12-*Oxygenated Pregnane Derivatives. Part II.* Preparation of* 21-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12 : 20-*trione from Hecogenin.*

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An attempt to convert hecogenin into 21-acetoxy-17α-hydroxypregn-4-ene-3 : 12 : 20-trione is recorded. No difficulty was experienced in preparing 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X) from (I). Introduction of the 4 : 5-unsaturated linkage into (X), however, could not be effected.

The conversion of deoxycholic acid into 12α : 17α : 21-trihydroxypregn-4-ene-3 : 20-dione (21-acetate), an analogue of *epi*hydrocortisone(*epi*cortisol), was recorded in Part I.* The present communication describes further experiments having as their object the conversion of hecogenin acetate (I) into 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X) and thence into 17α : 21-dihydroxypregn-4-ene-3 : 12 : 20-trione (21-acetate), the 12-oxygenated analogue of cortisone (acetate).

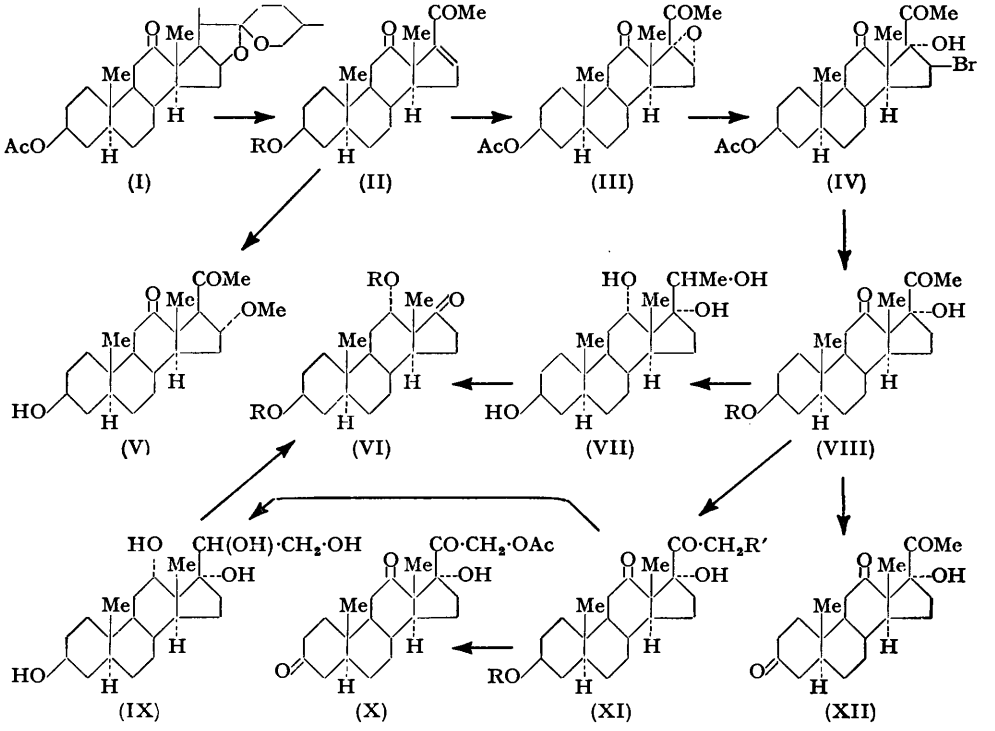
Hecogenin acetate (I) was readily degraded to 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = Ac) by methods developed by Marker and Rohmann (*J. Amer. Chem. Soc.*, 1940, **62**, 518) and Wagner, Moore, and Forker (*ibid.*, 1950, **72**, 1856). It was first converted into ψ-hecogenin diacetate which passed smoothly on oxidation with chromic acid into 3β-acetoxy-16β-(δ-acetoxy-γ-methylvaleroxy)*allo*pregnane-12 : 20-dione;

* Part I, *J.*, 1954, 1825.

careful hydrolysis of this "hecone diacetate" with aqueous-ethanolic potassium carbonate, followed by acetylation of the product, furnished (II; R = Ac).

