420. *Steroids and Related Compounds.. Part XIV.** 5β-*Methyl*-19-*norcoprost*-9(10)-*ene*-3β : 6β :-*diol.*

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Further study of the changes undergone by " Westphalen's diol " leads to its formulation as 5β-methyl-19-norcoprost-9(10)-ene-3β : 6β-diol (X; R′ = H). The revised structure is employed to illustrate the transformations undergone by this compound.

The constitution of a 5ξ-methyl-19-norcholest-8(9)-ene-3 : 6-diol for " Westphalen's diol " (Part II; Petrow, Rosenheim, and Starling, *J.*, 1938, 677) fails to accommodate certain transformations observed during the present investigation. We have, therefore, considered, *ab initio*, alternative structures for this product and, as a result, propose a revised formulation which seems to provide a better interpretation of available experimental data.

Work on the structure of Westphalen's diol, described in Part II (*loc. cit.*), led Petrow, Rosenheim, and Starling to conclude that forced dehydration of 3β : 6β-diacetoxycholestan-5α-ol (IX) results in a Wagner-type rearrangement of the *neo*pentyl group $C_{(10)}C_{(5)}C_{(1)}C_{(19)}C_{(9)}$ to give a 5ξ-methyl-19-norcholest-8(9)-ene-3 : 6-diol. The results described herein leave little doubt that this view is, in the main, correct. At the same time they show clearly that the unsaturated linkage of Westphalen's diol is located at $C_{(9)}$:$C_{(10)}$, and not at $C_{(8)}$:$C_{(9)}$, as previously thought. The arguments whereby this decision is reached, however, are too lengthy and involved for presentation *in extenso*. We shall, therefore, anticipate this conclusion in discussing the transformations examined in the course of the present study.

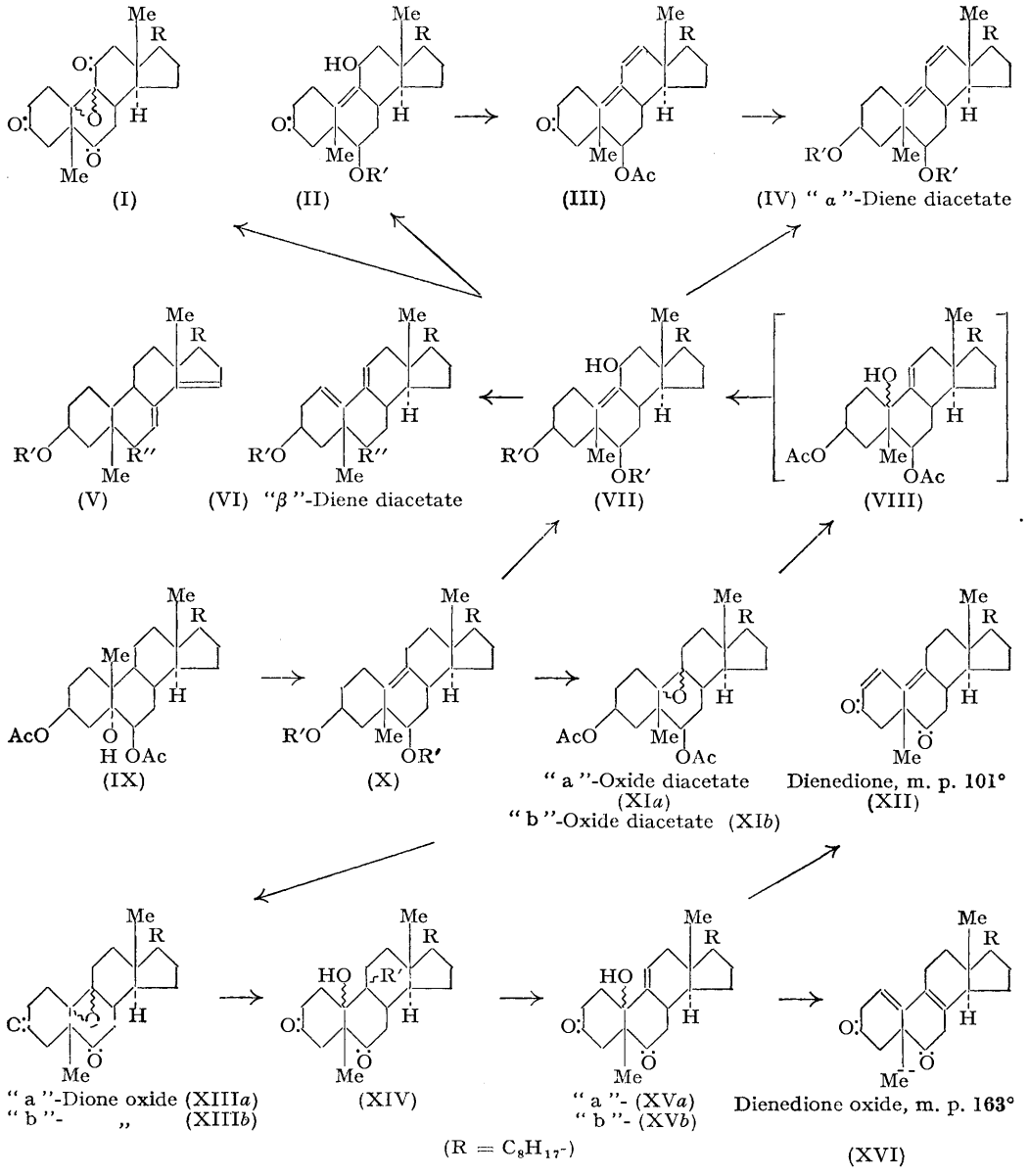
Wagner rearrangements are generally thought to involve a *trans*-interchange of groups (see de la Mare, *Ann. Reports*, 1950, **47**, 143). The β-configuration may therefore be assigned to the 5-methyl group of Westphalen's diol, which is accordingly formulated as 5β-methyl-19-norcoprost-9(10)-ene-3β : 6β-diol (X; R′ = H). Direct evidence for placing the methyl group at $C_{(5)}$, however, does not exist. Indirect evidence, on the other hand, strongly supports the view that this position is occupied by a group other than hydrogen. Thus, in contrast to 3β-hydroxycholestan-6-one and certain other 6-keto-steroids (see Part II), the 3β-methoxy-5β-methyl-19-norcoprost-9(10)-en-6-one [" 3-methoxy-5ξ-methyl-19-norcholest-8(9)-en-6-one "] of Davis and Petrow (*J.*, 1951, 2211) fails to give the Liebermann–Buchard reaction. It also differs from them in resisting all efforts at conversion into an enol benzoate. In addition, 5β-methyl-19-norcoprost-9(10)-ene-3 : 6-dione (" Westphalen diketone "; Part II) fails to form a pyridazine derivative with hydrazine (Windaus, Inhoffen, and Reichel, *Annalen*, 1934, **510**, 254), an observation which, though lacking structural significance (see Noller, *J. Amer. Chem. Soc.*, 1939, **61**, 2976), nevertheless reveals a point of difference between the Westphalen diketone and normal steroid 3 : 6-diones.

