24. *Compounds Related to the Steroid Hormones. Part XIII.*[1] *Preparation of 6α- and 6β-Methylcortisone Acetates.*

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6α- and 6β-Methylcortisone acetates have been prepared from cortisone acetate. Attack by Grignard reagent on the 5α,6α-epoxide has been used to introduce the 6-methyl group, the 3-keto-group being protected by ketalisation and the 20-keto-group by ketalisation or methoximation. Selective hydrolysis of the 3-ketal group and subsequent elimination of the 5α-hydroxyl group proceeded without epimerisation to give 6β-methylcortisone-20-ketal or -20-methoxyimine. Acid hydrolysis of the 20-ketal or 20-methoxyimine (VII) was accompanied by epimerisation of the 6-methyl group, resulting in formation of 6α-methylcortisone.

Removal of both ketal groups, with subsequent acetylation of the 21-hydroxy-group and dehydration with thionyl chloride in pyridine, gave 6β-methylcortisone acetate.

Cortisone acetate (I; R = Ac, R′ = O) has been converted into 6α- and 6β-methylcortisone acetates (VIII; R = Ac, R′ = O) and (VII; R = Ac, R′ = O). Attack by Grignard reagents on a 5α,6α-epoxy-3-ketal (III; R = H) has been utilised, as described earlier for the 11β-hydroxy-series,[2-4] to introduce the 6-methyl group, protection of the side-chain being achieved through formation of a 20-ketal derivative (II; R = H, R′ = O·[CH_2]$_2$·O) or a 20-methoxyimine (II; R = Ac, R′ = N·OMe).

Conversion of cortisone (I; R = H, R′ = O) into its 3,20-bisketal derivative (II; R = H, R′ = O·[CH_2]$_2$·O) proved inefficient, yields greater than 40% being difficult to sustain.[5] As in the bisketalisation of 4,5α-dihydrocortisone, formation of non-hydroxylic

[1] Part XII, preceding Paper.
[2] Spero, Thompson, Magerlein, Hanze, Murray, Sebek, and Hogg, *J. Amer. Chem. Soc.*, 1956, **78**, 6213.
[3] Bernstein and Littell, *J. Amer. Chem. Soc.*, 1960, **82**, 1235.
[4] Cooley, Ellis, Kirk, and Petrow, *J.*, 1957, 4112.
[5] Antonucci, Bernstein, Heller, Lenhard, Littell, and Williams, *J. Org. Chem.*, 1953, **18**, 70.

compounds may reduce the efficiency of 20-ketalisation,[6] but attack on the 11-oxo-group is also possible.[7]

Epoxidation of the ketal (II; R = H, R′ = O·[CH_2]$_2$·O) in ether–chloroform solution with monoperphthalic acid gave a mixture containing 5α,6α-epoxycortisone 3,20-bisketal (III; R = H, R′ = O·[CH_2]$_2$·O) and its 5β,6β-isomer (IV; R = H, R′ = O·[CH_2]$_2$·O). Crystallisation gave the α-epoxide in 60% yield. Differences in rotations and R_F values served to distinguish the two epoxides; the α-isomer, as expected, is the more lævorotatory and the more polar on paper chromatograms.[2,8]

The 5α,6α-epoxide (III; R = H, R′ = O·[CH_2]$_2$·O) reacted smoothly but slowly with methyl Grignard reagents in ether–tetrahydrofuran [9] to give the 5α-hydroxy-6β-methyl steroid (V; R = H, R′ = O·[CH_2]$_2$·O).[3] When benzene was used as solvent, yields of this product were low and variable. Recovery of the α-epoxide (III; R = H, R′ = O·[CH_2]$_2$·O) after treatment with magnesium bromide etherate in benzene suggested that the inefficiency with this solvent did not result from rearrangement of the epoxide [9] by this component of the Grignard reagent.[10]

The R_F value of the triol (V; R = H, R′ = O·[CH_2]$_2$·O) is much higher than expected for a steroid containing three hydroxyl groups,[11] and it provides an example of the Henbest–Kupchan 1,3-effect,[12] since hydrogen bonding occurs between the 5α-hydroxyl group and the pseudo-axial oxygen atom of the 3-ketal group. The 17- and 21-hydroxyl groups must participate in bonding with the 20-ketal group, but the paper-chromatographic behaviour of compounds (VI; R = H, R′ = O·[CH_2]$_2$O·) and (VI; R = H, R′ = O) indicates that this is of secondary importance.[13]

Selective hydrolysis with 2N-hydrochloric acid in acetone at room temperature [14] of the 3-ketal group in the bisketal (V; R = H, R′ = O·[CH_2]$_2$·O) gave the 5α-hydroxy-3-ketone (VI; R = H, R′ = O·[CH_2]$_2$·O), but for efficient regeneration of both the 3- and 20-ketones, treatment with 8½% sulphuric acid in refluxing acetone for 1 hour was required.[5,14] Shorter reflux periods [4] resulted in mixtures of 5α-hydroxy-6β-methyldihydrocortisone (VI; R = H, R′ = O) and its 20-ketal, which were not readily purified by crystallization. Acetylation of the mixtures gave the corresponding acetates (VI; R = Ac, R′ = O·[CH_2]$_2$·O) and (VI; R = Ac, R′ = O), from which removal of the less dextrorotatory ketal (VI; R = Ac, R′ = O·[CH_2]$_2$·O) proved equally difficult.