Conversion of 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = Ac) into 3β : 17α-dihydroxy*allo*pregnane-12 : 20-dione (VIII; R = H) followed the general pattern established in Part I. Epoxidation of (II; R = Ac) with hydrogen peroxide in aqueous-methanolic sodium carbonate (Kendall, *J. Biol. Chem.*, 1952, **194**, 237) gave 3β-acetoxy-16α : 17α-epoxy*allo*pregnane-12 : 20-dione (III) * in 85% yield. Reaction of the last compound with hydrogen bromide in chloroform–acetic acid at −18° led smoothly to 3β-acetoxy-16β-bromo-17α-hydroxy*allo*pregnane-12 : 20-dione (IV) † (cf. however, Experimental section). Bromine was then readily removed by catalytic reduction over 2% palladium–calcium carbonate (cf. Part I), 3β-acetoxy-17α-hydroxy*allo*pregnane-12 : 20-dione (VIII; R = Ac) being obtained, which was smoothly hydrolysed to the diol (VIII; R = H).

The 3β-acetate so obtained had m. p. 131—133°, $[\alpha]_D^{26}$ +55°. It thus differs from the compound, m. p. 176°, $[\alpha]_D^{20}$ +117°, prepared by Mueller *et al.* by reducing (IV) with Raney nickel in ethanol or with zinc in acetic acid and also assigned structure (VIII; R = Ac). The formulation of our material as (VIII; R = Ac), however, is unequivocally established by the transformations described below. We therefore attempted to prepare the product, m. p. 176°, for structural studies but without success. In our hands reduction of (IV) with Raney nickel (prepared at 110° as described by Adkins, "Reactions of Hydrogen," Univ. Wisconsin Press, Wisconsin, 1937) in ethanol led only to authentic (VIII; R = Ac), m. p.



131—133°, whilst treatment with zinc dust in acetic acid furnished 3β-acetoxy*allo*pregnane-12 : 20-dione as the sole isolatable product (cf. Part I, section D).

An alternative approach to (VIII; R = H), *via* (II; R = H), was also examined. An attempt to hydrolyse (II; R = Ac) with aqueous-methanolic potassium carbonate, how-

* Cf. the paper by Mueller, Stobaugh, and Winniford (*J. Amer. Chem. Soc.*, 1953, **75**, 4888) which appeared after completion of Part II and in which the preparation of (II; R = Ac), (III), and (IV) is independently recorded.

ever, led to 3β-hydroxy-16α-methoxy*allo*pregnane-12 : 20-dione (V) admixed with only 10% of 3β-hydroxy*allo*pregn-16-ene-12 : 20-dione (II; R = H). As aqueous-methanolic potassium carbonate smoothly converts 3α : 12α-diacetoxypregn-16-en-20-one into the 3α-hydroxy-compound without concomitant addition of methanol to the double bond (Part I), the behaviour of (II) must be related to the polar effect of the adjacent 12-carbonyl group on the reactivity of the 20-keto-16 : 17-unsaturated system (see also Mueller *et al.*, *loc. cit.*).

The constitution assigned to (VIII; R = Ac) was confirmed as follows: (*a*) Dehydration with phosphorus oxychloride in pyridine (Reichstein, *Helv. Chim. Acta*, 1940, **23**, 170; 1941, **24**, 401) gave 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione (II; R = Ac) identical with an authentic specimen (Wagner, Moore, and Forker, *loc. cit.*). Dehydration by Darzens's method surprisingly failed to yield (II; R = Ac), an abnormal product, $C_{23}H_{34}O_6S$, insoluble in sodium hydrogen carbonate solution, being formed. This result stands in contrast to the successful dehydration of 3α : 12α-diacetoxy-17α-hydroxypregnan-20-one to the 16-ene recorded in Part I. (*b*) Reduction with sodium borohydride yielded *allo*pregnane-3β : 12α : 17α : 20-tetrol (VII; R = H), and subsequent oxidation with sodium bismuthate (Norymberski, *Biochem. J.*, 1953, **55**, 371) and acetylation gave 3β : 12α-diacetoxyandrostan-17-one (VI; R = Ac) (see p. 2213 for evidence regarding the configuration at $C_{(12)}$). Hydrolysis of the last compound gave 3β : 12α-dihydroxyandrostan-17-one (VI; R = H) which was oxidised by *N*-bromoacetamide in aqueous *tert.*-butanol to a diketo-alcohol, tentatively formulated as 12α-hydroxyandrostane-3 : 17-dione.

