +58°; λ_{max}^{KBr} 3550, 1730, 1695 and 1235 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.37; H, 9.48; O, 17.14.

Room temperature acetylation of 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) with acetic anhydride and pyridine afforded the 20β-acetate XVIb, m.p. 174–176° from aqueous methanol, $[\alpha]_D$ +92°; λ_{max}^{KBr} 1725, 1700, 1245 and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 74.05; H, 9.28; O, 16.80.

3α,9α-Oxido-5β-pregnane-11,20-dione (XVIII).—A solution of 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) (75 mg.) in acetone (5 cc.) at 0° was treated with an excess of 8 *N* chromic acid[7] for 2–3 minutes. Addition of water, isolation with ether and crystallization from aqueous methanol gave 3α,9α-oxido-5β-pregnane-11,20-dione (XVIII) (41 mg.), m.p. 120–122°, raised by two further crystallizations from aqueous methanol to 125–127°, $[\alpha]_D$ +164°, λ_{max}^{KBr} 1700 and 995 cm.$^{-1}$; lit.[17] m.p. 126–127°, $[\alpha]_D$ +167°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 15.53. Found: C, 76.15; H, 8.99; O, 15.37.

Lead Tetraacetate Treatment of 5β-Pregnane-3α,11β,20β-triol (XIIIa).—Lead tetraacetate (20 g.) was added to a suspension of 5β-pregnane-3α,11β,20β-triol (XIIIa) (10 g.) in benzene (300 cc.) and heated under reflux for 18 hr. The reaction mixture was cooled and filtered and the residue was washed well with benzene. The combined benzene solutions were washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a residue, fraction A (6.1 g.). The benzene-insoluble solids were dissolved in methanol (75 cc.). Addition of ice-water to this solution and filtration afforded 5β-pregnane-3α,20β-diol-11-one (XIVa) (2.4 g.), m.p. 233–235°, $[\alpha]_D$ +36° (EtOH); the m.p. was undepressed upon admixture with an authentic sample and the infrared spectra were identical.

Fraction A was then adsorbed from benzene onto alumina (400 g.). Elution with benzene–ether (70:30, 750 cc.) and one crystallization from methylene dichloride–hexane afforded 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) (270 mg.), m.p. 203–205°, undepressed on admixture with the sample obtained previously (XIVa→XVIa); the infrared spectra were identical.

Further elution with benzene–ether (50:50, 750 cc.) and one crystallization from methylene dichloride–hexane gave a product (320 mg.), m.p. 167–185°. Further chromatography of this product over alumina furnished 5β-pregnane-3α,20β-diol-11-one 3-acetate (XVII) (200 mg.), m.p. 198–200°, raised by crystallizations from methylene dichloride–hexane to 207–208°, $[\alpha]_D$ +67°; λ_{max}^{KBr} 3400, 1730, 1685 and 1245 cm.$^{-1}$; lit.[12] m.p. 205–206°, $[\alpha]_D$ +66° (acetone).

Oxidation of XVII with 8 *N* chromic acid at 0° smoothly led to 5β-pregnane-3α-ol-11,20-dione acetate (XIa), m.p. 128–130°, $[\alpha]_D$ +133°. The m.p. was undepressed upon admixture with an authentic sample of XIa and the infrared spectra were identical.

5β-Pregnane-20β-ol-3α-tetrahydropyranyl Ether-11-one (XIVd).—*p*-Toluenesulfonic acid monohydrate (600 mg.) was added to a solution of 5β-pregnane-3α-ol-11,20-dione (XIb) (15 g.) in dry benzene (300 cc.) containing dihydropyran (30 cc.). After 20 hours at room temperature the solution was washed with sodium carbonate solution and water. Removal of the solvent after drying (Na_2SO_4) afforded an oil which was adsorbed from benzene–hexane (70:30) onto alumina (400 g.). Elution with benzene–hexane (50:50) afforded 5β-pregnane-3α-tetrahydropyranyl ether 11,20-dione (XIc) (7.6 g.) as an oil which could not be obtained crystalline, $[\alpha]_D$ +47°, $\lambda_{max}^{CHCl_3}$ 1710 cm.$^{-1}$.

Sodium borohydride (2.0 g.) was added to a solution of XIc (4.7 g.) in methanol (150 cc.) and kept at 20° for 1 hour. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto alumina (150 g.). Elution with benzene–ether (50:50; 1200 cc.) and one crystallization from hexane afforded 5β-pregnane-20β-ol-3α-tetrahydropyranyl ether-11-one (XIVd) (1.5 g.), m.p. 147–155°, raised by several crystallizations from hexane to 160–162°, $[\alpha]_D$ +5°; λ_{max}^{KBr} 3400, 1685 and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11; O, 15.29. Found: C, 74.38; H, 10.03; O, 15.11.

5β-Pregnane-20β-ol-3α-tetrahydropyranyl Ether-11-one Acetate (XIVe).—Acetic anhydride (0.5 cc.) was added to a solution of the 20β-alcohol XIVd (190 mg.) in pyridine (3.0 cc.). After 18 hours at room temperature addition of ice-water and filtration afforded the acetate XIVe (200 mg.), m.p. 145–150°, raised by crystallizations to 155–157°; λ_{max}^{KBr} 1730, 1700 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63; O, 20.15. Found: C, 72.81; H, 9.40; O, 19.73.

5β-Pregnane-3α,20β-diol-11-one 20-Acetate (XIVc).—Hydrochloric acid (0.05 cc., 2 *N*) was added to a solution of the tetrahydropyranyl ether (100 mg.) in acetic acid (3.0 cc.). After 5 hours at room temperature, addition of ice-water, isolation of the product with methylene dichloride, followed by one crystallization from acetone–hexane afforded 5β-pregnane-3α,20β-diol-11-one 20-acetate (XIVc) (35 mg.), m.p. 222–226°, raised by one further crystallization from acetone–hexane to 227–229°, $[\alpha]_D$ +60°. The m.p. was undepressed with the product isolated from the action of lead tetraacetate on XIVa and the infrared spectra were identical in every respect.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY, NEW BRUNSWICK, N. J.]

The Synthesis of Desoxyequilenin. The Stereochemistry of the C/D Ring Junction of Some Steroid Intermediates

BY RODERICK A. BARNES AND RICHARD MILLER[1]

RECEIVED JANUARY 13, 1960

2-Methyl-2-β(1'-naphthyl)-ethylcyclopentanone-3-carboxylic acid has been prepared and cyclized to yield 14,15-dehydroequilenane-17-β-carboxylic acid. The catalytic hydrogenation of the double bond of this latter substance produced *trans-d,l*-equilenane-17-β-carboxylic acid in good yield. The stereochemistry of the reduction product was determined by degradation to *trans-d,l*-3-desoxyequilenin.

A projected plan for the synthesis of 18-oxygenated- and 19-norsteroids involved the preparation of substances having a 14,15-double bond. The purpose of the work reported here was to explore some aspects of the basic synthetic scheme and particularly to investigate the stereochemistry of the products from the reduction of the double bond. The desoxyequilenin series was chosen for

(1) Abstracted from a thesis presented by R. Miller to the Graduate School for the Ph.D. degree, November, 1956.