Studies in the Synthesis of Cortisone. Part VII. The Preparation of* 3β : 17α-*Dihydroxy*allo*pregnane*-11 : 20-*dione.*

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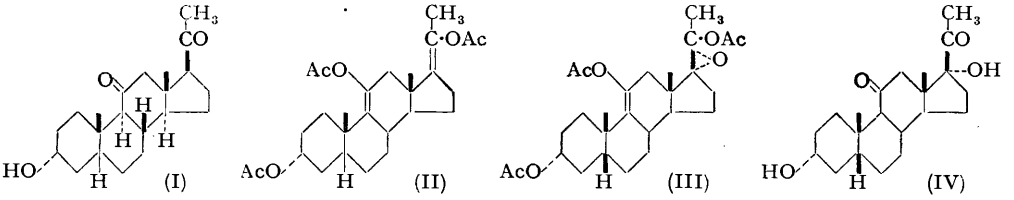
The 9(11)-double bonds in the dienol acetate (VI) of 3β-acetoxy*allo*pregnane-11 : 20-dione and the monoenol acetate of 3β-acetoxyergostan-11-one (VII) readily react with peracids. Conversion of 3β-acetoxy*allo*pregnane-11 : 20-dione (V) into the $\Delta^{17(20)}$-monoenol acetate (XIV) by treatment with acetic anhydride and perchloric acid in carbon tetrachloride, with subsequent epoxidation and hydrolysis, has given 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione (X; R = H) in high yield.

A new reaction sequence for the preparation of 3β-acetoxy*allo*pregnane-11 : 20-dione (V) was described in Part III of this series (*J.*, 1953, 3864). The present paper deals with methods for the introduction of a 17α-hydroxyl group into this compound. A very efficient procedure for this step with compounds of the normal series was described by Kritchevsky, Garmaise, and Gallagher (*J. Amer. Chem. Soc.*, 1952, **74**, 483) : they showed that 3α-hydroxypregnane-11 : 20-dione (I), when distilled with toluene-*p*-sulphonic acid and acetic anhydride, afforded a dienol acetate (II), which with perbenzoic acid gave the 17 : 20-monoepoxide (III); 3α : 17α-dihydroxypregnane-11 : 20-dione (IV) was obtained from this by the action of alcoholic sodium hydroxide. The preferential formation of a monoepoxide from (II) was taken as indicative of a 9(11)- rather than an 11(12)-ethylenic linkage. This has been confirmed recently by Hirschmann and Wendler (*ibid.*, 1953, **75**, 2361), who showed that, with compounds analogous to (II), more vigorous epoxidation conditions afford the 9α : 11α-epoxides.



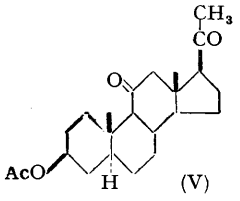
Chemerda, Chamberlin, Wilson, and Tishler (*ibid.*, 1951, **73**, 4052) and Pataki, Rosenkranz, and Djerassi (*ibid.*, 1952, **74**, 5615) applied this method to the *allo*-11 : 20-diketone, but they did not indicate the efficiency of the reactions. In our experience, the yield obtained by this method for the introduction of the 17α-hydroxyl group into 3β-acetoxy*allo*pregnane-11 : 20-dione (V) was only 25—30%, and it seemed that essential differences must exist between the reactions of such diketones in the normal and the *allo*-series.

The dienol acetate (VI), prepared by the method of Marshall, Kritchevsky, Lieberman, and Gallagher (*ibid.*, 1948, **70**, 1837), consumed more than 1 mol. of peracid, the 9(11)- and the 17(20)-bonds both reacting. This might be explained by the smaller steric hindrance of the 9(11)-double bond when rings A and B are *trans*-fused, or the unsaturated linkage might in this instance occupy the 11-position.