The resistance of the 20-ketal group to hydrolysis may account for the difference in the rotations given for two specimens of 6α-methylhydrocortisone.[2,4] The elemental analysis and lower dextrorotation of one specimen would befit the corresponding 20-ketal, but decisive tests cannot be made, because none of this specimen is left.[15]

Thionyl chloride in pyridine at −30° converted the 5α-hydroxy-steroid (VI; R = Ac, R′ = O) into 6β-methylcortisone acetate (VII; R = Ac, R′ = O), and the 20-ketal (VI; R = H, R′ = O·[CH_2]$_2$·O) was converted by 0·01N-sodium hydroxide into the 20-ketal of 6β-methylcortisone (VII; R = H, R′ = O·[CH_2]$_2$·O). The expected epimerisation of the 6-methyl group did not occur, for the product (VII; R = H, R′ = O·[CH_2]$_2$·O) had $\lambda_{max.}$

[6] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529; Bernstein, Heller, and Allen, *J. Org. Chem.*, 1961, **26**, 1333; Caspi, Wittstruck, and Grover, *ibid.*, 1963, **28**, 763.

[7] Magerlein and Levin, *J. Amer. Chem. Soc.*, 1955, **77**, 1904.

[8] Babcock, Gutsell, Herr, Hogg, Stucki, Barnes, and Dulin, *J. Amer. Chem. Soc.*, 1958, **80**, 2904; Bowers, Ibañez, and Ringold, *Tetrahedron*, 1959, **7**, 138.

[9] Gaylord and Becker, *Chem. Rev.*, 1951, **49**, 413; Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 5362; Kharasch and Reinmuth, "Grignard Reactions of Non-Metallic Substances," Constable, London, 1954, p. 961.

[10] Schlenk and Schlenk, *Ber.*, 1929, **62**, 920; Schlenk, *ibid.*, 1931, **64**, 735; Strohmeir and Seifert, *Chem. Ber.*, 1961, **94**, 2356; Dessy and Handler, *J. Amer. Chem. Soc.*, 1958, **80**, 5824; *J. Org. Chem.*, 1960, **25**, 2260.

[11] Kabasakalian and Basch, *Analyt. Chem.*, 1960, **32**, 458.

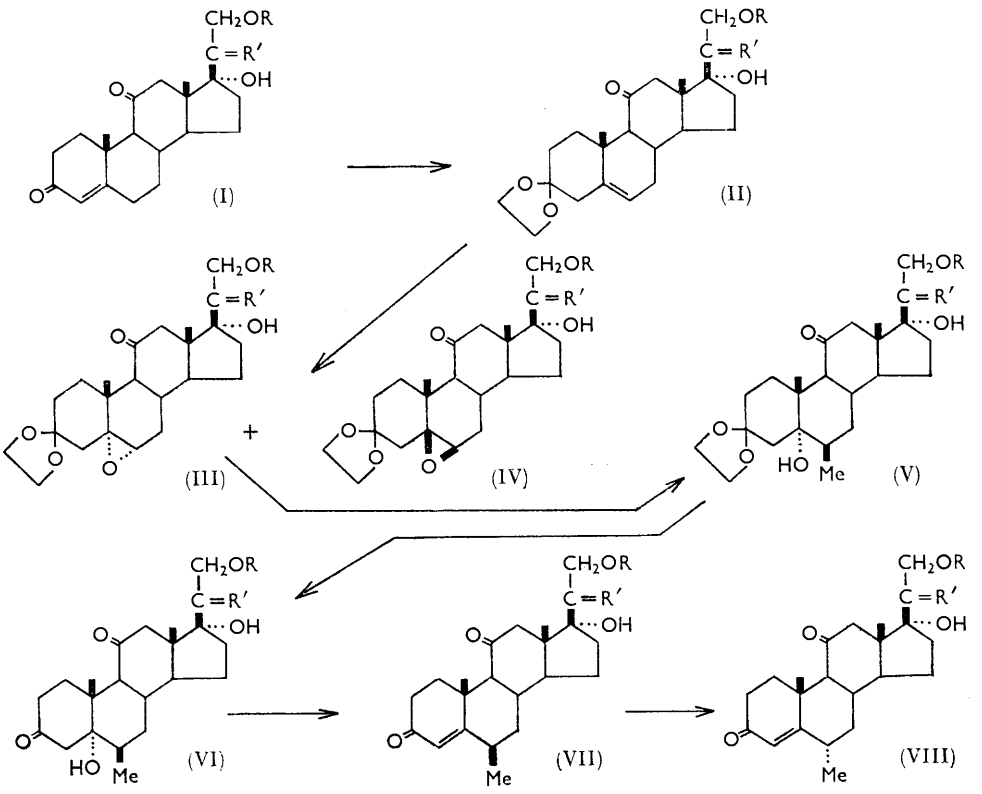
[12] West, Korst, and Johnson, *J. Org. Chem.*, 1960, **25**, 1976; Dobinson and Foster, *J.*, 1961, 2338.

[13] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175; Brooks, Evans, Green, Hunt, Long, Mooney, and Wyman, *J.*, 1958, 4614.

[14] Allen, Bernstein, and Littell, *J. Amer. Chem. Soc.*, 1954, **76**, 6116.

[15] Dr. V. Petrow, private communication.

238 mμ [16] (see below) and was converted on treatment with hot alkali into a compound that we did not isolate, though it appeared from its paper-chromatographic behaviour to be the less polar 6α-methyl-20-ketal (VIII; R = H, R′ = O·[CH_2]$_2$·O). Bernstein and Littell [3] prepared this 20-ketal by treating the ketal acetate (VI; R = Ac, R′ = O·[CH_2]$_2$·O) with 0·05N-sodium hydroxide.



