ACID CATALYSED REARRANGEMENTS OF SOME 5α-ACETOXY STEROIDS

J.M. Coxon, M.P. Hartshorn, G.A. Lane, K.E. Richards and U.M. Senanayake.

Department of Chemistry, University of Canterbury, Christchurch, New Zealand.

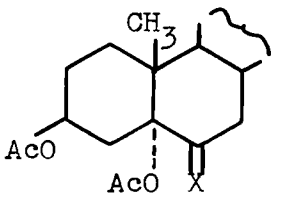
Received August 30, 1969

Abstract

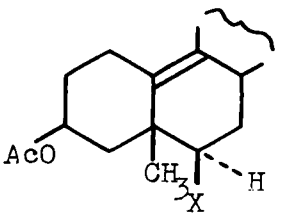
The influences of 6-substituents on the reactions of 3β,5α-diacetoxycholestanes with boron trifluoride-etherate in acetic anhydride are described.

As part of a study of the backbone rearrangement (1) of 5α-oxygenated steroids we required information about the effect of the variation of the 6-substituent on the acid-catalysed rearrangement of 5α-acetoxy steroids.

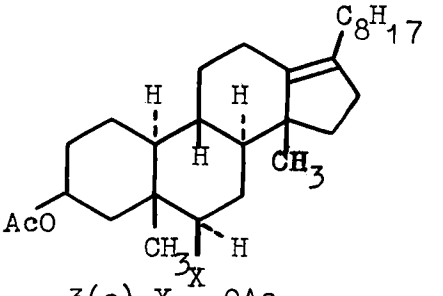
Reaction of the 3β,5α,6β-triacetate (1a) with boron trifluoride-etherate in acetic anhydride at 80° gave the rearranged Δ^{9}- (2a; 9%) and $\Delta^{13(17)}$- (3a; 54%) olefins with unchanged triacetate (1a; 28%), in accord with the earlier report (2).



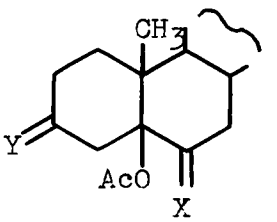
1(a) X = βOAc, H
(b) X = βCl, H
(c) X = O
(d) X = H, H
(e) X = αOAc, H



2(a) X = OAc
(b) x = Cl



3(a) X = OAc
(b) X = Cl
(c) X = H



4(a) X = αOAc, H; Y = βOAc, H
(b) X = αOH, H; Y = βOH, H
(c) X, Y = O.

Similar treatment of the 6β-chloro-3β,5α-diacetate (1b) gave the rearranged Δ^{9}- (2b; 15%) and $\Delta^{13(17)}$- (3b; 59%) compounds. In contrast the 6-keto-3β,5α-diacetate (1c) was recovered in nearly quantitative yield even after extended reaction times. This marked resistance to heterolysis of the C^{5}-O bond of a 5α-oxygenated-6-ketone under strong acid catalysis was earlier found (3) during the attempted Westphalen rearrangement of 5α-hydroxy-6-ketone derivatives.

Only brief treatment 3β,5α-diacetoxycholestane (1d) with boron trifluoride-etherate in acetic anhydride at 80° gave cholesteryl acetate (66%) and the $\Delta^{13(17)}$-olefin

(3c; 25%). The isolation of the backbone rearranged compound (3c) is noteworthy since the diacetate (1d) has no electron-withdrawing substituents at either the 4β- or 6β- positions, the apparent prerequisite (4) for the formation of 5β-methyl-Δ^9-compounds from 5α-hydroxy steroids under Westphalen rearrangement conditions.

The reaction of the 3β,5α,6α-triacetate (1e) under mild conditions gave, in addition to starting material (1e; 16%) and two unidentified materials (12% and 14%), the known (5) 3β,6α- and 3α,6α-diacetoxycholest-4-enes (21% and 18%) and a compound identified as the 3β,5β,6α-triacetate (4a; 10%). The structure of the triacetate (4a) was assigned on the basis of its NMR spectrum, and its conversion via the 3β,5β,6α-triol (4b) into the known (6) 5β-hydroxy-3,6-diketone (4c, with OH for OAc).