To distinguish between these two possibilities similar experiments were carried out on 3β-acetoxyergostan-11-one (VII). The enol acetate of (VII) reacted readily with either perbenzoic or monoperphthalic acid at 20°. The crude product, on hydrolysis, reacetylation, and chromatography, gave principally a hydroxy-compound, which with thionyl chloride in pyridine yielded 3β-acetoxyergost-8(9)-en-11-one (VIII) (cf. Hirschmann and Wendler, *loc. cit.*). It was thus apparent that the product from the hydrolysis of the epoxide was 3β-acetoxy-9α-hydroxyergostan-11-one (IX), that the double bond formed

* Part VI, *J.*, 1954, 468.

in the enol esterification occupied the 9(11)-position, and that it was readily attacked by peracids. The 9-hydroxy-group is given the α-configuration by analogy with the structure established for a similar compound in the normal series (Hirschmann and Wendler, *loc. cit.*). The smaller steric hindrance of the 9(11)-ethylenic linkage, in *trans*-A/B-compounds, relative to *cis*-A/B-compounds, revealed by our experiments, is readily understandable on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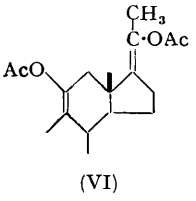
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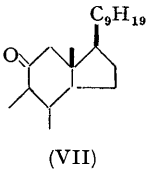
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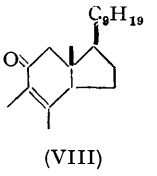
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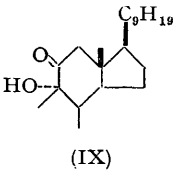
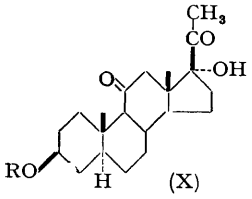

(IX)

a confirmational basis (Barton, *Experientia*, 1950, **6**, 316), and is in agreement with observations by Mattox, Turner, Engel, McKenzie, McGuckin, and Kendall (*J. Biol. Chem.*, 1946, **164**, 569) on the inability of 5α-sterols to form 3α : 9α-epoxides.

Chromatography of the reacetylated product from the epoxidation and further processing of the enol acetate derived from (V) gave a diol, in addition to (X; R = Ac). In view of its resistance to acetylation this diol must be ditertiary. For this reason, and from analogy with the above results, it is formulated as 3β-acetoxy-9α : 17α-dihydroxy*allo*pregnane-11 : 20-dione (XI). Consideration of molecular rotations confirms this. The contribution of the 17α-hydroxyl group is −279° {$[M]_D$ of (X) − (V)} and of the 9α-hydroxyl group +77° {$[M]_D$ of (IX) − (VII)}, and these $\Delta[M]_D$'s, when added to the $[M]_D$ of (V) (+330°), give a calculated value for (XI) of +128° compared with an observed value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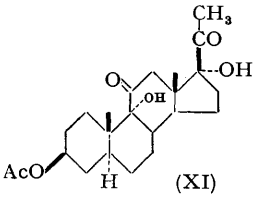
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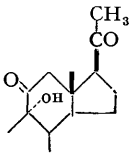
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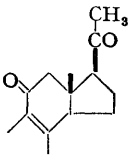
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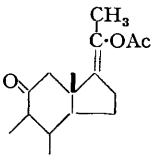

(XIV)

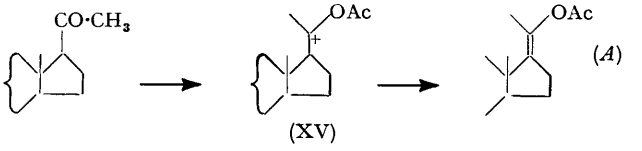
of +183°. Attempts to reduce the yield of this unwanted material by limiting the amount of peracid and terminating the reaction when 1 mol. had been utilised were unsuccessful and, as before, only 25% of (X; R = Ac) was obtained. Chromatography of the mother-liquors yielded an equivalent amount (30%) of 3β-acetoxy-9α-hydroxy*allo*pregnane-11 : 20-dione (XII), which was converted with thionyl chloride and pyridine into 3β-acetoxy*allo*-pregn-8(9)-ene-11 : 20-dione (XIII), whose structure was confirmed by its ultra-violet and infra-red spectra. It was thus apparent that the double bonds in (VI) are both reactive to peracids and that a satisfactory method for the preparation of (X; R = H) could best be achieved by the selective enol esterification of the 20-keto-group.

