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STEROIDS—CXXVI[1]

SOME FISSION REACTIONS OF STEROID 5,6-EPOXIDES INDUCED BY BORON TRIFLUORIDE ETHERATE

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Abstract—Steroid 5α,6α-epoxides in dimethyl formamide solution undergo fission in the presence of boron trifluoride etherate with solvent participation to afford 5α-hydroxy-6β-formates. The mechanism of this and related reactions is discussed. In dimethyl sulphoxide and acetone the corresponding 5α,6β-diols are obtained.

5β,6β-Epoxides are much more resistant to boron trifluoride etherate in dimethyl formamide but when reaction occurs the product is the corresponding 5α,6β-diol.

In a series of alcohols, pregnenolone acetate-α-epoxide (Ia) upon reaction with boron trifluoride etherate afforded either the corresponding 5α-hydroxy-6β-alkyl ether or in the case of the branched C-3 to C-5 alcohols the 5α,6β-diol. In phenol solution 6β-phenoxypregnan-3β,5α-diol-20-one 3-acetate (XIX) was obtained. The conversion of the latter compound into 6α-phenoxyprogesterone (XXII) is described.

THE fission of steroid 5α,6α-epoxides with boron trifluoride etherate in benzene or benzene–ether solutions has been studied in great detail[3–11] and dependent upon the nature and stereochemistry of the substituents at C-3 either the C-6-ketone[3] (rings A–B *cis*) or the 6β-fluoro-5α-hydroxy-fluorohydrin[4–11] was obtained.

In an attempt to determine the mechanism of this very unusual reaction[12] we have investigated the fission of steroid 5,6-epoxides in reaction media other than benzene or benzene–ether mixtures. This paper describes some of our findings.

Initial experiments were carried out with 5α,6α-oxidopregnan-3β-ol-20-one acetate (Ia) and the reaction of this epoxide with boron trifluoride etherate in dimethyl formamide, dimethyl acetamide, dimethyl sulphoxide, acetone, a series of alcohols and phenol was investigated.

Treatment of a solution of Ia in dimethyl formamide with boron trifluoride etherate for 2 hours at room temperature followed by addition of water precipitated a fluorine free reaction product (IIa).[13] The possibility that simple hydrolytic cleavage had occurred to yield the 5α,6β-diol (IVa) was eliminated by a direct comparison

[1] Steroids—CXXV: J. A. Zderic and D. Chavez Limon, *J. Amer. Chem. Soc.* **81**, 4570 (1959).
[2] Taken in part from the thesis submitted by R. Urquiza to the Instituto Politécnico Nacional, México for the degree of Químico Biólogo.
[3] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957).
[4] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).
[5] A. Bowers and H. J. Ringold, *Tetrahedron* **3**, 14 (1958).
[6] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 4423 (1958).
[7] A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron* **7**, 138 (1959).
[8] A. Bowers, E. Denot, M. B. Sánchez and H. J. Ringold, *Tetrahedron* **7**, 153 (1959).
[9] J. S. Mills, A. Bowers, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 1264 (1959).
[10] J. A. Edwards, A. Zaffaroni, H. J. Ringold and C. Djerassi, *Proc. Chem. Soc.* 87 (1959).
[11] J. A. Zderic, D. Chavez Limon, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 3120 (1959).
[12] For an analysis of the electronic and conformational factors involved in the fission of 3β-hydroxy, 3-keto or 3-cycloethylene-ketal-5α,6α-epoxides with boron trifluoride etherate cf. refs. 4 and 7.
[13] In the absence of BF_3 the epoxide was recovered unchanged.

with an authentic sample, in turn prepared by aqueous perchloric acid[14] hydrolysis of the epoxide (Ia) in acetone solution.

Treatment of IIa with acetic anhydride in pyridine solution for 48 hours at room temperature led only to the recovery of starting material in good yield, indicating the absence of a secondary hydroxyl group. It was then treated with an excess of lithium aluminum hydride and the reduction product without purification was oxidized with 8 N chromic acid in acetone solution.[15] A compound was obtained in

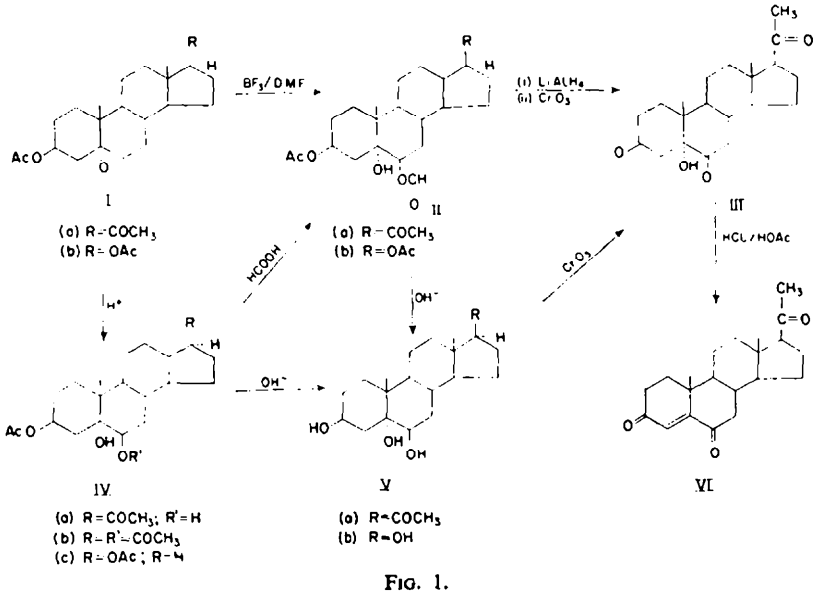


FIG. 1.

