# *Studies in the Steroid Group. Part LXV.* Reactions of 11-Hydroxy- and 11-Oxo-5α-steroids.*

By A. CRAWSHAW, H. B. HENBEST, and E. R. H. JONES.

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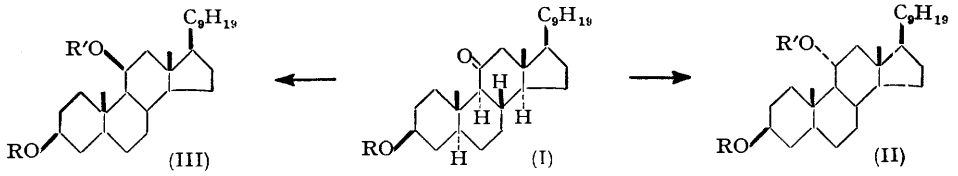
Reduction of 11-oxo-steroids gives 11α- or 11β-hydroxy-compounds. It is shown that the more hindered 11β-hydroxy-steroids can be acetylated with acetyl chloride. Phosphorus oxychloride–pyridine dehydration of epimeric 11-hydroxy-compounds affords the same $\Delta^{9(11)}$-olefin. As in the 5β-series, enol acetylation of 11-oxo-5α-steroids yields 11-acetoxy-$\Delta^{9(11)}$-steroids. The formation of $\Delta^{9(11)}$-compounds in these reactions indicates the relative difficulty of forming the strained $\Delta^{11}$-system.

THE starting material for most of the work described in this paper was 3β-acetoxyergostan-11-one (I), a compound first described by Heusser, Eichenberger, Kurath, Dällenbach, and Jeger (*Helv. Chim. Acta*, 1951, **34**, 2106). 11α-Hydroxy(equatorial)-compounds have been prepared recently by sodium–propanol reduction of 11-ketones (Heusser, Anliker, and Jeger, *ibid.*, 1952, **35**, 1537; Herzog, Jevnik, and Hershberg, *J. Amer. Chem. Soc.*, 1953, **75**, 269). This reduction has also been effected independently with sodium–ethanol, and although some starting material remains it is easily removed during chromatographic purification. The 3β : 11α-diol (II; R = R′ = H) was readily converted into its diacetate.

It is now well established that lithium aluminium hydride reduction of 11-ketones yields predominantly 11β-hydroxy(polar)-steroids, *e.g.*, (I) gives (III; R = R′ = H) in high yield. 11β-Hydroxy-groups have not been acylated hitherto.† 11β-Acetates (*e.g.*, III; R = R′ = Ac) can however be obtained in good yield by acetylation with acetyl chloride–dimethylaniline in chloroform (cf. formation of tertiary 5α-acetates; Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, 1944, **27**, 513; Part LVI of this series, *J.*, 1952, 4883). 11β-Hydroxy-$\Delta^7$-steroids are also acetylated by this method (to be published) (cf. Oliveto, Gerold, and Hershberg, *Arch. Biochem. Biophys.*, 1953, **43**, 234, who have also described acetylation of 11β-hydroxy-compounds by different methods).

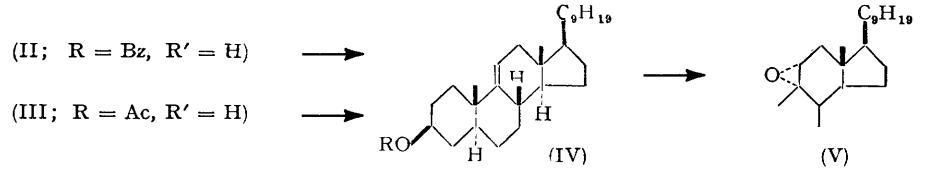



The behaviour of 11α- and 11β-hydroxy-compounds with phosphorus oxychloride in pyridine was then studied. This reagent usually affords trisubstituted olefins when the groups to be eliminated are *trans* and polar (cholestan-4β-ol ⟶ cholest-4-ene, Barton

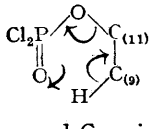
* Part LXIV, *J.*, 1954, preceding paper.

