491. *Steroids and Related Compounds. Part X. The Preparation of Pregna-5 : 17-diene-3β : 21-diol.*

By D. MAGRATH, D. S. MORRIS, V. PETROW, and R. ROYER.

The preparation of pregna-5 : 17-diene-3β : 21-diol (VI; R = H) from dehydro*epi*-androsterone acetate (I) by two novel routes is reported.

Dehydration of methyl 3β-acetoxy-17β-hydroxy-17-*iso*pregn-5-en-21-oate (IV; R = Ac, R′ = Me) with anhydrous formic acid leads to an abnormal product to which the structure of a methyl 3β-acetoxy-17-methylnorpregna-5 : 13(12)-dien-21-oate (IX; R = Ac, R′ = Me) is tentatively proposed.

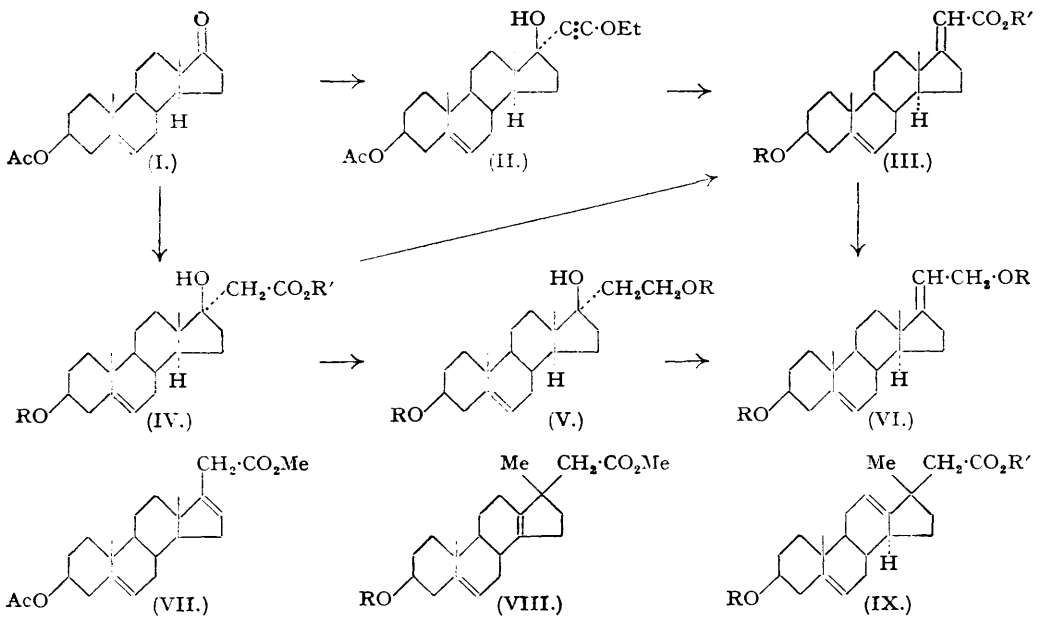
THE conversion of dehydro*epi*androsterone acetate (I) into pregna-5 : 17(20)-diene-3β : 21-diol (VI; R = H) has hitherto been achieved by reaction with acetylene and reduction to give 17α-vinylandrost-5-ene-3β : 17β-diol (Ruzicka and Hofmann, *Helv. Chim. Acta*, 1937, **20**, 1280); Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, 1938, **71**, 1024), followed by conversion into (VI; R = H) by treatment with (*a*) trichloroacetic acid in acetic anhydride (Miescher and Scholz, *Helv. Chim. Acta*, 1939, **22**, 120) or (*b*) phosphorus tribromide and then potassium acetate (Ruzicka and Müller, *ibid.*, p. 416). Both routes prove satisfactory with small quantities of

materials, but the experimental conditions required for optimum yields are rather critical and thus limit the value of the methods for large-scale working. As substantial quantities of (VI) were required for studies of methods of building up the ketol side chain present in the glucocorticoids (*e.g.*, Cortisone), model experiments were instituted on alternative approaches.