good yield which had strong carbonyl bands in the infrared at 1690 and 1718 cm^{-1} and also exhibited hydroxyl absorption at 3450 cm^{-1}. It showed no selective absorption in the ultraviolet and analyzed for $C_{21}H_{30}O_4$. Treatment of this compound with hydrogen chloride in acetic acid smoothly afforded 6-keto-progesterone[16] (VI), λ_{max} 250 mμ, log ε 4·00, identical in every respect with an authentic sample.[16b] This reaction sequence clearly established that the epoxide (Ia) cleaved to afford a C-6 oxygenated product and in view of its non-acylable nature it could best be formulated as a C-6 ester. A compound satisfying these requirements was the 5α-hydroxy-6β-formate (IIa), which upon lithium aluminum hydride reduction followed by oxidation would afford pregnan-5α-ol-3,6,20-trione (III). Acid catalyzed dehydration[17] would then yield 6-ketoprogesterone (VI). Indeed, alkaline hydrolysis of IIa afforded a triol (Va) identical with the product obtained from the alkaline hydrolysis of pregnan—3β,5α,6β-triol-20-one 3-acetate (IVa) and its derived diacetate (IVb). Also oxidation of the authentic triol (Va) with 8N chromic acid led to pregnan-5α-ol-3,6,20-trione (III) identical in every respect with the product obtained from compound IIa after

[14] F. Sondheimer, O. Mancera and G. Rosenkranz, *J. Amer. Chem. Soc.* **76**, 5020 (1954). These authors report a similar reaction in tetrahydrofuran solution.

[15] [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).

[16] [a] M. Ehrenstein, *J. Org. Chem.* **4**, 506 (1939); [b] C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 1226 (1954).

[17] For analogous dehydrations with hydrogen chloride in acetic acid cf. refs. 5–10.

successive treatment with lithium aluminum hydride and chromium trioxide (II → III). The structure of compound IIa (pregnan—3β,5α,6β-triol-20-one 3-acetate 6-formate) was confirmed unambiguously when it was prepared in good yield by reaction of the triol monoacetate (IVa) with formic acid.[18]

The formation of a 6β-formate ester from a 5α,6α-epoxide can perhaps best be represented as a pseudo nucleophilic attack of dimethyl formamide[19] at C-6β in the manner shown in Fig. 2 (I → VII → II), the reaction being assisted by coordination

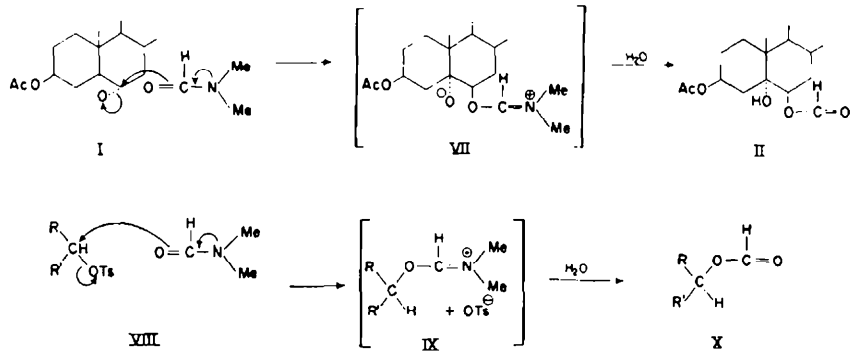


FIG. 2.

of electron deficient boron trifluoride with the epoxide oxygen atom. The aldimine type intermediate (VII) would be expected to hydrolyze readily in the presence of water[20] to afford the formate ester.[21]

Recently, two reports have appeared which lend credence to the idea that SN_2 attack by dimethyl formamide at electron deficient carbon atoms is not confined solely to 5α,6α-epoxides. Chang and Blickenstaff[22] have shown that a series of 3α or 3β-tosylates of saturated steroids were converted into their *epimeric* formates after treatment with dimethyl formamide at 78°. Similarly Paris and Hoffman[23] have obtained epi-estradiol ($\Delta^{1,3,5}$-estratriene-3β,17α-diol) by reacting the corresponding 17β-*tosylate* with potassium acetate in dimethyl formamide followed by an alkaline hydrolysis. Although the latter example is complicated by the addition of potassium acetate which conceivably could itself be the active displacing agent it should be pointed out that all previous attempts to displace a 17β-tosylate with acetate salts have been substantially unsuccessful.[24]

Walden inversion of this type can readily be explained on the basis of SN_2 attack at the carbon atom carrying the tosyloxy group to afford an aldimine type intermediate which reacts with water to generate the formate ester (Fig. 2) (VIII → IX → X). It is of interest to note that cholesterol tosylate affords cholesterol formate and not

[18] H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 816 (1956).

[19] The dimethyl formamide used for this work was carefully distilled immediately prior to use and was shown by titration with standard alkali to contain less than 0·0003 g/cc of formic acid.

