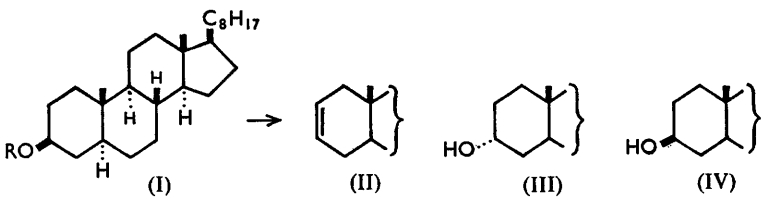
340. *Preparation of Axial Alcohols and Olefins from Equatorial Alcohols.*

By G. H. Douglas, P. S. Ellington, G. D. Meakins, and R. Swindells.

Cases in which the toluene-*p*-sulphonate of an equatorial alcohol is decomposed by contact with alumina to a mixture of the epimeric axial alcohol and an olefin are recorded (*e.g.*, cholestanyl toluene-*p*-sulphonate ⟶ cholestan-3α-ol and cholest-2-ene). The proportion of axial alcohol to olefin varies with the type of alumina used, thus giving convenient preparations of both products.

While cyclic alcohols with equatorial hydroxyl groups can generally be obtained by reduction of the corresponding ketones with dissolving metals or by equilibration of the axial epimers, preparation of the axial alcohols has frequently been troublesome. Catalytic reduction of a ketone in acidic media usually gives a preponderance of the axial isomer, but the ratio of equatorial to axial product varies widely with the keto-group's environment [1,2] and in some cases with the nature of the catalyst.[3] When reducible C=C bonds are present, chemical reduction of the ketone must be used. Recent investigations [2,4] have confirmed the generalisation [1] that reduction of highly hindered ketones with various hydrides gives mainly the axial alcohols, but with less hindered ketones prediction of the major product is difficult. In some important cases, such as 3-oxo-steroids and -triterpenes, reduction with hydrides or with agents of higher steric requirements (*e.g.*, aluminium alkoxides [5]) leads predominantly to the equatorial alcohols.



(I) (II) (III) (IV)

In work on steroids with unnatural stereochemistry [6] a method was required for converting 3β(equatorial)-alcohols into the 3α-epimers without proceeding through the related 3-ketones. The use of the sulphonic esters of the 3β-alcohols appeared promising since the ready elimination of the sulphonyloxy-group gives mixtures of olefins and derivatives of the epimeric alcohols. To evaluate the merits of various methods (see Table) the toluene-*p*-, *p*-bromophenyl-, and methane-sulphonic esters (I) of cholestan-3β-ol (IV) were studied. [The yields in the Table correspond to the weights of materials in the fractions obtained by chromatographic separation of the mixed products. These materials were characterised by their infrared spectra, and with one exception (see below) crystallisation gave products with satisfactory constants in greater than 70% recovery.]

By method 1 (acetolysis), cholest-2-ene (II) was the major product as recorded previously for the cholestanyl toluene-*p*-sulphonates,[7] and use of aqueous dimethylformamide as solvent [8] did not increase the yield of cholestan-3α-ol (III). This is to be

[1] Barton, *J.*, 1953, 1027.
[2] Dauben, Blanz, Jiu, and Micheli, *J. Amer. Chem. Soc.*, 1956, **78**, 3752.
[3] Djerassi, Manson, and Gorman, *ibid.*, 1955, **77**, 4925.
[4] Dauben, Fonken, and Noyce, *ibid.*, 1956, **78**, 2579; Henbest and Wilson, *J.*, 1956, 3289; Wicker, *J. Amer. Chem. Soc.*, 1958, **80**, 640.
[5] Biedeback, *Arch. Pharm.*, 1943, **281**, 49.
[6] Castells, Jones, Meakins, and Williams, *J.*, 1959, 1159, and unpublished work.
[7] King and Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 3338.
[8] Bharucha, Buckley, Cross, Rubin, and Ziegler, *Canad. J. Chem.*, 1956, **34**, 982.

contrasted with methanolysis of the toluene-*p*-sulphonate [9,10] which gives 3α-methoxycholestane (75%) and cholest-2-ene (25%). Alcoholysis with allyl alcohol and reductive fission of the products (mainly cholest-2-ene and cholestan-3α-yl allyl ether) with lithium in ethylamine (method 2) led to somewhat higher yields of cholestan-3α-ol. This method, however, required very careful control of the experimental conditions, and with the esters of 5α-lumist-7-en-3β-ol [6] considerable amounts of the 3β-alcohol were formed.

