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THE FAWORSKII REARRANGEMENT IN THE FORMATION OF 17-METHYL STEROIDS

THE CONFIGURATION OF C-17 BROMIDES*

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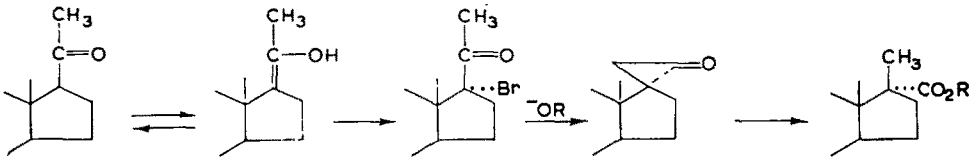
Abstract—The configuration of 17-bromo-20-keto pregnanes and the 17-methyletianic esters have been determined. The Faworskii rearrangement of the former to give the latter has been observed to be abnormal. It is suggested that C-17 → C-21 halogen transfer intervenes.

THE formation of 17-methyl etianates by Faworskii rearrangement of 17-bromo-20-keto steroids has been effected in a large number of cases.[1–4] In all instances the structure of the major product has been formulated as a 17α-methyl etianate principally on the basis of molecular rotation evidence and activity correlations.[5]

A consideration of the mechanics of the Faworskii rearrangement as set forth by the tracer work of Loftfield[6] suggested that the steroid acids should have a 17β-oriented methyl group. This conclusion was based on the assumption that bromination of a 20-keto steroid by way of its $\Delta^{17(20)}$-enol should, in keeping with all precedent, follow the rule-of-the-rear[7] and yield a 17α-bromo-20-keto product. Ensuing Faworskii rearrangement with attending inversion at C-17 in the formation of an intermediate *cyclo*propanone should, in its ultimate phase, yield a 17β-methyl etianate, thus,



In view of these considerations it was felt that chemical substantiation for the configuration of the 17-methyl Faworskii products would be desirable and further that their formation from a 17-bromo-20-keto pregnane of known stereochemistry should be sought.

The direct bromination of 3α-acetoxy pregnane-11,20-dione (I) has been reported recently by Engel to give a 17-bromo derivative, m.p. 168–170° of unknown configuration.[8] By treatment of the enol acetate derivative of I with N-bromsuccinimide, the Upjohn group[9,10] has also prepared in superior yield a 17-bromo derivative, m.p. 175–176°, which appeared to be the same as the product of direct bromination.[8]

* For a preliminary account of this work see: N. L. Wendler, R. P. Graber and G. G. Hazen, *Chem. Ind. (Rev.)* 847 (1956).

[1] R. E. Marker and R. B. Wagner, *J. Amer. Chem. Soc.* **64**, 216 (1942); **64**, 1273 (1942).

[2] Pl. Plattner, H. Heusser and S. E. Boyce, *Helv. Chim. Acta* **31**, 603 (1948).

[3] Pl. Plattner, H. Heusser and P. Th. Herzig, *Helv. Chim. Acta* **32**, 270 (1949).

[4] H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. Plattner, *Helv. Chim. Acta* **33**, 2229 (1950).

[5] Ch. R. Engel and G. Just, *J. Amer. Chem. Soc.* **76**, 4909 (1954).

[6] R. B. Loftfield, *J. Amer. Chem. Soc.* **73**, 4707 (1951).

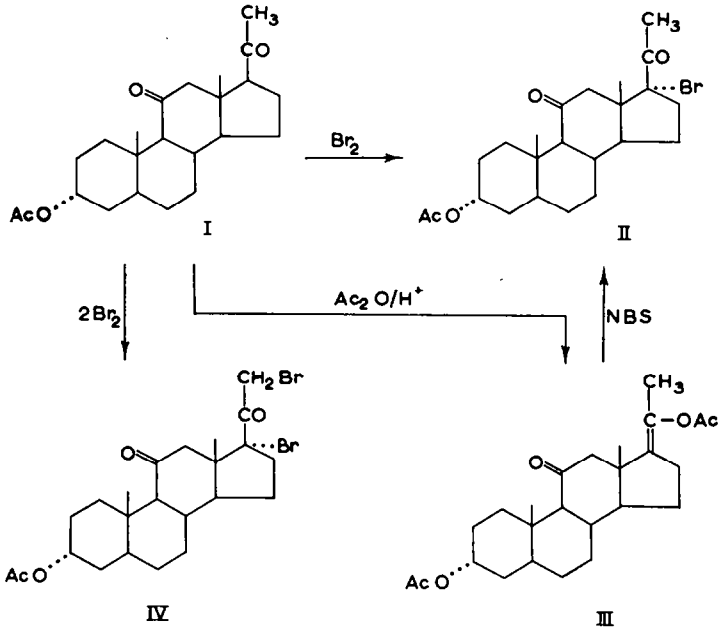
[7] T. F. Gallagher and T. H. Kritchevsky, *J. Amer. Chem. Soc.* **72**, 882 (1952).

[8] Ch. R. Engel, *J. Amer. Chem. Soc.* **78**, 4727 (1956).

[9] H. V. Anderson, E. R. Garrett, F. H. Lincoln, A. H. Nathan and J. A. Hogg, *J. Amer. Chem. Soc.* **76**, 743 (1954).

[10] B. J. Magerlein, D. A. Lyttle and R. H. Levin, *J. Org. Chem.* **20**, 1709 (1955).

We have repeated the above procedures and have found that the bromo derivatives obtained by the direct as well as the indirect method are indeed identical by mixed m.p. and infrared comparison. Further, it has been established that this 17-bromo derivative is a single individual by paper partition chromatography. In the latter connection dimethyl formamide was employed as the stationary phase and a 3 : 1 mixture of *cyclo*hexane in benzene as the mobile phase; the iodine-vapor technique[11] was used in tracing the compound. By this procedure 11-ketoprogesterone and 11-keto-17-*iso*progesterone as well as 11β-hydroxy progesterone and 11β-hydroxy-17-*iso*progesterone were found to be clearly and distinctly resolved.