[20] No vigorous attempts were made to dry the D.M.F. and S. R. Ross and M. M. Labes, *J. Amer. Chem. Soc.* 79, 4155 (1957) report that even when D.M.F. is distilled over barium oxide it still contains 0·09–0·13% of water, more than the equimolar proportion needed for reaction. Thus the aldimine intermediate (VII) could either have been hydrolyzed during the time of the reaction or when water was added to precipitate the product.

[21] This mechanism was outlined by A. B. at the Steroids and Natural Products section of the Gordon Research Conference, August 1958.

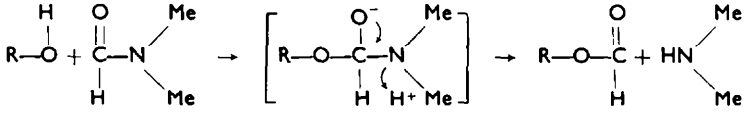
[22] F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.* **80**, 2906 (1958).

[23] A. A. Paris and C. Hoffman, *U.S. Pat.* 2,835,681.

[24] J. Elks and C. W. Shoppee, *J. Chem. Soc.* 241 (1953).

epi-cholesterol formate upon treatment with dimethyl formamide.[22] This is an expected result since it is well known that SN_2 type displacements at C-3 in cholesterol take place with an overall retention of configuration due to participation of the Δ^5-double bond.[25]

The direct formylation of a series of primary alcohols and cholesterol by iodine pentafluoride and dimethyl formamide has also been reported recently.[26] This reaction is probably of the same type and in the absence of double bond participation it should take place with inversion of configuration. Unfortunately, the author did not report a successful formylation of a secondary alcohol and in the absence of evidence to the contrary the possibility cannot be overlooked that formylation proceeded with retention of configuration, e.g.



A mechanism of this type could explain the formation of a 6β-formate from the BF_3-DMF fission of a 5α,6α-epoxide by assuming that the initial reaction is formation of the 5α,6β-diol and subsequent formylation at C-6 with retention of configuration. It was readily seen that this was not the case when IVa was recovered unchanged after treatment with boron trifluoride etherate in dimethyl formamide. Cholesterol was also stable to these reaction conditions.

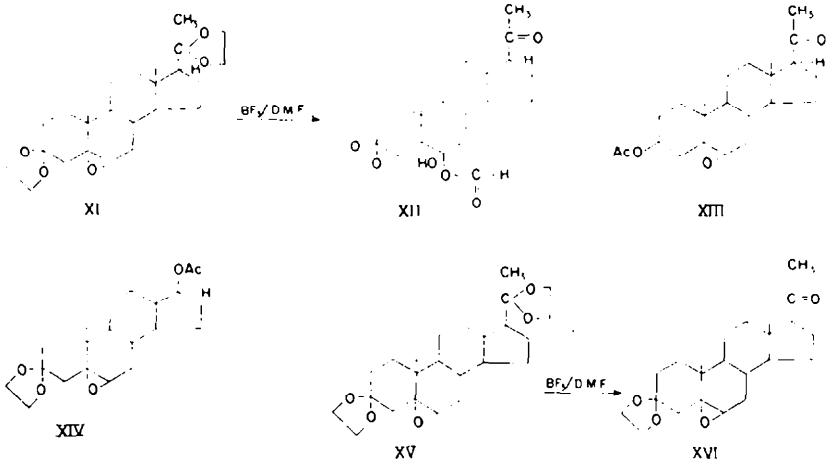


FIG. 3.

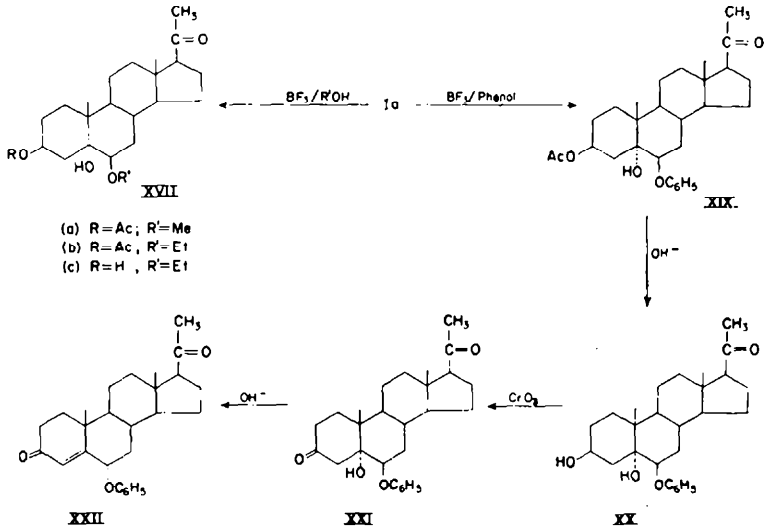
The general applicability of the boron trifluoride–dimethyl formamide reaction to 5α,6α-epoxides was shown when a similar reaction with 5α,6α-oxidoandrostan-3β, 17β-diol diacetate (Fig. 1) (Ib) afforded the 6β-formate (IIb). Alkaline hydrolysis of IIb gave the same tetrol (Vb) as was obtained from the alkaline hydrolysis of the tetrol-diacetate (IVc). The latter compound was obtained in good yield by the aqueous perchloric acid fission[14] of Ib. Formic acid treatment of the tetrol diacetate (IVc) readily gave the 6β-formate (IIb) identical in every respect with the product from the boron trifluoride in dimethyl formamide treatment of Ib.

