178. *The Use of Aprotic Solvents for Nucleophilic Substitution Reactions at $C_{(3)}$ and $C_{(17)}$ in Steroids.*

By H. B. Henbest and W. R. Jackson.

Cholestanes containing 3α-substituents (cyano, azido, bromo, fluoro, acetoxy) have been obtained in good yields (>70%) from reactions of cholestan-3β-yl toluene-*p*-sulphonate with nucleophiles in aprotic solvents. In comparison, reactions of cholestan-3α-yl toluene-*p*-sulphonate with cyanide and acetate ions gave more elimination, but the 3β-cyanide and 3β-acetate were obtained in 40% and 57% yields, respectively. Use of aprotic solvents inhibits structural rearrangement in nucleophilic replacement reactions at $C_{(17)}$, and good yields of 17α-azido-, -bromo-, -chloro-, and -fluoro-compounds were obtained from testosterone toluene-*p*-sulphonate. Reaction of this ester with acetate anion in *N*-methylpyrrolidone gave the 17α-acetate (34%) and 3-oxoandrosta-4,16-diene (57%).

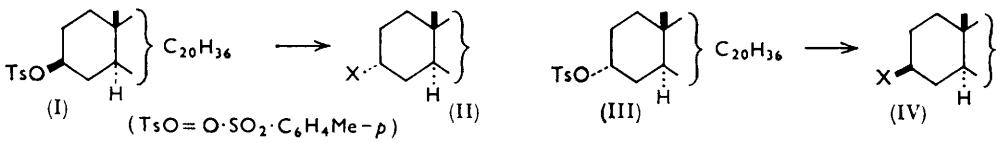
In connection with the synthesis of compounds required for studying intramolecular directing effects of polar substituents,[1,2] it became necessary to have reasonably efficient methods for introducing simple, dipolar substituents starting from alicyclic alcohols. 17α-Substituted 3-oxo-Δ^4-steroids were especially required in order to determine the effect of the remote $C_{(17)}$-group upon additions to the unsaturated ketone system. Such compounds should be available by replacement reactions of testosterone toluene-*p*-sulphonate (V) but, in view of the known [3,4] difficulties of effecting such reactions in this neopentyl type of system, pilot experiments were first carried out on cholestanyl toluene-*p*-sulphonate (I). Recent preparative [5] and kinetic [6] work has shown that nucleophilic reactions proceed well in aprotic dipolar solvents.

Reactions of Cholestanyl Toluene-p-*sulphonate* (I).—(a) *Cyanides.* Although cyanide ion

[1] Henbest, Nicholls, Jackson, Wilson, Crossley, Meyers, and McElhinney, *Bull. Soc. chim. France* 1960, 1365.
[2] Crossley, Darby, Henbest, Nicholls, McCullough, and Stewart, *Tetrahedron Letters*, 1961, 398.
[3] Madaeva and Lur'i, *Doklady Akad. Nauk, S.S.S.R.*, 1952, **84**, 713; *Chem. Abs.*, 1953, **47**, 3326.
[4] Elks and Shoppee, *J.*, 1953, 241.
[5] (*a*) Smiley and Arnold, *J. Org. Chem.*, 1960, **25**, 257; (*b*) Friedman and Shechter, *ibid.*, p. 877; Cava, Little, and Napier, *J. Amer. Chem. Soc.*, 1958, **80**, 2257; Newman and Otsuka, *J. Org. Chem.*, 1958, **23**, 797.
[6] Winstein, Savedoff, Smith, Stevens, and Gall, *Tetrahedron Letters*, 1960, No. 9, 24; Miller and Parker, *J. Amer. Chem. Soc.*, 1961, **83**, 117.

has a high nucleophilic constant,[7,8] reactions of secondary halides or sulphonates with alkali cyanides in aqueous or alcoholic solvents do not generally give more than 30% yields of nitriles.[9] Recently, by use of dimethyl sulphoxide as solvent, nitriles have been obtained in more than 70% yield from reactions between some secondary chlorides and sodium cyanide;[5a,b] no nitrile was, however, obtained from cyclohexyl chloride.[5b]