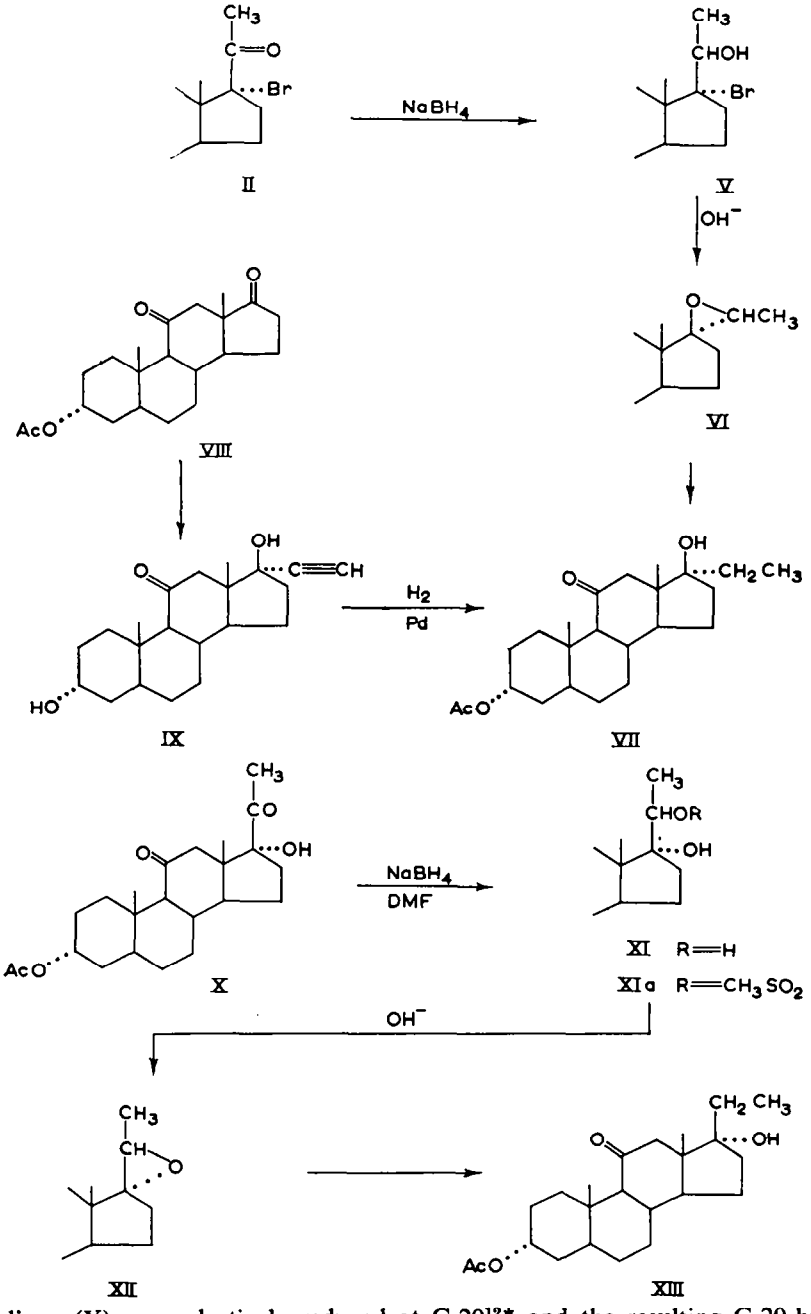


The configuration of the bromine substituent of II was established as being 17α in the following manner: II was reduced at C-20 by means of sodium borohydride; the resultant bromohydrin without isolation was converted by alkali with attending inversion at C-17 to the β-oxide (VI) and thence to 3α-acetoxy-17β-hydroxy-17-*iso*pregnane-11-one (VII) by successive reduction with lithium aluminum hydride, acetylation at C-3 and reoxidation at C-11. The carbinol VII thus produced was identical with an authentic sample prepared from 3α-acetoxyetiocholane-11,17-dione VIII with ethylmagnesium bromide or sodium acetylide followed by hydrogenation and acetylation.

The reduction of II $\rightarrow$ V was accompanied by considerable reductive loss of bromine to give as a by-product the corresponding C-20-hydroxy compound; the latter was identical with the corresponding C-20-reduction ($NaBH_4$) product of I.

The C-17-isomer of VII, namely XIII, was synthesized as a reference compound since its formation as a consequence of the above sequence would have been the case had the configuration of II been reversed at C-17. 3α-Acetoxy-17α-hydroxypregnane-

[11] G. B. Marini-Bettolo-Marconi and S. Guarino, *Experientia* 6, 309 (1950).



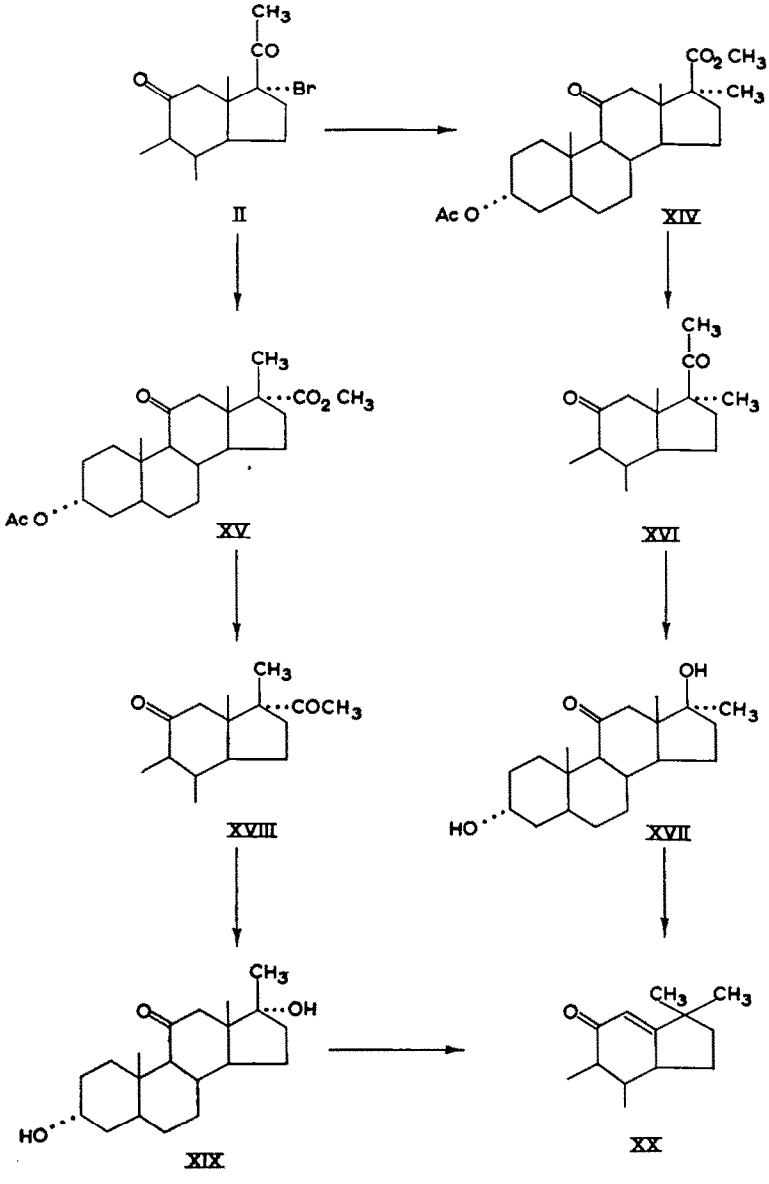
11,20-dione (X) was selectively reduced at C-20[12]* and the resulting C-20-hydroxy derivative (XI) in the form of its mesylate derivative (XIa) was converted to the α-oxide (XII) by means of sodium methoxide. Reductive scission of the oxide function

* Reductions carried out at room temperature with sodium borohydride in aqueous dimethyl formamide have been found to be highly specific, enabling e.g. the reduction of 20-CO in the presence of Δ^4-3-CO and 11-CO as well as a 21-acetoxyl function.