[25] S. Winstein and R. Adams, *J. Amer. Chem. Soc.* **70**, 838 (1948).
[26] T. E. Stevens, *Chem. & Ind.* 1090 (1958).

Extension of this reaction to a 3-cycloethylene ketal-5α,6α-epoxide led to a similar result, progesterone-bisketal-α-epoxide[27] (Fig. 3) (XI) yielding mainly pregnan—5α, 6β-diol-20-one 3-cycloethylene ketal 6-formate (XII), λ_{max}^{KBr} 3550 cm^{-1} (hydroxyl), 1725 and 1175 cm^{-1} (formate ester),[28] 1705 cm^{-1} (20-ketone) and 1125 cm^{-1} (ketal). In contrast to C-20, the cycloethylene ketal group at C-3 was stable to the conditions of the reaction. This marked difference in stability towards boron trifluoride of C-3 and C-20-ketal groups has been noted previously.[7]

In contrast to 5α,6α-epoxides the corresponding 5β,6β-epoxides were found to be much more resistant to cleavage by boron trifluoride etherate. For example, 5β,6β-oxidoandrostan-17β-ol 3-cycloethylene ketal acetate[7] (XIV) was recovered unchanged after 3 hours at room temperature with boron trifluoride etherate in dimethyl formamide and progesterone bisketal-5β,6β-epoxide (XV) underwent hydrolysis of the ketal group at C-20 to afford 5β,6β-oxidopregnan-20-one 3-cycloethylene ketal (XVI). However, pregnenolone acetate-5β,6β-epoxide[29] (XIII) under the same conditions was only recovered unchanged to the extent of 25 per cent, the corresponding 5α,6β-diol (IVa) being isolated in 36 per cent yield.

Replacement of dimethyl formamide with dimethyl acetamide in the boron trifluoride fission of pregnenolone acetate α-epoxide (Ia) led to the recovery of starting material and not to the 6β-acetate. Presumably steric factors inhibit the participation of dimethyl acetamide in a reaction of this type. However, in both dimethyl sulphoxide and acetone the room temperature treatment of the epoxide (Ia) with boron trifluoride etherate led to the 5α,6β-diol (IVa). Coordination of boron trifluoride with the epoxide oxygen followed by decomposition of this complex with water would afford the *trans*-diol (IVa).



XVII XIX XXII XXI XX

FIG. 4.

[27] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).

[28] The band at 1175 cm^{-1} is the C-O stretching vibration and is very characteristic for formate esters. The corresponding band of an acetate group lies between 1230 and 1250 cm^{-1} cf. L. J. Bellamy, *The Infrared Spectra of Complex Molecules* p. 161 Methuen, London (1956) and ref. 22.

[29] This compound was obtained by chromatography of the mother liquors from the preparation of Ia by the permonophthalic acid epoxidation of pregnenolone acetate. It was less polar towards alumina and had a specific rotation 32° more dextro-rotatory than Ia, in full accord with its assigned structure.[7]

The boron trifluoride induced fission of pregnenolone acetate α-epoxide was then investigated in a series of alcohols and with methanol and ethanol the corresponding 5α-hydroxy-6β-alkyl ethers (Fig. 4) (XVIIa) and (XVIIb) respectively were obtained. When isopropyl, *n*-butyl, tertiary butyl or tertiary amyl alcohol were used as solvents the product was the 5α-6β-diol (IVa), again emphasizing that substitution reactions at C-6β are sensitive to steric factors. However if the reaction was carried out in molten phenol at 50° the 6β-phenoxy ether (XIX) was obtained in fair yield and by appropriate manipulation it afforded 6α-phenoxyprogesterone (XXII). Mild alkaline hydrolysis of XIX gave the corresponding 3β-alcohol (XX) whence oxidation with 8 N-chromic acid led to the 5α-hydroxy-3-ketone (XXI). 6β-Substituted 5α-hydroxy-3-ketones are known to undergo elimination in the presence of small amounts of alkali with concomitant inversion of the 6β (axial) group to afford 6α-substituted-Δ^4-3-ketones[30] and in a like manner treatment of 6β-phenoxypregnan-5α-ol-3, 20-dione (XXI) with 0·25 per cent methanolic potassium hydroxide for 16 hours at room temperature gave 6α-phenoxyprogesterone (XXII).

EXPERIMENTAL

Melting points are uncorrected. Rotations were measured in chloroform unless stated otherwise and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Dr. L. J. Throop 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 elemental analyses were carried out by Dr. A. Bernhardt, Mülheim/Ruhr, Germany.

Treatment of pregnenolone acetate α-epoxide (Ia) *with boron trifluoride etherate in dimethyl formamide*

Boron trifluoride etherate (1·0 cc) (freshly distilled) was added to a solution of pregnenolone acetate epoxide (Ia, 500 mg) in dimethyl formamide[19,20] (20 cc) and kept at room temp for 4 hr. Addition of ice water and filtration afforded pregnan-3β,5α,6β-triol-20-one 3-acetate 6-formate (IIa, 450 mg), m.p. 195–201°, raised by one crystallization from acetone–hexane to 214–216°. The analytical sample from acetone–hexane had m.p. 215–217°, $[\alpha]_D \pm 0°$. λ_{max}^{KBr} 3500,1757 (sh), 1730,1690 1250 and 1155 cm^{-1}. (Found: C, 68·58; H, 8·44 $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·63%). IIa (150 mg) was recovered unchanged after treatment with acetic anhydride (0·5 cc) in pyridine (5 cc) at room temp for 48 hr.

