243. *Steroids and Related Compounds. Part VIII. Some Transformation Products of 5-Methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one.*

By M. Davis and V. Petrow.

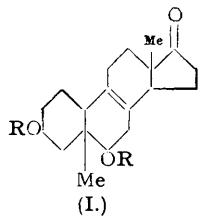
Interaction of 5-methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one (I; R = H) with methylmagnesium iodide, potassium acetylide in liquid ammonia, and hydrogen cyanide gave the expected 17β-*hydroxy*-derivatives, the transformations of which have been studied.

3 : 6-*Diacetoxy*-5-*methyl*-10-*norpregn*-8(9)-*en*-20-*one* (VII) has been obtained by pinacolinic rearrangement of 3β : 6β-diacetoxy*allo*pregnan-5α-ol-20-one following treatment with potassium hydrogen sulphate–acetic anhydride. Its constitution was indicated by collateral preparation of *pregn*-4-*ene*-3β : 6β-*diol*-20-*one* (VI).

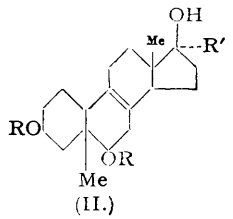
The methyl compound (III; R = H, R′ = Me) failed to show androgenic activity, or the ethynyl compound (III; R = H, R′ = ·C:CH) progestational activity.

Work on the relation between structure and biological activity in the 5-methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one series (I; R = H) (Davis and Petrow, *J.*, 1949, 2973) has been extended by a study of some transformations involving the 17-carbonyl grouping. These were undertaken with the object of enhancing any biological potentialities of (I), as it is known that reaction of dehydro*epi*androsterone with reagents such as methylmagnesium iodide (Ruzicka, Goldberg, and Rosenberg, *Helv. Chim. Acta*, 1935, **18**, 1487; 1936, **19**, 357) and acetylene (Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, 1938, **71**, 1024), followed by oxidation, affords tertiary carbinols of high androgenic and progestational activity, respectively.

Interaction of 5-methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one (I; R = H) with excess of methylmagnesium iodide in boiling ether–benzene gave 5 : 17α-*dimethyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17β-*triol* (II; R = H, R′ = Me), characterised by conversion into a *diacetate* (II; R = Ac, R′ = Me). The 17-hydroxyl grouping present in this compound is assigned the β-configuration relative to the 13β-methyl grouping on the assumption that the rules valid for the behaviour of 17-keto-steroids on reaction with Grignard reagents (see " Natural Products Related to Phenanthrene," Fieser and Fieser, 3rd Edition, p. 376) are not invalidated by the



(I.)



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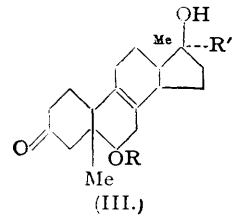

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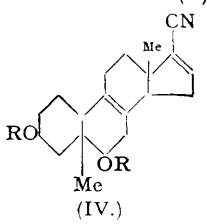

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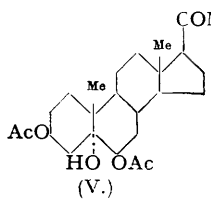

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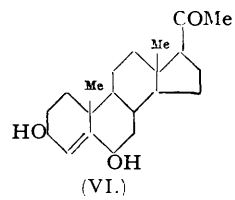

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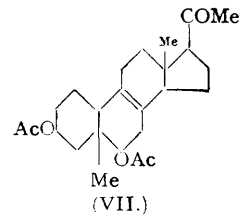

(VII.)

structural differences present in their 5-methylnorandrostene analogues. Oxidation of the triol (II; R = H, R′ = Me) by the Oppenauer method led to the formation of a *keto-diol*, characterised by conversion into a *monoacetate*. The constitution of a 5 : 17α-*dimethyl*-10-*norandrost*-8(9)-*ene*-6 : 17β-*diol*-3-*one* (III; R = H, R′ = Me) has been assigned to this compound from analogy with the sole formation of 3-keto-steroids from such compounds as deoxycholic and cholic acids under similar experimental conditions (Jones, Webb, and Smith, *J.*, 1949, 2164; cf. also Davis and Petrow, *loc. cit.*).

