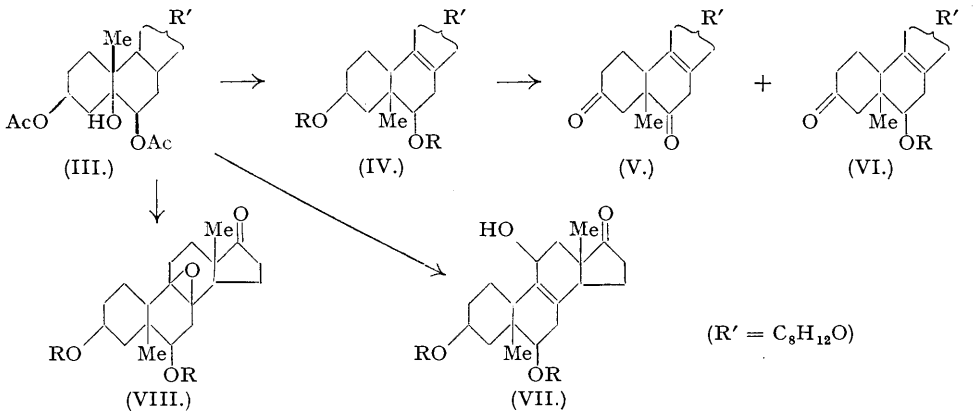
627. *Steroids and Related Compounds. Part VII. Some Derivatives of 5-Methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one.*

By M. Davis and V. Petrow.

Dehydration of 3β : 6β-diacetoxyandrostan-5α-ol-17-one (III) with potassium hydrogen sulphate–acetic anhydride leads to the diacetate of an unsaturated *diol* to which the constitution 5-*methyl*-10-*norandrost*-8(9)-*ene*-3 : 6-*diol*-17-*one* (IV; R = H) has been assigned. Evidence of an indirect character supporting this formulation has been obtained by a study of the transformation products of the diol. 3 : 6-*Diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*one* (IV; R = Ac), 5-*methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17-*trione* (V), and 3 : 6-*diacetoxy*-8 : 9-*epoxy*-5-*methyl*-10-*norandrostan*-17-*one* (VIII; R = Ac) have been examined for androgenic activity but are inactive.

By dehydrating cholestanetriol diacetate (I) with acetic anhydride containing a trace of concentrated sulphuric acid, Westphalen (*Ber.*, 1915, **48**, 1064) obtained the diacetate of an unsaturated diol (" Westphalen's diol ") (II) which Lettré and Müller (*Ber.*, 1937, **70**, 1947) formulated as a 5-methyl-10-norcholest-9(10)-ene-3 : 6-diol, but to which Petrow, Rosenheim, and Starling (*J.*, 1938, 677) assigned the constitution of a 5-methyl-10-norcholest-8(9)-ene-3 : 6-diol. Petrow (*J.*, 1939, 998) prepared substantial quantities of " Westphalen's diol " by dehydrating (I) with potassium hydrogen sulphate–acetic anhydride. He was thus able to study its transformations and his results, while not excluding a formula based on the conventional steroid skeleton, nevertheless provided strong indirect evidence supporting the 5-methyl-10-norcholestene-3 : 6-diol structure. The " Westphalen " series of compounds thus represents a new type of steroid and is, as such, worthy of further study, particularly from the standpoint of the relation between chemical structure and biological activity.

The preparation of 3β : 6β-diacetoxyandrostan-5α-ol-17-one (III), the androstane analogue of cholestanetriol diacetate (for configuration see Part VI; Davis and Petrow, this vol., p. 2536), has previously been described by, *inter alia*, Ehrenstein (*J. Org. Chem.*, 1941, **6**, 629), and the compound was readily obtained in satisfactory overall yield from dehydro*iso*androsterone. When (III) was heated with potassium hydrogen sulphate–acetic anhydride at 100° for 15 minutes, dehydration occurred to give a new unsaturated *diacetate* (A), $C_{23}H_{32}O_5$, in 40—60% yield. The dehydration residues yielded, by fractional crystallisation and chromatography, a further small quantity of the diacetate (A), a minute amount of 3β : 5α : 6β-triacetoxyandrostan-17-one, and traces of substance (B), probably $C_{25}H_{34}O_6$. A third dehydration product, an unsaturated *diacetate* (C), $C_{23}H_{32}O_5$, hydrolysable to a *diol*, was obtained in low yield from only one of the many experiments performed, but the quantities of (B) and (C) available were too small to permit of more than a very cursory examination.