Conversion of IIa *into pregnan-5α-ol-3,6,20-trione* (III)

A solution of IIa (750 mg) in dry ether (75 cc) and tetrahydrofuran (75 cc) was added over 10 mins to a stirred suspension of lithium aluminum hydride (750 mg) in ether (100 cc). After 16 hr at room temp ethyl acetate was added to destroy the excess of reagent. Saturated sodium sulphate solution (15 cc) was then added followed by anhydrous sodium sulphate (approx 20 g). The inorganic salts were removed by filtration and the residue washed well with chloroform. Removal of the solvent from the combined filtrates afforded a product which was dissolved in acetone (300 cc) and cooled to 0°. An excess of 8 N-chromic acid[15] was then added and the solution kept at 0° for a further 2 mins. Addition of water and filtration afforded pregnan-5α-ol-3,6,20-trione (III, 435 mg), m.p. 265–271°, raised by crystallizations from aqueous pyridine to 278–280°, $[\alpha]_D$ +31° (pyridine), λ_{max}^{KBr} 3450, 1718 and 1690 cm^{-1}. (Found: C, 73·15; H, 8·60; O, 18·19. $C_{21}H_{30}O_4$ requires: C, 72·80; H, 8·73; O, 18·47%).

Treatment of pregnan-5α-ol-3,6,20-trione (III) *with hydrogen chloride in acetic acid*

Dry hydrogen chloride was bubbled through a suspension of pregnan-5α-ol-3,6,20-trione (III, 250 mg) in acetic acid (20 cc) at 15–20° for 5 min when the flask was stoppered and kept at 20° for 4 hr. Addition of ice water and filtration afforded 6-ketoprogesterone (VI, 180 mg), m.p. 178–183° raised by crystallizations from acetone–hexane to 191–193°, undepressed on admixture with an authentic sample;[16b] λ_{max}^{EtOH} 250 mμ, ε 10,000, $[\alpha]_D$ +30°.

[30] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1958), and references cited therein.

Pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa)

Perchloric acid (0·6 cc of 7%) was added to a solution of pregnenolone acetate α-epoxide (Ia, 750 mg) in acetone (25 cc). After 16 hr at room temp addition of ice water and filtration afforded pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa, 690 mg) m.p. 214–222° raised by several crystallizations from acetone–hexane to 228–230°, $[\alpha]_D$ +36°. (Found: C, 70·12; H, 9·30; O, 20·82. $C_{23}H_{36}O_5$ requires: C, 70·37; H, 9·20; O, 20·50 %).

Acetylation of IVa (pyridine–acetic anhydride/room temp/16 hr) afforded pregnan-3β,5α,6β-triol-20-one 3,6-diacetate (IVb), m.p. 215–217°, $[\alpha]_D$ ±0°. Lit[31] reports m.p. 212–215°, $[\alpha]_D$ −7° (Found: C, 69·17; H, 8·89; O, 22·04. Calc. for $C_{26}H_{38}O_6$: C, 69·09; H, 8·81; O, 22·10%).

Stability of IVa *to boron trifluoride etherate in dimethyl formamide*

Boron trifluoride etherate (0·1 cc) was added to a solution of IVa (50 mg) in dimethyl formamide (20 cc). After 4 hr at room temp addition of water and filtration afforded IVa identical in every respect with starting material.

Pregnan-3β,5α,6β-triol-20-one (Va)

(a) Potassium hydroxide (800 mg) was added to a solution of pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa) in methanol (40 cc) and heated under reflux for 2 hr. After acidification with acetic acid and concentration to 10 cc addition of ice water precipitated pregnan-3β,5α,6β-triol-20-one (Va, 305 mg) m.p. 243–348° raised by several crystallizations from acetone–hexane to 253–255°, $[\alpha]_D$ +33° +32° (both in pyridine), $\lambda_{max}^{CHCl_3}$ 3438, and 1695 cm^{-1}. Lit[31] reports m.p. 252–255°, $[\alpha]_D$ +59° (pyridine). (Found: C, 71·85; H, 9·75; O, 18·15. Calc. for $C_{21}H_{34}O_4$: C, 71·96; H, 9·78; O, 18·26%).

(b) Alkaline hydrolysis of the diacetate (IVb) also afforded pregnan-3β,5α,6β-triol-20-one (Va) m.p. 250–253° identical in every respect with the product obtained from the preceding experiment.

Alkaline hydrolysis of pregnan-3β,5α,6β-triol-20-one 3-acetate 6-formate (IIa)

Potassium hydroxide (2·0 g) was added to a solution of IIa (1·0 g) in methanol (100 cc) and heated under reflux for 2 hr. After acidification with acetic acid the solution was concentrated to approximately 10 cc, when addition of ice water and filtration afforded pregnan-3β,5α,6β-triol-20-one (Va, 620 mg), m.p. 248–250°, raised by crystallizations from acetone–hexane to 251–253° undepressed on admixture with an authentic sample. The infrared spectrum was identical with the spectrum of the product obtained from the alkaline hydrolysis of IVa.