The use of acetic anhydride-acetic acid (3:1) as solvent instead of acetic anhydride resulted in a lower conversion of the triacetate (1a) into olefins (2a and 3a) (recovered triacetate, 64%). In addition, the relative yields of the Δ^9- (13%) and $\Delta^{13(17)}$ - (16%) olefins differed markedly. The Δ^9-compound (2a) is not converted into the $\Delta^{13(17)}$-compound (3a) on treatment with boron trifluoride etherate in acetic anhydride at 80°.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solutions at 20°. IR spectra were recorded for CS_2 solutions. Alumina used for chromatography was P. Spence, Grade H, deactiviated by addition of 5% of 10% acetic acid.

Reactions of 5α-Acetoxy-steroids with Boron Trifluoride.

(a) 3β,5α,6β-Triacetate (1a) in Acetic Anhydride. To a solution of steroid (1 5g) in acetic anhydride (240 ml) was added boron trifluoride-etherate (2 ml) and the mixture kept at 80° for 30 min. The reaction mixture was quenched with aqueous sodium bicarbonate at 0°. Isolation by means of chloroform gave a gum (14.1 g) which was adsorbed onto alumina (400 g). Elution with light petroleum-benzene (19:1) gave the rearranged Δ^9-compound (2a; 1.193 g), m.p. 125–126° (methanol) $[\alpha]_D$ + 85° (c 1.08) (Lit. values (7): m.p. 128°, $[\alpha]_D$ + 84°.

Elution with light petroleum-benzene (5:1) gave a gum identified as the $\Delta^{13(17)}$-compound (3a; 7.263 g), ν max 1750 and 1243 cm^{-1}. Reaction of diacetate (3a) with lithium aluminium hydride in ether gave the $\Delta^{13(17)}$-3β,6β-diol, m.p. 190–192°, $[\alpha]_D$ + 180 (c 1.00) (Lit. values (2): m.p. 192–193°, $[\alpha]_D$ + 21°).

Elution with benzene gave unchanged triacetate (1a; 3.989 g), m.p. and m.m.p. 148–149°, $[\alpha]_D$ - 27° (c 1.09).

(b) 3β,5α,6β-Triacetate (1a) in Acetic Anhydride-Acetic Acid. To a solution of steroid (5g) in acetic anhydride (60 ml) and acetic acid (20 ml) was added boron trifluoride-etherate (0.6 ml) and the mixture kept at 80° for 30 min. Quenching of the reaction mixture as above, isolation of the crude product by means of chloroform and crystallisation from light petroleum gave triacetate (1a; 2.94 g), m.p. and m.m.p. 148–149°. The residue (1.74 g) from the above crystallisation was adsorbed onto alumina (100 g). Elution with light petroleum gave the Δ^9-compound (2a; 558 mg), m.p. and m.m.p. 125–126°, $[\alpha]_D$ + 82° (c 1.07).

Elution with light petroleum-benzene (5:1) gave the $\Delta^{13(17)}$-compound (3a; 691 mg), ν_{max} 1750 and 1243 cm^{-1}, identical with an authentic sample.

Elution with benzene gave triacetate (1a; 283 mg), m.p. and m.m.p. 1490.

(c) 3β,5α-Diacetate (1d) in Acetic Anhydride. Boron trifluoride-etherate (1 ml) was added to a solution of the steroid (1 g) in acetic anhydride (100 ml) and the mixture

kept at 80° for 10 min. The crude product (980 mg), isolated by means of ether after quenching as above, was adsorbed onto alumina (50 g). Elution with light petroleum-benzene (20:1) gave the Δ13(17)- compound (3c; 223 mg) as a gum, $[\alpha]_D$ + 1° (c 1.01), ν_{max} 1735, 1245 and 1230 $cm.^{-1}$, ε197 nm 7650, M^+ 428, NMR ($CDCl_3$) 5.00 ppm ($W_h/2$ 8 cps; C^3-H); 2.02 ppm (OAc); 0.98 ppm (5β-CH_3); 0.96 ppm (J 6.5 cps; $C^{21}H_3$); 0.92 ppm (14β-CH_3); 0.92, 0.82 ppm ($C^{26}H_3$, $C^{27}H_3$).

Further elution with light petroleum-benzene (20:1) gave cholesteryl acetate (580 mg), m.p. and m.m.p. 114–115°, $[\alpha]_D$ - 38° (c 1.03).