Before proceeding with the next stage of the partial synthesis, *i.e.*, the introduction of a 21-acetoxy-group into (VIII; R = H), we examined the conversion of this compound into 17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (XII) and confirmed that this was readily effected with *N*-bromoacetamide in aqueous *tert.*-butanol. The way was thus open to the preparation of 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X).

Monobromination of (VIII; R = H) in chloroform in the presence of hydrogen bromide gave the monobromo-compound (XI; R = H, R′ = Br), which passed into the corresponding acetoxy-derivative on treatment with sodium iodide in acetone, followed by reaction of the iodo-compound *in situ* with potassium hydrogen carbonate–acetic acid (1 : 1). The constitution of 21-acetoxy-3β : 17α-dihydroxy*allo*pregnane-12 : 20-dione (XI; R = H, R′ = OAc) has been assigned to this product. Its alternative formulation as the 11ξ-acetoxy-derivative of (VIII; R = H) is excluded because reduction with borohydride gives *allo*pregnane-3β : 12α : 17α : 20ξ : 21-pentol (IX) which passes into 3β : 12α-diacetoxyandrostan-17-one (VI; R = Ac) on oxidation with sodium bismuthate followed by acetylation. Acetylation of (XI; R = H, R′ = OAc) gave the 3β : 21-diacetate (XI; R = Ac, R′ = OAc), also prepared directly from (VIII; R = Ac).

N-Bromoacetamide in aqueous *tert.*-butanol oxidised (XI; R = H, R′ = OAc) to 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (X). Attempts to effect the last stage of the partial synthesis by converting (X) into the Δ^4-derivative by the standard bromination–dehydrobromination techniques, however, were unsuccessful.

Experimental

Optical rotations were measured in $CHCl_3$ in a 1-dm. tube unless otherwise stated.

3β-*Hydroxy*allo*pregn*-16-*ene*-12 : 20-*dione* (II; R = H).—3β-Acetoxy*allo*pregn-16-ene-12 : 20-dione (2 g.) (Wagner, Moore, and Forker, *loc. cit.*) in methanol (65 ml.) was heated with potassium carbonate (400 mg.) and water (5 ml.) under reflux for 1 hr. The product (1·7 g.), isolated with ether, was chromatographed in benzene on alumina (50 g.; B.D.H., chromatography grade). Final acetone–ether and acetone eluates yielded 3β-*hydroxy*allo*pregn*-16-*ene*-12 : 20-*dione*, m. p. 210—211°, $[\alpha]_D^{24}$ +156° (*c*, 0·416) (Found: C, 76·7; H, 8·9. $C_{21}H_{30}O_3$ requires C, 76·4; H, 9·1%), after crystallisation from acetone–hexane. Reacetylation gave (II; R = Ac).

Early ether–acetone eluates yielded 3β-*hydroxy*-16α-*methoxy*allo*pregnane*-12 : 20-*dione* (V) (*ca.* 300 mg.), m. p. 142°, $[\alpha]_D^{25}$ +132° (*c*, 0·374) (Found: C, 73·1; H, 8·9. $C_{22}H_{34}O_4$ requires C, 72·9; H, 9·4%), after crystallisation from acetone–hexane.

