850. *Steroids and Related Natural Products. Part XVIII.*[1] *Synthesis of* 14α-*Methylprogesterone.*

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Isocholesterol (crude lanosterol) has been degraded to 14α-methylprogesterone, by a nineteen-step reaction sequence, as part of a study concerned with the evaluation of the biological importance of 14α-methyl-steroids.

ENZYMIC degradation of cholesterol to progesterone is now believed to proceed *in vivo* by way of 20β-hydroxycholesterol and pregnenolone. Progesterone, in turn, is an important precursor of the corticosteroids, androgens, and œstrogens.[2] Thus, a defect in the biosynthesis of cholesterol from lanosterol (I) might subsequently lead to biologically unfavourable hormones.[1] For this reason, 14α-methyl-androstane and -pregnane derivatives have been studied. Initially, a twenty-step reaction sequence for conversion of isocholesterol (crude lanosterol) into 14α-methyltestosterone was developed.[3] We have now degraded lanosterol to 14α-methylprogesterone.

Isocholesterol was transformed *via* methyl 3β-acetoxy-4,4,14α-trimethyl-7,11-dioxo-5α-cholanate (II) into 3β-hydroxy-4,4,14α-trimethyl-5α-pregnan-2-one (III) as previously described.[1] The diketone (II) was also a key intermediate in the synthesis of 14α-methyl-11-oxoprogesterone described by Heusser, Jeger, Voser, and Ruzicka.[4] The alcohol (III) was dehydrated and rearranged to the olefin (IV) (52%) by a phosphorous pentachloride[5] procedure. The 20-ketone (IV) was next reduced to the alcohol (V) by sodium borohydride. Reduction was considered necessary at this stage in order to preserve the pregnane side-chain during a subsequent Grignard reaction planned for ring A. Since reductions of 20-oxo-steroids with metal hydrides generally afford 20β-alcohols,[6] the product obtained in highest yield (66%) was tentatively assigned the 20*R*-configuration (cf. V).[7] Although a thin-layer chromatogram of the oily alcohol indicated the presence of only one component, ozonolysis led to a mixture of ketones. The expected 3-oxo-A-nor-steroid (VI) (27%) was separated from another oily ketonic ($\nu_{max.}$ 1720 cm.$^{-1}$) component,[5b] isolation of which suggested that reduction of the 20-ketone (IV) was

[1] Part XVII, Pettit, Hofer, Bowyer, Kasturi, Bansal, Kadunce, and Green, *Tetrahedron*, 1963, **19**, 1143.

[2] Wettstein, *Experientia*, 1961, **17**, 329; Pincus, "Proc. of the Fourth Internat. Congress of Biochemistry" ("Biochemistry of Steroids"), Vol. IV, ed. Mosettig, Pergamon Press, New York, 1959, p. 64.

[3] Pettit and Hofer, *Experientia*, 1963, **19**, 67.

[4] Heusser, Jeger, Voser, and Ruzicka, *Helv. Chim. Acta*, 1953, **36**, 299.

