his method of synthesis involving hydrogen sulfide and hexamethylenetetramine no halomethyl end groups can be present. This mechanism, based on sulfonium salt formation, was invoked by Bell, *et al.*[7] to explain "two classes" of poly(ethylene sulfides), namely, Class I which does not give *s*-dithiane on heating and Class II which gives the dithiane. We also observed the formation of dithiane on heating poly(ethylene sulfide) which was prepared by the reaction of 1,2-dibromoethane and sodium sulfide in equimolar proportions.

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Reduction of 3-Cholestanone with Lithium Aluminum Hydride–Aluminum Chloride

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In a previous paper from these laboratories[1b] it was shown that the reduction of 4-*t*-butylcyclohexanone with lithium aluminum hydride–aluminum chloride (1:4 ratio) in excess gives 80% of the *trans* (equatorial) 4-*t*-butylcyclohexanol, *i.e.*, less than the 89–91% *trans*-alcohol formed with lithium aluminum hydride alone.[1,2]

Compared to these results, the value of 99% 3-β-cholestanol reported by Wheeler and Mateos[3] for the reduction of 3-cholestanone with a mixture of lithium aluminum hydride–aluminum chloride seemed surprising, especially since the reduction of 3-cholestanone with lithium aluminum hydride alone is reported to give 88–91% of the (equatorial) alcohol[4] thus being very similar to the reduction of 4-*t*-butylcyclohexanone. This prompted us to restudy the reaction with the mixed hydride.

Preliminary experiments[5] indicated that in the presence of the usual excess (25–100%) of reducing agent (lithium aluminum hydride–aluminum chloride) variable amounts of unchanged 3-cholestanone were recovered. When a larger excess of hydride was used (10 equivalents of hydride per mole of ketone), the products of reduction were ketone-free and contained 18 ± 2% of 3-α-cholestanol (axial) according to the specific rotation of the acetate of the reaction product. Column chromatography of the reduction product yielded 15.3% of pure 3-α-cholestanol and suggested that the total proportion of this isomer was 17%.

The difference between these values, which are well in agreement with the published results[1] for the reduction of 4-*t*-butylcyclohexanone, and the amount of 3-α-cholestanol (less than 1%) reported earlier[3] might possibly be explained as the result of some ketone being left in the reduction product obtained in the earlier[3] investigation. It is known that in the presence of ketone, lithium aluminum hydride–aluminum chloride equilibrates a mixture of equatorial and axial alcohols (such as *trans*- and *cis*-4-*t*-butylcyclohexanol), and that at equilibrium almost the entire alcohol (99% or more) is in the form of a complex of the equatorial isomer. We were able to bring about such an equilibration by boiling the reaction product of 3-cholestanone (in excess) and lithium aluminum hydride–aluminum chloride overnight in ether solution. The only alcoholic material isolated from this reaction was 3-β-cholestanol.

The equilibration of the R-OAlCl$_2$ complex of the cholestanols (R-OH) must be distinguished (*cf.* ref. 1) from the equilibration of the free 3-cholestanols which gives 84% 3-β (equatorial) and 16% 3-α isomer,[4a] similarly to the equilibration of 4-*t*-butylcyclohexanol which gives 77–81% equatorial isomer.

EXPERIMENTAL[6]

Reduction with lithium aluminum hydride–aluminum chloride. (A) In a typical experiment, 0.88 g. (2.27 mmoles) of 3-cholestanone (m.p. 132–133°; $[\alpha]_D^{24}$ + 42.5°)[7] in 200 ml. of dry ether was added over a period of 2 hr. to the reducing agent prepared as described before[1] from 2.1 g. (15.7 mmoles) of aluminum chloride in 50 ml. of ether and 5 ml. (5.3 mmoles) of a 1.06*M* solution of lithium aluminum hydride in ether. The crude product, isolated in the usual manner, was heated for 3 hr. on a steam bath with 25 ml. of acetic anhydride and 15 ml. of dry pyridine to give 0.91 g. (95% overall yield) of crude 3-cholestanyl acetates, $[\alpha]_D^{24}$ + 16.8 ± 0.2° which corresponds to 18.0 ± 2% of the 3-α-isomer if the specific rotations are taken as +13.9°[8,9] for the 3-β isomer and +30.0°[8] for the 3-α isomer.

(1a) To whom inquiries regarding this note should be directed.

(1b) E. L. Eliel and M. N. Rerick, *J. Am. Chem. Soc.*, **82**, 1367 (1960).

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(3) O. H. Wheeler and J. L. Mateos, *Chem. & Ind. (London)*, 395 (1957); *Can. J. Chem.*, **36**, 1431 (1958).

(4) (a) H. R. Nace and G. L. O'Connor, *J. Am. Chem. Soc.*, **73**, 5824 (1951). (b) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 686 (1950). We repeated this reduction to check our analytical method and found 91% β-cholestanol (see Experimental).

(5) E. L. Eliel, M. N. Rerick, and L. A. Pilato, unpublished observations.

(6) All melting points were taken on a Kofler block and are uncorrected. Rotations were determined in a 2-dm. tube in 2–3% chloroform solution.