In addition to the 3β : 6β-diacetoxy-9 : 10-epoxy-5β-methyl-19-norcoprostane, m. p. 133·5° (hereafter termed the " a "-oxide diacetate) (XI*a*), obtained by the action of hydrogen peroxide on (X; R′ = Ac) (Part III, Petrow, *J.*, 1939, 998), we have now isolated an isomeric compound from the mother-liquors which we have designated the " b "-oxide diacetate (XI*b*). Both compounds readily undergo partial dehydration with alcoholic hydrochloric acid to give isomeric " α "-, m. p. 127°, $\lambda_{max.}$ 247 mμ (ε = 29,000), and " β "-3β : 6β-diacetoxy-5β-methyl-19-norcoprostadiene, m. p. 168°, $\lambda_{max.}$ 242 mμ (ε = 9200) (both spectra redetermined in *iso*propyl alcohol).

Comparison of the absorption spectra of the " α "- and the " β "-diene diacetate with those of homo- and hetero-annular dienes (see Woodward, *J. Amer. Chem. Soc.*, 1942, **64**, 72; also Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corpn., 2nd Edn., p. 185) leads to the conclusion that heteroannular conjugated systems are present in both these compounds. The low-intensity spectrum of the " β "-diene diacetate is similar to that of ergosteryl B_3 acetate (3β-acetoxyergosta-7 : 14 : 22-triene),

* Part XIII, *J.*, 1952, 161.

$\lambda_{max.}$ 242 mμ (ε = 9900) (Barton and Brooks, *J.*, 1951, 277), and to that of cholesteryl B_3 acetate (3β-acetoxycholesta-7 : 14-diene), $\lambda_{max.}$ 248 mμ (ε = 15,100) (Windaus, Linsert, and Eckhardt, *Annalen*, 1938, **534**, 22). The " β "-diene diacetate further resembles the last two compounds in readily forming a maleic anhydride adduct under non-forcing conditions (Part III, *loc. cit.*). It is thus reasonable to conclude that the " β "-diene



diacetate likewise possesses a *cisoid* dienic system spread over three rings, as indicated in (V) and (VI; R′ = Ac, R″ = β-OAc, H). A decision between these alternative formulations is possible from a study of certain transformations undergone by the 3β-methoxy-5β-methyl-19-norcoprost-9(10)-en-6-one of Davis and Petrow (*loc. cit.*).

Oxidation of this compound with hydrogen peroxide in acetic acid leads to the corresponding 9 : 10-epoxide in excellent yield. Hydrolysis of this epoxide with hot alcoholic

hydrochloric acid gives two isomeric methoxy-dienones of m. p. 70° and 85°, characterised by their absorption spectra [$\lambda_{max.}$ 248 (ε = 29,000) and 242 mμ ($\varepsilon_{max.}$ = 9200) respectively]. Comparison of these values with those given by the " α "- and the " β "-diene diacetate reveals the important fact that the two sets of spectra are indistinguishable. The conclusion may be drawn that the unsaturated linkages present in the two compounds, m. p. 70° and 85°, correspond exactly in position with those present in the " α "- and the " β "-diene diacetate, respectively. The dienic methoxy-ketone, m. p. 85°, should thus correspond structurally to the " β "-diene diacetate and should, therefore, be (V; R′ = Me, R″ = :O) or (VI; R′ = Me, R″ = :O) (see above). The former structure, however, is excluded by the spectroscopic data, which show that the dienic system is not conjugated with the carbonyl group at $C_{(6)}$. Formulation (VI; R′ = Me, R″ = :O) must therefore be assigned to the methoxy-keto-diene, m. p. 85°, and formulation (VI; R′ = Ac, R″ = β-OAc) to the " β "-diene diacetate.

Before proceeding further it is relevant to add that the production of (VI; R′ = Ac, R″ = β-OAc) from the " a " and the " b "-oxide diacetate (XI*a* and XI*b*) provided the first definite clue that the unsaturated linkage of Westphalen's diol is located at $C_{(9)}$:$C_{(10)}$. Formation of this diene from an 8 : 9-epoxide, though not impossible, requires bond migration of more complex character for which there is, at present, no *a priori* justification. The conclusion thus reached was strengthened by the observations, presented below, on the location of the unsaturated linkages in the " α "-diene diacetate.

Three correlated series of transformations are required to establish the structure of the " α "-diene diacetate :

(i) Reasons presented in Part III (*loc. cit.*) for assigning the 11-position to the hydroxyl group introduced into (X; R′ = H) by selenium dioxide rest largely on the observation that oxidation of the monounsaturated triol with chromic acid gives a trione oxide (cf. I) which does not contain a 1 : 3-diketone grouping. This conclusion, previously reached on chemical grounds alone, has now been finally confirmed by spectroscopic study of the trione oxide : this has no significant absorption in the ultra-violet region in both neutral and alkaline solution. The selenium dioxide oxidation product of (X; R′ = H) may therefore be formulated as a 5β-methyl-19-norcoprost-9(10)-ene-3β : 6β : 11-triol (VII; R′ = H), and the corresponding trione oxide as 9ξ : 10ξ-epoxy-5β-methyl-9-norcoprostane-3 : 6 : 11-trione (I).

(ii) The " a "- and the " b "-oxide diacetate (XI*a* and XI*b*) formed by treatment of (X; R′ = Ac) with hydrogen peroxide (see above) resemble each other in their behaviour towards alcoholic hydrochloric acid, an " α "- and a " β "-diene diacetate (VI; R′ = Ac, R″ = β-OAc) being formed. They differ, however, in their behaviour towards the periodic acid reagent recently introduced by Fieser and Rajagopalan (*J. Amer. Chem. Soc.*, **1949**, **71**, 3938) for conversion of cholesterol α-oxide into cholestane-3β : 5α : 6β-triol. Thus, in contrast to the " a "-isomer which is recovered unchanged, the " b "-oxide diacetate passes into (VII; R′ = Ac) when heated with this reagent in aqueous acetone. It is thus clear that careful acidic hydrolysis of the " b "-oxide diacetate (XI*b*) occurs through initial formation of (VIII) which then undergoes allylic rearrangement into (VII; R′ = Ac). The latter compound thus forms an essential intermediate in the conversion of the " b "-oxide acetate (XI*b*) into the " α "-diene diacetate.