Method 3, the most successful, is a one-stage process involving decomposition of the

Reactions of Cholestan-3β-yl Esters (yields to nearest 5%).

Ester group, R	Δ²-Compound	3α-Alcohol	3β-Alcohol	Unchanged
Method 1. Ester boiled with KOAc–AcOH, product saponified with KOH–EtOH.				
p-$C_6H_4Me\cdot SO_3$	55	35	—	—
p-$C_6H_4Br\cdot SO_2$.....	60	30	—	—
$Me\cdot SO_2$	60	25	5	—
Method 2. Ester boiled with $CH_2{:}CH\cdot CH_2\cdot OH$–$C_6H_6$, product treated with Li–$EtNH_2$.				
p-$C_6H_4Me\cdot SO_2$	40	50	—	—
p-$C_6H_4Br\cdot SO_2$	45	50	—	—
$MeSO_2$	45	45	—	—

Method 3. Ester in benzene adsorbed on a column of alumina.

Ester group, R	Type of alumina *	Contact time (hr.)	Δ²-Compound	3α-Alcohol	3β-Alcohol	Unchanged
p-$C_6H_4Me\cdot SO_2$ ...	*a*, *b*	18	70	25	5	—
,, ...	*c*, *d*, *e*	18	—	—	—	100
,, ...	*f*	18	65	35	—	—
p-$C_6H_4Br\cdot SO_2$ ...	*f*	18	65	30	—	—
$Me\cdot SO_2$	*f*	18	65	25	10	—
p-$C_6H_4Me\cdot SO_2$ ...	*g*	42	25	35	—	35
,, ...	*g*	66	40	60	—	—
p-$C_6H_4Br\cdot SO_2$ ...	*g*	66	50	45	—	—
$Me\cdot SO_2$	*g*	66	55	35	5	—

* Types *a* and *b* were untreated P. Spence's Grades O and H alumina respectively. Type *c* was prepared by shaking Grade H material (1 kg.) for 12 hr. with 10% aqueous acetic acid (50 c.c.). Type *d* was obtained by stirring Grade H material with an excess of ethyl acetate at 20° for 2 days, filtering it, washing it repeatedly with hot water, and drying it at 250° for 2 days. Type *e* was prepared by shaking Grade H material (1 kg.) for 12 hr. with a solution of potassium hydroxide (100 g.) in water (75 c.c.). Type *f* was Grade O material heated at 250° for 2 days. Type *g* was obtained by heating type *e* at 250° for 2 days.

esters on alumina.* In the few available analogies [9,11,12] inverted alcohols (up to *ca.* 30% yield) have been obtained from toluene-*p*-sulphonates by using slightly damp or alkaline alumina. The experiments summarised in the Table show that cholestan-3α-ol is best obtained (60% yield) from the 3β-toluene-*p*-sulphonate (rather than the other two esters) by contact with alumina previously impregnated with potassium hydroxide and dried at 250°. In practice the method involves adsorption of the ester on to a column of alumina which is left for 3 days and then developed with solvents in the standard chromatographic sequence. Ergosta-7,22-dien-3α-ol and several axial alcohols in the lumisterol series [6] were prepared (*ca.* 60% yields) in this way.

The proportion of axial alcohol to olefin varies with the type of alumina used: with untreated alumina cholest-2-ene is the major product (70% yield) from cholestanyl toluene-*p*-sulphonate. Comparable yields of Δ²-compounds were similarly obtained from the toluene-*p*-sulphonates of ergosta-7,22-dien-3β-ol, 3β-hydroxyergost-7-en-11-one, lupeol,

* We are indebted to Dr. A. Nickon for drawing our attention to the preparation of cholestan-7α-ol [11] by this method and for providing unpublished details of a further example.[12]

[9] Clayton, Henbest, and Smith, *J.*, 1957, 1982.
[10] Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937.
[11] Cremlyn and Shoppee, *J.*, 1954, 3515.
[12] 3α-Hydroxyallopregnan-3α-ol-20-one is formed in 25% yield from the corresponding 3β-toluene-*p*-sulphonate with slightly damp alumina (unpublished work by Dr. A. Nickon).

and β-amyrin. (In the two steroids the positions of the double bonds in ring A were not investigated, but the tentative Δ^2-formulations are more probable than the alternative Δ^3-structures.[9]) α-Amyrin toluene-*p*-sulphonate gave unsaturated material (75%) as a glass having an infrared spectrum almost identical with that of pure ursa-2,12-diene (α-amyrilene II).[13] The low yield (35%) finally obtained is thus probably due to the difficulty in crystallising this compound rather than to skeletal rearrangement[14] during the treatment with alumina.