[12] D. Taub, R. D. Hoffsommer and N. L. Wendler, *Abstracts of papers* p. 23. 132nd Meeting of the American Chemical Society, New York, Sept. 8–13 (1957).

with lithium aluminum hydride followed by acetylation at C-3 and reoxidation at C-11 provided XIII in good overall yield.

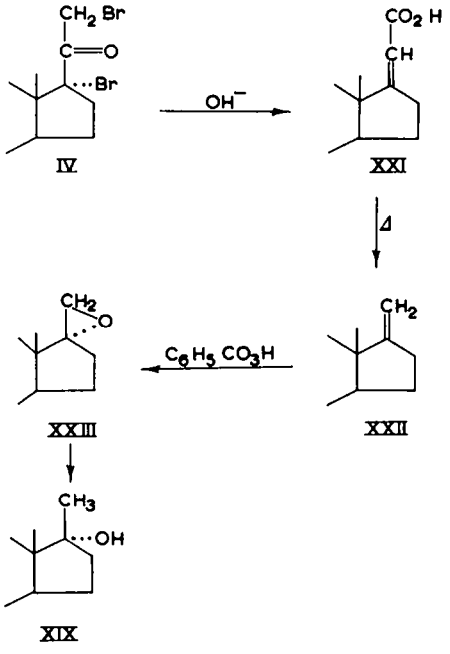
The Faworskii rearrangement of the 17α-bromoketone (II) was effected by refluxing with excess 3% sodium methoxide in methanol for 2 hr. The product was acety-



lated and chromatographed to yield ca. 60 per cent of the 17α-methyl etianate (XIV) and ca. 40 per cent of the 17β-methyl etianate (XV). The configuration of these esters was determined in the following manner: The 17α-methyl ester (XIV) was converted by saponification and acetylation to the corresponding 3α-acetoxy acid; the latter by

way of its acid chloride on treatment with diazomethane followed by hydrogen chloride and reduction with zinc afforded the methyl ketone (XVI).* Oxidation of XVI with peroxytrifluoroacetic acid[13] with subsequent saponification yielded 3α,17β-dihydroxy-17α-methyletiocholane-11-one (XVII) identical with authentic material prepared from 3α-acetoxyetiocholane-11,17-dione VIII with methylmagnesium iodide.†

In a similar manner the 17β-methyl ester (XV) was converted to the methyl ketone (XVIII) and thence with peroxytrifluoracetic acid and subsequent saponification to 3α,17α-dihydroxy-17β-methyletiocholane-11-one (XIX). An authentic sample of XIX was prepared by the method of Sondheimer *et al.*[14] in the following manner: Bromination of 3α-acetoxypregnane-11,20-dione (I) with 2 moles of bromine afforded the known 17,21-dibromide (IV).‡ Faworskii rearrangement of IV gave the unsaturated acid XXI which was decarboxylated to the olefin XXII. The latter was successively epoxidized with perbenzoic acid and reduced with lithium aluminum hydride according to the method of Sondheimer *et al.*[14] The product thus obtained was acetylated at C-3 and oxidized at C-11 followed by removal of the 3-acetate function to give XIX. The two samples of XIX prepared from XV and IV were found to be identical.



Both epimeric carbinols XVII and XIX were found to undergo the Kägi–Miescher rearrangement[15] to give the $\Delta^{\alpha,\beta}$ketone XX. Therefore the rearrangement to form XX is not dependent on the configuration at C-17 with the tertiary carbinols XVII and XIX in the manner found to be the case with the C-17-secondary carbinols.[15]

* Method of Pl. Plattner *et al.* (reference 3) has been used.

† When VIII was treated with excess methylmagnesium iodide at 65° an appreciable quantity of product was obtained which in all probability corresponds to reaction at both the C-11 and C-17 carbonyls. See Experimental.

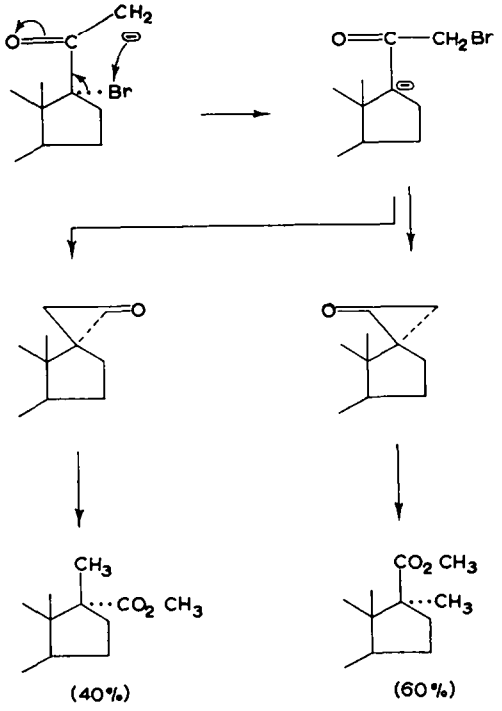
‡ Ch. Engel (reference 8) isolated this dibromide as a minor product from the preparation of II.

[13] W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.* **77**, 2287 (1955).

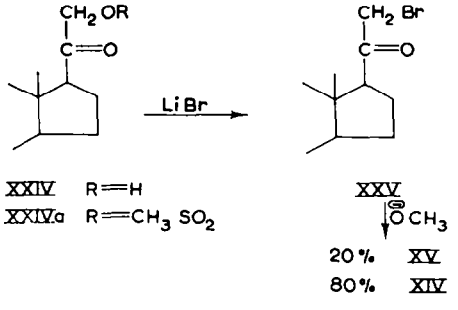
[14] F. Sondheimer, O. Mancera, M. Urquiza and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 4145 (1956).

[15] H. Kägi and K. Miescher, *Helv. Chim. Acta* **22**, 683 (1939); **32**, 761 (1949).