Condensation of (I) with ethoxyethynylmagnesium bromide to give 3β-acetoxy-17α-ethoxyethynyl-17-*iso*androst-5-en-17β-ol (II) has been described by Arens and van Dorp (Dutch P. 63,015/1949) and independently by Heusser, Eichenberger, and Plattner (*Helv. Chim. Acta*, 1950, **33**, 370), their results being identical with those obtained in this laboratory. In analogy with observations reported by Heilbron, Jones, Julian, and Weedon (*J.*, 1949, 1823) in the vitamin A field, we now find that (II) undergoes ready conversion into ethyl 3β-acetoxy*iso*pregna-5 : 17-dien-21-oate (III; R = Ac; R′ = Et) when heated with ethanolic sulphuric acid for two minutes on the water-bath. Alkaline hydrolysis of this product furnished 3β-hydroxypregna-5 : 17-dien-21-oic acid (III; R = R′ = H), identical with the acid described by Plattner and Schreck (*Helv. Chim. Acta*, 1939, **22**, 1178). Reduction of the acid, or of its ethyl ester, with lithium aluminium hydride (cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197) led to the formation of the required diol (VI; R = H).

Ethyl 3β-acetoxy-17β-hydroxy-17-*iso*pregn-5-en-21-oate (IV; R = Ac, R′ = Et) formed the starting point of a second novel approach to pregna-5 : 17-diene-3β : 21-diol (VI; R = R′ = H). The latter could clearly be obtained from (IV) by reduction and dehydration, which could presumably be carried out in either order. In practice, however, reduction followed by dehydration was preferable.

Preparation of compounds of type (IV) has been described by Reichstein, Müller, Meystre, and Sutter (*Helv. Chim. Acta*, 1939, **22**, 741) who condensed (I) with ethyl bromoacetate under Reformatsky conditions, but failed to isolate (IV; R = Ac, R′ = Et). Alkaline hydrolysis of the product furnished the crystalline acid (IV; R = R′ = H), converted into (IV; R = Ac, R′ = Me), from which, by Bouveault–Blanc reduction, they obtained (V; R = H) in low overall yield. We now find, in contrast, that direct crystallisation of the crude Reformatsky product readily yields the hitherto undescribed ethyl ester (IV; R = Ac, R′ = Et), which is converted into 17-*iso*pregn-5-ene-3β : 17β : 21-triol (V; R = H) by lithium aluminium hydride in yields exceeding 80%. Diacetylation of the triol, followed by treatment with thionyl chloride in pyridine (cf. Darzens, *Compt. rend.*, 1911, **152**, 601), resulted in the desired exocyclic dehydration with formation of the required 3β : 21-diacetoxypregna-5 : 17-diene (VI; R = R′ = Ac).



Dehydration of (IV) to (III), followed by reduction with lithium aluminium hydride, proved a less successful approach to (VI) owing to unexpected difficulties in achieving dehydration of

the 17β-hydroxyl grouping present in (IV). Methods such as reaction with thionyl chloride or phosphorus pentachloride in benzene, or distillation over anhydrous copper sulphate under reduced pressure, reported by Reichstein *et al.* (*loc. cit.*), proved incapable of consistent repetition. Similar results were obtained on employing the distillation procedure of Plattner and Schreck (*loc. cit.*), although in this case a 50% yield of (III; R = Ac, R′ = Me) was obtained in one instance. In general, however, the distillation products contained substantial quantities of (I).

Attempts to enforce dehydration of (IV; R = Ac, R′ = Me) with anhydrous formic acid under reflux were accompanied by marked colour changes of the solution which rapidly became an intense violet-blue. Termination of the experiment at this stage led to a new unsaturated acetoxy-ester (*A*) isomeric with methyl 3β-acetoxypregna-5 : 17-dien-21-oate (VI; R = Ac, R′ = Me). Its formulation as the Δ^{16}-dehydration product (VII) was rendered improbable by catalytic hydrogenation studies when two molecules of hydrogen were absorbed to give a tetrahydro-derivative not identical with methyl 3β-acetoxy*allo*pregnan-21-oate (Plattner and Schreck, *loc. cit.*). This observation, together with the formation of the intense purple-blue coloration during its formation (see above), led to the conclusion that dehydration had been accompanied by structural changes of a more profound character. Accordingly we propose the constitution of a methyl 3β-acetoxy-17-methylnorpregna-5 : 13(12)-dien-21-oate (IX; R = Ac, R′ = Me) for compound (*A*) on the basis of the following evidence : (*a*) 17α-hydroxyandrostane undergoes retropinacolinic rearrangement to ψ-androstene when heated with formic acid, the boiling solution likewise becoming deep violet (Miescher and Kägi, *Helv. Chim. Acta*, 1939, **22**, 761); (*b*) both ψ-androstene and compound (*A*) give intense blue-violet colours on treatment of their solutions in sulphuric acid–acetic acid with bromine–acetic acid (Miescher and Kägi, *loc. cit.*; see also Kägi and Miescher, *ibid.*, p. 683); and (*c*) the formulation of ψ-androstene as a retropinacolinic dehydration product is supported by chemical evidence (Miescher and Kägi, *loc. cit.*). A $\Delta^{13:17}$-structure is, of course, not possible in our case and, as compound (*A*) fails to give a blue nitrosochloride in the Thiele test (*Ber.*, 1894, **27**, 454) in contrast to ψ-androstene, we prefer to assign it structure (IX) rather than the isomeric structure (VIII).