(iii) Attempts to acetylate the free hydroxyl group of (VII; R′ = Ac) with acetic anhydride–sodium acetate led to the formation of the " α "-diene diacetate, admixed with smaller quantities of (VI; R′ = Ac, R″ = β-OAc). As free hydrogen ions are absent under these experimental conditions, it is unlikely that migration of unsaturated linkages in the " a "-diene diacetate would be facilitated by the dehydrating reagent. It is permissible to assume, in these circumstances, that the major product of the dehydration, the " α "-diene diacetate, is formed from (VII; R′ = Ac) by simple removal of the elements of water. If this is indeed the case the constitution of 3β : 6β-diacetoxy-5β-methyl-19-norcoprosta-9(10) : 11-diene (IV; R′ = Ac) may be assigned to the " α "-diene diacetate.

The formulation (IV; R′ = Ac) is supported by the spectrum of the compound which shows a high intensity band, $\lambda_{max.}$ 247 mμ (ε = 29,000), comparable with that given by 3β-acetoxycholesta-6 : 8(14)-dien-9-ol ($\lambda_{max.}$ 248 mμ; ε = 28,700) (Windaus, Linsert, and

Eckhardt, *Annalen*, 1938, **534**, 22). The structural relation postulated above between the " α "- (IV; R′ = Ac) and the " β "-diene diacetate (VI; R′ = Ac, R″ = β-OAc) is further strengthened by the observation that the " α "-isomer (IV; R′ = Ac), on treatment with dry hydrogen chloride in chloroform at 0°, passes into the " β "-isomer (VI; R′ = Ac, R″ = β-OAc), a change closely paralleled by the transformation of ergosterol B_2 into B_3 under similar experimental conditions (Windaus, Dithmar, Murke, and Suckfüll, *Annalen*, 1931, **488**, 91).

Oppenauer oxidation of (VII; R′ = H) with aluminium *iso*propoxide and *cyclo*hexanone leads to the formation of a dihydroxy-ketone, characterised by conversion into a monosemicarbazone, monoacetate, and monobenzoate. Its formulation as 6β : 11-dihydroxy-5β-methyl-19-norcoprost-9(10)-en-3-one (II; R′ = H) follows from the observation that it is not an αβ-unsaturated ketone, and that 3β-methoxy-5β-methyl-19-norcoprost-9(10)-en-6β-ol (Davis and Petrow, *loc. cit.*), in which oxidation at $C_{(3)}$ cannot occur, is recovered substantially unchanged under similar conditions (cf. Davis and Petrow, *J.*, 1949, 2973; 1950, 1185).

In contrast to (VII; R′ = Ac), (II; R′ = Ac) is not dehydrated when heated with sodium acetate–acetic anhydride for 3 hours. Brief treatment with anhydrous formic acid under reflux, however, converts (II; R′ = Ac) into 6β-acetoxy-5β-methyl-19-norcoprosta-9(10) : 11-dien-3-one (III), the constitution of which follows from (i) its ultra-violet absorption spectrum which shows absence of conjugation of the dienic system with the carbonyl group, (ii) its failure to give a potassium salt with ethanolic potassium hydroxide, and (iii) its conversion, by reduction with lithium aluminium hydride followed by acetylation, into (IV; R′ = Ac).

Alkaline hydrolysis of the " b "-oxide diacetate (XI*b*) gives the corresponding diol, which is oxidised with chromic acid to " b "-9 : 10-epoxy-5β-methyl-19-norcoprostane-3 : 6-dione (XIII*b*) characterised as the monosemicarbazone. Treatment of (XIII*b*) with (i) hot ethanolic hydrochloric acid, or (ii) hydrobromic acid in acetone at room temperature, affords the chlorohydrin (XIV; R′ = Cl) and the bromohydrin (XIV; R′ = Br), respectively. Both halogenohydrins are readily transformed by sodium acetate–acetic anhydride into (XIII*b*), and by hot ethanolic potassium hydroxide into an unsaturated hydroxy-diketone, also obtained directly from (XIII*b*) by treatment with hot ethanolic potash. This hydroxy-diketone is not an αβ-unsaturated ketone and is also stable to alkali (cf. 3-keto-œstr-5(10)-en-17-ol ⟶ 3-keto-œstr-4-en-17-ol; Birch, *J.*, 1950, 367), so that it is conveniently formulated as (XV*b*).

Attempts to dehydrate (XV*b*) by Darzens's method proved unsuccessful, gummy products admixed with much unchanged material being obtained. Boiling with acetic anhydride or with periodic acid in aqueous acetone were without effect. Dehydration of (XV*b*) was accomplished, however, by heating it (*a*) with ethanolic hydrochloric acid, a diene-dione, m. p. 163°, being obtained, and (*b*) with formic acid, which gave a diene-dione, m. p. 101°. The latter compound was also formed in excellent yield by treating (XIV; R′ = Cl) with thionyl chloride in pyridine at 0°.

Treatment of the isomeric " a "-9 : 10-epoxy-5β-methyl-19-norcoprostane-3 : 6-dione (XIII*a*; derived from the " a "-oxide diacetate) with ethanolic hydrochloric acid at room temperature likewise gives an unsaturated hydroxy-diketone, conveniently represented by (XV*a*), which passes into a mixture of the diene-diones, m. p. 101° and 163°, respectively, on treatment with hot ethanolic hydrochloric acid.

The ultra-violet absorption spectrum of the diene-dione, m. p. 163°, with $\lambda_{max.}$ 245 mμ (ε = 18,200), reveals the presence of a dienic chromophore, probably *transoid*, which is not conjugated with a carbonyl group. As, in addition, the compound forms a coloured potassium salt on solution in ethanolic potassium hydroxide, thereby showing that one of the double bonds is βγ to a carbonyl group, it is assigned the constitution 5β-methyl-19-norcoprosta-1(10) : 8(9)-diene-3 : 6-dione (XVI). This is supported by the observation that the diene-dione is reduced by lithium aluminium hydride to a non-crystalline mixture of diols showing ultra-violet absorption of $\lambda_{max.}$ 245 mμ (ε = 16,200), entirely compatible with formulation (XVI) for the parent diene-dione.