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(B) In another experiment the crude reduction product was chromatographed on alumina (Merck, for chromatographic purposes) and was separated as follows: 0.1498 g. (15.3% of the total) of 3-α-cholestanol, m.p. 187–189° (lit.[8] m.p. 186–187°), 0.0893 g. (8.8% of the total) of a mixture of 3-cholestanols, m.p. 137–177° and 0.7414 g. (75.7% of the total) of 3-β-cholestanol, double m.p. 127° and 145° (lit.[8] m.p. *ca.* 125° and 141–142°) which was acetylated as above to give a crude 3-β-cholestanyl acetate, $[\alpha]_D^{24}$ + 13.9.°

Reduction with lithium aluminum hydride.[4] This was carried out in the usual way and the crude reaction product was acetylated as described above. The rotation of the acetyl derivative $[\alpha]_D^{25}$ 14.8° rose to 15.4° upon further drying, corresponding to 9.4% cholestanyl-3-α acetate. In a second experiment the crude material was chromatographed. Of the eluate (96% recovery), 91% melted at 144–145° (3-β isomer) and 9% melted at 170–172° (slightly impure 3-α-isomer).

Reduction under equilibrating conditions. To a solution of 1.0 g. (7.5 mmoles) of aluminum chloride in 30 ml. of ether was added 6.0 ml (1.68 mmoles) of a 0.28*M* solution of lithium aluminum hydride in ether, followed by 2.3 g. (7.31 mmoles) of 3-cholestanone in ether solution. After refluxing overnight, the solution was worked up in the usual way and the residue chromatographed. There was obtained 0.24 g. (9% of the eluate) of an unidentified semisolid, followed by 1.39 g. (53% of eluate) of crude 3-cholestanone, m.p. 110–111° whose infrared spectrum indicated the absence of hydroxylated material and 0.98 g. (38%) of 3-β-cholestanol, m.p. 142–143°. No 3-α-cholestanol was detected.

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(9) Value reported in ref. 8 is +14.0°.

Fluorinated Steroids. III. Synthesis of 16ζ-Fluorotestosterone

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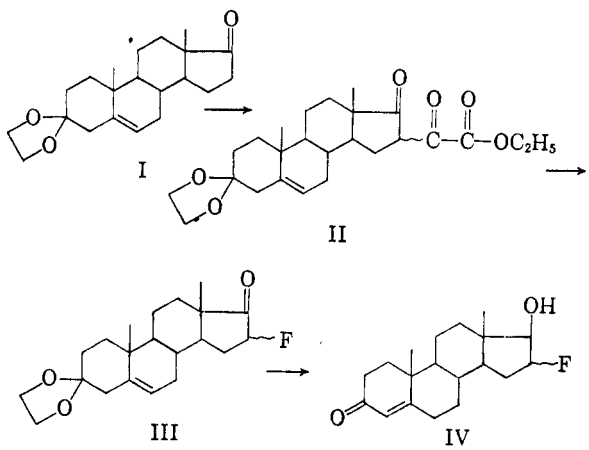
In previous papers[1] we have described a method for the introduction of fluorine into the steroid molecule which consists in the reaction of the sodio enolate of an α-alkoxalyl keto steroid with perchloryl fluoride[2] followed by removal of the alkoxalyl moiety under mildly alkaline conditions. In this note we wish to report the application of this method to the synthesis of 16ζ-fluorotestosterone (IV).[3]

A suitable starting material for the synthesis of a 16-alkoxalylandrostene derivative was 3-ethylenedioxy-5-androsten-17-one (I).[4] This compound was prepared by the chromic oxide–pyridine oxidation[5] of testosterone 3-ethylene ketal.[4d,6] Condensation of I with ethyl oxalate and sodium ethoxide in benzene afforded a white, crystalline ethoxalyl derivative II in 72% yield. Reaction of the sodio enolate of this substance with perchloryl fluoride in methanol followed by the potassium acetate-catalyzed cleavage of the ethoxalyl group gave 3-ethylenedioxy-16ζ-fluoro-5-androsten-17-one (III) in poor yield and also afforded a by-product, $C_{21}H_{29}FO_5 \cdot H_2O$, which has not been identified thus far. Compound III was converted to 16ζ-fluorotestosterone (IV)[3] by sodium borohydride reduction of the 17-keto group[7] followed by acid-catalyzed regeneration of the Δ^4-3-one system. The stereochemistry of the fluorine atom at C_{16} in III and IV is uncertain. However, the physical characteristics of the product are in good agreement with those reported in the patent literature[3] for 16α-fluorotestosterone.



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(2) We would like to thank the Pennsalt Chemicals Corporation for a generous sample of perchloryl fluoride.

(3) J. Fried and G. H. Thomas (U. S. Patent 2,857,403) prepared 16α- and 16β-fluorotestosterone in a reaction sequence which involved displacement of the mesyloxy group in 16α-mesyloxy-4-androstene-3,17-dione by fluoride ion.

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(6) A more direct preparation of I has been reported[4d] through the preferential 3-ketalization of 4-androstene-3,17-dione with 2-methyl-2-ethyl-1,3-dioxolane. However, in our hands, this procedure gave a product contaminated with 3,17-bisethylenedioxy-5-androstene.[4c]

(7) Metal hydride reductions of 16-halo 17-ketones have been reported by several workers to afford the 17β-hydroxy derivatives.[8] However, in a few instances, mixtures of the 17-epimeric alcohols have been obtained.[9]

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