Experimental.

M. p.s are uncorr. Microanalyses are by Drs. Weiler and Strauss, Oxford. Optical rotations were measured in chloroform solution in a 2-dm. tube unless stated otherwise.

Ethyl 3β-*Acetoxypregna*-5 : 17-*dien*-21-*oate* (III; R = Ac, R′ = Et).—3β-Acetoxy-17α-ethoxyethynylandrost-5-en-17β-ol (400 mg.; m. p. 140—141°) dissolved in ethanol (8 ml.) was treated with 3N-sulphuric acid (2 ml.), and the mixture heated on the steam-bath for 2 minutes. After the mixture had been poured into water the precipitated solids were collected, dried over potassium hydroxide, and crystallised from aqueous ethanol, giving *ethyl* 3β-*acetoxypregna*-5 : 17-*dien*-21-*oate* (55%), leaflets, m. p. 117°, $[\alpha]_D^{23}$ −69·8° (*c*, 0·394) (Found : C, 74·5; H, 8·8. $C_{25}H_{36}O_4$ requires C, 75·0; H, 9·1%).

3β-*Hydroxypregna*-5 : 17-*dien*-21-*oic Acid* (III; R = R′ = H).—The foregoing ester (500 mg.) was heated under reflux with methanolic sodium hydroxide (10 ml. of 2N.) for 1½ hours, after which the solution was poured into water (50 ml.). The mixture was boiled for 10 minutes and then acidified with hydrochloric acid until acid to Congo-red. The precipitated acid was collected, purified through the sodium salt, and finally crystallised from methanol. 3β-Hydroxypregna-5 : 17-dien-21-oic acid formed small crystals (37%), m. p. 245° (Found : C, 76·0; H, 9·1. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·2%). Plattner and Schreck (*loc. cit.*) give m. p. 249—250° (corr.); Marker *et al.* (*J. Amer. Chem. Soc.*, 1942, **64**, 1276) give m. p. 252—253°.

Pregna-5 : 17-*diene*-3β : 21-*diol* (VI; R = H).—The ester (III; R = Ac, R′ = Et) (170 mg.) in dry ether (10 ml.) was added to a solution of lithium aluminium hydride in dry ether (50 ml. of 0·2%), and the mixture heated under reflux for 15 minutes. Water was then carefully added followed by 3N-sulphuric acid, until the solution was acid to Congo-red. The ethereal layer was washed until neutral and dried ($MgSO_4$), and the ether removed. Crystallisation of the residue from methanol gave pregna-5 : 17-diene-3β : 21-diol (93%), as colourless leaflets, m. p. 191—192°, $[\alpha]_D^{19\cdot5}$ −57·6° (*c*, 0·544 in ethanol) (Found : C, 80·1; H, 10·1. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·2%). Miescher and Scholz (*loc. cit.*) give m. p. 198°; Ruzicka and Müller (*loc. cit.*) give m. p. 198—199° (corr.), $[\alpha]_D$ −59·5° ±1·5° (in ethanol).

Ethyl 3β-*Acetoxy*-17β-*hydroxy*-17-iso*pregn*-5-*en*-21-*oate* (IV; R = Ac, R′ = Et).—Ethyl bromoacetate (10 g.) was added as quickly as reaction permitted to a stirred mixture of dehydro*epi*androsterone acetate (20 g.), dry benzene (168 ml.), activated zinc (23·5 g.), and a crystal of iodine. The mixture was then heated on a steam-bath for 1½ hours, after which it was cooled in ice and the magnesium complex decomposed by the addition of 2N-hydrochloric acid (200 ml.). The product, extracted with ether ("crude Reformatsky product," see below), was taken up in methanol. *Ethyl* 3β-*acetoxy*-17β-*hydroxy*-17-iso*pregn*-5-*en*-21-*oate* separated slowly and, after crystallisation from methanol, formed needles, m. p. 112—113°, $[\alpha]_D^{22}$ −74·0° (*c*, 0·905) (Found : C, 71·1; H, 8·9. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%).