Oxidation of pregnan-3β,5α,6β-triol-20-one (Va)

The triol (250 mg) in acetone (60 cc) was treated with an excess of 8 N chromic acid[15] at 0° for 2–3 mins. Addition of water afforded a precipitate of pregnan-5α-ol-3,6,20-trione (III, 210 mg) m.p. 272–279°, raised by crystallization from aqueous pyridine to 278–280°, undepressed on admixture with the product described above (IIa → III), $[\alpha]_D$ +32° (pyridine). The infrared spectra were identical.

Formylation of pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa)

The triol monoacetate (IVa, 500 mg) in formic acid (60 cc) was heated at 65° for 2 hr. After concentrating this solution to 20 cc *in vacuo* addition of ice water and filtration gave a product which after one crystallization from acetone–hexane afforded pregnan-3β,5α,6β-triol-20-one 3-acetate 6-formate (IIa, 310 mg.), m.p. 214–216° undepressed on admixture with the product obtained from the BF_3-D.M.F. fission of the epoxide (Ia → IIa), $[\alpha]_D$ ±0°. The infrared spectra of these two compounds were identical.

Androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc)

Perchloric acid (1·2 cc of 7%) was added to a solution of 5α,6α-oxidoandrostan-3β,17β-diol diacetate (Ib, 1·5 g) in acetone (50 cc). After 16 hr at room temp addition of water and extraction with ether gave a product which after one crystallization from acetone–hexane afforded androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc, 980 mg), m.p. 180–182°, raised by several crystallizations from

[31] O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.* **16**, 192 (1951).

acetone-hexane to 184–185°, $[\alpha]_D$ −44°; −41° (pyridine). (Found: C, 67·34; H, 9·11. $C_{23}H_{36}O_6$ requires: C, 67·62; H, 8·88%).

Androstan-3β,5α,6β,17β-tetrol (Vb)

Potassium hydroxide (1·0 g) was added to a solution of androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc, 500 mg) in methanol (50 cc) and heated under reflux for 2 hr. After acidification with acetic acid the solution was concentrated to a small volume when a saturated solution of sodium chloride was added and the product was extracted with ethyl acetate. The combined extracts were washed with a saturated solution of sodium chloride and dried over sodium sulphate. Removal of the solvent afforded androstan-3β,5α,6β,17β-tetrol (Vb), m.p. 249–257° raised by one crystallization from acetone–hexane to 259–261°, 310 mg. The analytical sample from acetone–hexane had m.p. 262–264°, $[\alpha]_D$ −14° (pyridine). (Found: C, 69·99; H, 10·07. $C_{19}H_{32}O_4$ requires; C, 70·33 H, 9·94%).

Androstan-3β,5α,6β,17β-tetrol 3,17-*diacetate* 6-*formate* (IIb)

(a) Boron trifluoride etherate (4·0 cc) was added to a solution of 5α,6α-oxidoandrostan-3β,17β-diol diacetate (Ib, 2·0 g) in dimethyl formamide (80 cc). After 2 hr at room temp addition of water and filtration afforded androstan-3β,5α,6β,17β-tetrol 3,17-diacetate 6-formate (IIb,1·78 g), m.p. 169–173°, raised by crystallizations from benzene–hexane to 182–184°, $[\alpha]_D$ −60°. Crystallization from aqueous methanol afforded a solvated form, m.p. 174–177°, λ_{max}^{KBr} 3500, 1748, 1730, 1245 and 1170 (broad) cm^{-1} (Found: C, 66·25; H, 8·24; O, 25·13. $C_{24}H_{36}O_7$ requires: C, 66·03; H, 8·31; O, 25·56%).

(b) Androstan-3β,5α,6β,17β-tetrol 3,17-diacetate (IVc, 0·5 g) in formic acid (60 cc) was heated at 65° for 2 hr. The solution was then concentrated to 20 cc *in vacuo*, when ice water was added precipitating the 6β-formate (IIb, 415 mg), m.p. 164–166°, raised by crystallizations from aqueous methanol to 173–176°, undepressed on admixture with a sample prepared by method (a); $[\alpha]_D$ −64° The infrared spectra of the two products were identical.

Alkaline hydrolysis of androstan-3β,5α,6β,17β-tetrol 3,17-*diacetate* 6-*formate* (IIb)

The 6β-formate (IIb; prepared as in method (a) above) was hydrolyzed with methanolic potassium hydroxide exactly as described for the hydrolysis of IVc → Vb. The product was androstan-3β,5α,6β, 17β-tetrol (Vb), m.p. 258–260°, undepressed on admixture with an authentic sample; $[\alpha]_D$ −16°. The infrared spectra were identical.

Treatment of 5α,6α-*oxidopregnan*-3,20-*biscycloethylene-ketal* (XI) *with boron trifluoride*

Boron trifluoride etherate (1·0 cc) was added to a solution of the α-epoxide[27] (XI, 1·0 g) in dimethyl formamide (20 cc). After 3 hr at room temp addition of water and filtration afforded a product which was adsorbed from benzene–hexane (50 : 50; 100 cc) onto alumina (40 g). Elution with benzene–hexane (50 : 50; 600 cc) afforded pregnan-5α,6β-diol-20-one-3-cycloethylene ketal 6-formate (XII, 390 mg) m.p. 160–163°, raised by crystallizations from acetone to 170–172°, $[\alpha]_D$ +14°; XII did not exhibit selective absorption in the ultraviolet; λ_{max}^{KBr} 3550, 1725, 1712 and 1180 cm^{-1} (Found: C, 68·75; H, 8·41; O, 22·71. $C_{24}H_{36}O_6$ requires: C, 68·54; H, 8·63; O, 22·83%).