The ultra-violet absorption of the diene-dione, m. p. 101°, with $\lambda_{max.}$ 304 mμ (ε = 17,400),

reveals the presence of a dienic chromophore conjugated with a carbonyl group. The carbonyl group is probably not at $C_{(6)}$ as ethanolic hydrochloric acid converts 9 : 10-epoxy-3β-methoxy-5β-methyl-19-norcoprostan-6-one into two methoxy-dien-6-ones, neither of which is an αβ-unsaturated ketone (see above). The foregoing compound is therefore assigned the constitution 5β-methyl-19-norcoprosta-1 : 9(10)-diene-3 : 6-dione (XII). Its reduction with lithium aluminium hydride gives a non-crystalline mixture of diols with an ultra-violet absorption maximum at 247 mμ (ε = 22,000), in accord with this formulation.

Certain related observations required by us to reach the conclusion that Westphalen's diol is represented by (X; R′ = H) are reported upon briefly in the Experimental section.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. Optical rotations were measured in chloroform solution in a 2-dm. tube unless otherwise stated. Absorption spectra, measured in *iso*propyl alcohol, were kindly determined by Dr. R. E. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses, Ltd. Activated alumina, B.D.H. Laboratory Grade, was employed for all chomatographic work.

5β-*Methyl*-19-*norcoprost*-9(10)-*ene*.—5β-Methyl-19-norcoprost-9(10)-ene-3 : 6-dione (3 g.) was heated under reflux with semicarbazide hydrochloride (1·8 g.) and anhydrous sodium acetate (1·8 g.) in 95% alcohol (70 ml.) for 6 hours and the mixture poured into water. The crude granular semicarbazone (3·3 g.) obtained (softened at 170° and decomposed between 190° and 200°) was heated under reflux in diethylene glycol (50 ml.) containing hydrazine hydrate (1·5 ml. of 90% w/v) and potassium hydroxide (4·5 g.) for 30 minutes; the condenser was then removed and boiling continued until the temperature had reached 200°. The condenser was replaced and the mixture refluxed for a further 4 hours. The oily product so obtained was dissolved in light petroleum (b. p. 40—60°) (50 ml.), and the solution passed through a column (9 × 1·5 cm.) of alumina. Evaporation of the eluate gave a syrup (1·5 g.; $[\alpha]_D^{20}$ +62°). Purification was effected by strongly cooling a solution in boiling acetone. After three such treatments, 5β-*methyl*-19-*norcoprost*-9(10)-*ene* was obtained as a colourless viscous syrup distilling unchanged at 250°/1·5 mm., $[\alpha]_D^{22}$ +66·1° (*c*, 1·93) (Found: C, 87·4; H, 12·4. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%), which failed to crystallise during contact with solvents for many months.

It gave a characteristic violet colour in the Tortelli–Jaffé test and was recovered unchanged after treatment with dry hydrogen chloride in chloroform at 0°.

Cholest-8(9)-*en*-3-*one*.—A suspension of cholest-8(9)-en-3β-ol (1 g.) in benzene (10 ml.) was shaken for 5 hours with chromic acid (0·33 g.) in acetic acid (12 ml.; 70%). The neutral fraction of the oxidation product gave cholest-8(9)-en-3-one (50%), feathery needles, m. p. 124—125°, $[\alpha]_D^{20}$ +66·4° (*c*, 0·99), from aqueous acetone (Found: C, 84·3; H, 11·7. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%) (Wieland, Rath, and Benend, *Annalen*, 1941, **548**, 19, give $[\alpha]_D$ +71·5°, m. p. 124—125°).

Cholest-8(9)-*ene*.—The foregoing ketone (0·75 g.) in absolute ethanol (25 ml.) was heated with hydrazine hydrate (0·5 ml.; 90% w/v) for 30 minutes under reflux, whereafter the solvent was removed under reduced pressure and the crystalline residue was heated under reflux in diethylene glycol (20 ml.) containing potassium hydroxide (2 g.) and hydrazine hydrate (0·2 ml. of 90% w/v) for 1 hour. A solution of the product in light petroleum (b. p. 40—60°) was filtered through a column (8 × 1·3 cm.) of alumina. Evaporation of the filtrate gave a crystalline solid (0·55 g.; m. p. 88°), further purified by recrystallisation from acetone–methanol. Cholest-8(9)-ene formed lustrous plates, m. p. 90—91°, $[\alpha]_D^{24}$ +49·3° (*c*, 1·06) (Found: C, 87·4; H, 12·3. Calc. for $C_{27}H_{46}$: C, 87·5; H, 12·5%) (Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402, have independently given m. p. 92—93·5°, $[\alpha]_D$ +56°). It gave the normal green colour in the Tortelli–Jaffé test.

3β-*Methoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*en*-6-*one semicarbazone*, obtained in 90% yield by treating 3β-methoxy-5β-methyl-19-norcoprost-9(10)-en-6-one (5 g.) in absolute ethanol (100 ml.) with semicarbazide hydrochloride (1·5 g.) in water (5 ml.) and anhydrous sodium acetate (1·5 g.) in ethanol (15 ml.) for 3 days at room temperature, formed platelets, m. p. 187° (decomp.), from aqueous ethanol (Found: N, 8·9. $C_{29}H_{49}O_2N_3$ requires N, 8·9%). Only small quantities of the derivative could be isolated when the reactants were heated under reflux for several hours.

3β-*Methoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene*.—The foregoing semicarbazone (5 g.), potassium hydroxide (10 g.), and hydrazine hydrate (2 ml.; 90% w/v) in diethylene glycol (100 ml.) were heated in an open flask until the temperature reached 195—200°, whereafter the mixture was refluxed for 2 hours. The product was isolated with ether, its solution in light

petroleum (b. p. 40—60°) passed through a column (10 × 3·5 cm.) of alumina, and the filtrate evaporated, to give a waxy solid (2·9 g.), m. p. 61°. Crystallised from acetone–methanol, 3β-methoxy-5β-methyl-19-norcoprost-9(10)-ene formed long hard needles, m. p. 63—64°, $[\alpha]_D^{25}$ +64° (*c*, 2·34) (Found: C, 83·6; H, 11·7. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·1%) (Shealy and Dodson, *J. Org. Chem.*, 1951, **16**, 1427, have independently given m. p. 59·5—60·5°, $[\alpha]_D^{27}$ +61·7°). The compound gave a violet colour in the Tortelli–Jaffé test.