Reaction of the ester (I) with calcium or sodium cyanide gave the known 3α-cyanocholestane (II; X = CN), the best yield (80%) being obtained in *N*-methylpyrrolidone containing t-butyl alcohol (5%) at 90°, although the yield was only slightly lower in the absence of t-butyl alcohol. Small amounts of olefin (mainly or entirely cholest-2-ene



as indicated by infrared measurements [10]) and 3α-alcohol were also obtained from these reactions. As expected, the proportion of olefin was higher (*ca.* 55%) starting from the isomeric axial ester (III), but a 40% yield of the 3β-cyanide (IV; X = CN) was obtained from the reaction in *N*-methylpyrrolidone–t-butyl alcohol. The fractions of elimination observed in these reactions of the epimeric esters (I) and (III) are very similar to those found in the reactions of *trans*- and *cis*-4-t-butylcyclohexyl toluene-*p*-sulphonates [11] with sodium iodide in acetone.

Lower yields (40—50%) of the 3α-cyanide (II; X = CN) were obtained from the ester (I) when dimethylformamide–t-butyl alcohol (9 : 5) was used as solvent, mainly owing to production of the 3α-formate by reaction of the ester with dimethylformamide.[12]

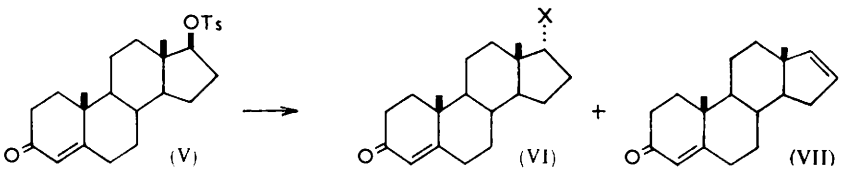
(b) *Azide.* Reaction of the ester (I) with sodium azide in dimethyl sulphoxide at 83—84° has been reported without full details.[13] Sodium azide being used in dimethylformamide at 153°, the 3α-azide (II; X = N_3) was obtained in 70% yield; this yield should be substantially improved by using *N*-methylpyrrolidone as solvent [cf. reactions of ester (V) below]. The structure of the 3α-azide was confirmed by reduction to the 3α-amine, which was isolated as its acetyl derivative.

(c) *Halides.* Reaction of the cholestane ester (I) with sodium iodide in acetone at 100° is unusual in giving the 3β-iodo-compound,[14] probably *via* the initially formed but very reactive axial 3α-iodide. However, lithium bromide in boiling acetone gave 3α-bromocholestane, although there was some evidence for its contamination by the 3β-bromide when longer reaction times were used. The ester (I) has not been treated with chloride, but an 80% yield of 3α-chloride has been obtained [15] from the related 3β-equatorial ester, hecogenin toluene-*p*-sulphonate, on reaction with lithium chloride in boiling ethyl methyl ketone–t-butyl alcohol (5 : 1). Recent work [6a] has shown that tetra-alkylammonium halides are more dissociated than lithium halides in organic solvents, revealing that the true order of increasing nucleophilic reactivity is iodide, bromide, chloride, fluoride. Tetrabutylammonium fluoride was therefore chosen as the source of fluoride ion for reaction with esters (I) and (III). In boiling acetone, the former ester gave the 3α-fluoride (II; X = F) in 75% yield, whereas the axial ester (III) gave the 3β-fluoride (IV; X = F) in 56% yield together with olefin (43%).

[7] Swain and Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.
[8] Hawthorne, Hammond, and Graybill, *J. Amer. Chem. Soc.*, 1955, **77**, 486.
[9] Wagner and Zook, "Synthetic Organic Chemistry," Wiley, New York, 1953, p. 591.
[10] Henbest, Meakins, and Wood, *J.*, 1954, 800.
[11] Winstein, Darwish, and Holness, *J. Amer. Chem. Soc.*, 1956, **78**, 2915.
[12] Chang and Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906.
[13] Hertler and Corey, *J. Org. Chem.*, 1958, **23**, 1221.
[14] Corey, Howell, Boston, Young, and Sneen, *J. Amer. Chem. Soc.*, 1956, **78**, 5036.
[15] Combe and Henbest, unpublished work.