† Cf. Fieser and Fieser ("Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, p. 408), but Reichstein and Steiger (*Helv. Chim. Acta*, 1937, **20**, 819) probably obtained an 11β-acetate by vigorous treatment with acetic anhydride and pyridine.

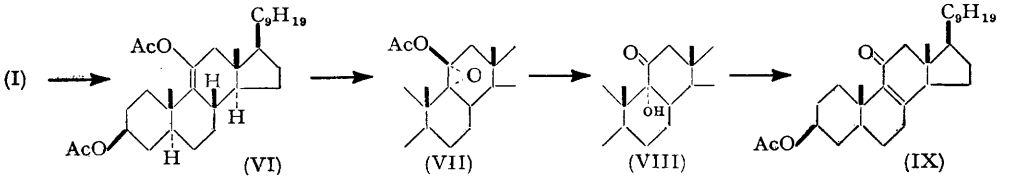
and Rosenfelder, *J.*, 1951, 1048; formation of $\Delta^7$-compounds from 7α-hydroxy-steroids, Buser, *Helv. Chim. Acta*, 1947, **30**, 1379; Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226; Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284—the last paper records that some 7β-chloro-compound may also be formed). Treatment of the 11β-hydroxy-compound (III; R = Ac, R′ = H) with phosphorus oxychloride in pyridine gave the expected olefin (IV; R = Ac) in 70% yield; the $\Delta^{9(11)}$-rather than the $\Delta^{11}$-structure is assigned from the infra-red absorption characteristics (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402; Henbest, Meakins, and Wood, *J.*, 1954, in the press). The homogeneity of this dehydration product was confirmed by its conversion (in high yield) into a single (9α : 11α-)epoxide (see Experimental section); the rotation contribution of the $\Delta^{9(11)}$-bond is also discussed in the Experimental section. Hydrogenation of the olefin in acetic acid (platinum catalyst) gave ergostanyl acetate.




The reaction of 11α-hydroxy-steroids with phosphorus oxychloride was less easy to predict. In analogous examples, cholestan-4α-ol gave a phosphate, and 7β-hydroxy-compounds yielded 7α-chloro-steroids (cf. refs. given above for 4β- and 7α-hydroxy-derivatives). The 3β : 11α-diol (II; R = R′ = H) was converted into its 3β-monobenzoate by selective acylation with benzoic anhydride in pyridine (Eckhardt, *Ber.*, 1938, **71**, 461). This, with phosphorus oxychloride–pyridine, also gave a $\Delta^{9(11)}$-compound (IV; R = Bz) (40% yield) as the only isolable product, hydrolysis yielding ergost-9(11)-en-3β-ol, identical with that obtained from the above 3β-acetate. The formation of a $\Delta^{9(11)}$-compound is unusual under these conditions, representing a *cis*-elimination of groups. The reaction may be an $E_1$ process occurring by loss of proton from $C_{(9)}$ from a positively charged $C_{(11)}$-intermediate, or a cyclic intermediate may possibly be involved (see inset). The further possibility (suggested by a referee) that a normal *E*2 reaction might follow the intermediate formation of an 11β-chloro-compound seems unlikely since Heusler and Wettstein (*loc. cit.*) record that 7α-chloro-steroids, of analogous stereochemistry, are stable in boiling collidine.



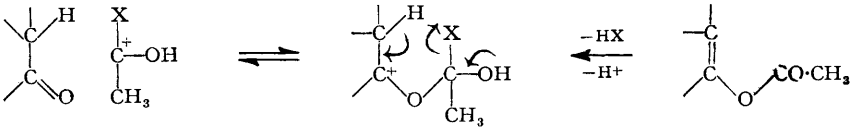

The direction of enol acetylation of 11-oxo-5α-steroids has also been investigated. Previous work on this type of reaction has been concerned with 5β-compounds, where recent studies (Hirschmann and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 2361) have shown that 11-acetoxy-$\Delta^{9(11)}$-5β-steroids are formed. The conversion of the 11-ketone (I) into its enol acetate was effected with acetic anhydride (Marshall, Kritchevsky, Lieberman, and Gallagher, *ibid.*, 1948, **70**, 1837) or with *iso*propenyl acetate (Moffet and Weisblat, *ibid.*, 1952, **74**, 2183). The enol acetate was separated from some unchanged 11-ketone by chromatography, and was then converted in high yield into the corresponding 9α : 11α-epoxide (VII).