Saponification values of the enol acetates obtained by the action of acetic anhydride and toluene-*p*-sulphonic acid on (V) and (VII) showed that they contained 2·7 and 1·7 acetyl groups per mole, respectively, whilst the infra-red spectrum of both indicated about 30% of unchanged carbonyl group. So the crude dienol acetate probably contained about 30% of the monoenol acetate (XIV), and the 25% of (X; R = H) formed in this reaction arose from the epoxide of this compound. The optimum yield of (X; R = H) (62%) was obtained by use of 0·1 part (by wt.) of toluene-*p*-sulphonic for 1·5 hours: the crude product then gave a crystalline monoenol acetate in low yield; this, since it is converted into (X; R = H) in 90% yield, must be 3β : 20-diacetoxy*allo*pregn-17(20)-en-11-one (XIV); as the crude enol acetate would be expected to contain 60—70% of (XIV), the low yield is probably due to the isolation of only one of the two possible geometric isomers (cf. Marshall *et al.*, *loc. cit.*). Removal by distillation of the acetic acid formed during the reaction is essential for the enol acetylation of an 11-ketone. When a solution of the ergostane derivative (VII) in acetic anhydride and toluene-*p*-sulphonic acid was heated under reflux,

the starting material was recovered unchanged. Similar treatment of the diketone (V) gave a product in which the 11-ketone was completely untouched, though some disruption of the side-chain had occurred. As no further improvement was achieved with these reagents attention was turned to alternative catalysts.

Polarimetric studies of the effect of small quantities of perchloric acid (cf. Whitman and Schwenk, *J. Amer. Chem. Soc.*, 1946, **68**, 1865; Burton and Praill, *J.*, 1950, 1203, and references there cited) on a solution of (V) in acetic anhydride at room temperature showed that a rapid reaction took place. The crude product was shown by its saponification value and infra-red spectrum to be essentially the monoenol acetate, and yielded by crystallisation 30% of pure monoenol acetate (XIV). Epoxidation succeeded by hydrolysis then gave a 60% yield of (X; R = H), and this yield was not altered by variation in the amounts of catalyst or the temperature of the reaction.

The mechanism for the enol-acetylation of 20-ketones by acetylium ions may be represented most simply as in (A). Consideration of this mechanism led us to the following simple working hypothesis. The intermediate ion (XV) could undergo two possible



(XV) (A)

reactions: (*a*) elimination of a proton to give the required enol acetate or (*b*) some alternative rearrangement, thus reducing the yield of the required product. On these grounds it seemed possible that, if the life-time of the ion could be reduced, the extent of the side reactions might be limited. Since suitable conditions would be likely to exist in a medium of low dielectric constant, the reaction was examined in a number of such solvents. As would be expected, the reaction was inhibited by ethers, which would have an affinity for the acetylium ion; maximum yields were obtained with solvents of low dielectric constant. The relation between these two factors is shown in the Table.

Solvent	Dielectric const. (approx.)	Yield of (X; R = H) (%)	Solvent	Dielectric const. (approx.)	Yield of (X; R = H) (%)
Acetic anhydride	20·5	67	Benzene	2·28	80
Methylene chloride.....	6·5 (100°)	73	Carbon tetrachloride...	2·2	85
Chloroform	5·0	77	*n*-Hexane	1·87	73
Trichloroethylene	3·4	80			

The result with *n*-hexane might appear at first sight to be anomalous, but since the reaction was carried out in a heterogeneous medium (all the other solvents listed gave a homogeneous medium) it is probable that the solvent was not exerting its full effect. Further investigation showed that the best results could be achieved by using carbon tetrachloride containing 5% of acetic anhydride, which gave a 92% yield of (X; R = H) from (V). Although the use of solvents in this reaction was originally based on the considerations outlined above, we would emphasize that these were only the basis of a working hypothesis and it is also possible that the different yields obtained are due to the influence of the solvent on the further reaction of acetic anhydride with the enol acetate (cf. Young, Frostick, Sanderson, and Hauser, *J. Amer. Chem. Soc.*, 1950, **72**, 3635).