(d) *Acetate.* The acetate anion has been considered to be a nucleophile of only moderate reactivity.[7] In reactions of 3-halogeno-steroids with potassium acetate in organic acids, the ratio of elimination to replacement is very high.[16] However, with use of ethyl methyl ketone as solvent and tetrabutylammonium acetate as nucleophile, the esters (I) and (III) have been converted into the 3α- and 3β-acetates, the yields being 85% and 57% respectively. The ratios of replacement to elimination in these reactions are therefore similar to those observed with tetrabutylammonium fluoride. The 3α-acetate was also obtained (79% yield) by using *N*-methylpyrrolidone as solvent at 160°; these conditions were also effective for replacement reactions at $C_{(17)}$ (see below).

*Reactions of Testosterone Toluene-*p*-sulphonate* (V).—(a) *Halides.* This ester was unchanged during an attempted replacement reaction using lithium bromide in boiling acetone. This difference in behaviour from that of the 3β-ester (I) may be due to the hindrance imposed by the neighbouring 18β-methyl and 12-methylene groups on the development of the required solvated, linear transition state; in less substituted structures, derivatives of cyclopentane are more reactive than those of cyclohexane in S_N2 reactions.[17] When ethyl methyl ketone (at 80°) was used in place of acetone, reaction between the



ester (V) and lithium bromide gave a crystalline bromo-compound (30%), but mostly a less polar non-crystalline material, probably olefin of rearranged structure (the product of direct elimination, the Δ^{16}-compound, is discussed below). The bromo-compound was reduced with sodium in ammonia and, after treatment of the product with chromic acid, 5α-androstan-3-one was obtained. This shows that the bromo-compound has the normal steroid skeleton, and it is therefore formulated as 17α-bromoandrost-4-en-3-one (VI; X = Br). A much improved yield of the bromo-compound was obtained by using tetrabutylammonium bromide as nucleophile in boiling ethyl methyl ketone. The 17α-chloro- and 17α-fluoro-3-oxo-Δ^4-compounds were obtained similarly from reactions of the ester (V) with the appropriate tetrabutylammonium halide in ethyl methyl ketone; the yields were high after allowing for unchanged starting material which could be easily separated from the 17α-halides by chromatography.

(b) *Azide.* A compound formulated as the 17α-azide (VI; X = N_3) was obtained from the reaction of the ester (V) and sodium azide, the yield being 92% in *N*-methylpyrrolidone–t-butyl alcohol and 45% in dimethylformamide.

(c) *Acetate.* No appreciable reaction occurred when tetrabutylammonium acetate was heated with ester (V) in ethyl methyl ketone for 14 days. However, reaction in *N*-methylpyrrolidone at 160° gave the 17α-acetate (VI; X = OAc) and the Δ^{16}-compound (VII), both crystalline. The latter gave a strong band in the infrared at 730 cm.$^{-1}$ due to the Δ^{16}-bond; the non-crystalline, presumably rearranged material referred to above as a by-product in the lithium bromide reaction showed no band of appreciable strength in this region. The formation of the 17-acetate of oestra-1,3,5(10)-triene-3,17α-diol from reaction of the related 17β-toluene-*p*-sulphonate with potassium acetate in dimethylformamide has been reported [18] without details.

Although no Δ^{16}-compound was detected in the product from reaction of ester (V) with

[16] Shoppee, *J.*, 1946, 1139; Bridgewater and Shoppee, *J.*, 1953, 1709.
[17] Eliel, " Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 124.
[18] Allais and Hoffman, U.S.P., 2,835,681; *Chem. Abs.*, 1958, **52**, 18531.

tetrabutylammonium chloride in boiling ethyl methyl ketone, the same reaction in *N*-methylpyrrolidone at 160° gave a 30% yield of this olefin as well as the 17α-chloride (67%). The difference between the behaviour of the two solvents might be due to the amides causing elimination independently of substitution. However, although the ester (V) partly decomposed in *N*-methylpyrrolidone under the conditions of the chloride reaction (except for the absence of the quaternary chloride) the product was the non-crystalline olefin, not the Δ^{16}-compound. The 17α-acetate was also stable in *N*-methylpyrrolidone under the conditions for replacement, showing that the Δ^{16}-compound was not produced by decomposition of the ester. Formation of the Δ^{16}-compound therefore appears to accompany replacement in the reactions of ester (V) with acetate or chloride ions in the amide solvent.

