Reactions of the Enol Sulphite of 3β-Acetoxy-5β-hydroxycholestan-6-one

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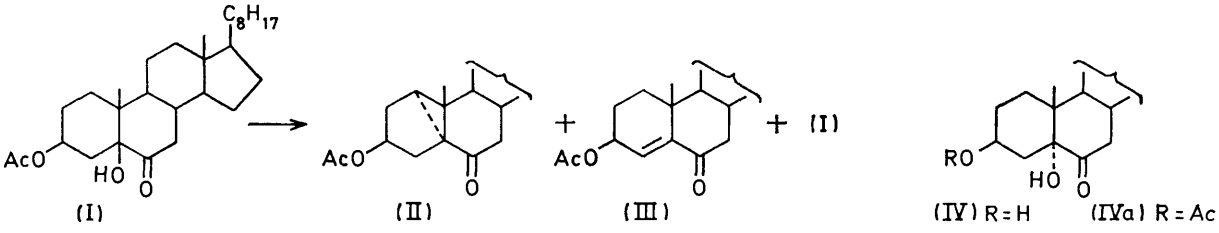
Treatment of 3β-acetoxy-5β-hydroxycholestan-6-one (I) with thionyl chloride in pyridine at 0° gave a highly reactive enol sulphite (V), which when chromatographed on aluminium oxide gave 3β-acetoxy-5α-hydroxycholestan-6-one (IVa), 3β-acetoxycholest-4-en-6-one (III), and cholesta-2,4-dien-6-one (VI). In 0·1N-hydrochloric acid the enol sulphite gave 3β-acetoxy-5α-hydroxycholestan-6-one, 3β-acetoxycholest-4-en-6-one, and 3β,7α-diacetoxy-5α-cholestan-6-one (VIII). A 1,3-dipolar intermediate is postulated to rationalise these reactions.

THE only reported preparation of 1α,5-cyclo-6-oxo-5α-cholestan-3β-yl acetate (II) involves the reaction of compound (I) with thionyl chloride in pyridine at 0° for 2 h, followed by chromatography on aluminium oxide; compounds (I), (II), and (III) were obtained in 50, 30, and 20% yield, respectively.[1] When we repeated this procedure, we were unable to isolate the cyclosteroid (II). We therefore reinvestigated the reaction.



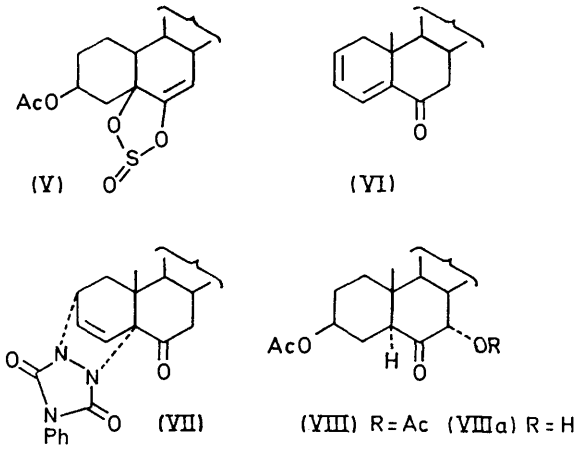
The 5β-hydroxy-ketone (I) was obtained by epimerisation[2] of the 5α-hydroxy-ketone (IVa)[3] in refluxing methanolic 10% potassium hydroxide for 72 h, followed by reactylation. The equilibrium mixture consisted of *ca.* 90% of (I) and 10% of (IVa), as ascertained from the n.m.r. signals of the 3β-acetate groups and from the optical rotation of the reacetylated mixture. The hydroxy-ketone (I) was also prepared by treating 5α-bromo-6-oxocholestan-3β-yl acetate with potassium hydroxide.[4]

Treatment of compound (I) with thionyl chloride in pyridine for 0·5—4 h at 0° followed by extraction with ether gave an oil which crystallised rapidly on immediate addition of hexane. The crystals (80—90% yield) slowly decomposed, giving off sulphur dioxide. The decomposition was rapid in solution, upon warming, or upon alumina or silica gel chromatography. The spectral and analytical data were consistent with structure (V), showing, in particular, i.r. absorptions at 1742 (acetate) and 1700 cm^{-1} (olefinic) and n.m.r. signals at δ 2·00 (3H, s, Ac), 4·98 (1H, d, *J* 2 Hz, olefinic), and 2·32 (1H, d, *J* 2 Hz). The spectral data corresponded to those reported for compound (II),[1] except for the doublet at δ 4·98.