3β-*Acetoxy*-16α : 17α-*epoxy*allo*pregnane*-12 : 20-*dione* (III).—(II; R = Ac) (2·5 g.) in methanol (310 ml.) was treated at 0° with water (37·5 ml.), 5% sodium carbonate solution

(5 ml.), and hydrogen peroxide (30 ml. of 30%). After 12 hr. at this temperature, water (300 ml.) was added, followed by dilute acetic acid until the mixture was neutral, and the mixture left at 0° for 16 hr. The separated solids on crystallisation from acetone and from chloroform–ether yielded 3β-acetoxy-16α : 17α-epoxy*allo*pregnane-12 : 20-dione, prisms, m. p. 235—237°, $[\alpha]_D^{26}$ +109° (*c*, 0·574) (Found : C, 71·4; H, 8·0. Calc. for $C_{23}H_{32}O_5$: C, 71·1; H, 8·2%). Mueller *et al.* give m. p. 234—235°, $[\alpha]_D^{32}$ +103° in dioxan.

3β-*Acetoxy*-16β-*bromo*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (IV).—The foregoing compound (2·3 g.) in chloroform (48 ml.) was treated at −20° with acetic acid (18 ml.) and hydrogen bromide (5 ml. of a saturated solution in acetic acid). After storage at 0° the product was isolated with ether and crystallised from chloroform–ether. 3β-Acetoxy-16β-bromo-17α-hydroxy*allo*pregnane-12 : 20-dione formed prismatic needles, m. p. 163—165° or 174—176°, $[\alpha]_D^{25}$ +8° (*c*, 0·74) (Found : C, 58·8; H, 6·9; Br, 16·9. Calc. for $C_{23}H_{33}O_5Br$: C, 58·8; H, 7·0; Br, 17·1%). Mueller *et al.* give m. p. 176—178°, $[\alpha]_D^{30}$ +39° in EtOH.

3β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (VIII ; R = Ac).—(i) The bromohydrin (12 g.) was reduced over 2% palladium–calcium carbonate (25 g.) in aqueous methanol (600 ml. ; 1 : 9). The crude product, after acetylation, was filtered in benzene through a short column of alumina and subsequently purified from hexane. 3β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* formed needles, m. p. 131—133°, $[\alpha]_D^{26}$ +55° (*c*, 0·57) (Found : C, 70·6; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·7%).

(ii) The bromohydrin (500 mg.) in ethanol (25 ml.) was stirred with Raney nickel (3 g.) on a steam-bath for 5 hr. The solution was filtered and concentrated, and the residue crystallised from ether–hexane. 3β-Acetoxy-17α-hydroxy*allo*pregnane-12 : 20-dione was obtained as needles, m. p. 131—132° not depressed on admixture with a sample prepared by (i) above.

(iii) The bromohydrin (500 mg.) in acetic acid (40 ml.) was stirred with zinc dust (1 g.) on a steam bath for 4 hr. The cooled solution was diluted with ether, filtered, and washed until neutral. From the crude product, after several recrystallisations from aqueous ethanol, 3β-acetoxy*allo*pregnane-12 : 20-dione was obtained, having m. p. and mixed m. p. 182—187° (Found : C, 73·7; H, 9·2. Calc. for $C_{23}H_{34}O_4$: C, 73·8; H, 9·1%). It was recovered unchanged after attempted acetylation.

3β-*Acetoxy*allo*pregnane*-12 : 20-*dione*.—3β-Acetoxy*allo*pregn-16-ene-12 : 20-dione (1·86 g.) was reduced over 1% palladium–calcium carbonate (1 g.) in methanol (70 ml.). By crystallisation of the product from acetone 3β-acetoxy*allo*pregnane-12 : 20-dione was obtained, having m. p. 190—192°, $[\alpha]_D^{25}$ +138° (*c*, 0·508) (Found : C, 74·2; H, 9·3%). Mueller *et al.* give m. p. 189—190°, $[\alpha]_D^{29}$ +139°.

3β : 17α-*Dihydroxy*allo*pregnane*-12 : 20-*dione* (VIII ; R = H), prepared by hydrolysing the compound (VIII ; R = Ac) with ethanolic sodium hydroxide at room temperature, or with aqueous-methanolic potassium carbonate under reflux for 1½ hr., formed prisms, m. p. 204—207°, $[\alpha]_D^{22}$ +71° (*c*, 0·51) (Found : C, 72·9; H, 9·5. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%), after crystallisation from acetone.