Experimental

Replacement reactions were carried out with the exclusion of water, purified solvents and either fused lithium halides or crystalline tetrabutylammonium salts being used. An atmosphere of nitrogen was kept over reactions on 3-oxo-Δ^4-steroids performed above 120°. Dimethylformamide was purified by Thomas and Rochow's method,[19] and *N*-methylpyrrolidone was dried with barium oxide followed by addition and distillation of one third of its volume of benzene; the fraction, b. p. 204—206°, was then collected. Calcium cyanide was purified *via* its ammonia complex.[20] Alumina (Spence, grade H), deactivated with aqueous acetic acid,[21] was used for chromatography. Light petroleum refers to the fraction of b. p. 40—60°. Most of the yields are based on the weights of almost pure materials obtained by chromatography. Rotations were determined for chloroform solutions, and m. p.s were determined on a hot stage. Infrared absorption measurements [10] were used to confirm that the once-crystallised olefin obtained from the reactions of esters (I) and (III) was essentially cholest-2-ene.

3α-*Cyano*-5α-*cholestane* (II; X = CN).—A stirred mixture of the ester (I) (0·5 g.) and calcium cyanide (0·93 g., 10 mol.) in *N*-methylpyrrolidone (47·5 ml.) and t-butyl alcohol (2·5 ml.) was maintained at 90° for 20 hr. Isolation with ether gave a product that was chromatographed on alumina (50 g.). Elution with light petroleum gave cholest-2-ene (25 mg., 8%), m. p. 69—71° (from methanol), followed by 3α-cyanocholestane (0·29 g., 81%), m. p. 167—169° (from acetone), $[\alpha]_D$ +20° (lit.,[22] m. p. 168°, $[\alpha]_D$ +21°). Elution with benzene–ether (9 : 1) gave cholestan-3α-ol (40 mg., 10%), m. p. and mixed m. p. 186—187° (from acetone). Repetition of the experiment with *N*-methylpyrrolidone (50 ml.) as solvent gave cholest-2-ene (30 mg.), 3α-cyanocholestane (0·27 g.), and cholestan-3α-ol (50 mg.); with sodium cyanide (0·51 g., 10 mol.), cholest-2-ene (28 mg.), 3α-cyanocholestane (0·29 g.), and cholestan-3α-ol (40 mg.) were obtained.

A mixture of ester (I) (1 g.) and calcium cyanide (1·8 g.) in dimethylformamide (90 ml.) and t-butyl alcohol (50 ml.) was heated under reflux for 15 hr. Isolation as before gave cholest-2-ene (0·13 g., 19%), 3α-cyanocholestane (0·36 g., 48%), and cholestan-3α-ol (0·27 g., 37%). Similar yields were obtained by using sodium cyanide (1 g.). The 3α-alcohol arises largely or wholly by hydrolysis of the 3α-formate during chromatography; the crude product before chromatography gave an absorption band at 1740 cm.$^{-1}$ due to formate.

3β-*Cyano*-5α-*cholestane* (IV; X = CN).—A stirred mixture of the ester (III) (0·49 g.), calcium cyanide (0·96 g.), *N*-methylpyrrolidone (47·5 ml.), and t-butyl alcohol (2·5 ml.) was kept at 90° for 20 hr. Chromatography on alumina (100 g.) gave cholest-2-ene (0·15 g., 53%), 3β-cyanocholestane (IV) (0·12 g., 40%), m. p. 151—152° (from acetone) (lit.,[22] m. p. 152°), and cholestan-3β-ol (20 mg., 5%), m. p. 139—142° (from ethyl acetate).