Chromatography of the crude or crystalline enol sulphite (V) on acidic, basic, or neutral alumina (activity I) gave the enone (III), the 5α-hydroxy-ketone (IVa), and a compound to which we assign structure (VI). On alumina of activity III, the main product was the 5β-hydroxy-ketone (I).

The structure (VI) followed from its spectral data (identical with those described by Fieser *et al.*[5]) and from the fact that it forms a 1,4-cycloadduct (VII) with 4-phenyl-1,2,4-triazoline-3,5-dione.[6]

When enol sulphite (V) was pyrolysed in a gas chromatograph at 295°, the major product had the same retention time as compound (VI). It was also shown that



stirring the enone acetate (III) with alumina (activity I) or pyrolysis in the gas chromatograph both gave the dienone (VI).

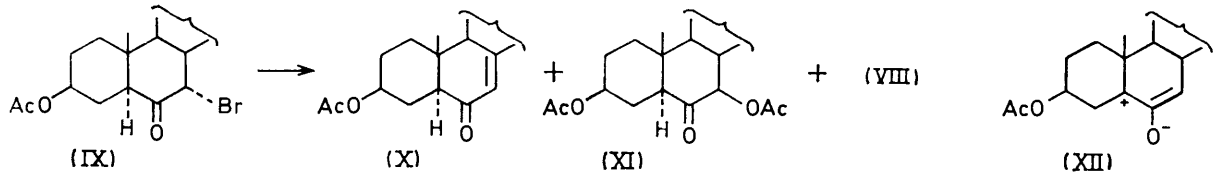
Reactions of the 5β-hydroxy-ketone (I) with sulphuryl chloride, methanesulphonyl chloride, or trifluoromethanesulphonyl chloride in pyridine did not give the cyclosteroid (II). The only positively identified compound from these reactions was the enone (III) obtained from treatment with sulphuryl chloride.

Treatment of a solution of the enol sulphite (V) in benzene with boron trifluoride–ether for 12 h at room

[1] S. B. Laing and P. J. Sykes, *J. Chem. Soc.* (*C*), 1968, 937.
[2] Y. Mazur and M. Nissum, *Tetrahedron Letters*, 1961, 817.
[3] L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.
[4] A. T. Rowland, *J. Org. Chem.*, 1962, **27**, 1135.
[5] L. F. Fieser, C. Yuan, and T. Goto, *J. Amer. Chem. Soc.*, 1960, **82**, 1996.
[6] R. C. Cookson, S. S. H. Giliani, and I. R. D. Stevens, *J. Chem. Soc.* (*C*), 1967, 1905.

temperature, gave the dienone (VI) and the enone (III) in 30 and 10% yield, respectively. Under identical conditions, the α-hydroxy-ketone (I) was stable.

When the enol sulphite (V) was stirred with hydrochloric acid diluted with aqueous tetrahydrofuran (0·1N) for 72 h, and the product was reacetylated, the enone (III), the 5α-hydroxy-ketone (IVa), and the diacetate (VIII) were obtained. Structure (VIII) was assigned from the following evidence. Its n.m.r. spectrum showed the α-protons of the acetates as a broad signal centred at δ 4·60 and a doublet at δ 4·65 p.p.m. (J 2 Hz). Partial hydrolysis gave a monoacetate (VIIIa), in which the doublet had shifted to δ 3·8 and was broadened. The broad signal at δ 4·60 remained. In mild oxidation of the monoacetate (VIIIa) 1 equiv. of oxidant was consumed rapidly, and a second more slowly, giving an acidic compound. Compound (VIII) therefore possessed an equatorial acetate group and an easily hydrolysable axial acetate which was most likely adjacent to a carbonyl function and a tertiary carbon atom (C-8). The magnitude of $J_{7,8}$ indicated that H-7 was equatorial.



The diacetate (VIII) was synthesised by treating the bromo-ketone (IX) [7] with potassium acetate in dimethyl sulphoxide at 70°. The products were an αβ-unsaturated ketone with spectral characteristics consonant with structure (X), and two diacetates (VIII) and (XI).