As a consequence of the above transformations, the configurations of the 17-bromo and 17-methyl pregnane derivatives have been placed on a firm basis, thereby permitting certain conclusions with regard to the *modus operandi* of the Faworskii rearrangement as applied to these systems. It has been seen that starting with a stereochemically pure 17α-bromo-20-keto steroid, the major product arising from Faworskii rearrangement is not the product to be expected from transformation according to the mechanism established by Loftfield.[6] Consequently it is suggested that the Faworskii change in the case of 17α-bromo-20-keto steroids is preceded by a bromine transfer from C-17 → C-21 to give a configurationally independent species capable of providing



either isomeric ester by way of its appropriate *cyclo*propanone precursor. As previously pointed out the ratio of 17β-methyl ester (XV) to 17α-methyl ester (XIV) formed from II is ca. 40 : 60. It has been shown further, however, that the Faworskii rearrangement of 3α-acetoxy-21-bromopregnane-11,20-dione (XXV) yields XV and



XIV in a ratio not greater than 20 : 80.* Therefore, it reasonably follows that the 17α-bromo-20-ketone (II) is capable of rearranging normally in a direct sense to the extent of at least 20 per cent.

These findings indicate that the act of bromine displacement leading to the appropriate *cyclo*propanone intermediate in the Faworskii change proceeds with greater facility in the geometrically α-sense, a consequence which is in agreement with expectations based on steric considerations.

EXPERIMENTAL

3α-Acetoxy-17α-bromopregnane-11,20-dione (II)

(a) Prepared by direct bromination of 3α-acetoxypregnane-3,11-dione (I) according to Engel;[8] crystallized from ether m.p. 168–71° (in reference 8 m.p. 168–70°).

(b) Prepared by treatment of the $\Delta^{17(20)}$-enol acetate derivative of 3α-acetoxypregnane-11,20-dione (III) with N-bromsuccinimide according to Anderson *et al.*[9] Crystallized from acetone m.p. 174–5° (in reference 9 m.p. 175–6°).

Samples of II prepared by methods (a) and (b) were not depressed on mixed melting point determination and were shown to have identical infrared spectra. A sample of II was submitted to paper-strip chromatography employing dimethyl formamide as the stationary phase and a 3 : 1 mixture of *cyclo*hexane and benzene as the mobile phase. The compound was traced by the iodine vapor technique[11] as well as by 2,4-dinitrophenyl hydrazine reagent subsequent to u.v. irradiation and found to be a single spot. As a control, 11-ketoprogesterone and 11-keto-17-*iso*progesterone were found to be cleanly and distinctly resolved in this system. Likewise 11β-hydroxyprogesterone and 11β-hydroxy-17-*iso*progesterone were unambiguously separated to give a two-spot paper chromatogram.

Conversion of 3α-acetoxy-17α-bromopregnane-11,20-dione (II) *to 3α-Acetoxy-17β-hydroxy-17-iso-pregnane-11-one* (VII)

A solution of 1·18 g of bromo derivative (II) (m.p. 174–5°) in 40 cm³ of tetrahydrofuran and 40 cm³ of methanol was treated with 100 mg of sodium borohydride and allowed to stand at room temperature for 1 hr. At the end of this period 0·75 cm³ of acetic acid was added and the reaction mixture evaporated to dryness. The product was extracted with ethyl acetate and the ethyl acetate extract washed with distilled water. Analysis of the aqueous layer revealed ionic bromine corresponding to reductive loss of bromine from II. Since the residue obtained on evaporation of the organic layer still gave a positive test with 2,4-dinitrophenylhydrazine reagent, indicating unreduced 20-carbonyl, this material was resubjected to reduction as before with 100 mg of sodium borohydride to give a product no longer exhibiting a positive reaction with 2,4-dinitrophenylhydrazine reagent.

The above reduction product (1 g) was dissolved in 30 cm³ of methanol, treated with 1 g of potassium hydroxide in 3 cm³ of water and 7 cm³ of methanol and allowed to stand at room temperature for 2 hr. The reaction mixture was evaporated to dryness and extracted with ethyl acetate to give 0·8 g of halogen-free product containing VI.

* Faworskii rearrangement of 21-halogenated 20-keto steroids was first carried out by Pl. Plattner, H. Heusser and S. E. Boyce (reference 2) and shown by these authors to be superior to the 17-bromo systems in the production of what is now established as being the 17α-methyl isomer.

The above product from base treatment (0·8 g) containing VI was dissolved in 90 cm³ of tetrahydrofuran, treated with 1 g of lithium aluminum hydride and refluxed for 3 hr. At the end of this time the excess lithium aluminum hydride was destroyed by dropwise addition of 5 cm³ ethyl acetate and finally 20 cm³ of saturated sodium sulfate solution. The organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was acetylated at room temperature with acetic anhydride in pyridine and the acetylated product oxidized with 230 mg of chromic anhydride in 25 cm³ of glacial acetic acid. The crude oxidation product was chromatographed on 50 g of acid-washed alumina and eluted with benzene–ether mixtures to give ca. 600 mg of 3α,20-diacetoxypregnane-11-one identical by infrared comparison with material obtained from I by reduction with sodium borohydride in aqueous dimethyl formamide at C-20, followed by acetylation. The fractions eluted with 20% and 50% ether in benzene corresponded to ca. 80 mg of 3α-acetoxy-17β-hydroxy-17-*iso*pregnane-11-one (VII) m.p. 203·5–205·5°. This material was not depressed in m.p. on admixture with an authentic sample of VII (see below) and was identical with it by infrared spectral comparison.

Synthesis of 3α-*acetoxy*-17β-*hydroxy*-17-iso*pregnane*-11-*one* (VII) *from* 3α-*acetoxyetiocholan*-11,12-*dione* (VIII)*

A 5 g sample of 17-ketone (VIII) was ethinylated according to the method of Stavely[16] as adapted by Sarett[17] to give 4·1 g of 17α-ethinyletiocholane-3α,17β-diol-11-one (IX) m.p. 210–15°. Crystallized from ethyl acetate m.p. 214–16° (in reference 17 m.p. 218·5–219°).

The above ethinyl carbinol (330 mg) was hydrogenated in 10 cm³ of absolute ethanol at 1 atm and 24°C, with 50 mg of 10% palladium-on-charcoal catalyst. The calculated uptake (2 moles) of hydrogen was complete in 40 min. The product was isolated and acetylated with acetic anhydride in pyridine at room temperature and the acetylated product crystallized from acetone–ether m.p. 203–6°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73·35; H, 9·64. Found: C, 73·56; H, 9·57.

The same substance (VII) was obtained in inferior yield by reaction of VII with ethyl magnesium bromide followed by acetylation.

3α-*Acetoxy*-17α,20-*oxidopregnane*-11-*one* (XII)

A solution of 5 g of 3α-acetoxy-17α-hydroxypregnane-11,20-dione (X) in 125 cm³ of dimethyl formamide was treated with 1·25 g of sodium borohydride in 12·5 cm³ of water and the reaction mixture allowed to stand for 1 hr at room temperature. At the end of the period the excess sodium borohydride was decomposed by cautious addition of acetic acid with cooling. The product was precipitated by addition of water and extracted with ether. The ether extract was evaporated to a foam and treated overnight at 0–5° with 2·5 cm³ of methanesulfonyl chloride in 10 cm³ of pyridine. The crude mesylate derivative was dissolved in 500 cm³ of warm methanol and treated with 15 g potassium hydroxide in 30 cm³ water for 2 hr at room temperature. At the end of this period the methanol was evaporated *in vacuo* and the residue extracted with ether–ethyl acetate. An aliquot of the product was chromatographed. The

* Performed by H. L. Slates of these Laboratories.