Dehydration of (VIII ; R = Ac) (1 g.) in pyridine (6 ml.) with phosphorus oxychloride (1 ml.) at 135° for 45 min. led to 3β-acetoxy*allo*pregn-16-ene-12 : 20-dione, m. p. 179—181° alone or on admixture with an authentic specimen (see above). Dehydration by Darzens's method gave a *product*, plates, m. p. 169—170° (Found : C, 63·5; H, 7·3; S, 7·3. $C_{23}H_{34}O_6S$ requires C, 63·1; H, 7·7; S, 7·3%), after crystallisation from acetone–ether.

Reduction of (VIII ; R = H).—The diketone (3·48 g.) in methanol (50 ml.) was reduced with sodium borohydride (400 mg.) in methanol (10 ml.). After acetylation, purification of the product yielded a *diacetate*, needles, m. p. 228—230°, $[\alpha]_D^{25}$ +25° (*c*, 0·406) (Found : C, 68·6; H, 9·3. $C_{25}H_{40}O_7$ requires C, 68·8; H, 9·2%).

3β : 12α-*Diacetoxyandrostan*-17-*one* (VI ; R = Ac).—The foregoing diacetate (1·3 g.) was hydrolysed in aqueous methanol (50 ml. ; 1 : 9) with potassium hydroxide (2·5 g.) for 1 hr. under reflux and the product (m. p. 236—240° ; 930 mg.) was treated with sodium bismuthate (5 g.) in 50% acetic acid (100 ml.) (Norymberski, *loc. cit.*). Acetylation of the oxidised material gave 3β : 12α-*diacetoxyandrostan*-17-*one*, needles, m. p. 197—199°, $[\alpha]_D^{25}$ +137° (*c*, 0·406) (Found : C, 70·4; H, 8·2. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·7%), after crystallisation from aqueous methanol.

3β : 12α-*Dihydroxyandrostan*-17-*one* (VI ; R = H), prepared by hydrolysing the foregoing compound (950 mg.) in aqueous methanol (50 ml. ; 1 : 9) with potassium hydroxide (1 g.) under reflux for 1 hr., formed needles, m. p. 195—197°, $[\alpha]_D^{22}$ +147° (*c*, 0·436) (Found : C, 74·7; H, 9·8. $C_{19}H_{30}O_3$ requires C, 74·5; H, 9·8%), after crystallisation from acetone. The compound gave a positive Zimmermann reaction for the 17-keto-group.

Configuration at $C_{(12)}$.—(i) $[M]_D$ of (VI; R = Ac) $-[M]_D$ of 3β-acetoxyandrostan-17-one = +274°. Molecular rotation increment of 12α-OAc = +280°, 12β-OAc = +76° (see Barton and Klyne, *Chem. and Ind.*, 1948, 755).

(ii) $[M]_D$ of (VI; R = H) $-[M]_D$ of 3β-hydroxyandrostan-17-one = +196°. Molecular rotation increment of 12α-OH = +93°, 12β-OH = +50°. Agreement is less satisfactory in this instance, presumably owing to vicinal action of the 17-keto-group.

12α-*Hydroxyandrostane*-3 : 17-*dione*.—3β : 12α-Dihydroxyandrostan-17-one (400 mg.) in *tert.*-butanol (15 ml.), kept with *N*-bromoacetamide (828 mg.) in water (1 ml.) for 16 hr. at room temperature, gave 12α-*hydroxyandrostane*-3 : 17-*dione*, m. p. 187—188°, $[\alpha]_D^{22}$ +221° (*c*, 0·462) (Found: C, 75·0; H, 9·2. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·2%). The presence of a hydroxyl group in this compound was revealed by its infra-red absorption spectrum and confirmed by conversion into the *acetate*, m. p. 200—202° (Found: C, 72·5; H, 9·0. $C_{21}H_{30}O_4$ requires C, 72·7; H, 8·7%).