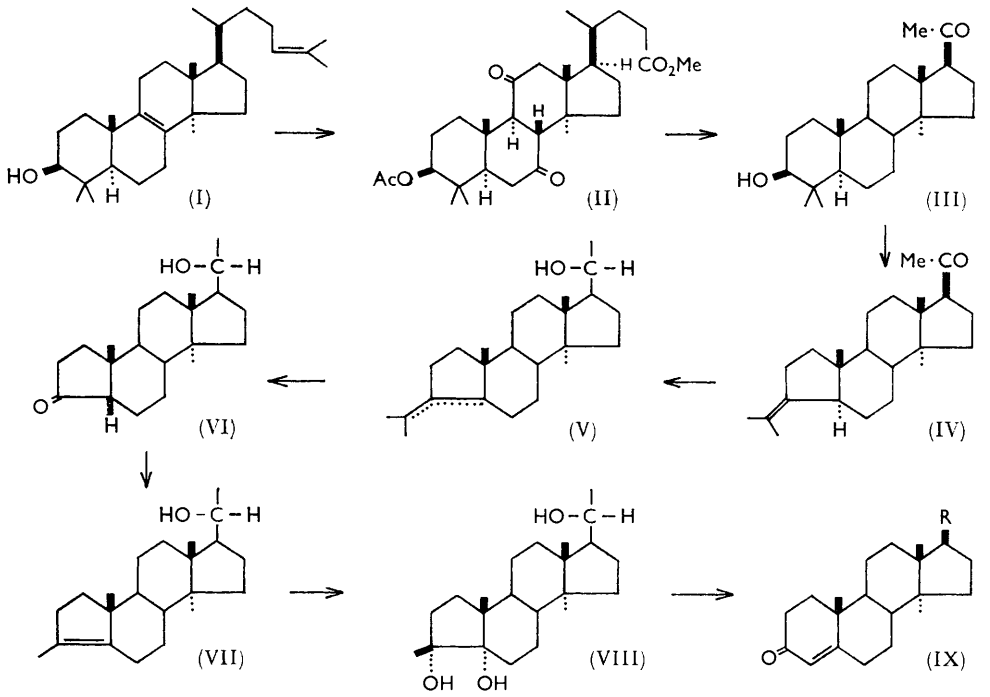
[5] (*a*) Biellman and Ourisson, *Bull. Soc. chim. France*, 1962, 311; (*b*) Pettit, Green, and Bowyer, *J. Org. Chem.*, 1961, **26**, 2879.

[6] Rakhit and Engel, *Canad. J. Chem.*, 1962, **40**, 2163.

[7] Pettit, *Experientia*, 1963, **19**, 124; Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

accompanied by partial isomerization of the A-ring olefin from an exocyclic to an endocyclic position. This observation, however, was not further substantiated.

Treatment [8] of the 3-ketone (VI) with methylmagnesium iodide, followed by acid-catalyzed dehydration, led to olefin (VII) (83%). The endocyclic olefin (VII) was oxidized



to the glycol (VIII) (70%) by an osmium tetroxide–hydrogen sulphide hydroxylation procedure.[5b] The crude diketone arising from lead tetra-acetate cleavage of the glycol (VIII) was next allowed to undergo intramolecular condensation [9] in methanol containing 3% of sodium methoxide. Selective oxidation of the condensation product, 20*R*-hydroxypregn-4-en-3-one (IX), employing an 8N-chromium trioxide reagent [10] gave 14α-methylprogesterone (X).*

Experimental

Activated alumina refers to Aluminum Co. of America's grade F-20 (80—200 mesh). Thin-layer chromatograms were prepared or silica gel G (E. Merck, A.G.) and developed with concentrated sulphuric acid.

A Kofler apparatus was used to observe the melting points of analytical samples. The optical rotation (chloroform solution) measurements by the microanalytical laboratory of Dr. C. Janssen, Beerse, Belgium. Ultraviolet (ethanol solution) and infrared spectral determinations were performed by Dr. R. A. Hill of this laboratory.

3-*Isopropylidene*-14α-*methyl*-A-*nor*-5α-*pregnan*-20-*one* (IV).—Phosphorus pentachloride (5·0 g.) was added to a cold (ice-bath) suspension of 3β-hydroxy-4,4,14α-trimethyl-5α-pregnan-20-one [2] (III) (4·3 g.) in benzene (1·5 l.)–toluene (500 ml.); after 15 min., dissolution was complete.

* Recently, Fried and his co-workers [11] have degraded eburicoic acid to 14α-methyl-A-nor-pregn-5-ene-3,11,20-trione and 3β,17β-dihydroxy-4,4,14α-trimethyl-5α-androstan-11-one.

[8] Crabbé, Ourisson, and Takahashi, *Tetrahedron*, 1958, **3**, 279.
[9] Wenkert, Youssefyeh, and Lewis, *J. Amer. Chem. Soc.*, 1960, **82**, 4675.
[10] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.
[11] Fried and Sabo, *J. Amer. Chem. Soc.*, 1962, **84**, 4356; Krakower, Brown, and Fried, *J. Org. Chem.*, 1962, **27**, 4710.