3β-*Toluene*-p-*sulphonyloxycholest*-8(9)-*ene*, obtained in small flat plates, m. p. 113° (sintering at 108°), from aqueous acetone (Found: C, 74·9; H, 9·7. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7%), was not converted into the methyl ether when its solution in methanol was refluxed for 8 hours, a gum being obtained.

3β-*Methoxycholest*-8(9)-*ene*.—A solution of cholest-8(9)-en-3β-ol (4 g.) in benzene (30 ml.) was added to a suspension of powdered potassium (1 g.) in benzene (30 ml.), and the reaction completed by warming. After addition of methyl iodide (20 ml.) the mixture was gently refluxed for 4 hours, cooled, and diluted with ether. The solution was washed and dried, the solvents were removed, and the residue in light petroleum was percolated through a column (10 × 3·5 cm.) of alumina. 3β-*Methoxycholest*-8(9)-*ene* separated in large thin plates (55%), m. p. 104°, $[\alpha]_D^{18}$ +40° (*c*, 1·17), from acetone–methanol (Found: C, 83·5; H, 11·8. $C_{28}H_{48}O$ requires C, 83·9; H, 12·1%).

3β : 6β-*Diacetoxy*-5β-*methyl*-19-*norcoprostan* 9 : 10-*Oxides*.—Westphalen's diacetate (30 g.) in acetic acid (750 ml.) was treated for 5 days at room temperature with hydrogen peroxide (30 ml.; 100 vol.), whereafter the mixture was poured into brine. When the precipitated solids were dissolved in warm aqueous methanol to which a little acetone had been added, 3β : 6β-diacetoxy-5β-methyl-19-norcoprostane " a "-9 : 10-oxide (40%) rapidly separated in flat needles, m. p. 132° (Part III, *loc. cit.*). Cautious dilution of the mother-liquors gave 3β : 6β-*diacetoxy*-5β-*methyl*-19-*norcoprostane* " *b* "-9 : 10-*oxide* (43%), flat needles, m. p. 101—102°, $[\alpha]_D^{20}$ +57·8° (*c*, 0·94) (from aqueous methanol) (Found: C, 74·4; H, 10·1. $C_{31}H_{50}O_5$ requires C, 74·1; H, 10·0%).

When the " b "-oxide diacetate was treated with alcoholic hydrochloric acid, and the product acetylated (cf. Part III, *loc. cit.*), 3β : 6β-diacetoxy-5β-methyl-19-norcoprosta-9(10) : 11- and 1(10) : 9-diene were obtained, identified by m. p.s and mixed m. p.s.

3β-*Methoxy*-5β-*methyl*-19-*norcoprostan*-6-*one* 9 : 10-*Oxide*.—3β-Methoxy-5β-methyl-19-norcoprost-9(10)-en-6-one (4·4 g.) in acetic acid (100 ml.) was treated for 24 hours at room temperature with hydrogen peroxide (4 ml.; 100 vol.). The product was poured into brine and the precipitated solids were crystallised from aqueous methanol–acetone. The *oxide* (90%) formed soft needles, m. p. 97°, $[\alpha]_D^{24}$ −6·3° (*c*, 1·27) (Found: C, 78·5; H, 10·8. $C_{28}H_{46}O_3$ requires C, 78·1; H, 10·8%).

Isomeric 3β-*Methoxy*-5β-*methyl*-19-*norcoprostadienones*.—The foregoing compound (2 g.) in ethanol (30 ml.) was refluxed for 10 minutes with concentrated hydrochloric acid (1·5 ml.). Crystallisation of the product from aqueous methanol–acetone gave 3β-*methoxy*-5β-*methyl*-19-*norcoprosta*-1(10) : 9-*dien*-6-*one* (35%) in hard needles, m. p. 85—86°, $[\alpha]_D^{24}$ −200° (*c*, 1·14) (Found: C, 81·8; H, 10·9. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%). Light absorption: $\lambda_{max.}$ 242 mμ, (ε = 9100). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in yellow needles, m. p. 137—139° (Found: N, 9·3. $C_{34}H_{48}O_5N_4$ requires N, 9·5%).

Removal of the solvents from the first mother-liquor gave a syrup which solidified only when its solution in absolute methanol was strongly cooled. Subsequent slow crystallisation from methanol gave 3β-*methoxy*-5β-*methyl*-19-*norcoprosta*-9(10) : 11-*dien*-6-*one* (20%), hard needles, m. p. 70°, $[\alpha]_D^{24}$ −105° (*c*, 1·07; *l*, 1) (Found: C, 81·4; H, 10·2. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·75%). Light absorption: $\lambda_{max.}$ 248 mμ (ε = 29,000). The 2 : 4-*dinitrophenylhydrazone* separated from ethanol in crystals, m. p. 148—150° (Found: N, 9·2. $C_{34}H_{48}O_5N_4$ requires N, 9·5%).

Action of Periodic Acid on 3β : 6β-*Diacetoxy*-5β-*methyl*-19-*norcoprostane* " *b* "-9 : 10-*Oxide* (XI*a*).—The " b "-oxide diacetate (4 g.) in acetone (120 ml.) was treated with a solution of periodic acid (2·4 g.) in water (40 ml.), and the mixture refluxed for 2 hours. The product, isolated with ether, was extracted with hot light petroleum (50 ml.) (b. p. 80—100°), and the insoluble fraction (1·3 g.) crystallised from acetone–light petroleum. 3β : 6β-Diacetoxy-5β-methyl-19-norcoprost-9(10)-en-11-ol formed small flat needles, m. p. 185° (Found: C, 74·1; H, 10·0. Calc. for $C_{31}H_{50}O_5$: C, 74·1; H, 10·0%) not depressed in admixture with an authentic specimen. Saponification with ethanolic potassium hydroxide gave 5β-methyl-19-norcoprost-9(10)-ene-3β : 6β : 11-triol, long hard needles, m. p. 253°, from ethanol (Found: C, 77·5; H, 10·8. Calc. for $C_{27}H_{46}O_3$: C, 77·5; H, 11·1%) [Petrow, *loc. cit.*, gives m. p. 223° (decomp.)].