Experimental

$[\alpha]_D$'s were determined on 1% solutions in $CHCl_3$ at room temperature unless otherwise stated: $\lambda_{max.}$ are for solutions in EtOH. A Perkin-Elmer Model 21 double-beam spectrophotometer equipped with rock-salt optics was used for the determination of infra-red spectra. The alumina used for chromatography was prepared as described in Part IV (*J.*, 1954, 451). M. p.s were determined on a Kofler block.

Enol Acetylations.—The dienol acetate (VI) and the enol acetate of (VII) were prepared as follows (cf. Marshall *et al.*, *loc. cit.*).

A solution of the ketone (10 g.), acetic anhydride (570 ml.), and toluene-*p*-sulphonic acid

(10 g.) was slowly distilled through a short column for 4 hr., the final volume being 200 ml. Most of the acetic anhydide was removed *in vacuo*, and the residue dissolved in ether, washed with ice cold 5% aqueous sodium hydroxide and water, and dried ($MgSO_4$). On evaporation both enol acetates were obtained as oils. They gave sap. val. of 2·7 and 1·7 respectively, and infra-red spectra indicated about 30% of unchanged keto-group [$\nu_{max.}$ 1706 cm.$^{-1}$ in CS_2 (ketone)].

3β-*Acetoxy*-9α-*hydroxyergostan*-11-*one* (IX).—3β-Acetoxyergostan-11-one (VII) (10 g.) was converted into the enol acetate as above and the resultant gum dissolved in light petroleum (200 ml.; b. p. 40—60°), the solution filtered through acid-washed alumina (20 g.), and the alumina washed with light petroleum (200 ml.); the combined filtrates were evaporated. The resulting gum (9·1 g.) was treated in chloroform (18 ml.) with 2·5N-monoperphthalic acid in ether (50 ml.) at room temperature for 18 hr. After washing of the solution with 5% aqueous sodium hydroxide and water, the solvent was removed and the residue dissolved in hot methanolic 0·8N-potassium hydroxide (60 ml.). After cooling and addition of water, a solid was collected, dried, and acetylated with acetic anhydride (20 ml.) and pyridine (30 ml.) at room temperature to give a solid (6·4 g.). A portion (6 g.) of this was chromatographed on alumina. A fraction was eluted with benzene (800 ml.) and then ether (300 ml.) which on evaporation yielded a solid (3·3 g.), m. p. 170—178°, $[\alpha]_D$ +50°. Recrystallisation from methanol yielded 3β-*acetoxy*-9α-*hydroxyergostan*-11-*one* (IX) as needles (2·1 g.), m. p. 181—182°, $[\alpha]_D$ +49° (Found: C, 76·4; H, 10·5. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%), $\nu_{max.}$ 3500 (hydroxyl), 1733 and 1240 (acetate), and 1694 cm.$^{-1}$ (ketone) in Nujol (C.S. no. 86).*

A portion of this solid (1·0 g.) was dissolved in dry pyridine (5 ml.), and redistilled thionyl chloride (1 ml.) was added. After 1·5 hr. at room temperature the mixture was poured into water and extracted with ether, the ethereal extract washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Removal of the solvent left a solid (0·85 g.) which recrystallised from methanol to give 3β-acetoxyergost-8(9)-en-11-one (VIII) as needles, m. p. 137—139°, $[\alpha]_D$ +121° (Found: C, 79·3; H, 10·5. Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%), $\lambda_{max.}$ at 254 mμ (log ε 3·94), $\nu_{max.}$ 1732 and 1240 (acetate), 1660 cm.$^{-1}$ (α : β-unsaturated ketone) in CS_2 (C.S. no. 87) (Laubach *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 1514, give m. p. 138—139°, $[\alpha]_D$ +125°).