Hydrolysis of the 20-ketal (VII; R = H, R′ = O·[CH_2]$_2$·O) with sulphuric acid in refluxing acetone was accompanied by epimerisation of the 6β-methyl group, yielding 6α-methylcortisone (VIII; R = H, R′ = O); acetylation gave the corresponding 21-acetate (VIII; R = Ac, R′ = O).

The stability and ease of epimerisation of 6β-methyl-Δ^4-3-ones depend upon small changes of alkali concentration [17,18] and upon the presence of other functional groups within the molecule.[2] The absorption maximum of our 6α-methyl-Δ^4-3-ones was consistently 1·5—2 mμ below that of their 6β-methyl epimers,[16,18] and the former were the less polar on paper chromatograms and had the higher dextrorotation.[2,8,19,20] The optical rotatory dispersion curve for 6α-methylcortisone acetate (VIII; R = Ac, R′ = O)[21] resembled closely that for cortisone acetate (I; R = Ac, R′ = O), but the curve for 6β-methylcortisone acetate (VII; R = Ac, R′ = O) displayed characteristic differences.[22,23]

[16] Ringold and Bowers, *Experientia*, 1961, **17**, 65.
[17] Upjohn Co., U.S.P. 2,867,633.
[18] Upjohn Co., U.S.P. 2,897,217.
[19] Ackroyd, Adams, Ellis, Petrow, and Stuart-Webb, *J.*, 1957, 4099.
[20] Ringold, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 99.
[21] Liisberg, Godtfredsen, and Vangedal, *Tetrahedron*, 1960, **9**, 149.
[22] Davies and Petrow, *Tetrahedron*, 1963, **19**, 1771.
[23] Djerassi, Halpern, Halpern, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

The utility of this route to 6-methylcortical hormones is limited by the inefficiency of ketalisation of the 20-ketone and the necessity for prior hydrolysis of the 21-acetate group. 20-Methoxyimines avoid these difficulties, and a test with the methoxyimino-ketal (II; R = Ac, R′ = N·OMe), under the conditions we applied to 5α,6α-epoxides, showed that it survived attack by Grignard reagents, save for hydrolysis of the 21-acetate group.* The work described below demonstrates further advantageous properties.

The 3-ketal (II; R = Ac, R′ = O) on treatment with *O*-methylhydroxylamine hydrochloride in pyridine [1] was converted efficiently into the methoxyimino-ketal (II; R = Ac, R′ = N·OMe). Epoxidation with monoperphthalic acid gave a mixture of epoxides, from which the predominating 5α,6α-isomer (III; R = Ac, R′ = N·OMe) was readily isolated by crystallisation. Perbenzoic acid proved less stereospecific.[24] Methoximation of the ketal epoxide (III; R = Ac, R′ = O) resulted in a lower yield of impure methoxyimino-epoxide (III; R = Ac, R′ = N·OMe). Treatment of the α-epoxide (III; R = Ac, R′ = N·OMe) with methyl Grignard reagent gave, after subsequent acid hydrolysis of the 3-ketal group and reacetylation at the 21-position, the 5α-hydroxy-6β-methyl-20-methoxyimine (VI; R = Ac, R′ = N·OMe).

Elimination of the 5α-hydroxyl group from the methoxyimine (VI; R = Ac, R′ = N·OMe) with dilute alkali gave the 6β-methyl-20-methoxyimine (VII; R = H, R′ = N·OMe); the 21-acetate group (which was introduced at the earlier stage to facilitate isolation) suffered hydrolysis, but epimerisation at the 6-position did not occur.

The resulting 6β-methyl-methoxyimine (VII; R = H, R′ = N·OMe), on treatment with hydrochloric acid in ethyl acetate and acetone gave, after acetylation, 6α-methylcortisone acetate (VIII; R = Ac, R′ = O). Also isolated was the corresponding 20-methoxyimine (VIII; R = Ac, R′ = N·OMe), the result of incomplete hydrolysis; its optical rotation and ultraviolet absorption served to show that epimerisation of the 6-methyl group had occurred. Since the increment in molecular rotation accompanying 21-acetylation of a 20-methoxyimino-21-ol is small, the difference between the 6-methyl-20-methoxyimines (VII; R = H, R′ = N·OMe) and (VIII; R = Ac, R′ = N·OMe) can be attributed mainly to the different configurations at the 6-position.

Experimental

Melting points were measured with a Kofler hot-stage apparatus. Solvents used in measurements of physical properties were chloroform (0·25—1% solutions at 18—23°) for optical rotations (a drop of pyridine was added for ketals), dioxan for optical rotatory dispersions, ethanol for ultraviolet spectroscopy, and bromoform for infrared spectroscopy (hydrolysis of ketal groups may occur in this solvent).

Solutions of steroids in organic solvents were washed with water and dried with sodium sulphate or magnesium sulphate before evaporation. Specimens were identified with other samples by mixed m. p. and by comparative paper chromatography and infrared spectroscopy. An atmosphere of nitrogen was maintained in experiments involving alkali or Grignard reagents. The latter were made by the usual means and the ethereal solutions set aside for the sludge to settle. A measured volume of the clear solution was run into water, an excess of standard hydrochloric acid was added, and the solution was back-titrated with standard sodium hydroxide solution (using Methyl Red indicator). The colour-change was slow, but the end-point was sharp. Methylmagnesium bromide was also assayed by Volhard titration of the bromide ion after adding the solution to an excess of dilute nitric acid and by direct titration with acid of the water-hydrolysed solution (care had to be taken that all the magnesium hydroxide dissolved).