After completion of this work the preparation of cholestan-3α-ol in high yield from cholestanyl toluene-*p*-sulphonate and dimethylformamide was briefly reported.[15]

Experimental

For general directions see *J.*, 1958, 2156.

Cholestan-3β-yl Esters.—A solution of cholestan-3β-ol (1 mol.) and the appropriate sulphonyl chloride (2 mol.) in an excess of pyridine (*ca.* 20 mol.) was kept at 0° for 24 hr. After dilution with water and filtration the product was washed with a little ethanol and crystallised from ethanol. The toluene-*p*-sulphonate had m. p. 133—135°, $\nu_{max.}$ 1189 and 1176 cm.$^{-1}$: the p-*bromobenzenesulphonate* had m. p. 120—122° (Found: C, 65·4; H, 8·6. $C_{33}H_{51}O_3SBr$ requires C, 65·2; H, 8·5%), $\nu_{max.}$ 1188 and 1175 cm.$^{-1}$: the *methanesulphonate* had m. p. 108—110° (Found: C, 72·3; H, 10·9. $C_{28}H_{50}O_3S$ requires C, 72·1; H, 10·8%), $\nu_{max.}$ 1189 and 1177 cm.$^{-1}$.

Reaction of Cholestan-3β-yl Esters.—(a) *With potassium acetate in acetic acid.* A solution of the toluene-*p*-sulphonate (1 g.) and potassium acetate (1 g.) in acetic acid (20 c.c.) was refluxed for 9 hr., then evaporated *in vacuo*. The residue was extracted with ether, and the ether solution dried and evaporated. The material (720 mg.) so obtained was refluxed with 5% ethanolic potassium hydroxide (20 c.c.) for 2 hr. and the product (660 mg.) was adsorbed on alumina (60 g.; Grade O). Elution with benzene (200 c.c.) gave cholest-2-ene (360 mg.), m. p. 74—75° after crystallisation from methanol, $[\alpha]_D$ +66° (*c* 0·5), identified by mixed m. p. and comparison of infrared spectra with an authentic specimen and by conversion into the dibromide,[16] m. p. 124—125°, $[\alpha]_D$ +64° (*c* 1·5).

Elution with ether–methanol (19 : 1; 300 c.c.) gave cholestan-3α-ol (260 mg.), m. p. 184—186° (from ethanol), $[\alpha]_D$ +23° (*c* 0·8), $\nu_{max.}$ 1037 (weak) and 1003 cm.$^{-1}$. (The peak at 1037 cm.$^{-1}$ was still present after purification through the 3 : 5-dinitrobenzoate, m. p. 160—161°. This band complicates analysis of cholestan-3β-ol–cholestan-3α-ol mixtures by infrared spectroscopy.) Further elution with ether–methanol (4 : 1) did not yield cholestan-3β-ol.

Similar treatment of cholestan-3β-yl *p*-bromobenzenesulphonate (1 g.) gave cholest-2-ene (360 mg.) and cholestan-3α-ol (190 mg.). The methanesulphonate (1 g.) afforded cholest-2-ene (490 mg.), cholestan-3α-ol (210 mg.), and cholestan-3β-ol (40 mg.), m. p. 142—143°, $[\alpha]_D$ +22° (*c* 1·0), $\nu_{max.}$ 1038 cm.$^{-1}$.

(b) *With allyl alcohol.* A solution of the toluene-*p*-sulphonate (1 g.) in dry allyl alcohol–benzene (1 : 1; 200 c.c.) was boiled for 48 hr. After repeated washing with water the benzene solution was dried, filtered through alumina (100 g.; Grade H), and evaporated. The residue was dissolved in anhydrous ethylamine–liquid ammonia (1 : 1; 100 c.c.), and lithium was added until the solution remained blue. After addition of methanol and then 4N-hydrochloric acid the mixture was extracted with ether. The material so obtained was chromatographed (as above) to give cholest-2-ene (290 mg.) and cholestan-3α-ol (390 mg.).

The *p*-bromobenzenesulphonate (1 g.) and the methanesulphonate (1 g.) similarly afforded cholest-2-ene (275 and 355 mg.) and cholestan-3α-ol (320 mg. and 405 mg. respectively).

(c) *With various types of alumina.* The general procedure was as follows. The ester (1 g.) in benzene (30 c.c.) was adsorbed on a column of the appropriate alumina (see Table; 100 g.). More benzene (10 c.c.) was run on to the column which was then stoppered for the required time.