Alkaline hydrolysis of (VII) afforded the ketol (VIII), in which the hydroxyl group was not acetylated under mild conditions. Thionyl chloride–pyridine dehydration of (VIII) yielded the $\Delta^8$-11-ketone (IX) (cf. Part LXII, *J.*, 1953, 2921), proving that the original enol acetate contained a $\Delta^{9(11)}$-linkage (VI). The 9β-11-ketone (Part LXII),

isomeric with (I), was recovered largely unchanged when subjected to conditions which gave 50% of enol acetate from (I); the non-epimerisation at $C_{(9)}$ under these acidic conditions is noteworthy (cf. Part LXII).

The results of enol acetylation experiments in the steroid series may be rationalised in terms of a transition complex (see formulæ), in which X may be OAc, O·CMe:$CH_2$, or halogen. The transformation of the intermediate complex into an enol acetate will be dependent upon steric factors; in particular, the accessibility of the hydrogen atom to be removed will be of great importance, as suggested by Cornforth (*Ann. Reports*, 1952, **49**, 197). The formation of $\Delta^{20(21)}$-20-acetates (in preference to the more stable $\Delta^{17(20)}$-20-acetates) in the lower-temperature (*iso*propenyl acetate) method of acetylating 20-ketones, and the more readily acetylation of 9α-11-ketones compared with the 9β-compounds (9β- less accessible than 9α-hydrogen) are reactions, both of which indicate the importance of the steric accessibility of a hydrogen atom adjacent to the ketone group. The higher reaction temperature employed in the acetic anhydride procedure may cause the ultimate




production of the thermodynamically more stable product (cf. conversion of $\Delta^{20(21)}$- into $\Delta^{17(20)}$-20-acetates). In this connection it may be noted that the direction of enol acetylation of a 7-oxo-5β-steroid (to give a $\Delta^{6}$-compound; Hirschmann and Wendler, *loc. cit.*) is analogous to the formation of a $\Delta^{3}$-3-acetate from a 3-oxo-5β-steroid (Dauben, Micheli, and Eastham, *J. Amer. Chem. Soc.*, 1952, **74**, 3852). A 7-oxo-5α-steroid should yield a $\Delta^{7}$-compound since 3-oxo-5α-steroids give $\Delta^{2}$-3-acetates (*loc. cit.*).

Infra-red absorption measurements indicate that the double bond in $\Delta^{11}$-steroids is appreciably strained (Henbest, Meakins, and Wood, *loc. cit.*), and there appears to be a growing amount of chemical evidence that the formation of a $\Delta^{11}$-compound will not take place if an alternative reaction path is available. The reactions described in this paper which have led to $\Delta^{9(11)}$-steroids indicate that the alternative formation of a $\Delta^{11}$-compound in each case is prevented by unfavourable energy relations. Difficulty in forming $\Delta^{11}$-steroids is also indicated by the rather poor yields (*ca.* 25%) of $\Delta^{11}$-compounds from base-assisted elimination of polar 12α-tosyloxy-groups (Meystre and Wettstein, *Helv. Chim. Acta*, 1948, **31**, 1890; von Euw and Reichstein, *ibid.*, p. 2076), and the ring-contraction reaction of 12β-toluene-*p*-sulphonates (Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1952, **74**, 2693) which occurs (solvolysis conditions) in preference to $E_1$ elimination to give a $\Delta^{11}$-compound.

## Experimental

General experimental directions are as given in Part LXI, *J.*, 1953, 2916; infra-red spectra were determined as mulls in Nujol unless stated otherwise.