Tetrahydrofuran was distilled over flakes of sodium hydroxide, then treated with sodium wire, distilled, and redistilled straight into the reaction vessel from a suspension containing lithium aluminium hydride.

* Eguchi and Ishii, *Bull. Chem. Soc. Japan*, 1963, **36**, 1434. Cf. Marxer and Horvath, *Helv. Chim. Acta*, 1964, **47**, 1101.

[24] Bowers and Ringold, *Tetrahedron*, 1958, **3**, 14.

Solvent system L was used for paper chromatography.[13] Comparisons were run at the same temperature; most results were obtained at 34°, but a few chromatograms were run at 26°. Means of detection were: spraying with TSTZ for α-ketols and their esters; exposure to the fumes over hydrochloric acid, then spraying with TSTZ [1,25] for compounds, such as the 20-methoxyimines and 20-ketals, which gave α-ketols or their esters by acid-catalysed hydrolysis; spraying with isonicotinic acid hydrazide [1] with subsequent inspection for spots which fluoresce yellow under irradiation with ultraviolet light (mostly of 365 mμ) [Δ^4-3-ketones were detectable within 15 min.; the oxides (III and IV; R = Ac, R′ = N·OMe) and the 5-hydroxy-ketone (V; R = Ac, R′ = N·OMe) were detectable only after the sprayed papers had been kept overnight]. Compounds were detected by all the appropriate tests, unless indication is given otherwise.

5α,6α-*Epoxy*-3,3:20,20-*bisethylenedioxy*-17,21-*dihydroxypregnan*-11-*one and its* 5β,6β-*Isomer* (III and IV; R = H, R′ = O·$[CH_2]_2$·O).—The 3,20-bisketal [5] (II; R = H, R′ = O·$[CH_2]_2$·O) (1·0 g.), R_F 0·63, in chloroform (20 ml.) was treated for 5 days at 20° with 0·485M-monoperphthalic acid in ether (13 ml., 1·4 mol). (Two days are probably enough.) The washed and dried solution was evaporated, and the residue crystallised from chloroform–ether, giving the 5α,6α-*epoxide* as rods (0·65 g., 62%), m. p. 232—241° (decomp.). Successive crystallisation from chloroform–ether and from ethyl acetate gave birefringent rods, m. p. 237—244° (decomp.), $[\alpha]_D$ −15°, R_F 0·20, $\nu_{max.}$ 3600 and 3500 (OH), 1700 (ketone), and 1058 cm.$^{-1}$ (C–O) (Found: C, 64·7; H, 7·5. $C_{25}H_{36}O_8$ requires C, 64·6; H, 7·8%). After isolation of the α-epoxide the residues from several experiments were combined (3·2 g.) and chromatographed on Florisil (35 g.). Benzene and benzene–chloroform mixtures containing up to 35% chloroform eluted the 5β,6β, *epoxide*, which crystallised from chloroform–ether as prisms (0·47 g.), m. p. 237—240°, R_F 0·20 (weak) and 0·39. Material eluted with benzene–chloroform (6 : 4) and more polar solvent mixtures contained the 5α-epoxide, which crystallised from chloroform–ether as rods (0·38 g.), m. p. 230—240° (decomp.). The residues (1·63 g.) from both crystallisations were rechromatographed on Florisil (16 g.) and provided more of the β-epoxide (0·25 g.), m. p. 215—225°, R_F 0·40. Recrystallisation of the β-epoxide (0·73 g.) from benzene gave blades (0·41 g.), m. p. 235—239°, $[\alpha]_D^{21}$ +7°, R_F 0·40, $\nu_{max.}$ 3560 (OH), 1698 (ketone), 1096 and 1056 cm.$^{-1}$ (ketal) (Found: C, 64·45; H, 7·8%). From the above evidence and by paper chromatography it is clear that the oxidation described gives the epoxides in the ratio α : β > 13 : 1.

3,3:20,20-*Bisethylenedioxy*-5α,17,21-*trihydroxy*-6β-*methylpregnan*-11-*one* (V; R = H, R′ = O·$[CH_2]_2$·O).—To a solution of the 5α,6α-epoxide (III; R = H, R′ = O·$[CH_2]_2$·O) (1·0 g.) in tetrahydrofuran (100 ml.) was added during 15 min. an ethereal solution of 2M-methylmagnesium bromide (35 ml., *ca.* 30 mol). The colourless solution was refluxed for 18 hr., the reflux temperature rising from 40 to 65°, owing to loss of ether. The solution was cooled to −20° and the excess of Grignard reagent destroyed by addition of saturated ammonium chloride solution (75 ml.). The product was extracted with methylene chloride and the combined extracts washed with water and dried. Crystallisation from chloroform–ether gave the *bisketal* (0·88 g.) as prisms, m. p. 186—190°, $[\alpha]_D$ 0°, R_F 0·58, $\nu_{max.}$ 3600 and 3500 (OH), 1700 (ketone), and 1060 cm.$^{-1}$ (C–O). A second crop (0·03 g.), m. p. 182—183°, brought the yield to 88%. Crystallisation of a specimen from ethyl acetate gave birefringent blades, m. p. 182—187° (Found: C, 64·7; H, 8·2. $C_{26}H_{40}O_8$ requires C, 65·0; H, 8·4%).