[13] Dieterle, Brass, and Schaal, *Arch. Pharm.*, 1937, **275**, 557; Winterstein and Stein, *Annalen*, 1933, **502**, 223.
[14] Noller, *J. Amer. Chem. Soc.*, 1950, **72**, 625; Burns, Cole, Parkes, and White, *Austral. J. Chem.*, 1956, **9**, 406.
[15] Chang and Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906.
[16] Barton and Rosenfelder, *J.*, 1951, 1048.

Elution with benzene (300 c.c.) gave cholest-2-ene and, in some cases, unchanged ester. (These compounds were separated by a separate chromatograph on Grade O alumina with pentane and pentane–benzene for elution.) The epimeric cholestanols were then eluted with ether–methanol as described above.

Preparation of 3α-*Alcohols*.—The following example illustrates the general procedure. A solution of ergosta-7,22-dien-3β-ol (1 g.; m. p. 174—175°) and toluene-*p*-sulphonyl chloride (1 g.) in pyridine (5 c.c.) was kept at 0° for 24 hr. The toluene-*p*-sulphonate, isolated by dilution with water and filtration, was washed with a little ethanol, dried *in vacuo*, and crystallised from ethyl acetate–methanol. The product (1·2 g.; m. p. 175—177°, $[\alpha]_D$ −21°, not analysed) was adsorbed on alumina [100 g., type (*g*) of Table] as described above. After 66 hr. the column was eluted with benzene (300 c.c.) to give *ergosta*-2(?),7,22-*triene* (360 mg.), m. p. 115—118° after crystallisation from ethyl acetate–methanol, $[\alpha]_D$ +0·6° (*c* 1·6) (Found: C, 88·6; H, 11·6. $C_{28}H_{44}$ requires C, 88·35; H, 11·65%). Ether–methanol (19 : 1; 350 c.c.) eluted ergosta-7,22-dien-3α-ol (590 mg.), m. p. 208—211° (from acetone), $[\alpha]_D$ +5° (*c* 1·2). (This m. p. is lower than that, 215—216°, previously recorded.[17] Infrared analysis showed that our product was free from any 3β-ol, and acetylation afforded an acetate with m. p. 154—156°, $[\alpha]_D$ +4° (*c* 0·9), in agreement with the literature.[17]

Similar experiments with lumisterol derivatives will be described later.[6]

Preparation of Ring A *Olefins*.—The preceding experiment on ergosta-7,22-dien-3β-ol (1 g.) was repeated, and the toluene-*p*-sulphonate decomposed by treatment with Grade H alumina for 18 hr. Elution with benzene (300 c.c.) gave the ergostatriene (720 mg.), m. p. 116—118° after crystallisation.

3β-Hydroxyergost-7-en-11-one (1 g.) similarly gave a toluene-*p*-sulphonate, m. p. 157—159°, and thence *ergosta*-2(?),7-*dien*-11-*one* (725 mg.), m. p. 113—114° (from acetone), $[\alpha]_D$ +81° (*c* 2·1) (Found: C, 84·4; H, 11·2. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

β-Amyrin (1 g.) yielded an olefinic fraction (705 mg.) which was crystallised from acetone and then ethyl acetate–methanol, to give oleana-2,12-diene (β-amyrilene II; Winterstein *et al.*[13]) (550 mg.), m. p. 148·5—150°, $[\alpha]_D$ +140° (*c* 1·4). Lupeol (1 g.) gave olefinic material (700 mg.) from which lupa-2,20(29)-diene [18] (580 mg.), m. p. 164—166°, $[\alpha]_D$ +57° (*c* 2·3), was obtained by crystallisation from ethyl acetate. Decomposition of the toluene-*p*-sulphonate from α-amyrin (1 g.) gave an olefinic fraction (760 mg.) which was chromatographed on alumina (100 g.; Grade O). Elution with pentane (5 × 20 c.c.) gave fractions which slowly solidified in contact with acetone. The combined solids were crystallised from acetone, to give ursa-2,12-diene (α-amyrilene II) (340 mg.), m. p. 116—118°, $[\alpha]_D$ +135° (*c* 1·0).

The authors are indebted to Professor E. R. H. Jones, F.R.S., for his interest and advice, to the Department of Scientific and Industrial Research for a grant (to R. S.), and to the Ministry of Education for research scholarships (to G. H. D. and P. S. E.).

The University, Manchester, 13.
Dyson Perrins Laboratory, Oxford. [*Received, December 15th*, 1958.]

[17] Windaus, Dithmar, Murke, and Suckfüll, *Annalen*, 1931, **488**, 91.
[18] Biedebach, *Arch. Pharm.*, 1939, **277**, 163.