(d) 3β,5α-Diacetoxycholestan-6-one (1c). Boron trifluoride-etherate (0.3 ml) was added to a solution of the steroid (2.5 g) in acetic anhydride (40 ml) and the mixture kept at 80° for 30 min. Quenching the reaction mixture as above and isolation by means of chloroform gave a gum (2.48 g), which on crystallisation gave the ketone (1c; 2.256 g), m.p. and m.m.p. 168–169°.

(e) 3β,5α,6α-Triacetoxycholestane (1e). Boron trifluoride-etherate (0.1 ml) was added to a solution of the steroid (1 g) in acetic anhydride (8 ml) and carbon tetrachloride (2 ml) and the mixture kept at 20° for 10 min. The crude product (900 mg), isolated by means of ether after quenching as above, was adsorbed onto alumina (100 g). Elution with light petroleum gave a complex mixture of non-polar compounds (120 mg).

Elution with light petroleum-benzene (9:1) gave 3β,6α-diacetoxycholest-4-ene as needles (methanol) (136 mg), m.p. and m.m.p. 163–165°, $[\alpha]_D$ + 19° (c 1.01).

Elution with light petroleum-benzene (4:1) gave 3α,6α-diacetoxycholest-4-ene as needles (methanol) (162 mg), m.p. 116–118°, $[\alpha]_D$ + 153° (c 1.03), NMR spectrum identical with that reported earlier (5) for a sample, m.p. 108–109°, $[\alpha]_D$ + 158°.

Elution with light petroleum-benzene (1:1) gave an unidentified gum (140 mg). Elution with benzene gave the 3β,5α,6α-triacetate (160 mg), m.p. and m.m.p. 122–123°, $[\alpha]_D$ + 13° (c 1.0).

Finally elution with benzene-ether mixtures gave the 3β,5β,6α-triacetate (4a) as a gum (100 mg), $[\alpha]_D$ + 6° (c 1.01), ν_{max} 1750, 1380 and 1260 cm^{-1}, NMR ($CDCl_3$) 5.38 ppm ($W_h/2$ ca. 20 cps; C^6-H); 5.15 ppm ($W_h/2$ 10 cps; C^3-H); 1.98 ppm (OAc); 1.05 ppm ($C^{19}H_3$); 0.92, 0.82 ppm (side chain CH_3); 0.67 ppm ($C^{18}H_3$). Reaction of the triacetate (4a) with lithium aluminium hydride in ether gave the 3β,5β,6α-triol (4b) as needles (methanol), m.p. 115–117°, $[\alpha]_D$ + 30° (c 1.06), ν_{max} 3615, 3585, 3505 cm^{-1}. (Found:

C, 76.98; H, 11.50. $C_{27}H_{48}O_3$ requires C, 77.09; H, 11.50%), NMR ($CDCl_3$) 4.27 ppm ($W_h/2$ 10 cps; C^3-H); 3.80 ppm ($W_h/2$ cps; C^6-H); 0.93 ppm ($C^{19}H_3$); 0.92, 0.82 ppm (sidechain CH_3); 0.67 ppm ($C^{18}H_3$). Oxidation of the triol (4b) with 8N-chromic acid in acetone gave 5β-hydroxycholesta-3,6-dione as needles (ethanol), m.p. 120–122°, $[\alpha]_D$ - 49° (c 0.68), ν_{max} 3615, 3495, 1723, 1715 cm^{-1}. (lit. values (6): m.p. 121–122.5°, $[\alpha]_D$ - 47.5°) NMR ($CDCl_3$) 0.91, 0.81 ppm (sidechain CH_3); 0.81 ppm ($C^{19}H_3$); 0.70 ppm ($C^{18}H_3$).

(f) 6β-Chloro-3β,5α-diacetoxycholestane (1b). Boron trifluoride-etherate (0.2 ml) was added to a solution of the steroid (2.5 g) in acetic anhydride (40 ml) and the mixture kept at 80° for 30 min. The crude product (2.1 g), isolated by means of chloroform as above, was adsorbed onto alumina (100 g). Elution with light petroleum gave the Δ^9-compound (2b; 330 mg) as needles (methanol), m.p. 137–138°, $[\alpha]_D$ + 128° (c 1.02) (Lit. values (8): m.p. 139–141°, $[\alpha]_D$ + 132° NMR ($CDCl_3$) 5.12 ppm ($W_h/2$ 9 cps; C^3-H); 4.03 ppm ($W_h/2$ 19 cps; C^6-H); 2.07 ppm (OAc); 1.27 ppm (5β-CH_3); 0.92, 0.82 ppm (sidechain CH_3); 0.82 ppm ($C^{18}H_3$).