Methylmagnesium iodide gave an insoluble white complex, but with little loss in the yield of the product. Inferior yields were obtained with benzene or ether as solvent; the trouble with the latter was not the action of magnesium bromide etherate in the Grignard reagent,[10] since the epoxide was stable to this compound in ether.[9] Methyl-lithium in ether–benzene gave products containing seven components detectable by chromatography; none could be crystallised out.

20,20-*Ethylenedioxy*-5α,17,21-*trihydroxy*-6β-*methylpregnane*-3,11-*dione* (VI; R = H, R′ = O·$[CH_2]_2$·O).—A solution of the 5-hydroxy-bisketal (V; R = H, R′ = O·$[CH_2]_2$·O) (0·50 g.) in acetone (20 ml.) and water (2·75 ml.) was treated with 2N-hydrochloric acid (0·5 ml.). The optical rotation increased and became constant within 19 hr.; the mixture was poured into saturated sodium hydrogen carbonate solution (15 ml.). Methylene dichloride extracted the 3-ketone, rods (0·38 g., 85%), m. p. 237—242° (from chloroform–methylene dichloride), $[\alpha]_D$ +20° {lit.,[25] m. p. 225—228°, $[\alpha]_D$ +19·8° (dioxan)}, R_F 0·06, $\nu_{max.}$ 3600 (OH), 1702 (ketone), and 1056 cm.$^{-1}$ (C–O) (Found: C, 65·7; H, 8·3. Calc. for $C_{24}H_{36}O_7$: C, 66·0; H, 8·3%).

[25] Sensi and Lancini, *Gazzetta*, 1959, **89**, 1965.

Refluxing N-sodium hydroxide converted this compound into a crude product, R_F 0·44, believed to be the 6α-methyl-20-ketal (VIII; R = H, R′ = O·[CH_2]$_2$·O).

20,20-*Ethylenedioxy*-17,21-*dihydroxy*-6β-*methylpregn*-4-*ene*-3,11-*dione* (VII; R = H, R′ = O·[CH_2]$_2$·O).—A solution of the 5-hydroxy-ketal (VI; R = H, R′ = O·[CH_2]$_2$·O) (0·30 g.) in dry methanol (63 ml.) was treated with 0·1N-sodium hydroxide (7 ml., 1 mol.). The optical rotation of the solution increased and became constant within 16 hr.; by addition of 0·1N-hydrochloric acid the pH was brought to 7, and the mixture was poured into water. Methylene dichloride extracted material (0·35 g.) that yielded the Δ^4-3-*ketone* (0·25 g., 86%), m. p. 199—204°, $[\alpha]_D$ +113°, R_F 0·35, $\lambda_{max.}$ 238 mμ (ε 15,200), $\nu_{max.}$ 3600 (OH), 1704 (ketone), 1664, 1616, and 874 (Δ^4-3-ketone), and 1054 cm.$^{-1}$ (C–O) (Found: C, 69·1; H, 8·2. $C_{24}H_{34}O_6$ requires C, 68·9; H, 8·2%).

N-Sodium hydroxide in aqueous methanol (see above) converted the Δ^4-3-ketone into a crude ketal, R_F 0·44, probably the 6α-isomer (VIII; R = H, R′ = O·[CH_2]$_2$·O).

5α,17,21-*Trihydroxy*-6β-*methylpregnane*-3,11,20-*trione and its* 21-*Acetate* (VI; R = H, Ac; R′ = O).—A solution of the bisketal (V; R = H, R′ = O·[CH_2]$_2$·O) (0·40 g.) in acetone (40 ml.) was treated with 8·5% (v/v) sulphuric acid (4 ml.). The solution was refluxed for 1 hr. under nitrogen, cooled, and poured into saturated sodium hydrogen carbonate solution (50 ml.) (pH finally 7·0). Methylene dichloride extracted a solid (0·33 g.), which crystallised from acetone–ether as rods (0·19 g., 57%) of the *trione*, m. p. 248—250°, $[\alpha]_D^{17}$ +44° [$CHCl_3$–EtOH (9 : 1)], R_F 0·03, $\nu_{max.}$ 3600 and 3450 (OH), 1706 cm.$^{-1}$ (ketone) (Found: C, 67·7; H, 8·8. $C_{22}H_{32}O_6$ requires C, 67·3; H, 8·2%). Traces of the 20-ketal (VI; R = H, R′ = O·[CH_2]$_2$·O) could be detected by paper chromatography in crude samples of this product.

Acetylation of the trione (0·315 g.) in acetic anhydride (3 ml.) and pyridine (2 ml.) for 18 hr. at 20°, with subsequent evaporation and dilution with ether, gave the crystalline 21-*acetate* (0·35 g.). Recrystallisation from chloroform gave 4 crops (0·28 g., 79%); the first crop had m. p. 247—249°, $[\alpha]_D$ +70°, R_F 0·23, $\nu_{max.}$ 1740 and 1232 (21-acetate), 1710 (3- and 20-ketones), and 1690 cm.$^{-1}$ (11-ketone) (Found: C, 66·0; H, 7·8. $C_{24}H_{34}O_7$ requires C, 66·3; H, 7·9%).