The products obtained, in particular (IVa) and (VIII), can be rationalised in terms of a 1,3-dipolar intermediate (XII) arising from the elimination of sulphur dioxide from the enol sulphite. A similar intermediate has been postulated [8] to explain the products formed in the reactions of a similar enol sulphite.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Optical rotations were determined for solutions in chloroform. I.r. spectra were taken for solutions in carbon tetrachloride and u.v. spectra for solutions in ethanol. N.m.r. spectra were recorded with a Varian T60 or HA 100 spectrometer (carbon tetrachloride as solvent and tetramethylsilane as internal reference). Mass spectra were run on an A.E.I. MS902 spectrometer. G.l.c. retention times were determined with a column of 4% SE-30 on Chromosorb G (100—120 mesh) at 296°. Woelm aluminium oxide was used for column chromatography and Merck silica gel $HF_{254+366}$ for preparative layer chromatography (p.l.c.) (20 × 20 cm plates 0·75 mm thick). Solutions were dried over anhydrous magnesium sulphate. Elemental analyses were carried out by Dr. C. Daessle, Montreal.

3β-Acetoxy-5β-hydroxycholestan-6-one (I).[2,4]—The general procedure of Mazur and Nissum [2] was used. 3β,5α-Dihydroxycholestan-6-one [3] (IV) (5 g) in methanolic 10% potassium hydroxide (800 ml) was refluxed for 72 h. The solution was concentrated, diluted with water, and neutralised with concentrated hydrochloric acid. The mixture was extracted with ether; the extracts were successively washed with water, saturated sodium hydrogen carbonate solution, and water and evaporated to dryness. The residue was acetylated with acetic anhydride in pyridine (50 ml) overnight. The residue obtained after the usual work-up crystallised from methanol to give compound (I) (2·80 g, 56%), identical with the compound obtained by the procedure of Rowland,[4] m.p. 143°, $[\alpha]_D^{21}$ −21·1° (c 4·41), {lit.,[6] m.p. 142—144°, $[\alpha]_D^{25}$ −22° (c 1·625)}; δ 0·64 (3H, s, 18-H_3), 0·72 (3H, s, 19-H_3), 0·88 (6H, d, J 7 Hz, 26- and 27-H_3), 1·94 (3H, s, 3-OAc), 3·75 (1H, s, 5β-OH), and 4·90 p.p.m. (1H, $W_{\frac{1}{2}}$ 7 Hz, 3α-H).

3β-Acetoxy-5β-hydroxycholest-6-ene-5,6-diyl Sulphite (V).—The hydroxy-ketone (I) (5 g) in dry pyridine (200 ml) at 0° was treated with freshly distilled thionyl chloride [9] (5·0 ml) and set aside at 0° for 2 h. The mixture was poured on ice and the steroids were extracted into ether. The solution was washed with dilute hydrochloric acid (2N) and then water, dried, and evaporated. The oily residue (5·03 g) crystallised upon addition of a few drops of hexane to give the *enol sulphite* (V), decomp. *ca.* 80°, $[\alpha]_D^{21}$ +33·2 (c 1·15), $\nu_{max.}$ 1742, 1700, 1250, and 1040 cm^{-1}; δ 0·67 (3H, s, 18-H_3), 0·89 (3H, s, 19-H_3), 0·88 (6H, d, J 7 Hz, 26- and 27-H_3), 1·96 (3H, s, 3-OAc), 2·32 (1H, d, J 2 Hz, 8-H), 4·98 (1H, d, J 2 Hz, 7-H), and 5·12br p.p.m. (1H, $W_{\frac{1}{2}}$ 6 Hz, 3α-H); m/e 442 ($M^+ - SO_2$), 398 (442 − SO), 382 ($M^+ - SO_2$ − HOAc), 64 (SO_2), and 48 (SO) (Found: C, 69·1; H, 9·2; S, 6·6. $C_{29}H_{46}O_5S$ requires C, 68·75; H, 9·15; S, 7·0%).