Further elution with light petroleum gave a gum (1.217 g) identified as the $\Delta^{13(17)}$-compound (3b), ν_{max} 1740, 1238 cm^{-1}, NMR (CCl_4) 5.03 ppm ($W_h/2$ 9 cps; C^3-H); 3.65 ppm (J 8 cps, J^1 9 cps; C^6-H); 1.06 ppm (5β-CH_3); 0.93 ppm (14β-CH_3); 0.93 ppm (J 6 cps; $C^{21}H_3$); 0.88 and 0.79 ppm (sidechain CH_3). Reaction of compound (3b) with lithium aluminium hydride in ether gave the 6β-chloro-3β-hydroxy-$\Delta^{13(17)}$-compound as needles (pentane), m.p. 110–112°, $[\alpha]_D$ + 48° (c 1.01), ν_{max} (nujol) 3350 cm^{-1}, ε 210 nm 7440, ε 205 9870, ε 200 11100, (Found: C, 77.2; H, 10.65; Cl, 8.3. $C_{27}H_{45}ClO$ requires C, 77.0; H, 10.8; Cl, 8.4%), NMR ($CDCl_3$) 4.15 ppm ($W_h/2$ 7 cps; C^3-H): 3.75 ppm (J 8 cps, J^1 9 cps; C^6-H); 1.20 ppm (5β-CH_3); 0.96 ppm (J 6 cps; $C^{21}H_3$); 0.93 ppm (14β-CH_3); 0.90, 0.80 ppm (sidechain CH_3).

Elution with benzene gave a complex mixture of compounds (TLC) as a gum (200 mg).

Reaction of 6β-Chloro-3β,5α-diacetoxycholestane (1b) with Hydrofluoroboric Acid - Acetic Anhydride (with F.W. Jones). Aqueous hydrofluoroboric acid (60%; 0.25 ml) was added to a solution of the steroid (4 g) in acetic anhydride

(80 ml) and carbon tetrachloride (10 ml). The mixture was kept at 80° for 15 min. The crude product (3.8 g), isolated by means of ether, was adsorbed onto alumina (160 g). Elution with light petroleum gave the Δ^9-compound (2b; 1.061 g), m.p. 139-141°, $[\alpha]_D$ + 126° (c 1.01).

Further elution with light petroleum gave a gum (1.256 g) identified as the $\Delta^{13(17)}$-compound, (3b) by conversion into the 3β-hydroxy-$\Delta^{13(17)}$-compound, m.p. and m.m.p. 110-112°, $[\alpha]_D$ + 48° (c 1.03).

Finally elution with light petroleum-benzene (1:1) and benzene gave the chloro-diacetate (1b; 876 mg), as needles (methanol), m.p. and m.m.p. 168-169°.

Acknowledgments: Acknowledgment is made to the Research Committee of the New Zealand Universities Grants Committee for grants, and a research fellowship to one of us (GAL).

REFERENCES

1. B.N. Blackett, J.M. Coxon, M.P. Hartshorn and K.E. Richards TETRAHEDRON, 25, in press (1969).

2. G. Snatzke and H.W. Fehlhaber, ANNALEN, 676, 188 (1964); J.W. Blunt, M.P. Hartshorn and D.N. Kirk, TETRAHEDRON LETTERS, 2125 (1966).

3. Y.F. Shealy and R.M. Dodson, J. ORG. CHEM., 16, 1426 (1951)

4. A.R. Davies and G.H.R. Summers, J. CHEM. SOC., (C), 1010 (1966).

5. M.P. Hartshorn and D.N. Kirk, TETRAHEDRON, 22, 1415 (1966).

6. A.T. Rowland, J. ORG. CHEM., 27, 1135 (1962).

7. V. Petrow, O. Rosenheim and W.W. Starling, J. CHEM. SOC., 677 (1938).

8. J.S. Mihina, J. ORG. CHEM., 27, 2807 (1962).