Addition of acetylene to 3 : 6-diacetoxy-5-methyl-10-norandrost-8(9)-en-17-one (I; R = Ac) in the presence of potassium *tert.*-amyloxide at room temperature gave only a small amount of the required 3 : 6-*diacetoxy*-5-*methyl*-17α-*ethynyl*-10-*norandrost*-8(9)-*en*-17β-*ol* (II; R = Ac, R′ = C≡CH). Somewhat better results were obtained by employing potassium acetylide in liquid ammonia. Yields fluctuated widely in successive experiments but the cause of this variation could not be determined. As before (cf. Fieser and Fieser, *op. cit.*, p. 328), the hydroxyl grouping at $C_{(17)}$ is provisionally assigned the 17β-configuration. Oppenauer oxidation of the

corresponding triol (II; R = H, R′ = C≡CH) gave a *monoketone*, characterised as the *monoacetate*, and assigned the formulation of a 5-*methyl*-17α-*ethynyl*-10-*norandrost*-8(9)-*ene*-6 : 17β-*diol*-3-*one* (III; R = H, R′ = C≡CH) (cf. Jones *et al.*, *loc. cit.*).

The conversion of 17-ketoandrostane derivatives into 20-ketopregnane derivatives by the "cyanohydrin" route has been described by, *inter alia*, Butenandt and Schmidt-Thomé (*Naturwiss.*, 1938, **26**, 265; *Ber.*, 1938, **71**, 1487; 1939, **72**, 182), and by Butenandt, Mamoli, and Heusner (*ibid.*, p. 1614). Similar treatment of (I; R = Ac) with potassium cyanide in boiling ethanol–acetic acid gave a poor yield of 17-*cyano*-3 : 6-*diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*ol* (II; R = Ac, R′ = CN), raised to >90% by carrying out the reaction at room temperature. The product was evidently a mixture of $C_{(17)}$-stereoisomers not readily separable by crystallisation, as the melting points varied somewhat in different preparations. Dehydration of the cyanohydrin with phosphorus oxychloride in pyridine, either under reflux or in a sealed tube at 155°, gave 17-*cyano*-3 : 6-*diacetoxy*-5-*methyl*-10-*norandrosta*-8(9) : 16-*diene* (IV; R = Ac) in yields never exceeding 45%, converted by alkaline hydrolysis into the *diol* (IV; R = H). Attempts to convert the nitrile (IV; R = Ac) into the corresponding 20-ketopregnane derivative by reaction with excess of methylmagnesium iodide in boiling benzene proved uniformly unsuccessful and further experiments in this direction were abandoned. Attempted hydrolyses of the nitrile (IV; R = H) to the corresponding acid were likewise unsuccessful. The compound was recovered essentially unchanged after prolonged heating with concentrated alcoholic potassium hydroxide, and reaction in a sealed tube at 150—160° led to profound decomposition. Accordingly, we turned our attention to the pinacolinic dehydration of 3β : 6β-diacetoxy*allo*pregnan-5α-ol-20-one (V), which possesses the essential stereochemical features associated with molecular rearrangements of this type (Davis and Petrow, *loc. cit.*).

*allo*Pregnane-3β : 5α : 6β-triol-20-one has previously been obtained in moderate yield by oxidation of pregn-5-en-3β-ol-20-one with hydrogen peroxide in acetic acid (Ehrenstein, *J. Org. Chem.*, 1939, **4**, 506; Ehrenstein and Stevens, *ibid.*, 1940, **5**, 318), or as the 6-monoacetate, by reaction of pregnenolone with perbenzoic acid to give some "α"-oxide, followed by acetolysis (Ehrenstein and Stevens, *ibid.*, 1941, **6**, 908). The preparation has now been improved, and (V) obtained in excellent yield, by treating pregn-5-en-3β-ol-20-one with monoperphthalic acid, whereby the "α"-oxide was obtained in nearly quantitative yield, followed by acetylation and acetolysis.