17-iso*Pregn*-5-*ene*-3β : 17β : 21-*triol* (V; R = H).—The foregoing ester (500 mg.) in dry ether (20 ml.) was added slowly with shaking to a solution of lithium aluminium hydride in ether (50 ml. of 0·6%). The

mixture was heated under reflux for 15 minutes, cooled, decomposed with ice, and shaken vigorously with 5N-hydrochloric acid (20 ml.). The white solid which separated was collected and united with the crystals which separated on concentration of the ethereal layer. Purification from ethanol yielded 17-*iso*pregn-5-ene-3β : 17β : 21-triol (82%) as glittering plates, m. p. 235—239° (Found : C, 75·0; H, 10·25. Calc. for $C_{21}H_{34}O_3$: C, 75·4; H, 10·25%). Similar results were obtained on using the " crude Reformatsky product." Reichstein *et al.* (*loc. cit.*) give m. p. 243—245° (corr.).

Acetylation of the triol gave the diacetate, m. p. 156—157°, $[\alpha]_D^{24}$ −59·8° (*c*, 0·413 in acetone). Reichstein *et al.* (*loc. cit.*) give m. p. 159—160° (corr.), $[\alpha]_D^{20}$ −65·3° ± 1·5° (in acetone).

3β : 21-*Diacetoxypregna*-5 : 17-*diene* (VI; R = Ac).—The foregoing diacetate (2·0 g.) in dry pyridine (10 ml.) was treated at 0° with thionyl chloride (0·44 ml.) added dropwise with shaking. The mixture was then poured into ice-water (50 ml.), and the precipitated gummy solids were thoroughly ground. After 2 hours the product was collected, dried over potassium hydroxide, and crystallised from ethanol, giving 3β : 21-diacetoxypregna-5 : 17-diene, colourless crystals, m. p. 135°, $[\alpha]_D^{21}$ −47·1° (*c*, 0·530). Miescher and Scholz (*loc. cit.*) give m. p. 136·5—137°. Ruzicka and Müller (*loc. cit.*) give m. p. 135—136° (corr.). Hydrolysis gave pregna-5 : 17-diene-3β : 21-diol, m. p. 194—196°, $[\alpha]_D^{23}$ −58·2° (*c*, 0·860 in ethanol) (Found : C, 79·1; H, 10·2. Calc. for $C_{21}H_{32}O_2$: C, 79·7; H, 10·2%), not depressed on admixture with the product prepared by the ethoxyacetylene route.

Preparation of Pregna-5 : 17-*diene*-3β : 21-*diol from Methyl* 3β-*Acetoxy*-17β-*hydroxy*-17-iso*pregn*-5-*en*-21-*oate*.—Hydrolysis of the " crude Reformatsky product " (10 g.) gave 3β : 17β-dihydroxy-17-*iso*pregn-5-en-21-oic acid (7·6 g.; m. p. 235°), converted into (IV; R = H, R′ = Me) (83%), m. p. 158°, by the method of Plattner and Schreck (*loc. cit.*). Dehydration of the ester by vacuum-distillation as described by Plattner and Schreck (*loc. cit.*) gave (III; R = Ac, R′ = Me) in poor yield, reduced to (VI; R = H) (91%), m. p. 194—198°, $[\alpha]_D^{22}$ −60·1° (*c*, 0·616 in ethanol) by lithium aluminium hydride. Dehydration by thionyl chloride or phosphoric oxide in benzene (Reichstein *et al.*, *loc. cit.*) likewise gave (III; R = Ac, R′ = Me) in poor yield, reduced to (VI; R = H).

Methyl 3β-*Acetoxy*-17-*methylnorpregna*-5 : 13(12)-*dien*-21-*oate* (IX; R = Ac, R′ = Me).—The ester (IV; R = Ac, R′ = Me) (1·0 g.) in formic acid (5 ml. of 98%) was heated on the steam-bath for 5 minutes, the colour changing from yellow to violet-blue. The mixture was poured into water, and the product extracted with ether and crystallised from ethanol. *Methyl* 3β-*acetoxy*-17-*methylnorpregna*-5 : 13(12)-*dien*-21-*oate* formed colourless leaflets (50%), m. p. 101° (Found : C, 74·2; H, 9·0. $C_{24}H_{34}O_4$ requires C, 74·6, H, 8·8%). Hydrolysis furnished the *hydroxy-acid* (IX; R = R′ = H) which, purified from acetone–light petroleum, had m. p. 163—165° (Found : C, 76·2, H, 9·0. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·2%).

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