397. *A New Preparation of Steroid Halides.*

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Aluminium and titanium halides have been shown to react with 3β-hydroxy-Δ^5-steroids, and their acetates, to give the corresponding halides in good yields. Reaction of androst-5-ene-3β : 17β-diol with aluminium chloride caused selective replacement of the 3β-hydroxyl group. A new preparation of aluminium iodide is described.

It has been known for some years [1] that simple aliphatic alcohols can be converted into the corresponding chlorides in good yields by treatment with aluminium chloride at 140—150°. Possibly owing to its vigorous nature this reaction has not been applied to more complex alcohols, nor have other aluminium halides been used. We now report its extension in a modified form to the halogenation of 3β-hydroxy-Δ^5-steroids, *viz.*, in refluxing ether in the presence of 10—15 mols. of aluminium halide for 8 hr. : the yields of halide were between 70 and 100%. Direct replacement by chlorine of the 3α-hydroxyl group in *epi*cholesterol failed, giving cholesta-3 : 5-diene as the sole product (cf. Evans and Shoppee [2]).

A new preparation of aluminium iodide has been developed which is more convenient for organic chemical purposes than that previously described.[3] This involves reaction of amalgamated aluminium with iodine under ether. The formation of cholesteryl iodide by use of this reagent constitutes a direct preparation superior to that reported by Landauer and Rydon [4] using triphenyl phosphite methiodide as the iodinating agent. It is noteworthy that the reaction is equally successful with the acetates of the above sterols.

Cholestan-3β-ol under similar conditions is recovered unchanged. Consequently the aluminium halide reagent has been used to replace selectively an activated hydroxyl group in a polyhydroxy-steroid. Thus androst-5-ene-3β : 17β-diol gave 3β-chloroandrost-5-en-17β-ol in a 56% yield. This reaction was slower than the corresponding reactions with

[1] Norris and Sturgis, *J. Amer. Chem. Soc.*, 1939, **61**, 1413.
[2] Evans and Shoppee, *J.*, 1953, 546.
[3] Eley and King, *Trans. Faraday Soc.*, 1951, **47**, 1288.
[4] Landauer and Rydon, *J.*, 1953, 2224.

monohydroxy-compounds and even after 24 hours some of the original diol was recovered. It seems evident that some interaction between a double bond near the hydroxyl group and the aluminium halide is essential for replacement to occur and retention of configuration results. This is reminiscent of the situation, already commented on,[5] in the reaction between ketones and the reagent aluminium chloride–lithium aluminium hydride. Some qualitative evidence for such interaction has been obtained from the observations that the ultraviolet spectrum, fluorescent properties, and optical rotation of cholesterol in ether change on the addition of aluminium chloride, whereas those of cholestan-3β-ol are unaffected. These effects are being investigated quantitatively.

Titanium tetrachloride and tetrabromide also convert cholesterol into the corresponding halides quantitatively.

Experimental

Cholesteryl Chloride.—(*a*) Cholesterol (568 mg.) in dry ether (40 ml.) was boiled under reflux for 8 hr. with anhydrous aluminium chloride (3·5 g.). The cold ethereal solution was shaken with 10% aqueous sodium hydroxide, washed with water, and dried. Evaporation of the ether gave a pale yellow oil (525 mg.) which quickly crystallised. Recrystallisation from acetone yielded cholesteryl chloride as colourless needles, m. p. and mixed m. p. 97°, $[\alpha]_D^{20}$ −26° (in $CHCl_3$) (Found : C, 79·8; H, 11·25. Calc. for $C_{27}H_{45}Cl$: C, 80·1; H, 11·1%).

(*b*) Cholesterol (1·00 g.) in dry ether (100 ml.) was treated with titanium tetrachloride (2·8 ml.). After an initial vigorous reaction the orange solution was boiled for 4 hr. The resulting brown solution, on being treated as above, gave a colourless oil which was dissolved in pentane, filtered through alumina, and crystallised from acetone to give cholesteryl chloride (940 mg.), m. p. 96—97° (Found : C, 79·6; H, 11·2%).

(*c*) A similar experiment, as in (*a*) but with cholesteryl acetate (382 mg.), yielded (after chromatography on alumina) cholesteryl chloride (345 mg.), m. p. and mixed m. p. 97—98° (Found : C, 79·8; H, 10·8%).

Cholesteryl Bromide.—(*a*) After reaction as in the preparation of the chloride but with cholesterol (560 mg.), aluminium bromide (3·5 g.), and ether (40 ml.), evaporation yielded a red oil which was dissolved in pentane and filtered through a column of alumina (20 g.). Evaporation gave a solid (635 mg.) which by recrystallisation from acetone gave cholesteryl bromide as colourless elongated plates, m. p. and mixed m. p. 102—103°, $[\alpha]_D^{17}$ −18° (in $CHCl_3$) (Found : C, 72·05; H, 10·2. Calc. for $C_{27}H_{45}Br$: C, 72·2; H, 10·0%).