Dehydration of (V) with acetic anhydride–potassium hydrogen sulphate (Petrow, *J.*, 1939, 998) gave a glass which showed little tendancy to crystallise. Eventually after chromatographic fractionation and long storage, a very small quantity of an unsaturated *diacetate*, $C_{25}H_{36}O_5$, m. p. 120°, crystallised out and was removed by hand. Its crystalline *semicarbazone* was obtained from the residual glass. The diacetate failed to give either the Tortelli–Jaffé reaction or a blue colour with trichloroacetic acid.

Negative colour reactions are unsatisfactory as a basis for the positive statement of identity, but they furnish useful evidence in this instance, for dehydration products of 3β : 5α : 6β-triols having the Δ^4-structure, *viz.*, 3β : 6β-diacetoxycholest-4-ene (Petrow, Rosenheim, and Starling, *J.*, 1938, 677) and 3β : 6β-diacetoxyandrost-4-en-17-one (Davis and Petrow, *J.*, 1949, 2536), give blue colours with trichloroacetic acid, in contrast to the pinacolic dehydration products 3 : 6-diacetoxy-5-methyl-10-norcholest-8(9)-ene and 3 : 6-diacetoxy-5-methyl-10-norandrost-8(9)-en-17-one. Acetic anhydride–potassium hydrogen sulphate dehydration, moreover, is known to enforce pinacolic dehydration in suitably constituted triols (Davis and Petrow, *J.*, 1949, 2973). Nevertheless, the preparation of 3β : 6β-diacetoxypregn-4-en-20-one was undertaken in order to effect a direct comparison with the unsaturated diacetate described above.

Treatment of (V) with acetic anhydride–toluene-*p*-sulphonic acid gave the oily triacetate, characterised as the crystalline 3β : 5α : 6β-*triacetoxy*allo*pregnan*-20-*one oxime*. When thionyl chloride in pyridine was employed, and the mixture heated under reflux, dehydration occurred to give, after hydrolysis and chromatography, a very low yield of pregn-4-ene-3β : 6β-diol-20-one (VI). The latter compound gave a blue colour with trichloroacetic acid, an observation which excludes a Δ^4-structure for the unsaturated diacetate, m. p. 120°, described above and leads to its formulation as a 3 : 6-*diacetoxy*-5-*methyl*-10-*norpregn*-8(9)-*en*-20-*one* (VII).

Dr. S. W. F. Underhill and Mr. W. S. Parr (Physiological Department, The British Drug Houses Ltd.) have kindly examined (III; R = H, R′ = Me) and (III; R = H, R′ = C≡CH) for biological activity. The former failed to show androgenic activity at a dose of 2 mg./rat,

but there was an indication that a dose of 20 mg./rat may have had a slight effect on one animal; the latter failed to show progestational activity in a dose of 10 mg. on infantile rabbits.

Experimental.

M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. Activated alumina (B.D.H. Laboratory Grade) was used for chromatographic work.

5 : 17*α*-*Dimethyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17*β*-*triol* (II; R = H, R′ = Me).—A solution of 5-methyl-10-norandrost-8(9)-ene-3 : 6-diol-17-one (700 mg.) in benzene (250 ml.) was added to a Grignard reagent prepared from magnesium (1·5 g.) and excess of methyl iodide, and the mixture heated under reflux for 2½ hours. After decomposition with ammonium chloride solution containing a little hydrochloric acid, and removal of the benzene layer, the solution was extracted with small quantities of chloroform (total 250 ml.). Concentration of the bulked and washed benzene and chloroform extracts, followed by addition of light petroleum, gave 5 : 17*α*-*dimethyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17*β*-*triol* (530 mg.; m. p. 183—188°), prisms (from acetone–light petroleum), m. p. 195° (Found : C, 74·9; H, 9·8. $C_{20}H_{32}O_3$ requires C, 75·0; H, 10·1%). The 3 : 6-*diacetyl* derivative, prepared by treatment of the foregoing triol with acetic anhydride–pyridine for 2 days at room temperature, formed prismatic needles, m. p. 142—144° (Found : C, 70·7; H, 8·8. $C_{24}H_{36}O_5$ requires C, 71·2; H, 9·0%), from ether–light petroleum.