*Preparation of* 11α-*Hydroxy-compounds.*—Sodium (25 g.) was added during 1 hr. to a solution of 3β-acetoxyergost-22-en-11-one (2 g.) in absolute ethanol (500 c.c.). When the sodium had dissolved, the steroid was isolated with ether and chromatographed on deactivated alumina (100 g.). Benzene–ether (20 : 1) (800 c.c.) eluted 3β-hydroxyergost-22-en-11-one (500 mg.), m. p. 171—173°, which on acetylation gave starting material, m. p. 125—126°, $[\alpha]_D$ +12°. Continued elution with benzene–ether (1 : 1) (600 c.c.) gave ergost-22-ene-3β : 11α-diol (1·01 g.) (crystals from nitromethane), m. p. 165—167°, $[\alpha]_D$ −21° (Found: C, 80·5; H, 11·5. Calc. for $C_{28}H_{48}O_2$: C, 80·7; H, 11·6%). Heusser *et al.* (*Helv. Chim. Acta*, 1952, **35**, 950) record m. p. 156—157°, $[\alpha]_D$ −16°. Acetylation of the 3β : 11α-diol gave the diacetate, crystallising from methanol as needles, m. p. 137—138°, $[\alpha]_D$ −35° (Found: C, 76·65; H, 10·5. Calc. for $C_{32}H_{52}O_4$: C, 76·75; H, 10·45%). Heusser *et al.* (*loc. cit.*) give m. p. 126—127°, $[\alpha]_D$ −36°.

A solution of the 3β : 11α-diol (750 mg.) in dioxan (40 c.c.) and acetic acid (40 c.c.) was shaken with hydrogen in the presence of Adams catalyst (300 mg.). Crystallisation from nitromethane afforded *ergostane*-3β : 11α-*diol* (II; R = R′ = H) (650 mg.), m. p. 158·5—160°, $[\alpha]_D$ −2° (Found: C, 80·35; H, 12·1. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·05%). Acetic anhydride and

pyridine (overnight at 20°) gave the *diacetate* (II; R = R′ = Ac), m. p. 89—91°, $[\alpha]_D$ −21° (Found: C, 76·15; H, 10·95. $C_{32}H_{54}O_4$ requires C, 76·45; H, 10·85%).

A solution of ergostane-3β : 11α-diol (1·3 g.) and benzoic anhydride (1·3 g.) in pyridine (60 c.c.) was heated under reflux for 24 hr. The steroid was isolated with ether and chromatographed on alumina (140 g.). Benzene–ether (9 : 1) (1·5 l.) eluted solid (830 mg.) which on crystallisation from methanol gave 3β-*benzoyloxyergostan*-11α-ol (II; R = Bz, R′ = H) (640 mg.), m. p. 176—178°, $[\alpha]_D$ −5° (Found: C, 80·1; H, 10·55. $C_{35}H_{54}O_3$ requires C, 80·4; H, 10·4%). Infra-red spectrum (in $CCl_4$): peaks at 3630 (OH), 1715 and 1275 cm.$^{-1}$ (benzoate). Further elution of the column with ether yielded starting material (550 mg.).

*Preparation of* 11β-*Hydroxy-compounds.*—3β-Acetoxyergost-22-en-11-one (1·5 g.) in dry ether (30 c.c.) was treated with lithium aluminium hydride (2 mols.) in ether (20 c.c.), the mixture then being heated under reflux for 1 hr. Ethyl acetate (5 c.c.) was added, followed by aqueous tartaric acid. Isolation with ether and acetylation of the product with acetic anhydride and pyridine at 20° overnight gave material (1·37 g.), which yielded 3β-*acetoxyergost*-22-*en*-11β-*ol* (1·2 g.) (as needles from methanol), m. p. 170—171°, $[\alpha]_D$ −6° (Found: C, 78·55; H, 10·8. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%). Hydrogenation of this compound with Adams catalyst in acetic acid gave 3β-*acetoxyergostan*-11β-*ol* (III; R = Ac, R′ = H) (needles from methanol), m. p. 134—135°, $[\alpha]_D$ +25° (Found: C, 78·05; H, 11·45. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%).

3β : 11β-*Diacetoxyergostane* (III; R = R′ = Ac).—A solution of ergostane-3β : 11β-diol (0·5 g.) in dimethylaniline (12 c.c.), acetyl chloride (6 c.c.), and chloroform (18 c.c.) was heated under reflux for 16 hr. The steroid was isolated with ether, and then percolated in benzene solution through alumina (30 g.). Crystallisation from methanol gave the *diacetate* (250 mg.), m. p. 118—119°, $[\alpha]_D$ +31° (Found: C, 76·6; H, 11·15. $C_{32}H_{54}O_4$ requires C, 76·45; H, 10·85%). Infra-red spectrum (in $CCl_4$): peaks at 1735 and 1235 cm.$^{-1}$ (acetate); no hydroxyl band.