Chromatography of the Enol Sulphite (V).—(a) *On aluminium oxide (neutral) activity* III. The enol sulphite (V) (100 mg) was chromatographed on aluminium oxide (neutral) activity III (6 g). Elution with hexane–benzene (1 : 1) gave 3β-acetoxy-5β-hydroxycholestan-6-one (I) (70 mg), identified by spectral data.

(b) *On aluminium oxide (neutral) activity I.* The enol sulphite (V) (100 mg) was placed on a column of aluminium oxide (neutral) activity I (6 g) but could not be eluted, even with benzene–ether (1 : 1). The column was therefore stripped with methanol and the residue chromatographed on aluminium oxide (neutral) activity III (6 g). Elution with hexane–benzene (1 : 1) gave cholesta-2,4-dien-6-one (VI), which gave plates (8 mg), m.p. 109—110° (from acetone), $[\alpha]_D^{21}$ +17° (c 0·98), $\lambda_{max.}$ 315 nm (ε 7100), $\nu_{max.}$ 3040, 1685, 1630, and 1280 cm^{-1} (lit.,[5] m.p. 125—126°, $\lambda_{max.}$ 317 nm), further characterised by formation of the 1,4-cycloadduct with 4-phenyl-1,2,4-triazoline-3,5-dione (VII).

Elution with hexane–benzene (1 : 4) gave 3β-acetoxycholest-4-en-6-one (III), which gave plates (17 mg), m.p. 108—109° (from acetone), $[\alpha]_D^{21}$ −48° (c 1·04), $\lambda_{max.}$ 236 nm

[7] D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 1954, 4224.
[8] J. Levisalles, E. Rose, and I. Tkatchenko, *Chem. Comm.*, 1969, 445.
[9] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1967, vol. 1, p. 1158.

(ε 6000) {lit.,[10] m.p. 110°, $[\alpha]_D^{21}$ −50°}. Elution with methanol gave 3β-acetoxy-5α-hydroxycholestan-6-one (IVa), which gave plates (30 mg), m.p. 238° (from methanol), identical (mixed m.p. and spectral data) with an authentic sample prepared by the method of Fieser and Rajagopalan.[3]

(c) *On aluminium oxide (acidic) activity I.* The enol sulphite (V) (1 g) was stirred with aluminium oxide (acidic) activity I (20 g) in benzene (30 ml) for 1 h. The mixture was filtered and the aluminium oxide washed with methanol. The solvent was evaporated off and the residue chromatographed on aluminium oxide (neutral) activity III (40 g). Elution with hexane–benzene (1 : 1) gave cholesta-2,4-dien-6-one (VI) (77 mg). Elution with hexane–benzene (1 : 4) gave 3β-acetoxycholest-4-en-6-one (II) (105 mg). Elution with methanol gave 3β-acetoxy-5α-hydroxycholestan-6-one (IVa) (200 mg).

(d) *On aluminium oxide (basic) activity I.* The enol sulphite (300 mg) was stirred with aluminium oxide (basic) activity I (10 mg) in benzene (20 ml) for 1 h. The mixture was filtered and the aluminium oxide washed with methanol. The solvent was evaporated off and the residue chromatographed on aluminium oxide (neutral) III (8 g). Elution with hexane–benzene (1 : 1) gave compound (VI) (30 mg). Elution with hexane–benzene (1 : 4) gave compound (III) (70 mg). Elution with methanol gave compound (IVa) (100 mg).

Conversion of 3β-Acetoxycholest-4-en-6-one (III) *into Cholesta-2,4-dien-6-one* (VI) *on Aluminium Oxide.*—The enone (III) (14 mg) was stirred with aluminium oxide (acidic) activity I (0·5 g) for 0·5 h. The mixture was filtered and the aluminium oxide washed with methanol. The solvent was evaporated off and the extinction coefficients of the residue (12 mg) were determined. Compounds (III) and (VI) were present in a 60 : 40 ratio as calculated from the extinction coefficients of the 236 and 315 nm absorptions.