The chemical properties of compound (A), the main dehydration product, are consistent with its formulation as a 3 : 6-*diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*one* (IV; R = Ac), removal of the $C_{(5)}$-hydroxy grouping from (III) being accompanied by a pinacolic rearrangement. Thus the compound is unsaturated to tetranitromethane but does not give a colour with the trichloroacetic acid reagent. It differs from the known 3 : 6-diacetoxyandrost-4-en-17-ones recently described by Davis and Petrow (*loc. cit.*). It exhibits strong dextrorotation, the molecular-rotation differences between the " Westphalen " type of compounds belonging to

the androstane and cholestane series showing fair agreement. It differs from the " Westphalen " diacetate, however, in failing to give a Tortelli–Jaffé reaction, resembling in this respect the behaviour of the " Westphalen " diketone, 5-methyl-10-norcholest-8(9)-ene-3 : 6-dione (Petrow, Rosenheim, and Starling, *loc. cit.*).

Molecular-rotation Differences.

	$[M]_D$.						
	3 : 6--Diol.	3 : 6-Diacetate.	3 : 6-Dione.	3 : 6-Diacetate 8 : 9-oxide.	Δ_1.	Δ_2.	Δ_3.
5-Methyl-10-norcholest-8(9)-en	+478° [1]	+408° [1]	−182° [1]	+44° [2]	−70°	−660°	−434°
5-Methyl-10-norandros-8(9)-en-17-one	+702	+612	0	+238	−90	−702	−464

[1] Petrow, Rosenheim, and Starling (*loc. cit.*). [2] Petrow, *J.*, 1939, 1001.

5-*Methyl*-10-*norandrost*-8(9)-*ene*-3 : 6-*diol*-17-*one* (IV; R = H), obtained by hydrolysis of the diacetate, was characterised by conversion into the *dibenzoate* (IV; R = Bz). Its oxidation with chromic acid furnished 5-*methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17-*trione* (V) in low yield, converted into a *tris-dinitrophenylhydrazone*. When a limited quantity of chromic acid was employed for the oxidation, a partial oxidation product formulated as a 5-*methyl*-10-*norandrost*-8(9)-*en*-6-*ol*-3 : 17-*dione* (VI; R = H) was formed in addition to the triketone (V), its separation being rendered possible by its stronger adsorption on alumina. The same diketo-alcohol was the sole product when the diol (IV; R = H) was oxidised by the Oppenauer method, the compound being characterised by conversion into a *monoacetate* (VI; R = H) and *monobenzoate* (VI; R = Bz).

Oxidation of (IV; R = H) with selenium dioxide followed the pattern established for the 5-methyl-10-norcholestene analogue (see Petrow, *loc. cit.*), a *triol* being obtained, although in very low yield. The presence of three active hydrogen atoms in this compound was confirmed by a Zerewitinoff determination. It has therefore been assigned the constitution of a 5-*methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 11-*triol*-17-*one* (VII; R = H) and, in accordance with this formulation, gave what was apparently only a *diacetate* (VII; R = Ac) on gentle acetylation, although analysis of the product was not entirely satisfactory.

Treatment of (IV; R = Ac) with monoperphthalic acid gave 3 : 6-*diacetoxy*-8 : 9-*epoxy*-5-*methylnorandrostan*-17-*one* (VIII; R = Ac), alkaline hydrolysis of which gave the corresponding *diol* (VIII; R = H). Attempts to hydrolyse the oxide ring of the latter compound with dilute acid, were however, uniformly unsuccessful.

Attempts to carry out the " Westphalen " rearrangement on 3β : 6α-diacetoxyandrostan-5α-ol-17-one and 3β : 6α-diacetoxycholestan-5α-ol led to the isolation of the corresponding Δ^4-compounds in low yields.