Treatment of 5β,6β,-*oxidoandrostan*-17β-*ol*-3-*cycloethylene-ketal* 17-*acetate* (XIV) *with boron trifluoride*

Boron trifluoride etherate (1·5 cc) was added to a solution of the β-epoxide[7] (XIV, 1·5 g) in dimethyl formamide (30 cc). After 3 hr at room temp addition of water and filtration afforded a product (1·39 g) m.p. 144–148°, undepressed on admixture with starting material. After one crystallization from acetone it had m.p. 144–146°, $[\alpha]_D$ ±0°. Lit[7] records m.p. 146–148°,$[\alpha]_D$ −4°.

Treatment of 5β,6β-*oxidopregnan*-3,20-*biscycloethylene-ketal* (XV) *with boron trifluoride*

Boron trifluoride etherate (2·0 cc) was added to a solution of the β-epoxide[7] (XV, 1·5 g) in dimethyl formamide (25 cc). After 3 hr at room temp addition of water and isolation with ethyl acetate gave a product which was adsorbed from benzene–hexane (1 : 1; 200 cc) onto alumina (75 g). Elution with benzene (800 cc) afforded 5β,6β-oxidopregnan-20-one-3-cycloethylene-ketal (XVI, 590 mg), m.p. 153–159°, raised by crystallizations from ethyl acetate–methanol containing a trace of pyridine to 159–161°, $[\alpha]_D$ +88°, λ_{max}^{KBr} 1710 cm^{-1} (Found: C, 73·55; H, 9·15; O, 17·29. $C_{23}H_{34}O_4$ requires: C, 73·76; H, 9·15; O, 17·09%).

5β,6β-Epoxidopregnan-3β-ol-20-one acetate (XIII)

The epoxidation of pregnenolone acetate (50 g) with permonophthalic acid (35 g) was carried out as described previously.[6] Crystallization of the product from methanol afforded 5α,6α-epoxidopregnan-3β-ol-20-one 3-acetate (31 g), m.p. 162–164° and a second crop (7·8 g) m.p. 117–165°. Evaporation of the mother liquors gave a noncrystalline product (10·5 g) which was adsorbed from hexane–benzene (70 : 30; 250 cc) onto alumina (350 g). Elution with hexane-benzene (1 : 1; 2 l.) and one crystallization from acetone–hexane gave 5β,6β-epoxidopregnan-3β-ol-20-one acetate (XIII, 3·25 g) m.p. 126–128°, raised by crystallizations from acetone–hexane to 137–139°, $[\alpha]_D$ +43°. (Found: C, 73·69; H, 9·27; O, 17·27. $C_{23}H_{34}O_4$ requires: C, 73·76, H, 9·15; O, 17·09%).

Treatment of 5β,6β-epoxidopregnan-3β-ol-20-one acetate (XIII) *with boron trifluoride*

Boron trifluoride etherate (0·5 cc) was added to a solution of 5β,6β-epoxidopregnan-3β-ol-20-one acetate (500 mg) in dimethyl formamide (10 cc) at room temp. After 3 hr at room temp addition of water and filtration afforded a product (450 mg) which was adsorbed from hexane–benzene (50 : 50; 100 cc) onto alumina (30 g). Elution with benzene (200 cc) gave starting material (125 mg) m.p. 133–136°, raised by one crystallization from acetone–hexane to 136–139° undepressed on admixture with an authentic sample. Further elution with benzene–ether (90 : 10; 600 cc) afforded pregnan-3β, 5α,6β-triol-20-one 3-acetate (IVa, 180 mg), m.p. 221–226° raised by crystallizations from acetone to 227–228°, undepressed on admixture with an authentic sample; $[\alpha]_D$ +38°. The infrared spectra of the two samples were identical.

6β-Methoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIa)

Boron trifluoride etherate (1·0 cc) was added to a solution of 5α,6α-oxidopregnan-3β-ol-20-one 3-acetate (Ia, 500 mg) in methanol (20 cc). After 2 hr at room temp addition of water afforded a product which after one crystallization from acetone–hexane gave 6β-methoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIa, 340 mg), m.p. 198–210° raised by crystallizations from acetone–hexane to 213–215°, $[\alpha]_D$ +20°, λ_{max}^{KBr} 3370, 1725, 1685 and 1245 cm^{-1} (Found: C, 71·13; H, 9·35; O, 19·25. $C_{24}H_{38}O_5$ requires: C, 70·90; H, 9·42; O, 19·68%).

6β-Ethoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIb)

Repetition of the previous experiment with ethanol instead of methanol led to 6β-ethoxypregnan-3β,5α-diol-20-one 3-acetate (XVIIb, 470 mg), m.p. 168–170°, raised by crystallizations from acetone–hexane to 177–179°, $[\alpha]_D$ +17°, λ_{max}^{KBr} 3400, 1725, 1685 and 1243 cm^{-1} (Found: C, 71·58; H, 9·47; O, 18·69. $C_{25}H_{40}O_5$ requires: C, 71·39; H, 9·59; O, 19·02%).