1,4-Cycloaddition of 4-Phenyl-1,2,4-triazoline-3,5-dione to Cholesta-2,4-dien-6-one (VI).—4-Phenyl-1,2,4-triazoline-3,5-dione [from 4-phenyl-1,2,4-triazole-3,5-dione (30 mg, 0·168 mmol)] in dry acetone (2 ml) at −70° was stirred and treated with cholesta-2,4-dien-6-one (VI) (50 mg, 0·131 mmol) in acetone (5 ml). The mixture was allowed to warm to room temperature, filtered, and evaporated to dryness. The *adduct* (VII) crystallised as needles m.p. 209—210° (from ethanol), $[\alpha]_D^{21}$ +82·6 (*c* 0·26), $\nu_{max.}$ 1740, 1415, and 1075 cm^{-1} (Found: C, 75·1; H, 8·6; N, 7·7. $C_{35}H_{47}N_3O_3$ requires C, 75·4; H, 8·5; N, 7·5%).

Reaction of 5β-Acetoxy-5β-hydroxycholestan-6-one (I) *with Sulphuryl Chloride.*—The hydroxy-ketone (I) (100 mg) dissolved in pyridine (5 ml) at 0° was treated with sulphuryl chloride (0·1 ml) and set aside at 0° for 2 h. The mixture was poured on ice and the steroids were extracted with ether. The solution was washed with dilute hydrochloric acid (2N) and then water, dried, and evaporated. G.l.c. showed the presence (>80%) of one major component having the same retention time as (III). P.l.c. [hexane–ether (4 : 1) as eluant] gave compound (III) (80 mg), identical (mixed m.p. and spectral data) with an authentic sample prepared by the reaction of 3β-acetoxy-5α-hydroxycholestan-6-one with thionyl chloride in pyridine.[10]

Reaction of the Enol Sulphite (V) *with Boron Trifluoride–Ether.*—The enol sulphite (V) (1·085 g) in dry benzene (50 ml) at room temperature was treated with boron trifluoride–ether (1 ml) and set aside at room temperature for 12 h. The solution was washed with water, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated to give a black tar (899 mg). P.l.c. [ether–benzene (1 : 9) as eluant] afforded two bands visible under u.v. light at R_F 0·75 and 0·40. Extraction of these bands afforded compounds (VI) (175 mg) and (III) (60 mg), respectively.

Reaction of 5β-Acetoxy-5β-hydroxycholestan-6-one with Boron Trifluoride–Ether.—The hydroxy-ketone (I) (192 mg) in dry benzene (110 ml) at room temperature was treated with boron trifluoride–ether (1 ml) and set aside at room temperature for 3·5 h. The solution was washed with water, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated to afford unchanged starting material (I).

Reaction of the Enol Sulphite (V) *with Hydrochloric Acid in Aqueous Tetrahydrofuran.*—The enol sulphite (V) (1·05 g) in 10% aqueous tetrahydrofuran (40 ml) was treated with concentrated hydrochloric acid (0·5 ml) and set aside at room temperature for 72 h, with stirring. The solution was diluted with ether and the ethereal solution washed with water, saturated sodium hydrogen carbonate solution, and water, dried, and evaporated to afford an oily residue which was immediately treated with acetic anhydride (5 ml) and pyridine (5 ml) for 2 h at 60°. After the usual work-up the residue was purified by p.l.c. [ether–benzene (1 : 9) as eluant]. Three major bands, R_F 0·5, 0·38, and 0·25 (112, 150, and 100 mg, respectively) were separated. The compound having R_F 0·5 was identified as (III) and that at R_F 0·25 was identified as (IVa) by comparison (mixed m.p.s and spectral data) with authentic samples.

The compound having R_F 0·38 gave needles of 3β,7α-*diacetoxy-5α-cholestan-6-one* (VIII) (150 mg), m.p. 112—113° (from aqueous ethanol), $[\alpha]_D^{21}$ −40° (*c* 0·06), $\lambda_{max.}$ 300 nm (ε 95), $\nu_{max.}$ 1760, 1740, 1735, 1260, and 1255 cm^{-1}; δ 0·67 (3H, s, 18-H_3), 0·75 (3H, s, 19-H_3), 0·91 (6H, d, *J* 7 Hz, 26- and 27-H_3), 1·94 (3H, s, 3-OAc), 2·06 (3H, s, 7-OAc), 4·60br (1H, 3α-H), and 4·65 p.p.m. (1H, d, *J* 2 Hz, 7β-H); *m/e* 502 (M^+), 460 (M^+ − CH_2=C=O), 442 (M^+ − HOAc), 400 (442 − CH_2=C=O), and 382 (442 − HOAc) (Found: C, 74·2; H, 10·2. $C_{31}H_{50}O_5$ requires C, 74·1; H, 10·0%).