*Dehydration* of 11-*Hydroxy-compounds.*—(*a*) Phosphorus oxychloride (4 c.c.) was added to a solution of 3β-benzoyloxyergostan-11α-ol (640 mg.) in pyridine (14 c.c.) with external cooling. The solution was kept at 20° overnight and the steroid was isolated with ether. The solid product (560 mg.) was chromatographed on alumina (55 g.); light petroleum–benzene (9 : 1) (500 c.c.) eluted material which, on crystallisation from methanol–chloroform, afforded 3β-*benzoyloxyergost*-9-*ene* (250 mg.), m. p. 153·5—154·5°, $[\alpha]_D$ +16° (Found: C, 83·1; H, 10·65. $C_{35}H_{52}O_2$ requires C, 83·3; H, 10·4%). Infra-red spectrum: peaks at 1715, 1285 (benzoate), 845 and 820 cm.$^{-1}$ ($\Delta^9$-H bending). Hydrolysis gave *ergost*-9-*en*-3β-*ol* (IV; R = H) (crystals from methanol), m. p. 147·5—149°, $[\alpha]_D$ +29° (Found: C, 83·7; H, 12·1. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%). Acetylation yielded 3β-*acetoxyergost*-9-*ene* (needles from methanol), m. p. 128—132°, $[\alpha]_D$ +17° (Found: C, 81·3; H, 11·3. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Infra-red spectrum (supercooled melt): peaks at 1730, 1235 (acetate), 3045 (sh), 1640, 840, and 820 cm.$^{-1}$ ($\Delta^9$).

(*b*) Phosphorus oxychloride (0·75 c.c.) was added to 3β-acetoxyergostan-11β-ol (150 mg.) in pyridine (4 c.c.), and the solution kept at 20° for 12 hr. Isolation of the steroid as usual followed by crystallisation from methanol afforded 3β-acetoxyergost-9-ene, with physical properties (including infra-red spectrum) identical with those of the specimen prepared by method (*a*). Hydrolysis yielded the same 3β-hydroxy-compound.

Since these compounds are the simplest $\Delta^{9(11)}$-5α-steroids yet prepared it was of interest to calculate the rotation contribution of the $\Delta^{9(11)}$-bond. With the 3β-hydroxy-compounds, ΔE = + 44, and with the 3β-acetates, ΔE = + 58°. These figures are similar to those given by Barton and Klyne (*Chem. and Ind.*, 1948, 755), for 5β-compounds. Fieser and Huang (*J. Amer. Chem. Soc.*, 1953, **75**, 5356) have reported ΔE values of +15° and +36° for cholest-9-en-3β-ol and its acetate respectively.

*Hydrogenation* of *Ergost*-9-*en*-3β-*ol.*—A solution of the sterol (30 mg.) in acetic acid (3 c.c.) was shaken with Adams catalyst (30 mg.) and hydrogen for 1 hr. Crystallisation of the product from methanol gave ergostan-3β-ol, m. p. and mixed m. p. 143—146°, $[\alpha]_D$ +18°. Hydrogenation in ethyl acetate solution for 90 min. afforded partly reduced material, m. p. 149—150°, $[\alpha]_D$ +23°.

3β-*Acetoxy*-9α : 11α-*epoxyergostane* (V).—Solutions of 3β-acetoxyergost-9-ene (1·2 g.) in ether (15 c.c.) and monoperphthalic acid (0·6N in ether) (2 mols.) were mixed and then kept at 20° for 5 days. The 9α : 11α-*epoxide* (0·85 g.), isolated as usual, crystallised from methanol–chloroform as needles, m. p. 167—168°, $[\alpha]_D$ −12° (Found: C, 78·8; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·5; H, 11·0%). Chromatography of part (125 mg.) of the mother-liquor material yielded a further amount (100 mg.) of the pure epoxide.

