SECTION C
Organic Chemistry

New Method for the Preparation of Unsaturated Axial 3-Sterols

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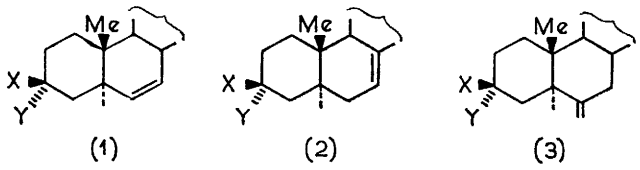
The reaction of 3β-steroidal tosylates with tetrabutylammonium acetate in acetone has been developed as a route to unsaturated axial 3-sterols.

In the course of investigations into the effect of conformational transmission on the solvolysis of steroidal tosylates,[1] we needed to synthesise a number of cholesten-3α-ols. Frequently, pairs of epimeric alcohols have been prepared by metal hydride reduction of the appropriate ketone. However, the proportions of the alcohols formed are well known to be dependent on the steric environment of the carbonyl group,[2] and in the cholestane series reduction of the 3-ketone gives predominantly the equatorial alcohol.[3] Catalytic hydrogenation of the carbonyl function often yields a greater proportion of the axial alcohol than does hydride reduction [3] but such an approach is obviously excluded for unsaturated alcohols.



a; X = OTs, Y = H
b; X = H, Y = OAc
c; X = H, Y = OH

A convenient route to 5α-cholest-6- and 1-7-en-3α-ols and 6-methylene-5α-cholestan-3α-ol (1c, 2c, and 3c) was found in an adaptation of a method used by Winstein and his co-workers,[4] reaction of the corresponding 3β-tosylate (1a, 2a, and 3a) with an excess of tetrabutylammonium acetate in acetone to give acetate with predominantly inverted configuration (1b, 2b, and 3b).

Products from reaction of tetrabutylammonium acetate with 3β-tosylate in acetone

	Acetate (%)	Olefin (%)
5α-Cholest-6-en-3β-yl tosylate (1a)	79·8	20·2
5α-Cholest-7-en-3β-yl tosylate (2a)	92·5	7·5
6-Methylene-5α-cholestanyl tosylate (3a)	89·2	10·8

Although the reaction time for the steroidal tosylates is fairly long (10—14 days), the 3α-acetate is obtained in good yield (80—90%), together with some olefin (Table).

The alcohol obtained by reduction of the acetate fraction with lithium aluminium hydride was examined for its epimeric purity by g.l.c. analysis of the trimethylsilyl ether derivative [5] and shown to contain 95—98% of the 3α-epimer in each case (the remainder being the 3β-ol).

The reaction appears to be a nucleophilic bimolecular S_N2 displacement by acetate in acetone. Although the small amount of olefin formed may be satisfactorily accounted for in terms of a competing bimolecular E_2 elimination, possibly the presence of acetic acid (from the tetrabutylammonium acetate; see Experimental section) could lead to some acetolysis of the tosylate, which is known [6] to give substantial amounts of olefin. This would also account for the small amount of retention of configuration observed. (The inversion : retention ratio obtained in the acetolysis of the 3β-tosylates suggested this as a possible route to the 3α-epimers but the proportion of elimination in this reaction limited its application.)

EXPERIMENTAL

Gas chromatographic analyses were carried out with a Pye-Unicam series 104 gas chromatograph equipped with a flame ionisation detector and a glass column (5 ft. × ¼ in.) packed with 1% cyclohexane–dimethyl succinate on a 80—100 mesh Celite support and operated at 235°.

Hydrogenation of commercial 7-dehydrocholesterol over Raney nickel gave cholest-7-en-3β-ol, m.p. 120—121° (lit.,[3] 126°). Cholest-6-en-3β-ol,[3] m.p. 122° (lit.,[3] 131°), was prepared from 6-oxocholestan-3β-yl acetate *via* bromination, borohydride reduction, and dehydrobromination with zinc dust and acetic acid.[3] A Wittig reaction on 6-oxocholestan-3β-yl acetate [7] gave 6-methylenecholestan-3β-ol, after hydrolysis; m.p. 121° (lit.,[7] 113°).

Tetrabutylammonium Acetate (*TBAA*).—Tetrabutylammonium hydroxide (40%; 80 ml.) was neutralised with glacial acetic acid (12 ml., 2 mol. to allow for acetic acid of crystallisation [4]). Benzene was added and the solvent was evaporated off below 40°. The moist solid was placed in a desiccator (P_2O_5) under vacuum for 2—3 days. The acetate so prepared was used without further purification.

Reaction of 3β-Tosylates with TBAA.—The 3β-tosylate

[1] R. Baker and J. Hudec, *Chem. Comm.*, 1967, 479.
[2] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965.
[3] L. F. and M. Fieser, 'Steroids,' Reinhold, New York, 1959, and references cited therein.
[4] S. Winstein, E. C. Friedrich, R. Baker, and Yang-i Lin, *Tetrahedron*, 1966, Suppl. 8, 621.
[5] T. Luukainen, W. J. A. Vanden Heuvel, E. O. A. Haahti, and E. C. Horning, *Biochim. Biophys. Acta*, 1961, **52**, 599.
[6] R. Baker, J. Hudec, and K. L. Rabone, unpublished work.
[7] G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, 1965, **98** [2], 604.

(5 g., 9·3 mmoles) was heated under reflux in an inert atmosphere (N_2) with a solution of TBAA [from the hydroxide (12 ml.)] in acetone (100 ml.) for 10—14 days, after which the mixture was poured into water and extracted with ether. The combined extracts were washed successively with water and hydrogen carbonate solution and dried ($MgSO_4$). G.l.c. of the product (Table) indicated that the major product was the 3α-acetate. The crude product was separated on an alumina column made up in light petroleum (b.p. 40—60°) into hydrocarbon and acetate fractions. Reduction of the acetate with lithium aluminium hydride in ether gave the sterol, a sample (5—10 mg) of which was treated with hexamethyldisilazane and trimethylchlorosilane in tetrahydrofuran to give the trimethylsilyl ether,[5] which was analysed by g.l.c. [relative retention times of ethers (3β : 3α) 1·39 for Δ^6- and 1·43 for Δ^7-cholestenols, and 1·56 for 6-methylenecholestanols).

The 3α-cholestenols were freed from the small amount of the 3β-epimer by chromatography on alumina, with benzene and benzene–ethyl acetate (97 : 3) as eluants, and characterized by their i.r. spectra [$\nu_{max.}$ (Nujol) 1000 cm.$^{-1}$] and by relative retention times (of the silyl ether) on g.l.c. The tosylates of 3α-cholest-6- and 1-7-enols were prepared (tosyl chloride–pyridine) and recrystallised from light petroleum. *5α-Cholest-6-en-3α-yl tosylate* had m.p. 135—136° (decomp) (Found: C, 75·35; H, 9·6; S, 5·85. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7; S, 5·95%), and 5α-cholest-7-en-3α-yl tosylate had m.p. 139—140° (decomp.) (lit.,[8] 136°) (Found: C, 75·75; H, 9·75; S, 6·0. Calc. for $C_{34}H_{52}O_3S$: C, 75·5; H, 9·7; S, 5·95%).

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[8] D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 1956, 4821.