17α-*Hydroxy*allo*pregnane*-3 : 12 : 20-*trione* (XII).—The diol (VIII; R = H) (6·4 g.) in *tert.*-butanol (150 ml.) was oxidised with *N*-bromoacetamide (4 g.) in water (7·5 ml.) for 16 hr. at room temperature. After precipitation with water, the product was collected, debrominated by brief treatment with zinc dust–acetic acid, and purified from chloroform–ether. 17α-*Hydroxy*allo*pregnane*-3 : 12 : 20-*trione* had m. p. 222—224°, $[\alpha]_D^{24}$ +79° (*c*, 0·454) (Found: C, 72·9; H, 8·4. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

21-*Bromo*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = H, R′ = Br).—The diol (VIII; R = H) (3·60 g.) in chloroform (50 ml.) was treated at room temperature with bromine in chloroform (87 ml.; 0·1204M) during 90 min. Bromination was slow even in the presence of hydrogen bromide. Purification of the product from chloroform–ether gave 21-*bromo*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-dione, m. p. 183—184°, $[\alpha]_D^{24}$ +57° (*c*, 0·50) (Found: C, 61·5; H, 7·6; Br, 15·7. $C_{21}H_{31}O_4Br$ requires C, 59·0; H, 7·2; Br, 18·7%), which decomposed on storage.

21-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = H, R′ = OAc).—The foregoing bromo-compound (3·15 g.) in acetone (102 ml.) was treated with sodium iodide (1·8 g.) for 20 min. under reflux under nitrogen. After filtration to remove sodium bromide, the solution was poured on sodium hydrogen carbonate (15 g.) admixed with acetic acid (9 ml.), and refluxing under nitrogen was continued for a further 16 hr. After removal of acetone the product was extracted with ether and crystallised from acetone–hexane. 21-*Acetoxy*-3β : 17α-*dihydroxy*allo*pregnane*-12 : 20-*dione* formed needles, m. p. 206—209°, $[\alpha]_D^{23}$ +50° (*c*, 0·52) (Found: C, 68·2; H, 8·4. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

Reduction of (XI; R = H, R′ = OAc) with sodium borohydride, followed by oxidation of the total reduction product [presumably (IX)] with sodium bismuthate, and acetylation, furnished 3β : 12α-diacetoxyandrostan-17-one, m. p. 197—199°, alone or on admixture with a sample prepared from (VII; R = H) (above).

3β-*Acetoxy*-21-*bromo*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = Ac, R′ = Br), prepared by bromination of (VIII; R = Ac), had m. p. 172—174° (softening at 168°) (Found: C, 58·2; H, 6·8; Br, 17·7. $C_{23}H_{33}O_5Br$ requires C, 58·8; H, 7·0; Br, 17·1%).

3β : 21-*Diacetoxy*-17α-*hydroxy*allo*pregnane*-12 : 20-*dione* (XI; R = Ac, R′ = OAc).—(i) Prepared from the foregoing compound, the *product* formed needles, m. p. 161—163°, $[\alpha]_D^{23}$ +41° (*c*, 0·53) (Found: C, 66·7; H, 7·9. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·0%), after crystallisation from acetone–hexane; (ii) prepared by acetylation of (XI; R = H, R′ = OAc), the compound had m. p. 161—163°, not depressed on admixture with a sample prepared as in (i) (above).

21-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12 : 20-*trione* (X).—The diacetate (XI; R = H, R′ = OAc) (4·06 g.) in *tert.*-butanol (120 ml.) was treated at room temperature with water (4 ml.) and *N*-bromoacetamide (2·76 g.). After being shaken for 5 hr. in absence of light, the mixture was poured into water, and the product isolated with ether and debrominated with zinc dust (3·5 g.) in acetic acid (15 ml.) for 15 min. on the water-bath. 21-*Acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12 : 20-*trione* had m. p. 207—210°, $[\alpha]_D^{26}$ +66° (*c*, 0·482) (Found: C, 68·9; H, 8·1. $C_{23}H_{32}O_6$ requires C, 68·3; H, 7·9%), after purification from acetone–ether. The compound depressed the m. p. of (XI; R = H, R′ = OAc).

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