3α-*Azido*-5α-*cholestane* (II; X = N_3).—A solution of ester (I) (1 g.) and sodium azide (0·7 g., 5 mol.) in dimethylformamide (130 ml.) was heated under reflux for 20 hr. The product was isolated with ether and its solution in light petroleum was filtered through alumina (100 g.). 3α-*Azidocholestane* (0·59 g., 70%) had m. p. 50—52° (from ethanol), $[\alpha]_D$ +24° (Found: C, 78·55; H, 11·4; N, 9·55. $C_{27}H_{47}N_3$ requires C, 78·4; H, 11·45; N, 10·15%).

[19] Thomas and Rochow, *J. Amer. Chem. Soc.*, 1957, **79**, 1843.
[20] Christmann and Houpt, U.S.P. 2,386,434; *Chem. Abs.*, 1946, **40**, 684.
[21] Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657.
[22] Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705.

For reduction, the azide (1 g.) in dry ether (100 ml.) was added to a suspension of lithium aluminium hydride (0·3 g.) in dry ether (200 ml.), and the mixture was heated under reflux for 8 hr. Isolation with ether gave the 3α-amine (0·9 g.) which was treated with acetic anhydride (3 ml.) in ether (10 ml.). 3α-Acetamidocholestane (0·94 g., 90%) had m. p. 216—217° (from acetone–ethyl acetate), $[\alpha]_D$ +37° (lit.,[23] m. p. 217—218°, $[\alpha]_D$ +36°).

3α-Bromo-5α-cholestane (II; X = Br).—A solution of ester (I) (0·25 g.) and lithium bromide (0·2 g.) in acetone (15 ml.) was heated under reflux for 36 hr. The steroid was isolated in light petroleum, this extract being filtered through alumina (20 g.) to give a product (0·16 g.), m. p. 99—100°. Crystallisation from methanol–isopropyl ether gave 3α-bromocholestane (0·15 g., 75%), m. p. 101—102°, $[\alpha]_D$ +26° (lit.,[22] m. p. 103°). Increase of the reaction time to 72 hr. gave the bromo-compound, m. p. 82—100°.

3α-Fluoro-5α-cholestane (II; X = F).—A solution of ester (I) (0·5 g.) and tetrabutylammonium fluoride (1·4 g., 6 mol.) in acetone (10 ml.) was heated under reflux for 5 days. Isolation with ether and chromatography (elution with light petroleum) on alumina (100 g.) gave cholest-2-ene (66 mg., 19%), m. p. 70—71°, and then *3α-fluorocholestane* (0·28 g., 78%), m. p. 104—106° (from isopropyl ether–methanol), $[\alpha]_D$ +32° (Found: C, 83·3; H, 11·9. $C_{27}H_{47}F$ requires C, 83·1; H, 12·0%).

3β-Fluoro-5α-cholestane (IV; X = F).—The reaction between the ester (III) and tetrabutylammonium fluoride was carried out as in the preceding experiment. Chromatography gave cholest-2-ene (0·15 g., 43%), m. p. 70—72° (from methanol), and the 3β-fluoride (0·19 g., 56%), m. p. 80·5—82·5°, $[\alpha]_D$ +22° (from acetone) (lit.,[24] m. p. 80—82°, $[\alpha]_D$ +23°).

3α-Acetoxy-5α-cholestane.—A solution of ester (I) (0·5 g.) and tetrabutylammonium acetate (1·65 g., 6 mol.) in ethyl methyl ketone (10 ml.) was heated under reflux for 7 days. Chromatography on alumina (100 g.) gave cholest-2-ene (50 mg., 14%), m. p. 72—74° (from methanol), 3α-acetoxycholestane (0·32 g., 81%), m. p. 94—95° (from methanol), $[\alpha]_D$ +30°, and cholestan-3α-ol (16 mg., 4%), m. p. 181—183° (from acetone). The compounds were eluted by light petroleum, benzene–light petroleum (1 : 19), and benzene–ether (9 : 1), respectively.