5 : 17*α*-*Dimethyl*-10-*norandrost*-8(9)-*ene*-6 : 17*β*-*diol*-3-*one* (III; R = H, R′ = Me).—The foregoing triol (300 mg.) in acetone (15 ml.) and aluminium *tert.*-butoxide (1 g.) in benzene (25 ml.) were heated under reflux for 24 hours. After decomposition with dilute sulphuric acid, the benzene layer was removed and washed with dilute acid and water. The aqueous portion was extracted three times with chloroform (total 90 ml.), and the bulked benzene–chloroform extracts taken to dryness. The residue was dissolved in benzene–light petroleum and purified by chromatography. Elution with benzene containing a small amount of ether yelded 5 : 17*α*-*dimethyl*-10-*norandrost*-8(9)-*ene*-6 : 17*β*-*diol*-3-*one* (120 mg.), prisms (from acetone–light petroleum), m. p. 144—145°, $[\alpha]_D^{23}$ +54·1° ± 1° (*c*, 0·426 in chloroform) (Found : C, 75·1; H, 9·4. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). Its 6-*acetyl* derivative, obtained by treatment with acetic anhydride–pyridine for 18 hours at room temperature, formed prismatic needles, m. p. 146—147° (Found : C, 72·8; H, 8·9. $C_{22}H_{32}O_4$ requires C, 73·3; H, 9·0%), from ether–light petroleum.

3 : 6-*Diacetoxy*-5-*methyl*-17*α*-*ethynyl*-10-*norandrost*-8(9)-*en*-17*β*-*ol* (II; R = Ac, R′ = C≡CH).—Acetylene (washed with concentrated sulphuric acid) was passed into liquid ammonia (50 ml.) (cylinder gas, dried over potassium hydroxide and recondensed). Potassium (400 mg.) was added during several minutes, passage of acetylene being maintained. After one hour a solution of (I; R = Ac) (400 mg.) in dry benzene (25 ml.) was added, followed by a little dry ether. Passage of acetylene was discontinued after a further 1¾ hours, and the ammonia was then allowed to evaporate off spontaneously at room temperature, solid ammonium chloride being added to destroy any residual potassium. The mixture was decomposed with saturated ammonium chloride solution, and the benzene layer removed, washed, and dried, and the solvent removed. The residue (335 mg., 79%), after crystallisation from chloroform–light petroleum or from methanol, yielded 3 : 6-*diacetoxy*-5-*methyl*-17*α*-*ethynyl*-10-*norandrost*-8(9)-*en*-17*β*-*ol*, m. p. 225—227° (Found : C, 72·0; H, 8·2. $C_{25}H_{34}O_5$ requires C, 72·4; H, 8·3%). The compound failed to give a Tortelli–Jaffé reaction, but gave a yellow colour with tetranitromethane when kept.

5-*Methyl*-17*α*-*ethynyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17*β*-*triol* (II; R = H, R′ = C≡CH).—(*a*) The foregoing diacetate was hydrolysed with ethanolic potash yielding 5-*methyl*-17*α*-*ethynyl*-10-*norandrost*-8(9)-*ene*-3 : 6 : 17*β*-*triol*, dimorphic needles, m. p. 129—131° or 170—172° (Found : C, 75·3, 75·3; H, 8·9, 9·1. $C_{21}H_{30}O_3,\frac{1}{4}H_2O$ requires C, 75·3; H, 9·2%), from acetone–light petroleum. (*b*) A solution of potassium (400 mg.) in dry *tert.*-amyl alcohol (15 ml.) was added to dry ether (20 ml.) saturated with acetylene, followed by a solution of 3 : 6-diacetoxy-5-methyl-10-norandrost-8(9)-en-17-one (300 mg.) in dry ether (20 ml.). Acetylene was passed through the mixture for 12 hours and it was then decomposed with ammonium chloride solution. The ether-soluble fraction was treated with Girard's reagent *P* to remove ketonic material and was then hydrolysed with alcoholic potassium hydroxide. The product was dissolved in benzene–chloroform (1 : 1) and chromatographed. Treatment of the column with benzene removed oily material, after which elution with benzene–ether (1 : 1) gave (II; R = H, R′ = C≡CH) (30 mg.), needles, m. p. 130—132°, not depressed in admixture with a sample prepared by method (*a*).