6α-*Methylcortisone and its* 21-*Acetate* (VIII; R = H, Ac, R′ = O).—(*a*) 8·5% (v/v) Sulphuric acid (7·4 ml.) was added to a solution of the 6β-methyl-ketal (VII; R = H, R′ = O·[CH_2]$_2$·O) (0·74 g.) in acetone (74 ml.), refluxed for 1 hr. under nitrogen, cooled, and poured into saturated sodium hydrogen carbonate solution (100 ml.). Methylene dichloride extracted material (0·74 g.) which crystallised from acetone–ether to give 6α-methylcortisone (0·27 g.), m. p. 215—218°, $[\alpha]_D$ +177°, R_F 0·26, $\lambda_{max.}$ 236·5 mμ (ε 14,500), $\nu_{max.}$ 3620 and 3520 (OH), 1708 (ketones), 1660, 1610, and 870 cm.$^{-1}$ (Δ^4-3-ketone). Two recrystallisations from acetone gave birefringent prisms, m. p. 225—228° (samples were dried at 100° *in vacuo* to remove tenaciously held solvent) (Found: C, 70·2; H, 8·2. Calc. for $C_{22}H_{30}O_5$: C, 70·6; H, 8·1%). [Lit.,[2,25] m. p. 212·5—215°; m. p. 209—212°, $[\alpha]_D$ +150°, $\lambda_{max.}$ 242 mμ (ε 14,600). The latter set of properties are more in keeping with those expected for the 6β-isomer (VII; R = H, R′ = O).]

Acetylation (see above) of 6α-methylcortisone (0·20 g.) gave, after evaporation of the reagents, a solid which crystallised from ethyl acetate in clumps (0·09 g., 40%) and gave the 21-acetate, m. p. 231—232° (from ethyl acetate), $[\alpha]_D^{16}$ +202·5°, $[\alpha]_{318}$ (max.) +2600° (*c* 0·11), R_F 0·69, $\lambda_{max.}$ 236·5 mμ (ε 15,600) {lit.,[21,26] m. p. 225—227°, $[\alpha]_D$ +178° (dioxan), $\lambda_{max.}$ 238 mμ (ε 15,500); m. p. 240—241·5°, $[\alpha]_D$ +219°}, $\nu_{max.}$ 3600 and 3500 (OH), 1744 and 1232 (21-acetate), 1726 (20-ketone), 1706 (11-ketone), 1658, 1610, and 868 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 69·1; H, 8·0. Calc. for $C_{24}H_{32}O_6$: C, 69·2; H, 7·7%).

(*b*) A solution of the methoxyimine (VII; R = H, R′ = N·OMe) (0·705 g.) in acetone (70·5 ml.), ethyl acetate (35 ml.), and 2N-hydrochloric acid (70·5 ml.) was kept at room temperature for 24 hr. Neutralisation with sodium hydrogen carbonate, extraction with ethyl acetate, and acetylation of the product with acetic anhydride (5 ml.) and pyridine (8 ml.) yielded material which separated as crystals (0·24 g.) from ether–ethyl acetate. The residues were chromatographed on Florisil (30 g.); benzene–ethyl acetate (3 : 1) eluted material which separated as crystals (0·07 g.) from ether containing a trace of ethyl acetate. Recrystallisation of the combined crops gave 6α-methylcortisone acetate (0·20 g., 28%), m. p. 233—236°, $[\alpha]_D$ +201°, $\lambda_{max.}$ 236 mμ (ε 13,900). Ethyl acetate–benzene (12 : 100) eluted another fraction (0·255 g.). Crystallisation from cyclohexane–ethyl acetate and twice from aqueous acetone gave birefringent needles (0·09 g., 12%) of the 6α-*methyl*-20-*methoxyimine* (VIII; R = Ac, R′ = N·OMe), m. p. 180—183°, $[\alpha]_D^{25}$ +160°, R_F 0·87, $\lambda_{max.}$ 234 mμ (ε 15,900), $\nu_{max.}$ 3600 and 3500 (OH), 1737 and

[26] Bowers and Ringold, *J. Amer. Chem. Soc.*, 1958, **80**, 3091.

1240 (21-acetate), 1702 (ketone), 1654 and 1608 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 66·4; H, 7·9; N, 3·2. $C_{25}H_{35}NO_6$ requires C, 67·4; H, 7·9; N, 3·2%) (repetition of the analysis gave the same result).

21-*Acetoxy*-17-*hydroxy*-6β-*methylpregn*-4-*ene*-3,11,20-*trione* (VII; R = Ac, R′ = O).—A solution of the dihydroxy-trione (VI; R = Ac, R′ = O) (0·25 g.) in pyridine (2·5 ml.) at −30° in an atmosphere of nitrogen was treated with a solution of thionyl chloride (0·2 ml.) in pyridine (5 ml.), prepared and kept at −30°. The mixture was shaken at this temperature and in 5 min. crystals began to separate. The mixture was poured into sodium hydrogen carbonate solution (50 ml.), and the steroid was extracted into methylene dichloride. After having been washed successively with 2N-hydrochloric acid and sodium hydrogen carbonate solution, the extract yielded, on evaporation, a solid (0·25 g.) which crystallised from ethyl acetate–hexane to give the *acetate* (0·20 g., 85%), R_F 0·27 (weak) and 0·68, $\lambda_{max.}$ 239 mμ (ε 13,600). Two recrystallisations from ethyl acetate afforded birefringent rods and spikes, m. p. 239—244°, $[\alpha]_D$ +172° (*c* 0·15), $[\alpha]_{295}$ 0°, $[\alpha]_{318}$ (max.) +1400°, $[\alpha]_{340}$ (min.) +820°, $[\alpha]_{352}$ (max.) +1200° (*c* 0·193), R_F 0·66, $\lambda_{max.}$ 238 mμ (ε 16,200), $\nu_{max.}$ 1742 and 1230 (21-acetate), 1726 (20-ketone), 1706 (ketone), 1660, 1608, and 868 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 68·9; H, 7·7. $C_{24}H_{32}O_6$ requires C, 69·2; H, 7·7%).