Stirring and cooling were continued for 45 min. before addition of 2N-sodium carbonate (200 ml.). The organic phase was washed with water, dried over activated alumina, and concentrated *in vacuo*, and the residue (in hexane) chromatographed on activated alumina. After crystallization from ether–methanol, the fraction (3·25 g.) eluted with 4 : 1 hexane–benzene, weighed 1·37 g. and had m. p. 133—135°. Concentration of the mother-liquors gave a product (0·74 g.) of m. p. 100—103°. The lower-melting substance appeared to be a mixture of A-ring exo- and endo-cyclic olefins and was not further investigated. The higher-melting fraction crystallized from ether–methanol as colourless needles, m. p. 139—141°, $[\alpha]_D^{20}$ +88·6° (*c* 0·89), $\nu_{max.}$ (KBr) 1700 cm.$^{-1}$ (Found: C, 84·1, H, 11·15. $C_{24}H_{38}O$ requires C, 84·15; H, 11·2%).

20R-*Hydroxy*-14α-*methyl*-A-*nor*-5β-*pregnan*-3-*one* (VI). A solution of sodium borohydride (2·0 g.) in methanol (20 ml.)–isopropyl alcohol (80 ml.) was added to the 20-ketone (IV) (1·0 g.) in isopropyl alcohol (80 ml.). After 18 hr. at room temperature, the mixture was diluted with water, concentrated *in vacuo*, and the aqueous residue extracted with chloroform. Evaporation of the chloroform extract gave a crude material (1·0 g.). A hexane–benzene (1 : 1) solution of the combined product (4·4 g.) from four similar reductions was chromatographed on activated alumina. Elution with the same solvent gave a viscous oil (2·9 g., 66%); a thin-layer chromatogram (9 : 1 hexane–ethyl acetate mobile phase) showed only one component. A similar chromatogram of the fraction (0·67 g.) eluted with benzene indicated a mixture of epimeric pregnan-20-ols.

A solution of the 1 : 1 hexane–benzene fraction (2·9 g.) in chloroform (300 ml.) was cooled to −50° and treated with a stream of ozone in oxygen until oxidation appeared complete (blue solution for 30 min.). The mixture was then diluted with acetic acid (100 ml.) and treated (0·5 hr.) with zinc dust (3 g.). After filtration, the solution was washed with water and dried (Na_2SO_4). Following removal of solvent, a solution of the residue in 4 : 1 hexane–benzene was chromatographed on activated alumina. Elution with benzene, and re-chromatography of the mother-liquors, gave 20R-*hydroxy*-14α-*methyl*-A-*nor*-5β-*pregnan*-3-*one* (total 1·21 g.), needles, m. p. 201—204° (from acetone–hexane), $[\alpha]_D^{20}$ +149·7° (*c* 0·69), $\nu_{max.}$ (KBr) 3450 and 1726 cm.$^{-1}$ (Found: C, 79·15; H, 10·65; O, 9·95. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·75; O, 10·05%).

Continued elution of the above chromatogram with benzene–chloroform (9 : 1) gave a viscous oil (0·67 g.) whose infrared spectrum exhibited carbonyl absorption at 1720 cm.$^{-1}$, attributable to the diketone which would arise from an endocyclic isomer of the olefin (V).