*Enol Acetylation of* 11-*Oxo-steroids*.—(a) *With acetic anhydride*. A mixture of 3β-acetoxyergostan-11-one (0·9 g.), toluene-*p*-sulphonic acid (0·38 g.), and acetic anhydride (70 c.c.) was distilled slowly for 5 hr., the solution becoming pale-brown and decreasing in volume to about 10 c.c. The steroid product (0·94 g.) was chromatographed on deactivated alumina (95 g.). Development with light petroleum–benzene (9 : 1) (1 l.) gave starting material (260 mg.), m. p. 139—140°, and further elution with the same solvent yielded an oil (500 mg.), which crystallised slowly from methanol, to give 3β : 11-*diacetoxyergost*-9-*ene* (VI) (350 mg.) as prisms, m. p. 78—80·5°, $[\alpha]_D$ +39° (Found : C, 76·8; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). Infra-red spectrum (in $CCl_4$) : peaks at 1745, 1220 (11-acetate), 1735, 1235 (3-acetate), and 1650 cm.$^{-1}$ ($\Delta^9$). Similar treatment of 3β-acetoxy-9β-ergostan-11-one for 6 and for 20 hr. periods gave 80% and 70% yields respectively of starting material, no enol acetate being isolated.

(b) *With* iso*propenyl acetate*. A mixture of 3β-acetoxyergostan-11-one (250 mg.), toluene-*p*-sulphonic acid (50 mg.), and *iso*propenyl acetate (10 c.c.) was distilled slowly for 10 hr. As the volume of solution reached about 5 c.c., fresh portions (5 c.c.) of *iso*propenyl acetate were added (3 times). Chromatography of the product afforded starting material (160 mg.), m. p. 138—140°, and 3β : 11-diacetoxyergost-9-ene (50 mg.), m. p. and mixed m. p. 75—79°.

3β : 11β-*Diacetoxy*-9α : 11α-*epoxyergostane* (VII).—An ethereal solution of monoperphthalic acid (2 mols.) was added to 3β : 11-diacetoxyergost-9-ene (300 mg.) in dry ether (4 c.c.), and the mixture was kept at 0° for 1 day and then at 20° for 6 days. Isolation with ether followed by crystallisation from methanol afforded the *epoxide* (250 mg.) as fine needles, m. p. 162·5—163·5°, $[\alpha]_D$ +32° (Found : C, 74·0; H, 10·15. $C_{32}H_{52}O_5$ requires C, 74·35; H, 10·15%). Infra-red spectrum : peaks at 1740, 1235 (11-acetate), 1730 and 1245 cm.$^{-1}$ (3-acetate).

3β-*Acetoxy*-9α-*hydroxyergostan*-11-*one* (VIII).—Methanolic potassium hydroxide (8 c.c.; 5%) was added to the foregoing epoxide (200 mg.) dissolved in methanol (10 c.c.), the mixture being heated under reflux for ¾ hr. Isolation with ether and crystallisation from nitromethane gave a high yield of 3β : 9α-*dihydroxyergostan*-11-*one*, m. p. 189—190°, $[\alpha]_D$ +59° (Found : C, 77·6; H, 11·15. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). Infra-red spectrum : peaks at 3150, 3580 (OH), and 1695 cm.$^{-1}$ (11-ketone). Acetylation with acetic anhydride–pyridine at 20° overnight afforded the 3β-*acetate* (crystals from nitromethane–methanol), m. p. 181—182°, $[\alpha]_D$ +48° (Found : C, 75·7; H, 10·7. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). Infra-red spectrum : peaks at 3000—3500 (OH), 1740, 1245 (acetate), and 1700 cm.$^{-1}$ (11-ketone).

3β-*Acetoxyergost*-8-*en*-11-*one* (IX).—Thionyl chloride (0·05 c.c.) was added to 3β-acetoxy-9α-hydroxyergostan-11-one (20 mg.) in pyridine (0·3 c.c.) with external cooling. The solution was kept at 20° for 1 hr. and the steroid was then isolated with ether. The methanol solution of the product, when kept overnight, deposited needles of 3β-acetoxyergost-8-en-11-one, m. p. and mixed m. p. 138—140°, $[\alpha]_D$ +116°. The physical constants given in Part LXII (*loc. cit.*) are m. p. 138—140°, $[\alpha]_D$ +119°.

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