5β-*Methyl*-19-*norcoprostane*-3 : 6 : 11-*trione* 9 : 10-*Oxide* (I).—A suspension of 5β-methyl-19-norcoprost-9(10)-ene-3β : 6β-11-triol (0·85 g.) in benzene (15 ml.) was shaken for 5 hours with chromium trioxide (0·7 g.) in acetic acid (20 ml.; 80%). The neutral fraction, from aqueous methanol, yielded 5β-methyl-19-norcoprostane-3 : 6 : 11-trione 9 : 10-oxide (60%), flat needles, m. p. 168—169° (Found : C, 75·5; H, 9·1. Calc. for $C_{27}H_{40}O_4$: C, 75·7; H, 9·3%) (Petrow, Part III, *loc. cit.*, gives m. p. 165·5—166·5°). Examined in neutral and in alkaline *iso*propyl alcohol, the compound did not show any significant absorption in the region 230—400 mμ. The *monosemicarbazone* formed small needles, m. p. 229—230° (decomp.), from aqueous ethanol (Found : N, 8·9. $C_{28}H_{43}O_4N_3$ requires N, 8·7%).

Isomerisation of 3β : 6β-*Diacetoxy*-5β-*methyl*-19-*norcoprosta*-9(10) : 11-*diene* (IV; R′ = Ac) *with Hydrogen Chloride.*—A stream of dry hydrogen chloride was passed during 45 minutes through a solution of the diene (1·3 g.) in chloroform (30 ml.) at 0°. Thereafter the violet solution was washed with ice-cold aqueous sodium hydrogen carbonate and dried, the solvent removed *in vacuó*, and the residue crystallised from aqueous acetone. 3β : 6β-Diacetoxy-5β-methyl-19-norcoprosta-1(10) : 9-diene (35%) was obtained, having m. p. and mixed m. p. 168°.

6β : 11-*Dihydroxy*-5β-*methyl*-19-*norcoprost*-9(10)-*en*-3-*one* (II; R′ = H).—5β-Methyl-19-norcoprost-9(10)-ene-3β : 6β : 11-triol (8 g.) and aluminium *iso*propoxide (12·5 g.) in toluene (100 ml.) and *cyclo*hexanone (60 ml.) were heated under reflux for 1 hour. The mixture was washed with dilute sulphuric acid, then with water, and the solvents were removed by steam-distillation. The product on crystallisation from aqueous ethanol gave 6β : 11-*dihydroxy*-5β-*methyl*-19-*norcoprost*-9(10)-*en*-3-*one* (60%) in long flat needles, m. p. 180°, $[\alpha]_D^{20}$ −14·6° (*c*, 1·01) (Found : C, 77·8; H, 10·1. $C_{27}H_{44}O_3$ requires C, 77·8; H, 10·4%). The compound did not show significant absorption in the region 220—300 mμ. The *semicarbazone* separated from aqueous ethanol in needles, m. p. 220—221° (decomp.) (Found : N, 9·4. $C_{28}H_{47}O_3N_3$ requires N, 8·9%). The 6β-*monoacetate*, prepared by refluxing the dihydroxy-ketone (2 g.) with acetic anhydride (15 ml.) for 30 minutes, crystallised from aqueous methanol in small hard prisms, m. p. 124°, $[\alpha]_D^{25}$ −30° (*c*, 1·1; *l*, 1) (Found : C, 76·3; H, 9·8. $C_{29}H_{46}O_4$ requires C, 75·9; H, 10·1%). The 6β-*monobenzoate*, prepared by heating the dihydroxy-ketone (0·45 g.) with benzoyl chloride (1·5 ml.) in pyridine (3 ml.) for 30 minutes at 100°, crystallised from aqueous acetone as hard rods, m. p. 138° (Found : C, 78·3; H, 8·8. $C_{34}H_{48}O_4$ requires C, 78·4; H, 9·3%).

6β-*Acetoxy*-5β-*methyl*-19-*norcoprosta*-9(10) : 11-*dien*-3-*one* (III).—6β-Acetoxy-11-hydroxy-5β-methyl-19-norcoprost-9(10)-en-3-one (1·4 g.) was treated for 5 minutes at 100° with anhydrous formic acid (7 ml.). The product, on crystallisation from aqueous acetone, gave 6β-*acetoxy*-5β-*methyl*-19-*norcoprosta*-9(10) : 11-*dien*-3-*one* (30%), long thin needles, m. p. 137°, $[\alpha]_D^{24}$ −57·6° (*c*, 0·85; *l*, 1) (Found : C, 79·2; H, 10·3. $C_{29}H_{44}O_3$ requires C, 79·0; H, 10·1%). Light absorption : $\lambda_{max.}$ 248 mμ (ε = 23,100). Reduction of the foregoing dienone (185 mg.) with lithium aluminium hydride (400 mg.) in ether (60 ml.) under reflux for 45 minutes, followed by acetylation and crystallisation from aqueous acetone, gave 3β : 6β-diacetoxy-5β-methyl-19-norcoprosta-9(10) : 11-diene (55 mg.), soft needles, m. p. 126° (Found : C, 76·8; H, 10·0. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 9·9%), not depressed in admixture with an authentic specimen.

3β : 6β-*Dihydroxy*-5β-*methyl*-19-*norcoprostane* " *b* "-9 : 10-*Oxide.*—Obtained from the corresponding diacetate by hydrolysis with ethanolic potassium hydroxide, this *oxide* separated from light petroleum–acetone in felted hair-like needles, m. p. 148—149° (Found : C, 77·4; H, 11·1. $C_{27}H_{46}O_3$ requires C, 77·5; H, 11·1%).

5β-*Methyl*-19-*norcoprostane*-3 : 6-*dione* " *b* "-9 : 10-*Oxide* (XIII*b*).—The foregoing diol " b "-oxide (2 g.) in benzene (20 ml.) was shaken for 5 hours with chromium trioxide (1·4 g.) in acetic acid (30 ml. of 80%). The neutral fraction crystallised from methanol, to give 5β-*methyl*-19-*norcoprostane*-3 : 6-*dione* " *b* "-9 : 10-*oxide* (60%), long hard needles, m. p. 147°, $[\alpha]_D^{20}$ +70° (*c*, 1·01) (Found : C, 78·0; H, 10·1. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·1%). The *monosemicarbazone* formed needles, m. p. 225° (decomp.), from ethanol–chloroform (Found : N, 8·7. $C_{28}H_{45}O_3N_3$ requires N, 8·9%).

Chlorohydrin (XIV; R′ = Cl).—When the dione " b "-oxide (XIII*b*) (200 mg.) in ethanol (5 ml.) was heated under reflux with concentrated hydrochloric acid (1 ml.) for 5 minutes, the *chlorohydrin* (130 mg.) was obtained; it formed hard needles, m. p. 219—220° (effervescence), from aqueous ethanol (Found : C, 71·8; H, 9·6; Cl, 8·3. $C_{27}H_{43}O_3Cl$ requires C, 71·9; H, 9·6; Cl, 7·9%). When the compound (60 mg.) and anhydrous sodium acetate (100 mg.) were heated under reflux for 30 minutes in acetic anhydride (1 ml.) the dione " b "-oxide (40 mg.) was regenerated (m. p. and mixed m. p. 147°).