When this experiment was carried out for 24 hr instead of 2 hr concomitant hydrolysis of the 3β-acetate occurred to afford 6β-ethoxypregnan-3β,5α-diol-20-one (XVIIc), m.p. 218–220°, $[\alpha]_D$ +38°. (Found: C, 73·02; H, 10·12; O, 16·91. $C_{23}H_{38}O_4$ requires: C, 72·97; H, 10·12; O, 16·91%).

Acetylation of XVIIc (acetic anhydride/pyridine/room temperature/24 hr) smoothly afforded XVIIb.

When the epoxide (Ia) was treated with boron trifluoride etherate as described above (Ia → XVIIa) in either acetone, dimethyl sulphoxide, isopropyl alcohol, t-butyl alcohol or t-amyl alcohol the product in good yield was pregnan-3β,5α,6β-triol-20-one 3-acetate (IVa).

In dimethyl acetamide Ia was recovered unchanged.

6β-Phenoxypregnan-3β,5α-diol-20-one 3-acetate (XIX)

Boron trifluoride etherate (4·0 cc) was added to a solution of pregnenolone acetate 5α,6α-epoxide (Ia, 4·0 g) in anhydrous phenol (20 g) at 50°. After 5 min at 50° water (300 cc) was added and sufficient 5% KOH solution to give an alkaline solution. The product was then extracted from this solution with ether (3 × 250 cc) and the combined ether extracts were washed well with water and dried over sodium sulphate. Removal of the solvent gave a product which was absorbed from benzene–hexane (1 : 1; 200 cc) onto alumina (200 g). Elution with benzene–hexane (80 : 20; 1500 cc) afforded 6β-phenoxypregnan-3β,5α-diol-20-one 3-acetate (XIX, 2·32 g), m.p. 165–169°, raised by one crystallization from methanol to 170–172° (1·85 g). The analytical sample from methanol had m.p. 172–174°, $[\alpha]_D$ −35°, λ_{max}^{EtOH} 222, 274 and 280 mμ, ε 9,500, 1350 and 1200 respectively; λ_{max}^{KBr} 3400, 1720, 1685, 1595, 1585 and 1240 cm^{-1} (Found: C, 74·42; H, 9·00; O, 16·75. $C_{29}H_{40}O_5$ requires: C, 74·32; H, 8·60; O, 17·08%).

Mild alkaline hydrolysis of XIX (1% methanolic potassium hydroxide/reflux 30 min) afforded 6β-phenoxypregnan-3β,5α-diol-20-one (XX). The analytical sample from acetone–hexane had m.p. 182–183, $[\alpha]_D \pm 0°$, λ_{max}^{EtOH} 224, 274 and 280 mμ, ε 7590, 1180 and 978 respectively; λ_{max}^{KBr} 3450, 3300, 1690 and 1588 cm^{-1} (Found: C, 75·67; H, 9·05; O, 15·18. $C_{27}H_{38}O_4$ requires: C, 76·02; H, 8·98; O, 15,00%).

6β-Phenoxypregnan-5α-ol-3,20-dione (XXI)

An excess of 8 N chromic acid [15] (permanent orange color) was added to a solution of 6β-phenoxypregnan-3β,5α-diol-20-one (XX, 1·0 g) in acetone (50 cc) at 0°. After a further 2 min at 0° ice water was added and the precipitate of 6β-phenoxypregnan-5α-ol-3,20-dione (XXI), m.p. 213–220° was removed by filtration. One crystallization from acetone afforded 770 mg with m.p. 228–232°, raised by several crystallizations from acetone to 232–234°, $[\alpha]_D \pm 0°$, λ_{max}^{EtOH} 222, 272 and 280 mμ, ε 8,300, 1260 and 980 respectively; λ_{max}^{KBr} 3400, 1703, 1685, 1588 and 1575 cm^{-1} (Found: C, 76·14; H, 8·53, O, 15·80. $C_{27}H_{36}O_4$ requires: C, 76·38; H, 8·55; O, 16·07%).

6α-Phenoxyprogesterone (XXII)

Potassium hydroxide (200 mg) in methanol (4·0 cc) was added to a solution of 6β-phenoxy-pregnan-5α-ol-3,20-dione (XXI, 500 mg) in methanol (30 cc) and heated under reflux in a nitrogen atmosphere for 30 min. After neutralizing the solution with acetic acid it was evaporated to a small volume when addition of water afforded a precipitate which was removed by filtration and adsorbed from hexane–benzene (80 : 20; 50 cc) onto alumina (25 g). Elution with benzene–hexane (70 : 30; 400 cc) afforded 6α-phenoxyprogesterone (XXII, 250 mg) m.p. 95–100°, raised by crystallizations from aqueous methanol to 108–110°, $[\alpha]_D + 114°$, λ_{max}^{EtOH} 222 mμ, ε 15,000; λ_{max}^{KBr} 1690, 1665, 1615 and 1585 cm^{-1} (Found: C, 79·37; H, 8·66; O, 11·62. $C_{27}H_{34}O_3$ requires: C, 79·76; H, 8·46; O, 11·78%).

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