(*b*) Cholesterol (200 mg.) in ether (20 ml.) was boiled with titanium tetrabromide (700 mg.) for 3·5 hr. Isolation of the product in the usual way gave an oil which after filtration of a pentane solution through alumina gave an oil (198 mg.) which by crystallisation from acetone gave cholesteryl bromide, m. p. 98—99° (Found : C, 71·95; H, 10·1%).

Cholesteryl Iodide.—Aluminium powder (3·0 g.) was shaken with a 1% solution of mercuric chloride in commercial ether (25 ml.) for about 2 min. The resulting grey powder was washed by decantation with dry ether and treated gradually with iodine (38 g.) in ether (350 ml.) so that the reaction did not become too vigorous. The reaction was completed under reflux for 30 min., all the aluminium dissolving. (In a quantitative experiment in which the excess of iodine was determined by titration, 0·269 g. of aluminium reacted with 3·74 g. of iodine.) (Found : I, 93·3. Calc. for AlI_3 : I, 93·4%).

Cholesterol (5·5 g.) in ether (50 ml.) was added to the aluminium iodide solution and the mixture was boiled for 8 hr., then decomposed at 0° with aqueous sodium hydroxide. The ether layer was separated and washed successively with water, aqueous sodium hydrogen sulphite, and water, and dried. Evaporation yielded a dark brown oil (5·1 g.) which was dissolved in pentane and filtered through a column of alumina (140 g.). Evaporation of the eluate (500 ml.) and crystallisation of the residue from acetone yielded cholesteryl iodide (4·7 g.) as colourless needles, m. p. and mixed m. p. 107—108°, $[\alpha]_D^{17}$ −12° (in $CHCl_3$) (Found : C, 65·7; H, 9·1. Calc. for $C_{27}H_{45}I$: C, 65·3; H, 9·05%).

Stigmasteryl Chloride.—Stigmasterol (50 mg.) in ether (5 ml.) was boiled with anhydrous aluminium chloride (300 mg.) for 4 hr. Working up in the usual way gave stigmasteryl chloride (48 mg.) which by crystallisation from acetone gave plates, m. p. 88—89° (Found : C, 80·9; H, 10·7; Cl, 8·3. Calc. for $C_{29}H_{47}Cl$: C, 80·8; H, 11·0; Cl, 8·2%).

[5] Broome and Brown, *Chem. and Ind.*, 1956, 1307.

β-Sitosteryl Chloride.—β-Sitosterol (100 mg.) in ether (25 ml.) was boiled with anhydrous aluminium chloride (700 mg.) for 8 hr. Isolation of the product in the usual way gave an oil (94 mg.) which by crystallisation from acetone gave β-sitosteryl chloride as prisms, m. p. 87—88° (Found : C, 80·5; H, 11·4; Cl, 8·0. Calc. for $C_{29}H_{49}Cl$: C, 80·4; H, 11·4; Cl, 8·2%).

β-Sitosteryl Bromide.—This was prepared as above from sitosterol (100 mg.) and aluminium bromide (800 mg.). The oil (101 mg.) by crystallisation from acetone gave β-sitosteryl bromide as plates, m. p. 77—78° (Found : C, 73·0; H, 10·6; Br, 16·5. Calc. for $C_{29}H_{49}Br$: C, 72·9; H, 10·35; Br, 16·7%).

3β-Chloroandrost-5-en-17β-ol.—Androst-5-ene-3β : 17β-diol (180 mg.) in ether (100 ml.) was boiled with aluminium chloride (3·0 g.) for 24 hr. The mixture was worked up as usual, to yield an oil. This was dissolved in benzene and put on a column of alumina. Elution with 4 : 1 benzene–ether (200 ml.) yielded colourless crystals (80 mg.). 3β-Chloroandrost-5-en-17β-ol, purified by recrystallisation from methanol or by sublimation at 150°/17 mm., was obtained as colourless needles, m. p. 163—164°, $[\alpha]_D^{16}$ −45° (in $CHCl_3$) (Found : C, 74·1; H, 9·5; Cl, 11·1. Calc. for $C_{19}H_{29}OCl$: C, 73·9; H, 9·4; Cl, 11·5%). Kuwada and Miyasaka [6] give m. p. 163°.

Further elution with ether (300 ml.) gave unchanged starting material (45 mg.), m. p. and mixed m. p. 177—178°.

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[6] Kuwada and Miyasaka, *J. Pharm. Soc. Japan*, 1937, **57**, 234.