Epoxidation of (VI) *and Hydrolysis of the Product.*—(a) *Excess of peracid.* The enol acetate of (V) (9·3 g.), prepared as above, was dissolved in chloroform (20 ml.), 2·2N-monoperphthalic acid in ether (50 ml.) was added, and the mixture kept at room temperature overnight. After being washed with 5% aqueous sodium hydroxide and water, the solution was dried and evaporated. The resulting gum was dissolved in hot methanolic 0·8N-potassium hydroxide (60 ml.), then cooled, water (500 ml.) was added, and the precipitated solid was collected, dried, and acetylated with acetic anhydride (25 ml.) and pyridine (50 ml.) at room temperature. A solid product (6·1 g.) was isolated and a portion (4·0 g.) of this was chromatographed on alumina. A fraction eluted with 50% benzene–ether (1 l.) yielded crude 3β-acetoxy-17α-hydroxy*allo*pregnane-11 : 20-dione (X; R = Ac) (1·95 g.), m. p. 145—155°. Ether eluted another solid (2·9 g.) which, crystallised from benzene, yielded 3β-*acetoxy*-9α : 17α-*dihydroxy*allo*pregnane*-11 : 20-*dione* (XI) as needles (1·35 g.), double m. p. 216—218° and 250—253°, $[\alpha]_D$ +45° in $CHCl_3$, +67° in $COMe_2$ (Found: C, 68·2; H, 8·5. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%), $\nu_{max.}$ 3550 (hydroxyls), 1730, 1248 (acetate), and 1704 and 1710 cm.$^{-1}$ (ketones) in Nujol (C.S. no. 88). This solid (0·4 g.) was dissolved in methanol (10 ml.), and methanolic 0·9N-potassium hydroxide (5 ml.) added. The solution was warmed for a few minutes, then evaporated almost to dryness, water was added and the precipitated 3β : 9α : 17α-*trihydroxy*allo*pregnane*-11 : 20-*dione* was collected; it had m. p. 305—308°, $[\alpha]_D$ +88° (*c*, 1·0 in dioxan) (Found: C, 69·2; H, 8·9. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·8%).

(b) 1 *Mol. of peracid.* The dienol acetate (VI), prepared as described above, was oxidised overnight in ether with 1 mol. of 0·3N-monoperphthalic acid. Titration showed that approx. 90% of the available oxygen had been used. The epoxide was isolated by the addition of more ether, washing of the organic layer with three portions of ice-cold sodium hydrogen carbonate solution and then with water, drying ($MgSO_4$), and removal of the solvent *in vacuo*. The gummy epoxide was hydrolysed by dissolving it in warm dry ethanol (630 ml.), adding 10 ml. of tetrahydrofuran, followed by aqueous 0·6N-sodium hydroxide (630 ml.). The solution was kept at room temperature for 1 hr., then some solvent was removed *in vacuo* and the solid which was precipitated was removed and washed with a little water and acetone. The solid was then warmed with a little chloroform and the mixture cooled and filtered. The residual solid was

* Spectra thus marked have been deposited with the Society. Photocopies, price 3*s.* 0*d.* per copy per spectrum, may be obtained on application to the General Secretary, quoting the C.S. no.

recrystallised from methanol, to give 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione (X; R = H) (8 g.), double m. p. 267—271° and 286—289°, $[\alpha]_D$ +65° in dioxan (Found: C, 72·6; H, 9·4. Calc. for $C_{21}H_{32}O_4$: C, 72·4; H, 9·2%), $\nu_{max.}$ 3400, 3330 (hydroxyl), 1692 and 1702 cm.$^{-1}$ (ketone) in Nujol (C.S. no. 89). The mother-liquors from the hydrolysis and the washings were combined, more water was added, and the organic material was extracted with chloroform. Removal of the chloroform gave a gum which was acetylated with acetic anhydride and pyridine at room temperature to yield a solid (17·7 g.) which was chromatographed on alumina. A fraction was eluted with light petroleum (b. p. 40—60°)–ether (1 : 1) which on evaporation gave a solid (7·6 g.) which crystallised from acetone–petrol to give 3β-*acetoxy*-9α-*hydroxy*allo*pregnane*-11 : 20-*dione* (XII) (5·3 g.), m. p. 209—211°, $[\alpha]_D$ +105° in $COMe_2$ (Found: C, 71·2; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·8%). A second fraction (3·1 g.), eluted with light petroleum and ether containing 1% of methanol, and crystallised from benzene, gave 3β-acetoxy-9α : 17α-dihydroxy-*allo*pregnane-11 : 20-dione (XI), double m. p. 216—218° and 250—253°, $[\alpha]_D$ +45°.