3β,14α-*Dimethyl*-A-*norpregnane*-3α,5α,20R-triol (VIII).—A tetrahydrofuran (65 ml.) solution of the 3-ketone (VI) (0·70 g.) was added to a Grignard reagent prepared from methyl iodide (10 ml.), magnesium (1·3 g.), and ether (50 ml.). The mixture was heated under reflux for 12 hr., diluted with aqueous ammonium chloride, and concentrated *in vacuo*, and the aqueous residue was extracted with chloroform. The combined extracts were washed with 0·1N-sodium thiosulphate and water, and evaporated. A solution of the residue in methanol (30 ml.) containing concentrated hydrochloric acid (2 ml.) was heated under reflux for 1 hr. The mixture was neutralized with 2N-sodium carbonate, concentrated, and extracted with chloroform. After removal of solvent from the combined extracts, a 1 : 1 hexane–benzene solution of the residue was chromatographed on activated alumina (24 g.). The oily fraction (0·58 g. total) eluted by 1 : 1 and 1 : 3 hexane–benzene exhibited only one spot on a thin-layer chromatogram (17 : 3 hexane–ethyl acetate mobile phase). A solution composed of the olefin (VII) (0·58 g.), osmium tetroxide (1·0 g.), and benzene (25 ml.) was maintained at room temperature for 50 hr. After dilution with methanol (25 ml.) a stream of hydrogen sulphide was passed (20 min.) into the solution. Chloroform (50 ml.) was added and the solution was filtered. The filtrate was passed through activated alumina and evaporated to dryness. Crystallization of the residue (0·53 g.) from chloroform–acetone gave 3β,14α-*dimethyl*-A-*norpregnane*-3α,5α,20R-*triol* (0·32 g.), m. p. 212—215°. A second crop (0·10 g.) (70% total yield) had m. p. 202—204°. In 4 : 1 hexane–ethyl acetate, both specimens exhibited the same mobility on a thin-layer chromatogram. The higher-melting fraction yielded leaflets, m. p. 212—215° (from chloroform–acetone), $[\alpha]_D^{20}$ +26·6 (*c* 0·81), $\nu_{max.}$ (KBr) 3400, 3350, and 3260 cm.$^{-1}$ (Found: C, 75·55; H, 10·75; O, 13·35. $C_{22}H_{38}O_3$ requires C, 75·4; H, 10·95; O, 13·7%).

Since the major hydroxylation product should arise from attack by osmium tetroxide at the less hindered α-side of the olefin (VII), the substance of m. p. 212—215° has been assigned an α-*cis*-glycol structure.

20R-*Hydroxy*-14α-*methylpregn*-4-*en*-3-*one* [IX; R = CH(OH)·Me].—To a solution of the *cis*-glycol (VIII) (0·38 g.) in chloroform (30 ml.) was added lead tetra-acetate (0·60 g.) in acetic

acid (30 ml.). After 45 min. at room temperature, several drops of ethylene glycol were added and the reaction was allowed to continue for 15 min. The solution was then washed with water and concentrated to dryness *in vacuo*. A solution of the residue (0·38 g.) in methanol (40 ml.) containing 3% of sodium methoxide was heated (steam-bath) until the mixture became pale yellow (2—3 min.). After 1 hr. at room temperature, the mixture was diluted with water and concentrated *in vacuo*, and the aqueous residue extracted with chloroform. Evaporation of solvent, and crystallization of the product from ether–hexane, yielded the *ketone* [IX; R = CH(OH)·Me] (0·28 g., 78%), m. p. 161—163°, $[\alpha]_D^{20}$ +224·7° (*c* 0·16), $\lambda_{max.}$ 241 mμ (log ε 4·23), $\nu_{max.}$ (KBr) 3450, 1660, and 1615 cm.$^{-1}$ (Found: C, 80·3; H, 10·15; O, 9·55. $C_{22}H_{34}O_2$ requires C, 79·95; H, 10·35; O, 9·7%).

14α-*Methylpregn*-4-*ene*-3,20-*dione* (IX; R = COMe).—An 8N-chromium trioxide reagent (0·80 ml.) [10] was added to a cool (ice-bath) solution of the alcohol [IX; R = CH(OH)·Me] (0·20 g.) in acetone (15 ml.). After 5 min. the mixture was diluted with aqueous sodium acetate (15 ml.) and concentrated (*in vacuo*) to *ca.* 15 ml. The crude ketone (X; R = COMe) (0·20 g.), extracted with chloroform and crystallized from acetone–hexane, gave two crops of crystals (total 0·18 g., 90·5%). Recrystallization from the same solvent yielded elongated prisms, m. p. 200—205° (sublimation at 196°), $[\alpha]_D^{20}$ +215·9° (*c* 0·81), $\lambda_{max.}$ 241 and 302 mμ (log ε 4·22 and 0·95), $\nu_{max.}$ 1700, 1670, and 1620 cm.$^{-1}$ (Found: C, 80·45; H, 9·7; O, 9·6. $C_{22}H_{32}O_2$ requires C, 80·45; H, 9·85; O, 9·75%).

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