Partial Hydrolysis of the Diacetate (VIII).—The diacetate (VIII) (75 mg) dissolved in 90% methanol–water containing sodium hydrogen carbonate (200 mg) was kept at room temperature for 3 h. The mixture was diluted with water, neutralised with dilute acid, extracted with ether, and worked up in the usual manner. The residue (60 mg) was crystallised from hexane; m.p. 143°, $[\alpha]_D^{21}$ −24° (*c* 0·15). Spectral data are consistent with structure (VIIIa): $\nu_{max.}$ 1740, 1720, and 1250 cm^{-1}, δ 0·72 (3H, s, 18-H_3), 0·78 (3H, s, 18-H_3), 2·08 (3H, s, 3-OAc), 3·80 (1H, d, *J* 2 Hz, 7β-H), and 3·75br p.p.m. (1H, 3α-H); *m/e* 460 (M^+), 418 (M^+ − CH_2=C=O), and 400 (M^+ − HOAc).

Oxidation of the Hydroxy-acetate (VIIIa).—The hydroxy-acetate (VIIIa) (18·6 mg) was dissolved in 100 ml of 10^{-3}M-chromium trioxide in 90% acetic acid. The course of the oxidation was followed by observation in the change in ε of the 380 nm absorption.[11] One equiv. of oxidant was consumed in 6 h and a second after a further 12 h. Dilution of the mixture with water and extraction with ether followed by the usual work-up gave a compound (11 mg) having $\nu_{max.}$ 3500—3000br, 1740, 1720, 1710, and 1245 cm^{-1} and which was acidic.

[10] I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, 1937, 801.

[11] J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1529.

3β-*Acetoxy*-7α-*bromo*-5α-*cholestan*-6-*one* (IX).— The bromo-ketone (IX), prepared according to the procedure of James and Shoppee,[7] had m.p. 130° (from acetic acid), $[\alpha]_D^{21}$ +35° (*c* 0·21) (lit.,[7] m.p. 145°, $[\alpha]_D$ +39°), $\nu_{max.}$ 1742, 1725, and 1250 cm^{-1}; δ 0·67 (3H, s, 18-H_3), 0·74 (3H, s, 19-H_3), 1·96 (3H, s, 3-OAc), 4·05 (1H, $W_{\frac{1}{2}}$ 4 Hz, 7-H), and 4·60br p.p.m. (1H, 3α-H).

Reaction of the Bromo-ketone (IX) *with Potassium Acetate in Dimethyl Sulphoxide.*—The bromo-ketone (IX) (400 mg) was dissolved in a mixture of dimethyl sulphoxide (50 ml) and potassium acetate (5 g). The mixture was heated at 70° for 12 h, then diluted with water and extracted with ether. The extracts were washed with brine, dried, and evaporated. The residue was separated by p.l.c. Three major bands, R_F 0·60, 0·50, and 0·40 (48, 183, and 52 mg, respectively), were separated. The compound having R_F 0·60 had $\lambda_{max.}$ 236 nm (ε 7800), $\nu_{max.}$ 1740, 1700, and 1245 cm^{-1}, consistent with structure (X). The compound having R_F 0·50 was an oil, $[\alpha]_D^{21}$ +12·7 (*c* 0·79), $\nu_{max.}$ 1758, 1742, and 1250 cm^{-1}; δ 0·70 (3H, s, 18-H_3), 0·76 (3H, s, 19-H_3), 1·93 (3H, s, 3-OAc), 0·90 (6H, d, *J* 7 Hz, 26- and 27-H_3), 2·03 (3H, s, 7-OAc), 4·60br (1H, 3α-H), and 4·80 p.p.m. (1H, d, *J* 11 Hz, 7α-H), consistent with structure (XI). The compound having R_F 0·40 was identified as (VIII) by spectral and t.l.c. comparison.

This work was supported by the National Research Council of Canada and by the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service. One of us (P. E. G.) gratefully acknowledges receipt of a N.R.C. Post-graduate Scholarship.

[2/1580 *Received*, 5*th July*, 1972]