Reaction between the ester (I) (6 g.) and tetrabutylammonium acetate (20 g.) in *N*-methylpyrrolidone (120 ml.) at 160° for 4 hr. gave cholest-2-ene (0·83 g., 20%), 3α-acetoxycholestane (3·64 g., 76%), and cholestan-3α-ol (0·1 g., 3%).

3β-Acetoxy-5α-cholestane.—Reaction of ester (III) as in the preceding experiment gave cholest-2-ene (0·14 g., 43%), m. p. 72—73° (from methanol), and the 3β-acetate (0·22 g., 57%), m. p. 110—111° (from methanol–isopropyl ether).

17α-Bromo-3-oxoandrost-4-ene (VI; X = Br).—A solution of the testosterone ester (V) (0·5 g.) and tetrabutylammonium bromide (2·1 g., 6 mol.) in ethyl methyl ketone (10 ml.) was heated under reflux for 72 hr. Isolation with ether followed by chromatography on alumina (100 g.) gave, on elution with benzene–light petroleum (3 : 1), *17α-bromo-3-oxoandrost-4-ene* (0·20 g., 55%), m. p. 153—155° (from isopropyl ether), $[\alpha]_D$ +18° (Found: C, 64·9; H, 7·55; Br, 23·05. $C_{19}H_{27}BrO$ requires C, 64·95; H, 7·7; Br, 22·8%). Elution with benzene–ether (9 : 1) gave the starting material (0·22 g., 44%).

Extension of the reaction time to 8 days gave less-pure bromide (0·285 g.), m. p. 140—146° (one crystallisation from isopropyl ether).

Reaction between the ester (V) (3 g.) and lithium bromide (9 g., 10 mol.) in boiling ethyl methyl ketone (90 ml.) for 24 hr. gave an oil (1·2 g., eluted from alumina by light petroleum) and the 17α-bromo-compound (0·74 g., 30%), m. p. 153—154° (eluted with benzene–light petroleum).

For reduction, the bromo-compound (0·3 g.) in ether (75 ml.) was added to a stirred solution of sodium (0·75 g.) in ether (45 ml.) and liquid ammonia (150 ml.), and the mixture was stirred for a further 10 min. Methanol was added, the ammonia was allowed to evaporate, and the steroid (0·28 g.) was isolated with ether. The product was dissolved in acetone, oxidised with 8N-chromic acid in sulphuric acid, and then extracted with ether. Filtration through alumina (20 g.) of a solution of the product in light petroleum gave 3-oxoandrostane (0·25 g.), m. p. 103—104°, $[\alpha]_D$ +24° (from aqueous acetone) (lit.,[25] m. p. 104—105°, $[\alpha]_D$ +25°).

17α-Chloro-3-oxoandrost-4-ene (VI; X = Cl).—A solution of the ester (V) (0·5 g.) and tetrabutylammonium chloride (1·94 g., 6 mol.) in ethyl methyl ketone (10 ml.) was heated

[23] Shoppee, Evans, Richards, and Summers, *J.*, 1956, 1649.
[24] Shoppee and Summers, *J.*, 1957, 4816.
[25] Ruzicka and Kagi, *Helv. Chim. Acta*, 1937, **20**, 1557.

under reflux for 14 days. Isolation with ether and chromatography on alumina (100 g.) gave, on elution with benzene–light petroleum (4 : 1), 17α-*chloro*-3-*oxoandrost*-4-*ene* (0·28 g., 87%), m. p. 152—153° (from isopropyl ether), $[\alpha]_D$ +44° (Found: C, 74·6; H, 8·9. $C_{19}H_{27}ClO$ requires C, 74·4; H, 8·8%). Elution with benzene gave the starting material (60 mg., 12%).

Similar reaction in *N*-methylpyrrolidone (10 ml.) at 160° for 4 hr. gave the 17α-chloride, m. p. 149—151°, $[\alpha]_D$ +45°, and 3-oxoandrosta-4,16-diene, m. p. 129—132°, $[\alpha]_D$ +119° (see below). The diene was eluted before the chloro-compound but complete separation was difficult to achieve. With the rotations of mixed fractions taken into account, the approximate yields were: diene 27%, chloride 67%.