[16] H. Stavely, *J. Amer. Chem. Soc.* **61**, 79 (1939).

[17] L. H. Sarett, *J. Biol. Chem.* **162**, 601 (1940).

fractions eluted with benzene and 10% ether in benzene afforded XII as colorless, transparent prisms from ether which on melting lose solvent of crystallization at 80° and undergo a phase change at 112° producing needles that melt at 128–9°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73·80; H, 9·10, Found: C, 74·01; H, 9·00.

Later fractions from the chromatogram yielded 3α,20-diacetoxy-17α-hydroxypregnane-11-one, m.p. 244–46·5°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69·44; H, 8·33. Found: C, 69·72; H, 8·76.

3α-*Acetoxy*-17α-*hydroxypregnane*-11-*one* (XIII)

In the conversion of the oxide XII to the pregnane derivative XIII it was found unnecessary to purify by chromatography at that stage. Therefore the crude oxide obtained above by alkali treatment of its mesylate precursor was reduced with 2·5 g of lithium aluminum hydride in 200 cm³ of refluxing tetrahydrofuran for 3 hr. The product was worked up as described previously, acetylated with acetic anhydride in pyridine and the acetylated product oxidized in 50 cm³ of acetic acid with 1 g of chromium trioxide. The crude oxidation product on chromatography afforded 1·85 g of 3α-acetoxy-17α-hydroxypregnane-11-one (XIII), m.p. 147·5°, $\lambda_{max}^{CCl_4}$ 2·82 μ (OH); 5·79 μ (OAc); 5·87 μ (C=O).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73·40; H, 9·57. Found: C, 73·37; H, 9·52.

Later fractions from the chromatography again produced 3α,21-diacetoxy-17α-hydroxypregnane-11-one as experienced at the purification stage of this oxide (XII) (see above).

Methyl 3α-*acetoxy*-11-*keto*-17α-*methyletianate* (XIV) *and methyl* 3α-*acetoxy*-11-*keto*-17β-*methyl*-17-iso*etianate* (XV). *Faworskii rearrangement of* 3α-*acetoxy*-17α-*bromo-pregnane*-11,20-*dione* (II)

To a solution of 1 g of sodium metal in 30 cm³ of methanol was added 1 g of purified bromoketone (II), m.p. 172–173·5°. The reaction mixture was refluxed for 3·5 hr. At the end of this period the methanol was evaporated *in vacuo* and the product dissolved in ethyl acetate–water. The ethyl acetate solution was dried and concentrated to dryness. The residue was acetylated with 2 cm³ of acetic anhydride in 2 cm³ of pyridine and a 700 mg sample of the acetylated product chromatographed on 35 g of acid-washed alumina. The eluates corresponding to 20–50% benzene in petroleum ether afforded 236 mg (40 per cent) of methyl 3α-acetoxy-11-keto-17β-methyl-17-*iso*etianate (XV) as long needles from ether–petroleum ether, m.p. 156–7° $[\alpha]_D^{25}$ +46° (1·0 chf.).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71·25; H, 8·99. Found: C, 71·63; H, 8·95.

The eluates corresponding to benzene and 5% ether in benzene afforded 361 mg (60 per cent) of methyl 3α-acetoxy-11-keto-17α-methyletianate (XIV) as plate-like prisms from ether m.p. 168–70° with phase change to form massive prisms, m.p. 182–4°, $[\alpha]_D^{CHCl_3}$ +62 (in reference 8 m.p. 184° $[\alpha]_D^{25°}$ +63·7°(chf.)).

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71·25; H, 8·99. Found: C, 71·17; H, 8·80.

The eluates (50% benzene in petroleum ether–benzene) representing overlap fractions of XIV and XV amounted to 92 mg were shown by infrared analysis to consist of essentially equal amounts of the two isomers.

A Faworskii rearrangement carried out on 21·3 g of bromoketone (II), m.p. 168·5–172°, afforded after due processing 7·3 g of XV and 8·6 g of XIV.

3α-Hydroxy-11-keto-17α-methyletianic acid

The total crude amorphous residue from the bromination of 50·0 g (0·134 mole) of pregnane-11,20-dione-3α-ol 3-acetate with 21·5 g (0·135 mole) of bromine in a mixture of chloroform and methanol was treated with 1·4 l. of methanolic sodium methoxide containing 12·5 g (0·231 mole) of sodium methoxide. The mixture was heated under reflux for 3 hr, cooled and a cold solution of 240 g (4·28 moles) of potassium hydroxide in 300 ml of water added. Reflux was continued for an additional 40 hr, concentrated *in vacuo* to 300 ml and diluted with 400 ml of water. The insoluble gum which separated was removed by extraction with 2 portions of chloroform. The aqueous layer was filtered through Supercel and then acidified with 2 N hydrochloric acid. The precipitated acid was removed by filtration, washed with water and dried, weight 28·0 g (59·9 per cent), m.p. (cap.) 210–240°. Recrystallization from acetone afforded 13·9 g (29·7 per cent), m.p. (cap.) 280–281·5°, $[\alpha]_D^{25}$ +36° (1·0, dioxane) (in reference 8 m.p. 285–286°, $[\alpha]_D^{25}$ +29·5° (1·0, dioxane)); an additional recrystallization did not raise the m.p. An additional 2·5 g was obtained from the mother liquors to bring the total yield to 35 per cent.

Hydrolysis of the 17α-methylacetoxy ester (XIV) with refluxing aqueous methanolic potassium hydroxide as described below for the hydrolysis of the 17β-methyl ester (XV) gave material m.p. (cap.) 280–282°, undepressed on admixture with that prepared above.

The corresponding *methyl ester* was prepared by treating a slurry of 400 mg of the acid above in 20 ml of ether with excess ethereal diazomethane. The solid dissolved and nitrogen was evolved. Evaporation of the solvent and recrystallization from ether gave material, m.p. (cap.) 163·5–165°, $[\alpha]_D^{25}$ +42° (1·0, $CHCl_3$) (reference 8 m.p. 165°, $[\alpha]_D^{22}$ +41·5° (1·01, $CHCl_3$)).