Treatment of the foregoing triol (15 mg.) in pyridine with benzoyl chloride (100 mg.) at 100° for 1 hour afforded the 3 : 6-*dibenzoyl* derivative, plates (from aqueous methanol), m. p. 215—216° (Found : C, 77·3, 77·2; H, 7·0, 7·0. $C_{35}H_{38}O_5,\frac{1}{4}H_2O$ requires C, 77·4; H, 7·1%).

5-*Methyl*-17*α*-*ethynyl*-10-*norandrost*-8(9)-*ene*-6 : 17*β*-*diol*-3-*one* (III; R = H, R′ = C≡CH), prepared by oxidising (II; R = H, R′ = C≡CH) (110 mg.) with aluminium *tert.*-butoxide (250 mg.) in acetone–benzene for 44 hours, followed by chromatography in benzene and elution with benzene–ether, formed crystals, m. p. 218—219° (Found : C, 75·9, 76·0; H, 8·6, 8·7. $C_{21}H_{28}O_3,\frac{1}{4}H_2O$ requires C, 75·8; H, 8·6%), from acetone–light petroleum. The 6-*acetyl* derivative, obtained by treatment of the foregoing compound (15 mg.) with acetic anhydride–pyridine for 12 hours at room temperature, formed feathery needles, m. p. 209—211° (Found : C, 74·2; H, 8·4. $C_{23}H_{30}O_4$ requires C, 74·5; H, 8·2%), from ether–light petroleum.

17-*Cyano*-3 : 6-*diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*ol* (II; R = Ac, R′ = CN).—A mixture prepared from (I; R = Ac) (720 mg.) and finely powdered potassium cyanide (4 g.) in absolute ethanol (15 ml.) and glacial acetic acid (4 ml.) was kept overnight at room temperature and then poured into water. Crystallisation of the product from ether–light petroleum gave 17-*cyano*-3 : 6-*diacetoxy*-5-*methyl*-10-*norandrost*-8(9)-*en*-17-*ol* (740 mg.) as prisms, m. p. 148—152° (effervescence) (Found : N, 3·2. $C_{24}H_{33}O_5N$ requires N, 3·4%). The m. p. varied for different preparations.

17-*Cyano*-3 : 6-*diacetoxy*-5-*methyl*-10-*norandrosta*-8(9) : 16-*diene* (IV; R = Ac).—(*a*) The foregoing

cyanohydrin (100 mg.) in dry pyridine (4 ml.) and phosphorus oxychloride (0·3 ml.) was heated in a sealed tube at 155° for 1 hour. The product was purified by chromatography in benzene–light petroleum, yielding 17-*cyano*-3 : 6-*diacetoxy*-5-*methyl*-10-*norandrosta*-8(9) : 16-*diene* (45 mg.), needles, m. p. 165° (Found: N, 3·7. $C_{24}H_{31}O_4N$ requires N, 3·5%), from ether–light petroleum or aqueous methanol. (*b*) The cyanohydrin (70 mg.) in dry pyridine (1 ml.) was heated under reflux (oil-bath) with redistilled phosphorus oxychloride (0·3 ml.) for 15 minutes. The diene (20 mg.), purified as before, had m. p. 166—167°, not depressed on admixture with a sample prepared by method (*a*).

17-*Cyano*-5-*methyl*-10-*norandrosta*-8(9) : 16-*diene*-3 : 6-*diol*, prepared by hydrolysis of the foregoing diacetate with boiling methanolic potash for 15 minutes, formed needles, m. p. 211—213° (Found, after drying at 100°: C, 75·2; H, 8·4. $C_{20}H_{27}O_2N,\frac{1}{4}H_2O$ requires C, 75·3; H, 8·7%), from chloroform–light petroleum.

5α : 6α-*Epoxyallopregnan*-3β-*ol*-20-*one*.—A solution of pregn-5-en-3β-ol-20-one (2 g.) in chloroform (25 ml.) was treated with monoperphthalic acid (2·03 g.; 1·76 mols.) in ether (70 ml.) at room temperature for 2 days. After the mixture had been washed free from acid, the solvent was removed and the residue crystallised from acetone, giving 5α : 6α-epoxy*allo*pregnan-3β-ol-20-one (1·47 g., 70%), m. p. 184—186°. A further quantity (0·56 g., 28%; m. p. >166°) was obtained from the mother-liquors. Recrystallisation raised the m. p. to 190—190·5° (acetate, m. p. 167°) (Ehrenstein and Stevens, *loc. cit.*, give m. p. 180—184° for the α-oxide and m. p. 167—168° for the acetate). Chromatographic fractionation of the residues failed to reveal the presence of any β-oxide.