17α-*Fluoro*-3-*oxoandrost*-4-*ene* (VI; X = F).—A solution of the ester (V) (2 g.) and tetrabutylammonium fluoride (7·3 g., 6 mol.) in ethyl methyl ketone (20 ml.) was heated under reflux for 10 days. Isolation with ether and chromatography on alumina (100 g.) gave, on elution with benzene–light petroleum (4 : 1), a mixture (0·26 g.) [probably Δ^{16}-compound (VII) and 17α-fluoride] followed by 17α-*fluoro*-3-*oxoandrost*-4-*ene* (0·63 g., 52%), m. p. 149—151° (from isopropyl ether), $[\alpha]_D$ +110° (Found: C, 78·9; H, 9·5. $C_{19}H_{27}FO$ requires C, 78·6; H, 9·3%). Elution with benzene–ether (9 : 1) gave unchanged ester (0·64 g., 32%).

17α-*Azido*-3-*oxoandrost*-4-*ene* (VI; X = F).—A mixture of the ester (V) (0·5 g.), sodium azide (0·43 g.), and *N*-methylpyrrolidone (10 ml.) was heated at 160° for 4 hr. Isolation with ether, and chromatography on alumina (100 g.) gave, on elution with benzene–light petroleum, the 17α-*azide* (0·33 g., 92%), m. p. 100—101° (from isopropyl ether), $[\alpha]_D$ +44° (Found: C, 73·0; H, 8·4; N, 13·7. $C_{19}H_{27}N_3O$ requires C, 72·8; H, 8·7; N, 13·4%). The ester (V) (1 g.) and sodium azide (1·8 g.) in boiling dimethylformamide for 16 hr. gave the 17α-azide (0·38 g., 45%).

17α-*Acetoxy*-3-*oxoandrost*-4-*ene* (VI; X = OAc).—The ester (V) (0·5 g.) and tetrabutylammonium acetate (2·1 g., 6 mol.) were heated in *N*-methylpyrrolidone (10 ml.) at 160° for 4 hr. Isolation with ether and chromatography on alumina gave, on elution with benzene–light petroleum (4 : 1), 3-oxoandrosta-4,16-diene (0·17 g., 57%), m. p. 131—133° (from light petroleum–isopropyl ether), $[\alpha]_D$ +121° (lit.,[26] m. p. 131·5—133·5°, $[\alpha]_D$ +123°). Elution with benzene gave the 17α-acetate (0·12 g., 34%), m. p. 112—114° (from isopropyl ether), $[\alpha]_D$ +110° (lit., m. p. 115·5—116·5° for 17α-acetate; m. p. 140—141°, $[\alpha]_D$ +91° for 17β-acetate). The 17α-acetate (50 mg.) was unchanged (49 mg., m. p. 111—113°) after being kept in *N*-methylpyrrolidone (3 ml.) containing tetrabutylammonium acetate (0·2 g.) for 4 hr. at 160°.

The ester (V) (0·5 g.) was heated in *N*-methylpyrrolidone (10 ml.) at 160° for 4 hr. Isolation with ether gave a product (0·38 g.) that was chromatographed on alumina (100 g.). Elution with benzene–light petroleum (3 : 1) gave a gum (0·11 g.) showing a broad band at 670—680 cm.$^{-1}$ but no peak at 730 cm.$^{-1}$ (absence of Δ^{16}-bond) (Found: C, 83·7; H, 9·4. $C_{19}H_{26}O$ requires C, 84·4; H, 9·7%). The analysis suggests that this product is formed from the starting material by elimination of toluene-*p*-sulphonic acid. Elution with benzene–ether gave the starting material (0·20 g.).

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King's College, London, W.C.2.
The Queen's University of Belfast. [*Received, July 17th,* 1961.]

[26] Prelog, Ruzicka, Meister, and Wieland, *Helv. Chim. Acta*, 1945, **28**, 618.