Biological Results.—Dr. S. W. F. Underhill and Mr. W. S. Parr (Physiological Department, The British Drug Houses Ltd.) have kindly examined (IV; R = Ac), (V), and (VIII; R = Ac) for androgenic action and report as follows : The method used for determining androgenic activity was the response of castrated rats, the criterion being the increase in weight of the prostate and seminal vesicles. All three compounds failed to show androgenic activity, even in doses of 10 mg. This result may be due to the presence of the 6-acetoxy- or 6-keto-grouping in the molecule. Thus Butenandt *et al.* (*Ber.*, 1936, **69**, 1163, 1158) showed that androst-4-ene-3 : 6 : 17-trione and androst-4-en-17-ol-3 : 6-dione (6-ketotestosterone) are devoid of androgenic activity, whilst androst-4-ene-3 : 17-dione and androst-4-en-17-ol-3-one (testosterone) are highly active.

Experimental.

M. p.s are corrected. Microanalyses and the Zerewitinoff determination are by Drs. Weiler and Strauss, Oxford. Optical rotations were measured in chloroform solution in a 2-dm. tube, limits of experimental error being given as the polarimeter employed could only be read to 0·03°. Activated alumina was used for all chromatographic work.

3β : 6β-Diacetoxyandrostan-5α-ol-17-one (III) was prepared by the method of Ehrenstein (*loc. cit.*) from 3β-acetoxy-5α : 6α-epoxyandrostan-17-one (Ruzicka and Muhr, *Helv. Chim. Acta*, 1944, **27**, 503).

3β-*Benzoyloxy*-6β-*acetoxyandrostan*-5α-*ol*-17-*one*.—(*a*) 3β-Benzoyloxy-5α-6α-epoxyandrostan-17-one (100 mg.; m. p. 242—243°; Ruzicka, Grob, and Raschka, *Helv. Chim. Acta*, 1940, **23**, 1518, give m. p. 218—220°) was heated under reflux with glacial acetic acid (5 ml.) for 2 hours. The residue left on removal of the solvent *in vacuo* was crystallised from ether–light petroleum, giving 3β-*benzoyloxy*-6β-*acetoxyandrostan*-5α-*ol*-17-*one*, prisms, m. p. 124° (decomp.) (Found : C, 72·0; H, 8·1. $C_{28}H_{36}O_6$ requires C, 71·8; H, 7·7%). (*b*) The same compound, m. p. 120—124° (decomp.), not depressed in admixture with the product obtained as in (*a*), was formed when 6β-acetoxyandrostane-3β : 5α-diol-17-

one (Ehrenstein, *J. Org. Chem.*, 1941, **6**, 626) was heated with benzoyl chloride in pyridine under reflux for 45 minutes.

3 : 6-*Diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*one* (IV; R = Ac) *and Related Compounds.*—A solution of 3β : 6β-diacetoxyandrostan-5α-ol-17-one (2 g.) in acetic anhydride (10 ml.) containing powdered potassium hydrogen sulphate (0·5 g.) was heated on the water-bath for 15 minutes. The product obtained on pouring the solution into brine and keeping the mixture overnight was crystallised from methanol, giving 3 : 6-*diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*one* (40—60%), needles, m. p. 155—156°, $[\alpha]_D^{22}$ + 158° ± 1° (*c*, 1·486) (Found : C, 71·1; H, 8·1. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%).

The residues from the mother-liquors of several experiments were dissolved in benzene–light petroleum (1 : 1), and the solution was passed through a column of alumina. Elution with the same solvents, followed successively by benzene, benzene–ether, and ether, yielded small quantities of the above diacetate, of 3β : 5α : 6β-triacetoxyandrostan-17-one, m. p. 183—184° [alone or in admixture with an authentic specimen (Ehrenstein, *loc. cit.*)], and a trace of *compound* (*B*), fine needles from ether–light petroleum, m. p. 205° (Found : C, 69·9; H, 8·4. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%). Compound (*B*) failed to give a Tortelli–Jaffé colour reaction and gave only a brownish colour with trichloroacetic acid. It was saturated towards tetranitromethane. Hydrolysis with ethanolic potassium hydroxide gave a product which did not crystallise satisfactorily and was reconverted into the original acetate, m. p. 203°, on acetylation.