Bromohydrin (XIV; R′ = Br).—The dione " b "-oxide (XIII*b*) (100 mg.) in acetone (5 ml.) was treated for 1 hour at room temperature with hydrobromic acid (0·2 ml.; 48%). The

crystalline deposit (60 mg.), purified from aqueous methanol, gave the *bromohydrin* as needles, m. p. 174° (decomp.) (Found : C, 66·0; H, 8·9. $C_{27}H_{43}O_3Br$ requires C, 65·4; H, 8·75%). The dione " b "-oxide was regenerated from this compound by boiling acetic anhydride–sodium acetate.

The Hydroxy-diketone (XV*b*).—(*a*) The chlorohydrin (XIV; R′ = Cl) or the bromohydrin (XIV; R′ = Br) (200 mg.) in ethanolic potassium hydroxide (5 ml.; 4%) was refluxed for 10 minutes, and water was added to turbidity. The *hydroxy-diketone* (100—125 mg.) separated and crystallised from aqueous ethanol as small blades or long needles, m. p. 210—212° [Found : C, 78·1; H, 10·0; active H (Zerewitinoff), 0·29. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·1; active H, 0·24%).

(*b*) The dione " b "-oxide (XIII*b*) (500 mg.) was heated under reflux for 5 minutes with ethanolic potassium hydroxide (12 ml. of 4%), to give the foregoing product (400 mg.), m. p. 210—212°, not depressed in admixture with a specimen prepared by method (*a*).

The compound did not show selective absorption in the region 220—300 mμ. It was recovered unchanged after being heated under reflux for 15 minutes with sodium acetate–acetic anhydride, and for 30 minutes with periodic acid in aqueous acetone.

5β-*Methyl*-19-*norcoprosta*-1(10) : 8(9)-*diene*-3 : 6-*dione* (XVI).—The foregoing substance (XV*b*) (100 mg.) in ethanol (2·5 ml.) containing concentrated hydrochloric acid (5 drops) was refluxed for 30 minutes and the product in light petroleum (b. p. 40—60°) chromatographed on a column (5 × 0·8 cm.) of alumina. Development with the same solvent furnished several fractions, giving yellow intractable gums. Further development with ether gave a gum that solidified when rubbed with methanol. Purified from aqueous acetone, the *diene-dione* (10 mg.) formed leafy plates, m. p. 163°, $[\alpha]_D^{24}$ +3° (*c*, 0·97; *l*, 1) (Found : C, 81·4; H, 10·1. $C_{27}H_{40}O_2$ requires C, 81·8; H, 10·2%). Light absorption : $\lambda_{max.}$ 245 mμ (ε = 18,200). The compound dissolved in 6% ethanolic potassium hydroxide with production of an intense orange-yellow colour and separation of a micro-crystalline potassium salt. The diene-dione was regenerated on acidification.

5β-*Methyl*-19-*norcoprosta*-1 : 9(10)-*diene*-3 : 6-*dione* (XII).—(*a*) The hydroxy-diketone (XV*b*) (200 mg.) was treated for 5 minutes at 100° with anhydrous formic acid (5 ml.). The product, in light petroleum (b. p. 40—60°), was chromatographed on a column (5 × 1·3 cm.) of alumina. Elution with light petroleum–acetone gave the *diene-dione* (30 mg.) in hard prismatic needles, m. p. 100—101°, $[\alpha]_D^{24}$ +238° (*c*, 1·14; *l*, 1) (Found : C, 81·4; H, 9·9. $C_{27}H_{40}O_2$ requires C, 81·8; H, 10·2%). Light absorption : $\lambda_{max.}$ 304 mμ (ε = 17,400).

(*b*) The chlorohydrin (XIV; R′ = Cl) (130 mg.) in dry pyridine (1 ml.) was treated at 0° with thionyl chloride (0·06 ml.). After 10 minutes at room temperature, ice-water was added and the precipitated solids were crystallised from aqueous ethanol, giving the diene-dione (82 mg.), needles, m. p. 100°, not depressed in admixture with a specimen prepared by method (*a*). The 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–ethanol in dark red needles, m. p. 198° (Found : N, 9·4. $C_{33}H_{44}O_5N_4$ requires N, 9·7%). An enol *benzoate* was obtained in low yield when the diene-dione (400 mg.) in pyridine (1 ml.) and benzoyl chloride (1 ml.) was refluxed for 20 minutes. It crystallised from aqueous acetone in hard plates, m. p. 140° (Found : C, 81·8; H, 9·1. $C_{34}H_{44}O_3$ requires C, 81·6; H, 8·8%). Light absorption : $\lambda_{max.}$ 324 mμ (ε = 13,700).

The Hydroxy-diketone (XV*a*).—Concentrated hydrochloric acid (0·8 ml.) was added to a suspension of the dione " a "-oxide (XIII*a*) (0·8 g.) in ethanol (50 ml.). The mixture was diluted after 3 hours at room temperature, and the product dissolved in aqueous ethanol from which crystals (0·5 g.) slowly separated. Recrystallised from aqueous acetone–methanol, the *compound* formed hard needles, m. p. 175—176° (Found : C, 77·2; 77·3; H, 10·2, 10·2. $C_{27}H_{42}O_3,\frac{1}{4}H_2O$ requires C, 77·35; H, 10·2%).

Hydrolysis of the Dione " a "-Oxide (XIII*a*) *by Hot Alcoholic Hydrochloric Acid.*—The oxide (XIII*a*) (7·5 g.) was heated under reflux for 30 minutes with ethanol (100 ml.) and concentrated hydrochloric acid (5 ml.). Chromatography of the product in light petroleum (b. p. 40—60°) on a column (12 × 3·5 cm.) of alumina gave much yellow intractable gum as the first fraction. Subsequent fractions, which solidified when rubbed with methanol, were combined and crystallised from aqueous acetone, giving the diene-dione, m. p. 100—101° (270 mg.). Elution with light petroleum–ether (4 : 1) gave further intractable gums. Finally, development with ether afforded solids which, purified from aqueous acetone, gave the diene-dione, m. p. 163° (400 mg.).

Reduction of the Isomeric Diene-diones.—(*a*) The diene-dione (XVI) (220 mg.) in ether (80 ml.) was refluxed for 1 hour with lithium aluminium hydride (300 mg.). The amorphous product, m. p. 70—80°, had light absorption $\lambda_{max.}$ 245 mμ (ε = 16,200). It failed to crystallise before or after acetylation followed by chromatography.