17α-Methylpregnane-11,20-dione-3α-ol 3-acetate (XVI)

A solution of 2·0 g of the 17α-methyl acid, m.p. (cap.) 278–280°, in 10 ml of pyridine and 4·3 ml of acetic anhydride was heated for 1 hr at 70°, then 5 ml of water added and heating continued at 45° for an additional hour. The solution was poured into 200 ml of ice water, and acidified with concentrated hydrochloric acid. The colorless crystalline precipitate was removed by filtration, washed thoroughly with water and dried, weight 2·2 g (93·7 per cent), m.p. (cap.) 254–260°. One recrystallization from acetonitrile gave 1·7 g of *3α-acetoxy-11-keto-17α-methyletianic acid*, m.p. (cap.) 262–264·5°, $[\alpha]_D^{25}$ +58° (1·0 $CHCl_3$). Further recrystallization did not raise the m.p.

A 1·0 g sample of the acetoxy acid above in 25 ml of dry benzene was cooled to 10° and 4·0 ml of oxalyl chloride added. The solution was allowed to warm to room temperature for 2 hr and then heated briefly under reflux. Concentration *in vacuo* gave a crystalline residue which was dissolved in 20 ml of ether and reconcentrated. Recrystallization from ether afforded 0·7 g (66·8 per cent) of 3α-acetoxy-11-keto-17α-methyletianic acid chloride, m.p. (cap.) 189–192°.

Anal. Calcd. for $C_{23}H_{33}O_4Cl$: Cl, 8·67. Found: Cl, 8·62.

An ethereal solution of diazomethane was prepared from 2·5 g of N-nitroso-N-methylurea. This solution was added to an ice cold solution of 1·0 g of the acid chloride above in 10 ml of dry benzene and 20 ml of dry ether and the mixture stored at 0° for 15 hr. Then 20 ml of ether was distilled and after cooling to 0°, a solution of

0·5 g of hydrogen chloride in 10 ml of ether added. The evolution of nitrogen ceased in 0·5 hr. The excess acid was removed by washing with dilute aqueous sodium bicarbonate, the solution dried over sodium sulfate, filtered and the solvents removed *in vacuo* to give a brown gummy residue. Crystallization from acetonitrile afforded 0·40 g (38·5 per cent) of 21-*chloro*-17α-*methylpregnone*-11,20-*dione*-3α-*ol* 3-*acetate*, m.p. (cap.) 165–175°.

Anal. Calcd. for $C_{24}H_{35}O_4Cl$: Cl, 8·38. Found: Cl, 8·41.

Reductive removal of the 21-chlorine was carried out as follows: A solution of 2·0 g of the 17α-methyl chlorketone in 20 ml of glacial acetic acid was warmed to 40° and 2·0 g of zinc dust added portion-wise. After 1 hr, 100 ml of water was added and the precipitate collected on a filter, washed with water and dried, m.p. (cap.) 150–185°. A solution of this product in 40 ml of 1 : 1 benzene–hexane was poured into a column of 40 g of acid-washed alumina (Harshaw chromatographic grade). Elution with 2 l. of 1 : 1 benzene–hexane gave 1·1 g (59·8 per cent) of the 17α-methylpregnane (XVI), m.p. (cap.) 187–190°. Recrystallization from acetone, then from ethyl acetate, raised the m.p. (cap.) to 189·5–191°. The infrared spectrum in the solid state exhibited bands at 5·74 and 5·85 μ indicating the presence of acetate and carbonyl functions.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74·23; H, 9·28. Found: C, 74·18; H, 9·28.

When the preparation of XVI was carried out without isolation of the 21-chloro compound a 43 per cent yield was obtained from the acid chloride.

3α,17β-*Dihydroxy*-17α-*methyletiocholane*-11-*one* (XVII)

(*a*) *Via peroxytrifluoroacetic acid oxidation of* XVI. To a mixture of 0·41 ml of 90% hydrogen peroxide and 2·5 ml of methylene chloride at 0° was added with stirring 2·54 ml of trifluoroacetic anhydride over a period of 18 min. After about half of the anhydride had been added, the mixture became a single phase. The mixture was stirred for a few minutes more and then transferred to a dropping funnel and added dropwise with stirring to an ice-cold solution of 388·5 mg 17α-methylpregnane-11,20-dione-3α-ol 3-acetate (XVI) in 7·5 ml of methylene chloride containing 6·5 g of disodium hydrogen phosphate. The addition required 10 min and at the end, the slurry had become very thick. After an additional 10 min, the mixture was allowed to warm to 25° and stirring continued for 2 hr. During this time, considerable frothing was observed and 30 ml of methylene chloride was added in 3 portions at intervals. Finally, the mixture was heated under reflux for ½ hr, then 50 ml of water was added to dissolve the salts. The mixture was shaken vigorously, separated, and the aqueous layer extracted with an additional 25 ml of methylene chloride. The combined methylene chloride extracts were washed once with saturated salt solution, filtered through anhydrous magnesium sulfate and the solvent removed *in vacuo* to give 405 mg of colorless crystalline residue, m.p. (micro) 158–178° with previous softening. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 212·6 mg of crystals, m.p. (micro) 168–175°; the m.p. on admixture with the starting material (XVI) was 170–189°.

Since the product appeared to be a mixture, it was combined with its mother liquor and concentrated to dryness. The residue was heated under reflux for 2 hr and 40 min with 20 ml of methanol and 10 ml of 30% aqueous potassium hydroxide. The methanol was removed *in vacuo*, 25 ml of water added, and the product extracted with 4 portions of chloroform. The combined extracts were washed with water until

neutral, then filtered through magnesium sulfate and the solvent removed *in vacuo* to give 270 mg of amorphous solid. This material was chromatographed over 13·5 g of neutral alumina. The fractions eluted with benzene, 10%, 20% and 50% ether in benzene weighed 165 mg and crystallized as needles upon addition of ether. A portion of this material was recrystallized from ether–petroleum ether (b.p. 30–60°) and had the m.p. (micro) 76–81° with evolution of gas, resolidification as prismatic needles, remelting 130–133°, resolidification as plates, remelting 146–148·5°. This material was shown to be 17α-methylpregnane-11,20-dione-3α-ol by acetylation of a sample with acetic anhydride and pyridine for 5 hr at 100°. The product, after one recrystallization from ether–petroleum ether (b.p. 30–60°), had the m.p. 189–190·5°, undepressed on admixture with the starting material (XVI).

The fractions eluted with ether, 10% acetone–ether and with acetone crystallized spontaneously as prisms. These fractions were combined, weight 48 mg, and recrystallized twice from acetone–ether–petroleum ether (b.p. 30–60°) to give prisms, m.p. (micro) 203·5–205·5°, undepressed on admixture with 3α,17β-dihydroxy-17α-methyletiocholane-11-one prepared in part B below. The identity was confirmed by infrared comparison.