Dehydration of 3β-*Acetoxy*-9α-*hydroxy*allo*pregnane*-11 : 20-*dione* (XII).—The hydroxy-compound (XII) (2 g.) in dry pyridine (10 ml.) was kept at room temperature with thionyl chloride (2 ml.) for 1 hr., then poured into a large volume of water. The organic material was extracted into ether, the extract washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the resulting gum on alumina and elution with 1 : 1 light petroleum (b. p. 40—60°)–benzene gave a solid (1·13 g.) which after two crystallisations from aqueous methanol gave 3β-*acetoxy*-allo*pregn*-8(9)-*ene*-11 : 20-*dione* (XIII) (0·59 g.), m. p. 129—131°, $[\alpha]_D$ +194° in $COMe_2$ (Found: C, 73·8; H, 8·6. $C_{23}H_{32}O_4$ requires C, 74·15; H, 8·7%), $\lambda_{max.}$ 254 mμ (log ε 3·95), $\nu_{max.}$ 1734 and 1240 (acetate), 1712 (ketone), 1668 cm.$^{-1}$ (α : β-unsaturated ketone) in CS_2 (C.S. no. 90)

Isolation of 3β : 20-*Diacetoxy*allo*pregn*-17(20)-*en*-11-*one* (XIV).—(a) *With toluene*-p-*sulphonic acid.* A solution of 3β-acetoxy*allo*pregnane-11 : 20-dione (V) (5 g.), toluene-*p*-sulphonic acid (0·5 g.), and acetic anhydride (100 ml.) was slowly distilled for 1·5 hr., further acetic anhydride being added to keep the volume constant. The solution was cooled, ether added, and the solution washed with ice-cold 5% sodium hydroxide solution and water, and dried ($MgSO_4$), and the solvent evaporated. The residual gum dissolved in light petroleum (b. p. 40—60°) was filtered through acid-washed alumina, and the solution concentrated and set aside at 0°. The resulting solid was crystallised twice more from the same solvent, to give the *monoenol acetate* (XIV; 1 g.), m. p. 152—154°, $[\alpha]_D$ +7° (Found: C, 72·3; H, 8·6%; OAc, 1·02 equiv. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%), $\nu_{max.}$ 1756 and 1215 (enol acetate), 1735, 1242 (acetate) and 1708 cm.$^{-1}$ (ketone) in CS_2 (C.S. no. 91). This was converted into (X; R = H) in 92% yield by the method described below.

(b) *With perchloric acid.* 3β-Acetoxy*allo*pregnane-11 : 20-dione (V) (10 g.) in carbon tetrachloride (95 ml.) was treated at room temperature with 50% aqueous perchloric acid (0·2 ml.) in acetic anhydride (5 ml.). After 1·5 hr. at room temperature, the solution was washed with ice-cold 5% sodium hydroxide solution and water, then dried ($MgSO_4$), and the solvent removed *in vacuo*. The semicrystalline residue was taken up in light petroleum (b. p. 40—60°). A solid gradually separated, which, twice recrystallised from light petroleum, yielded the enol acetate (XIV) (3·2 g.) (Sap. val., 0·98)

3β : 17α-*Dihydroxy*allo*pregnane*-11 : 20-*dione* (X; R = H).—3β-Acetoxy*allo*pregnane-11 : 20-dione (V) (10 g.) was converted into its enol acetate as described in the previous experiment. The crude residue was taken up in chloroform (20 ml.) and a solution of monoperphthalic acid in ether (2N; 55 ml.) added. After 3 hr. at room temperature, the product was isolated in the usual manner. The gummy material remaining after removal of the solvent was treated with hot methanolic 0·8N-potassium hydroxide (80 ml.) with rapid swirling and further heating. The solution became clear and almost immediately crystalline material started to separate. The solution was cooled rapidly to room temperature, water added, and the solid filtered off, washed with water, and dried *in vacuo* (P_2O_5) at room temperature, to give pure (X; R = H) (8·4 g., 92%), double m. p. 267—271° and 286—289°, $[\alpha]_D$ +65° in dioxan (*c*, 0·5), $\nu_{max.}$ 3400, 3330 (hydroxyls), 1692 and 1702 cm.$^{-1}$ (ketones) in Nujol.

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