In one dehydration experiment with 2 g. of (III), a second crop of crystals (60 mg.) was obtained after removal of the main product (IV; R = Ac) (820 mg.). This fraction melted at 130—140° and, on crystallisation from aqueous methanol and ether–light petroleum, afforded *compound* (*C*), m. p. 164° (Found : C, 71·3; H, 8·3. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). The compound gave a pale yellow colour with tetranitromethane, but did not give positive reactions with trichloroacetic acid or the Tortelli–Jaffé reagent. It was evidently a *diacetate*, as hydrolysis with methanolic potassium hydroxide, followed by crystallisation from benzene–light petroleum, gave a *diol*, m. p. 183—184° (Found : C, 75·2; H, 9·7. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%), reconverted by acetic anhydride–pyridine into the diacetate, m. p. 164°.

5-*Methyl*-10-*norandrost*-8(9)-*ene*-3 : 6-*diol*-17-*one* (IV; R = H), obtained by hydrolysis of (IV; R = Ac) with 5% ethanolic potassium hydroxide, formed prisms from benzene, m. p. 235—236°, $[\alpha]_D^{22}$ + 230° ± 2° (*c*, 0·499) (Found : C, 74·6; H, 9·1. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%).

3 : 6-*Dibenzoyloxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*one* (IV; R = Bz), obtained by treating the foregoing diol with excess of benzoyl chloride in pyridine for 45 minutes on the water-bath, formed feathery needles, m. p. 218° (Found : C, 76·7; H, 6·7. $C_{33}H_{36}O_5$ requires C, 77·3; H, 7·1%).

5-*Methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17-*trione* (V).—The foregoing diol (400 mg.) in glacial acetic acid (15 ml.) was treated dropwise with a solution of chromium trioxide (250 mg.) in 80% acetic acid (6 ml.). After 6 hours at room temperature, methanol (2 ml.) was added and the solution set aside overnight. The neutral fraction of the oxidation product yielded 5-*methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17-*trione* as hard prisms (110 mg.) (from benzene–light petroleum), m. p. 175—177° (Found : C, 75·9; H, 8·0. $C_{19}H_{24}O_3$ requires C, 76·0; H, 8·1%). The compound did not give the Tortelli–Jaffé reaction.

The orange-coloured *tris*-2 : 4-*dinitrophenylhydrazone*, prepared by warming the triketone (15 mg.) with 2 : 4-dinitrophenylhydrazine (40 mg.) and concentrated hydrochloric acid (3 drops) in alcohol (5 ml.) on the water-bath, and crystallised from chloroform–methanol, had m. p. 202—204° (decomp.) (Found : N, 19·5. $C_{37}H_{36}O_{12}N_4$ requires N, 20·0%).

5-*Methyl*-10-*norandrost*-8(9)-*en*-6-*ol*-3 : 17-*dione* (VI).—(*a*) The diol (IV; R = H) (160 mg.), dissolved in benzene (3 ml.), was shaken with a solution of chromium trioxide (85 mg.) in acetic acid (2 ml.) and water (1 ml.) for 5 hours at room temperature. The neutral fraction of the oxidation product was chromatographed in benzene containing a little light petroleum. Fractions 1 and 2 of the eluate yielded the triketone (25 mg.). Fractions 3 and 4 gave a trace of a mixture. Fraction 5, eluted with benzene, gave 5-*methyl*-10-*norandrost*-8(9)-*en*-6-*ol*-3 : 17-*dione*, prisms (from ether–acetone–light petroleum), m. p. 180—182° (Found : C, 74·9; H, 8·6. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7%). depressed to 140° by admixture with the triketone. (*b*) The diol (IV; R = H) (65 mg.) and aluminium *iso*propoxide (300 mg.) in acetone–benzene were heated under reflux for 52 hours. The solution was washed with dilute sulphuric acid and then water and dried, and the solvent was removed. The residue in benzene solution, after chromatographic purification and crystallisation from chloroform–light petroleum, yielded 5-methyl-10-norandrost-8(9)-en-6-ol-3 : 17-dione (32 mg.), m. p. 183—184°, not depressed on admixture with a sample prepared by method (*a*). The *monoacetate* formed needles, m. p. 153—154°, from ether–light petroleum (Found : C, 73·0; H, 8·5. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%). The *monobenzoate* likewise formed needles, m. p. 189—191°, from ether–light petroleum (Found : C, 76·3; H, 8·2. $C_{26}H_{30}O_4$ requires C, 76·7; H, 7·4%). The red 2 : 4-dinitrophenylhydrazone had m. p. 176—178°, but there was insufficient material for analysis.