3β : 6β-*Diacetoxyallopregnan*-5α-*ol*-20-*one*.—The α-oxide (1·16 g.) was acetylated with acetic anhydride and then boiled with glacial acetic acid for 2 hours. The residue, obtained by removal of the solvent *in vacuo*, was crystallised from aqueous methanol, giving 3β : 6β-diacetoxy*allo*pregnan-5α-ol-20-one (1·17 g., 77%), m. p. 212—214°, raised to 217° by further purification.

The *semicarbazone*, prepared by boiling the triolone diacetate (30 mg.) with semicarbazide hydrochloride (50 mg.) and sodium acetate (50 mg.) in alcohol for 2 hours, was dissolved in benzene and purified by chromatography. After elution with benzene–ether and crystallisation from chloroform–light petroleum, it had m. p. 265° (Found: N, 8·4. $C_{26}H_{41}O_6N_3$ requires N, 8·6%).

3β : 5α : 6β-*Triacetoxyallopregnan*-20-*one*.—(*a*) A solution of 3β : 6β-diacetoxy*allo*pregnan-5α-ol-20-one (95 mg.) and toluene-*p*-sulphonic acid (25 mg.) in acetic anhydride (1 ml.) was heated under reflux for 15 minutes. As the product failed to crystallise after chromatography, it was heated with hydroxylamine hydrochloride (100 mg.) and sodium acetate (100 mg.) in alcohol for 2¼ hours. Chromatography in benzene, followed by elution with benzene–ether and crystallisation from ether–light petroleum, gave 3β : 5α : 6β-*triacetoxyallopregnan*-20-*one oxime*, needles, m. p. 248—250° (Found: C, 66·2; H, 8·7. $C_{27}H_{41}O_7N$ requires C, 66·0; H, 8·4%). (*b*) The above oxime, m. p. 253—255°, not depressed on admixture with a sample prepared by method (*a*), was obtained when dry hydrogen chloride was passed for 1 hour through a solution of the triolone in acetic anhydride under reflux.

Pregn-4-*ene*-3β : 6β-*diol*-20-*one* (VI).—A solution of 3β : 6β-diacetoxy*allo*pregnan-5α-ol-20-one (170 mg.) in dry pyridine (6·4 g.) was heated with freshly distilled thionyl chloride (0·5 ml.) for 25 minutes under reflux (oil-bath). The product, after hydrolysis, chromatography in benzene, and elution with benzene–ether, yielded *pregn*-4-*ene*-3β : 6β-*diol*-20-*one* (30 mg.), m. p. 198—200° after crystallisation from ether–light petroleum (Found: C, 73·1; H, 9·7. $C_{21}H_{32}O_3,\frac{3}{4}H_2O$ requires C, 72·9; H, 9·8%).

3 : 6-*Diacetoxy*-5-*methyl*-10-*norpregn*-8(9)-*en*-20-*one* (VII).—A solution of 3β : 6β-diacetoxy*allo*pregnan-5α-ol-20-one (120 mg.) in acetic anhydride (1 ml.) containing potassium hydrogen sulphate (30 mg.) was heated on the water-bath for 1 hour. The product, in benzene–light petroleum (1 : 1; 50 ml.) was passed over alumina, elution being carried out with benzene (25 ml. portions). The fourth fraction thus obtained deposited, after being kept for several days, a small quantity of 3 : 6-*diacetoxy*-5-*methyl*-10-*norpregn*-8(9)-*en*-20-*one* as large prisms which, removed by hand, had m. p. 120° (Found: C, 72·5; H, 9·1. $C_{25}H_{36}O_5$ requires C, 72·1 H, 8·7%). The *semicarbazone* was purified by chromatography in ether. After crystallisation from ether–light petroleum it formed needles, m. p. 213—219° (Found: N, 9·1. $C_{26}H_{39}O_5N_3$ requires N, 8·9%). The m. p. varied with the rate of heating.

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