(*b*) Reduction of the diene-dione (XII) likewise gave an amorphous product, m. p. 60—70°.

Light absorption: $\lambda_{max.}$ 247 mμ ($\varepsilon = 22{,}000$). Crystalline fractions were not obtained by chromatography of the acetylated material.

The following derivatives were prepared for *X*-ray studies, the results of which will be reported elsewhere.

3β : 6β-*Bischloroacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene* (85%), prepared by treating Westphalen's diol (1·6 g.) with chloroacetic anhydride (5 g.) for 15 minutes at 100°, formed needles, m. p. 101—102°, $[\alpha]_D^{24}$ +81·2° (*c*, 2·52), from ethanol (Found: C, 66·6; H, 8·7. $C_{31}H_{48}O_4Cl_2$ requires C, 67·0; H, 8·7%).

3β : 6β-*Bisiodoacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene* was obtained when the foregoing bischloroacetate (1 g.) was heated under reflux for 15 minutes with sodium iodide (3 g.) in acetone (30 ml.). It separated from ethanol as a jelly but was obtained in soft felted needles, m. p. 114°, $[\alpha]_D^{24}$ +69·2° (*c*, 2·57), when methanol was added to its concentrated acetone solution (Found: C, 50·8; H, 6·8. $C_{31}H_{48}O_4I_2$ requires C, 50·4; H, 6·6%).

6β-*Acetoxy*-3β-*chloroacetoxycholestan*-5α-*ol*, prepared by chloroacetylation of 6β-acetoxycholestane-3β : 5α-diol (Ellis and Petrow, *J.*, 1939, 1078), crystallised from aqueous acetone in hard glistening needles, m. p. 198°, $[\alpha]_D^{24}$ −36·5° (*c*, 1·82) (Found: C, 68·9; H, 9·1. $C_{31}H_{51}O_5Cl$ requires C, 69·05; H, 9·5%).

6β-*Acetoxy*-3β-*chloroacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene*.—A solution of 6β-acetoxy-3β-chloroacetoxycholestan-5α-ol (7·5 g.) in acetic anhydride (35 ml.) containing potassium hydrogen sulphate (2 g.) was heated under reflux for 10 minutes. The mixture was poured into brine, then set aside overnight, and the gummy product isolated with ether and crystallised from acetone–methanol, to give 6β-*acetoxy*-3β-*chloroacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene* (30%), prisms m. p. 110—111°, $[\alpha]_D^{24}$ +84·5° (*c*, 1·94) (Found: C, 71·2; H, 9·5. $C_{31}H_{49}O_4Cl$ requires C, 71·4; H, 9·5%). The compound gave a green colour in the Tortelli–Jaffé test.

6β-*Acetoxy*-3β-*iodoacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene*, prepared from the foregoing chloroacetate, crystallised from aqueous ethanol in long hard needles, m. p. 130—131°, $[\alpha]_D^{24}$ +71·1° (*c*, 1·78) (Found: C, 61·1; H, 8·45; I, 20·7. $C_{31}H_{49}O_4I$ requires C, 60·8; H, 8·1; I, 20·75%). On hydrolysis with methanolic potash, Westphalen's diol was obtained, identified by m. p. and mixed m. p. with an authentic specimen.

3β-*Acetoxy*-6β-*chloroacetoxycholestan*-5α-*ol*, obtained on chloroacetylation of 3β-acetoxycholestan-5α : 6β-diol (Pickard and Yates, *J.*, 1908, **93**, 1678), crystallised from aqueous ethanol in needles, m. p. 144—145°, $[\alpha]_D^{24}$ −43·6° (*c*, 1·86) (Found: C, 69·2; H, 9·6. $C_{31}H_{51}O_5Cl$ requires C, 69·05; H, 9·5%).

3β-*Acetoxy*-6β-*iodoacetoxycholestan*-5α-*ol* formed needles, m. p. 113—115°, $[\alpha]_D^{24}$ −33·2° (*c*, 1·16), from aqueous ethanol (Found: C, 59·1; H, 8·4. $C_{31}H_{51}O_5I$ requires C, 59·0; H, 8·15%).

3β-*Acetoxy*-6β-*iodoacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene*.—(*a*) 3β-Acetoxy-6β-chloroacetoxycholestan-5α-ol (3·5 g.) in acetic anhydride (20 ml.) containing potassium hydrogen sulphate (1 g.) was heated under reflux for 10 minutes. The product, isolated with ether, did not crystallise and was, therefore, treated with sodium iodide (5 g.) in acetone (50 ml.) for 30 minutes under reflux. 3β-*Acetoxy*-6β-*iodoacetoxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene* (900 mg.) was obtained as felted hair-like needles, m. p. 127—128°, $[\alpha]_D^{24}$ +72° (*c*, 1·55), from aqueous alcohol (Found: C, 60·3; H, 8·0. $C_{31}H_{49}O_4I$ requires C, 60·8; H, 8·1%).

(*b*) When 3β-acetoxy-6β-iodoacetoxycholestan-5α-ol was treated with acetic anhydride and potassium hydrogen sulphate, the corresponding Westphalen diester was obtained from aqueous acetone in hair-like needles, m. p. 128°, not depressed in admixture with a specimen prepared by method (*a*). The compound gave a positive Tortelli–Jaffé test, and Westphalen's diol on saponification.

6β-*Acetoxy*-3β-p-*iodobenzoyloxycholestan*-5α-*ol* (70%) was obtained when 6β-acetoxycholestane-3β : 5α-diol (2 g.) was heated under reflux for 45 minutes with *p*-iodobenzoyl chloride (4 g.) in dry pyridine (25 ml.) and crystallised from acetone–methanol in soft silky needles, m. p. 162° (sinters 117—120°), $[\alpha]_D^{24}$ −13·3° (*c*, 1·80) (Found: C, 61·7; H, 7·4. $C_{36}H_{53}O_5I$ requires C, 62·4; H, 7·7%).

6β-*Acetoxy*-3β-p-*iodobenzoyloxy*-5β-*methyl*-19-*norcoprost*-9(10)-*ene* (30%), prepared from the foregoing compound, crystallised in tiny plates, m. p. 197°, $[\alpha]_D^{24}$ −103° (*c*, 1·84), from acetone (Found: C, 63·8; H, 7·5. $C_{31}H_{51}O_4I$ requires C, 64·1; H, 7·6%). It gave Westphalen's diol on saponification.

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