5-*Methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 11-*triol*-17-*one* (VII; R = H).—Solutions of selenium dioxide (270 mg.) in water (3 ml.) and (IV; R = H) (270 mg.) in ethanol (10 ml.) were mixed and kept at room temperature for 7 days [35 mg. of Se deposited ≡ 0·5 atom of Se]. The mixture was poured into water and extracted thoroughly with chloroform, and the extracts were freed from traces of selenium by washing them with potassium cyanide solution. The residue (260 mg.) left on removal of the chloroform was heated under reflux with light petroleum and kept overnight; the crystalline deposit was boiled with benzene and crystallised 3 times from chloroform–benzene. 5-*Methyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 11-*triol*-17-*one* formed prisms, m. p. 202—203° [Found : C, 70·8; H, 8·3%; active hydrogen (Zerewitinoff), 2·74 atoms. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%; active hydrogen, 3 atoms]. The Tortelli–Jaffé reaction was negative. The *diacetate* (VII; R = Ac) formed needles, m. p. 116—118°, from benzene–light petroleum (Found : C, 71·9; H, 8·3. $C_{23}H_{32}O_6$,C_6H_6 requires C, 72·2; H, 7·9%), depressed below 100° on admixture with (IV; R = Ac).

3 : 6-*Diacetoxy*-8 : 9-*epoxy*-5-*methyl*-10-*norandrostan*-17-*one* (VIII; R = Ac).—The diacetate (IV; R = Ac) (1·14 g.) in ether (10 ml.) was treated with an ethereal solution of monoperphthalic acid (12

ml. of 0·335N.) for 2 days at room temperature. The product, on crystallisation from benzene–light petroleum, gave **3** : 6-*diacetoxy*-8 : 9-*epoxy*-5-*methyl*-10-*norandrostan*-17-*one* (520 mg.), clusters of prismatic needles, m. p. 200—201°, $[\alpha]_D^{17}$ + 59° ± 2·6° (*c*, 1·883) (Found : C, 68·0; H, 7·9. $C_{23}H_{32}O_6$ requires C, 68·2; H, 8·0%).

8 : 9-*Epoxy*-5-*methyl*-10-*norandrostane*-3 : 6-*diol*-17-*one* (VIII; R = H), obtained by hydrolysis of the foregoing diacetate with 4% ethanolic potassium hydroxide, formed prisms (from ethanol–benzene–light petroleum), m. p. 253—255° (Found : C, 70·7; H, 8·6. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

Dehydration of 3β : 6α-*Diacetoxycholestan*-5-*ol*.—The triol diacetate (110 mg.) and potassium hydrogen sulphate (25 mg.) in acetic anhydride (1 ml.) were heated on the water-bath for 15 minutes. The product, on repeated crystallisation from methanol, gave 3β : 6α-diacetoxycholest-4-ene (30 mg.), m. p. 164—166°, not depressed on admixture with an authentic specimen.

Dehydration of 3β : 6α-*Diacetoxyandrostan*-5-*ol*-17-*one*.—The diacetate (85 mg.) and potassium hydrogen sulphate (20 mg.) were heated in acetic anhydride for 2 hours on the water-bath. The product, which gave a blue colour with trichloroacetic acid, failed to crystallise, even after chromatography. It was therefore hydrolysed and, after chromatographic fractionation and repeated crystallisation, gave impure androst-4-ene-3β : 6α-diol-17-one, m. p. 168—180° (Found : C, 74·8; H, 9·4. Calc. for $C_{19}H_{28}O_3$: C, 75·0; H, 9·3%), not depressed on admixture with an authentic specimen (Davis and Petrow, *loc. cit.*).

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