21-*Acetoxy*-5α,6α-*epoxy*-3,3-*ethylenedioxy*-17-*hydroxypregnane*-11,20-*dione* (III; R = Ac, R′ = O).—The ketal [5] (II; R = Ac, R′ = O) (1·0 g.), dissolved in AnalaR chloroform (170 ml.), was treated at room temperature with 0·388M-perbenzoic acid in chloroform (7·2 ml., 1·25 mol.). After 68 hr. the crystals (0·31 g.) of the epoxide were collected, m. p. >315° (decomp.), $[\alpha]_D$ +30° (pyridine), $\nu_{max.}$ (Nujol) 3450 (OH), 1748 and 1234 (21-acetate), 1728 (20-ketone), 1706 (ketone), 1106 and 1046 cm.$^{-1}$ (ketal) (Found: C, 65·1; H, 7·3. Calc. for $C_{25}H_{34}O_8$: C, 64·9; H, 7·4%). The mother-liquor was washed with sodium hydrogen carbonate solution and water; addition of hexane precipitated another crop (0·45 g., total 74%), $[\alpha]_D$ +24° (pyridine). This compound was too insoluble for paper chromatography. Sondheimer *et al.*[27] give m. p. >300°, $[\alpha]_D$ +62° (pyridine) for this oxide; we cannot explain the discrepancy in rotation. We obtained similar material by oxidation with 1·11M-monoperphthalic acid in ether, with crystallisation of the product from aqueous pyridine.

21-*Acetoxy*-5α,6α-*epoxy*-3,3-*ethylenedioxy*-17-*hydroxy*-20-*methoxyiminopregnan*-11-*one and its* 5β,6β-*Epimer* (III and IV; R = Ac, R′ = N·OMe).—The methoxyimine [1] (II; R = Ac, R′ = N·OMe) (42·8 g.) and 0·98M-monoperphthalic acid in ether (120 ml., 1·2 mol. equiv.) were dissolved in AnalaR chloroform (1070 ml.), and set aside at room temperature for 1 weekend, during which a precipitate settled out. The mixture was washed with sodium hydrogen carbonate solution, treated with a drop of pyridine (to preserve the ketal group from hydrolysis), and evaporated. The residue was rubbed with ethanol, and a first crop (31·6 g.) of the 5α,6α-*epoxide*, m. p. 245—248°, $[\alpha]_D$ −6°, R_F 0·77, was filtered off; a second crop (4·9 g., total 83%), with similar properties, was obtained by crystallisation from aqueous pyridine of the material in the mother-liquors. Recrystallisation from this solvent gave birefringent rectangles, m. p. 248—249°, $[\alpha]_D$ −7°, R_F 0·79, $\nu_{max.}$ 3600 and 3470 (OH), 1738 and 1244 (21-acetate), 1702 (ketone), and 1048 cm.$^{-1}$ (C–O) (Found: C, 63·7; H, 7·2; N, 2·8. $C_{26}H_{37}NO_8$ requires C, 63·5; H, 7·6; N, 2·85%).

The remaining mother-liquors yielded on evaporation a yellow oil, which was dissolved in ethanol (25 ml.); seeding with a crystal of the β-epoxide (IV; R = Ac, R′ = N·OMe) then prompted the separation of crystals (2·21 g., 5%), m. p. 188—191°, R_F 0·85. Recrystallisation from aqueous pyridine afforded the β-*epoxide*, m. p. 198—199°, $[\alpha]_D^{25}$ +17·5°, R_F 0·87, $\nu_{max.}$ (Nujol) 3420 (OH), 1738 and 1226 (21-acetate), 1698 (ketone), 1102 and 1046 cm.$^{-1}$ (ketal) (Found: C, 63·3; H, 7·4; N, 3·0%). Paper chromatography indicated an α : β ratio of 9 : 1 in the crude oxide.

Oxidation with perbenzoic acid (2·5 mol.) gave the α- and β-*epoxides* in yields of 30 and 16%, respectively; paper chromatography indicated an α : β ratio in the crude product of 6 : 4. 21-Acetoxy-3,3-ethylenedioxy-17-hydroxy-20-methoxyimino-5α-pregnan-11-one was unaffected by perbenzoic acid under the conditions described above.

Attempts to make the epoxy-methoxyimine (III; R = Ac, R′ = N·OMe) by methoximation of the oxide (III; R = Ac, R′ = O) gave a crude product (66%), m. p. 234—251°, $[\alpha]_D^{24}$ −10°, R_F 0·55 (weak), 0·77 and 0·86 (weak), the weak spots reducing TSTZ without prior exposure to acid.

[27] Sondheimer, Mancera, and Rosenkranz, *J. Amer. Chem. Soc.*, 1954, **76**, 5020.