(b) *Via the reaction of methylmagnesium iodide with* 3α-*acetoxyetiocholane*-11,17-*dione* (VIII). Methylmagnesium iodide was prepared from 2·4 g of magnesium and 20 g of methyl iodide. The ether was distilled off and replaced with benzene until the temperature reached 60°. To the resulting solution of methylmagnesium iodide was added 1·75 g of 3α-acetoxyetiocholan-11,17-dione and the homogeneous solution was refluxed 2 hr. The reaction product was worked up by hydrolysis with water and ammonium chloride, acetylated and chromatographed. The eluates consisting of 1–5% ether in benzene afforded what is probably slightly impure 11α,17α-*dimethyletiocholane* 3α,11β,17β-*triol* 3-*acetate** as needles m.p. 140–2°, λ_{max} 2·95 μ (OH), 5·8 μ (OAc), 5·84 μ (very weak).

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 73·02; H, 10·05. Found: C, 73·15; H, 9·73.

The eluates representing 10—20% ether in benzene afforded 3α-*acetoxy*-17β-*hydroxy*-17α-*methyletiocholane*-11-*one* as prisms m.p. 210–13°. λ_{max} 2·92 μ (OH), 5·8 μ (OAc), 5·86 μ (C=O).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72·93; H, 9·46. Found: C, 73·25; H, 9·35.

A solution of 135 mg of the above 3α-acetoxy-17β-hydroxy-17α-methyletiocholone-11-one in 10 cm³ of methanol was refluxed for 2 hr with 1 g of potassium hydroxide in 1 cm³ of water. The product was crystallized from acetone–hexane to give 3α,17β-*dihydroxy*-17α-*methyletiocholane*-11-*one*, m.p. 203–5°.

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 75·00; H, 10·00. Found: C, 75·15; H, 9·81.

This material was found to be identical with that obtained in Part A above by mixed m.p. and infrared comparison.

3α-*Hydroxy*-11-*keto*-17β-*methyl*-17-iso*etianic acid*

A solution of 4·85 g (12·0 mmoles) of the 17β-methyl ester (XV), m.p. 156–7°, in 242·5 ml of 10% methanolic potassium hydroxide was heated in a nitrogen atmosphere at 170° for 48 hr in a glass-lined hydrogenation bomb. The methanol was then removed *in vacuo*, 450 ml of water added and the solution extracted with 3 portions of ether which were discarded. The aqueous layer was acidified with 80 ml of 6 N

* See footnote (†) p. 148.

hydrochloric acid and the solid which separated extracted with 3 portions of ethyl acetate. The combined extracts were washed 4 times with water, once with saturated salt solution, filtered through anhydrous magnesium sulfate and the solvent removed *in vacuo* to give 4·325 g of light brown crystalline residue. Recrystallization from ethyl acetate gave 3·18 g (76 per cent) of prisms, m.p. (micro) 260–263°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72·30; H, 9·26. Found: C, 71·93; H, 9·31.

The hydrolysis of the 17β-methyl ester (XV) was also carried out by hydrolysis with aqueous methanolic potassium hydroxide. A solution of 400 mg of XV in 40 ml of methanol was mixed with a solution of 6 g of potassium hydroxide in 7·5 ml of water. The mixture was heated under reflux for 48 hr, concentrated *in vacuo* to 7 ml, diluted with 10 ml of water and acidified with 2 N hydrochloric acid. The crystalline precipitate was filtered, washed with water and dried, m.p. (cap.) 255·5–259°. Recrystallization from acetonitrile raised the m.p. (cap.) to 258–259·5°.

17β-*Methyl*-17-iso*pregnane*-11,20-*dione*-3α-*ol* 3-*acetate* (XVIII).

A 2·09 g (6·0 mmole) sample of the 17β-methyl acid was treated with 10 ml of pyridine and 10 ml of acetic anhydride. After standing at 25° for 3 hr, the excess reagents were removed *in vacuo*. The residual oil was dissolved in ethyl acetate, concentrated to an oil, and this procedure repeated twice with ethyl acetate, twice with dry ether, and twice with dry benzene to remove the acetic anhydride and pyridine. Then 75 ml of dry benzene was added, the solution heated to reflux and a small amount distilled to thoroughly dry the solution. This solution, after cooling to 0°, was treated with a solution of 9·93 ml of freshly distilled oxalyl chloride in 24·6 ml of benzene and stored at 25° for 3 hr. The mixture was then concentrated *in vacuo* to a colorless amorphous residue which was dissolved in 25 ml of dry benzene and reconcentrated.

A solution of this residue in 65 ml of dry benzene was added dropwise with stirring over a period of 10 min to about 170 ml of ethereal diazomethane cooled to −15°; the diazomethane was prepared from 8·85 ml of ethyl N-nitroso-N-methyl urethane. The yellow mixture was held at −15° for an additional 0·5 hr, then stored at 0° overnight. After standing at 25° for 1·5 hr, the solvents were removed *in vacuo*. The amorphous residue dissolved in 30 ml of dry ether and reconcentrated.

The pale yellow product in 103·5 ml of dry ether was treated with 24·1 ml of 1·368 N hydrogen chloride in ether and the mixture stored at 25° overnight. The initial evolution of nitrogen had ceased. The solution was poured onto 100 g of ice with stirring and the product extracted with 2 portions of ether. The combined extracts were washed free of acid with 3 portions of water, then washed once with saturated salt solution, filtered through magnesium sulfate and the ether removed *in vacuo* to give 2·71 g of amorphous residue which crystallized on adding ether. Recrystallization of a portion of this material from ether gave 21-*chloro*-17β-*methyl*-17-iso*pregnane*-11,20-*dione*-3α-*ol* 3-*acetate* as prism, m.p. (micro) (ca. 173°).

Anal. Calcd. for $C_{24}H_{35}O_4Cl$: Cl, 8·38. Found: Cl, 8·05.

A 2·50 g sample of the chloroketone above was dissolved in 27·5 ml of glacial acetic acid at 25°. The solution was swirled and 3·59 g of zinc dust added in portions over 15 min. The temperature of the mixture slowly rose to 33°, then dropped to 25°. After about one-quarter of the zinc had been added, the solution became bright yellow and then faded to nearly colorless. Finally the mixture was heated at 100° for

1 hr with occasional swirling, 150 ml of water was added and the product extracted with 3 portions of ether. The combined extracts were washed successively with water twice, with 5% aqueous sodium bicarbonate until neutral, again with water 3 times and finally with saturated salt solution. The washed extracts were filtered through magnesium sulfate and the solvent removed *in vacuo* to give a crystalline residue, weight 2·03 g. This was chromatographed over 152 g of acid-washed alumina. After development with 1:3 and 1:2 benzene–petroleum ether (b.p. 30–60°), crystalline material was eluted with 1:1 and 2:1 benzene–petroleum ether and with benzene. All these fractions melted in the range 160–173° and were combined, weight 1·805 g. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 1·39 g of the 17β-methyl-17-*iso*pregnane-11,20-dione-3α-ol 3-acetate (XVIII), m.p. (micro) 171–174°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74·23; H, 9·28. Found: C, 73·99; H, 9·38.

3α,17α-*Dihydroxy*-17β-*methyletiocholane*-11-*one* (XIX)

(a) *Via peroxytrifluoroacetic acid oxidation of* XVIII. A solution of peroxytrifluoroacetic acid was prepared as described above from 1·64 ml of 90% hydrogen peroxide and 10·16 ml of trifluoroacetic anhydride. This was added to a solution of 777·0 mg (2·0 mmoles) of 17β-methyl-17-*iso*pregnane-11,20-dione-3α-ol 3-acetate (XIX) in 30 ml of methylene chloride containing 26·0 g of disodium hydrogen phosphate; the addition required 20 min. The mixture was allowed to stand at 25° overnight, then heated under reflux for 1 hr. Addition of water and extraction as described above gave 0·79 g of amorphous residue. This was hydrolyzed by heating under reflux for 3 hr with 20 ml of methanol and 10 ml of 30% aqueous potassium hydroxide. Removal of the methanol *in vacuo*, dilution with water and extraction with ether gave 0·39 g of an amorphous mixture which was chromatographed over 19·5 g of neutral alumina. The fractions eluted with 10, 20 and 50% ether in benzene and with ether were combined, weight 231 mg. A portion of this oily material on acetylation with acetic anhydride and pyridine at 25° for 2 hr and recrystallization from petroleum ether (b.p. 30–60°) had the m.p. 164–170·5°, undepressed on admixture with the starting acetate (XVIII).

After further development of the column with 10, 25 and 50% acetone in ether, the fractions eluted with acetone were combined, weight 99·5 mg. Recrystallization from acetone–ether followed by recrystallization from ethyl acetate gave 26·0 mg of prisms, m.p. (micro) 196–199·5°, undepressed on admixture with a sample of 3α,17α-dihydroxy-17β-methyletiocholane-11-one prepared in part (b) below and showing identical infrared spectra.

(b) *Via the sequence originating from* 3α-*acetoxy*-17α,21-*dibromopregnane*-11-*one* (IV). A solution of 14·96 g of 3α-acetoxypregnane-11,20-dione in 290 cm^3 glacial acetic acid was brominated with 13 g of bromine at room temperature. After complete addition of bromine the reaction mixture was heated at 40–50° for 30 min and the product precipitated with water and filtered. The product was extracted with ethyl acetate (500–600 cm^3) and the ethyl acetate extract washed with dilute aqueous potassium bicarbonate solution. The solvent was concentrated *in vacuo* and the dibromide (IV) crystallized from acetone, wt. 16 g, m.p. 173–175° (reported ref. 8 m.p. 177°)

The above dibromide in 650 cm^3 of methanol refluxed 2 hr with 35 g of potassium

hydroxide in 35 cm³ of water. At the end of this period the methanol was removed *in vacuo* replaced with water and the aqueous solution extracted twice with ether. Acidification precipitated the crude acid III. The latter was dissolved in ethyl acetate, dried over magnesium sulfate and concentrated to the point of crystallization. There was obtained 8 g of the $\Delta^{\alpha,\beta}$-acid XXI recrystallized from acetone–hexane, m.p. 247°. λ_{max}^{Nj} 3 μ, 5·80 μ, 6·02 μ, 5·93 μ.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72·83; H, 8·67. Found: C, 73·02; H, 8·65.

The $\Delta^{\alpha,\beta}$-acid XXI (3·5 g) in 15 cm³ of quinoline and 0·35 g of copper powder was heated under reflux for 1 hr. Evolution of carbon dioxide had ceased after 30 min. The reaction product was diluted with ether, filtered through Supercel, and the quinoline removed by extraction with dilute hydrochloric acid. Concentration of the ether produced 3·1 g of crystalline product which appeared to be homogeneous by alumina chromatography m.p. 145–146°. Recrystallization from ether–petroleum ether afforded the *exomethylene derivative* (XXII), m.p. 147–147·5°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79·39; H, 10·00. Found: C, 79·47; H, 9·93.

A solution of 1·5 g of the olefin XXII in 5 cm³ of benzene was treated with 26 cm³ of 0·21 M perbenzoic acid in benzene for 18 hr. At the end of this period the reaction mixture was washed free of acid with 5% aqueous sodium carbonate solution. Concentration produced 1·2 g of a crystalline product which did not melt sharply (135–150°) and was therefore processed without further purification.

The above epoxidized olefin (1 g) was dissolved in 60 cm³ of tetrahydrofuran and refluxed with 1 g of lithium aluminum hydride for 2 hr. The reduction product was acetylated with acetic anhydride in pyridine and the acetylated product oxidized in acetic acid with 300 mg of chromic acid. Chromatography of the oxidized product afforded oily fractions which were saponified to give crystalline 3α,17α-dihydroxy-17β-methyletiocholane-11-one (XIX) m.p. 195–197·5° $[\alpha]_D^{25°}$ +39·6° (1·0 acetone).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 75·00; H, 10·00. Found: C, 74·96; H, 10·00.

This material was found to be identical in mixed m.p. and infrared comparison with XIX obtained above in part (a).

3α-*Acetoxy*-21-*methanesulfonyloxypregnane*-11,20-*dione* (XXIVa)

A solution of 2 g of 3α-acetoxy-21-hydroxypregnane-11,20-dione[18] (XXIV) in 9 cm³ of pyridine was treated with 3 cm³ of methanesulfonyl chloride at 0–5° for 18 hr. The reaction mixture was decomposed with ice-water extracted with ether and the ether solution washed with dilute aqueous hydrochloric acid, potassium bicarbonate solution and finally dried and concentrated. The residue was crystallized from acetone ether m.p. 164·5–166°.

Anal. Calcd. for $C_{24}H_{36}O_7S$: C, 61·54; H, 7·69. Found: C, 61·85; H, 7·94.

3α-*Acetoxy*-21-*bromopregnane*-11,20-*dione* (XXV)

A solution of 2 g of the 21-mesylate derivative XXIVa in 10 cm³ of acetone was refluxed for 2 hr with 4 g of lithium bromide. The product crystallized as needles from ether, m.p. 164–165·5°.

Anal. Calcd. for $C_{23}H_{33}O_4Br$: C, 60·93; H, 7·28; Br. 17·66. Found: C, 61·18; H, 7·26; Br, 17·59.

[18] Huang-Minlon and R. Pettebone, Unpublished work.

Rearrangement of carbinols XVII and XIX

Samples of XVII and XIX (100 mg) were heated in 10 cm^3 of formic acid on a steam bath for 2 hr according to the method of Kägi and Miescher.[15] The product was identical in both instances giving XX as prisms from ligroin, m.p. 129–131·5°. $\lambda_{max}^{CH_3OH}$ 240 mμ ε = 17,200 λ_{max} 5·79 (OAc), 6·00 (conj. C=O).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76·78; N, 9·31. Found: C, 76·52; H, 9·58.

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