21-*Acetoxy*-5α,17-*dihydroxy*-20-*methoxyimino*-6β-*methylpregnane*-3,11-*dione* (VI; R = Ac, R′ = N·OMe).—A solution of the α-epoxide (III; R = Ac, R′ = N·OMe) (20 g.) in tetrahydrofuran (1 l.) was treated with 2·91M-methylmagnesium bromide in ether (348 ml., 25 mol.), added in 5 min. The solution became warm. It was heated (57°) under reflux for 9 hr., cooled to 0°, and the excess of Grignard reagent (Gilman test [28]) destroyed with ammonium chloride solution. The steroid was extracted with methylene dichloride, washed with ammonium chloride solution, and recovered by evaporation. Part (18·2 g.) of the product (19·2 g.) was dissolved in acetone (900 ml.), water (126 ml.), and N-hydrochloric acid (23 ml.). After 18 hr. at room temperature this solution was neutralised with sodium hydrogen carbonate, the acetone was evaporated off *in vacuo*, the volume made up to 600 ml. with water, and the solution kept overnight at 0°. The crystals that separated (the mother-liquors were kept; see below) were treated for 18 hr. with acetic anhydride (20 ml.) and pyridine (70 ml.) at room temperature, and the solution poured on to ice, giving crystals (9·2 g., 51%) of the 6β-*methyl-ketone*, m. p. 234—240°, R_F 0·35 (weak) and 0·60. (The component, R_F 0·35, was detected only with isonicotinic acid hydrazide, the fluorescence appearing only after some hours; see introduction to Experimental section.) Crystallisation from ethyl acetate (with a trace of pyridine) gave homogeneous material, m. p. 248—249°, $[\alpha]_D^{24}$ +25°, R_F 0·60, $\nu_{max.}$ 3600 (OH), 1760, 1740, and 1244 (acetate), and 1708 cm.$^{-1}$ (ketones) (Found: C, 64·6; H, 7·95; N, 3·35. $C_{25}H_{37}NO_7$ requires C, 64·8; H, 8·0; N, 3·0%). Highly polar material, R_F 0·06, extracted with ethyl acetate from the mother-liquors mentioned above, may have been a 5α,6β,17,21-tetraol resulting from cleavage of the epoxide ring.

The 21-acetoxy-20-ketone (II; R = Ac, R′ = O) was recovered in 60 and 33% yields after treatment for 20 min. in dioxan with 2 and 3 mol., respectively, of ethereal methylmagnesium iodide; 15 mol. gave an intractable gum and hydrolysis of the 21-acetoxy-group occurred. Treatment of the 21-acetoxy-20-methoxyimine (II; R = Ac, R′ = N·OMe) in tetrahydrofuran with methylmagnesium bromide (25 mol.) in ether, with subsequent hydrolysis (see above) with acetone and hydrochloric acid, gave blades of 17,21-*dihydroxy*-20-*methoxyimino*-*pregn*-4-*ene*-3,11-*dione* (I; R = H, R′ = N·OMe) (37%), m. p. 249—252° (this material separated from the hydrolysis mixture when it was set aside for 63 hr.). Crystallisation from acetone and from ethanol yielded prisms, m. p. 259—262°, $[\alpha]_D$ +183°, R_F 0·59, $\lambda_{max.}$ 235·5 mμ (ε 16,750), $\nu_{max.}$ (Nujol) 3400 (OH), 1702 (ketone), 1644, 1616, and 868 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 67·85; H, 7·6; N, 3·7. $C_{22}H_{31}NO_5$ requires C, 67·8; H, 8·0; N, 3·6%). Acetylation with acetic anhydride and pyridine gave the 21-acetate (I; R = Ac, R′ = N·OMe), m. p. 179—182°, $[\alpha]_D$ +181°, R_F 0·82, $\lambda_{max.}$ 235·5 mμ (ε 17,700), identified with material made before.[1]

After separation of the methoxyimine described in the last paragraph, the mother-liquors yielded, by extraction with methylene chloride and acetylation of the extract, crystalline cortisone acetate (I; R = Ac, R′ = O) (27%). Most of the residues consisted of this compound, R_F 0·61. These results demonstrated the resistance of the 20-methoxyimino-group to a Grignard reagent.

17,21-*Dihydroxy*-20-*methoxyimino*-6β-*methylpregn*-4-*ene*-3,11-*dione* (VII; R = H, R′ = N·OMe).—The 5-hydroxy-ketone (VI; R = Ac, R′ = N·OMe) (1·0 g.), dissolved in methanol (200 ml.), was treated with 0·5N-sodium hydroxide solution (13 ml., 3 mol.). After 3·5 hr. at room temperature, an excess of acetic acid was added and the solution was evaporated to dryness. The crude product yielded, from aqueous pyridine, crystals (0·42 g., 48%) of the Δ^4-3-*ketone*. Two crystallisations from aqueous pyridine afforded prisms, m. p. 243—246° (with darkening), $[\alpha]_D$ +111°, R_F 0·66, $\lambda_{max.}$ 237·5 mμ (ε 16,400), $\nu_{max.}$ (Nujol) 3500 and 3400 (OH), 1702 (ketone), and 1644 and 1600 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 68·1; H, 8·0; N, 3·8. $C_{23}H_{33}NO_5$ requires C, 68·5; H, 8·2; N, 3·5%).

Refluxing the 5-hydroxy-ketone (VI; R = Ac, R′ = N·OMe) in acetic acid for 70 min. gave, presumably, the 21-acetate (VII; R = Ac, R′ = N·OMe). Pyridine at 100°, or stirring of a solution in benzene with alumina, caused no change detectable by ultraviolet spectroscopy or paper chromatography.

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[28] Gilman and Schultze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.