[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S.A.]

Steroids. XCV.[1] Synthesis of 6α-Methyl-21-desoxycortisone. A New Route to 6α-Methylcortisone

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RECEIVED DECEMBER 21, 1957

21-Desoxycortisone (II) has been synthesized from cortisone in high yield. Ketalization and epoxidation of II led to the 3,20-bis-ketal-5α,6α-epoxide V. Cleavage of V with the methyl Grignard reagent followed by acid hydrolysis of the ketal groups and alkaline dehydration of the 5α-hydroxy-3-ketone VII afforded 6α-methyl-21-desoxycortisone (VIII) in an over-all yield of 30% from cortisone. Finally, direct introduction of the C-21-hydroxyl group completed a new and shorter route to the important 6α-methylcortisone.[2]

Recently we and others[2-8] have reported on the synthesis of 6α-methyl hormone analogs, certain of which exhibit enhanced or more favorable biological activities than the parent compounds. The syntheses in general[9] are based on the cleavage of a 3-hydroxy- or 3-cycloethylenedioxy-5α,6α-oxidosteroid with methylmagnesium halide to afford the 5α-hydroxy-6β-methyl system, a reaction first reported by the Russian workers Ushakov and Madaeva[10] and subsequently confirmed by Fieser and Rigaudy[11] and later by Turner.[12]

From this system the 6α-methyl (equatorial) Δ^4-3-ketone may be formed readily by conversion of the 3-hydroxyl or 3-ketol to the 3-ketone, dehydration of the 5-hydroxyl and inversion of the 6β-methyl group.

The 6α-methyl cortical hormone analogs have been prepared by a lengthy sequence from 11α-hydroxyprogesterone[2] and by a more direct route from cortisone-3,20-bisketal.[2,7]

The latter direct route would appear to be unsuitable for large scale application in view of the low yield and irreproducibility[13a,b] in the formation of the bisketal of cortisone.

It appeared to us that the most feasible route to 6α-methyl corticoids would be one starting with 21-desoxycortisone, for, if the 3,20-bisketal-5α,6α-epoxide of this compound could be formed in high yield, the preparation of 6α-methylcortisone or hydrocortisone would seem to be straightforward. Conversion of these 21-desoxy compounds or their Δ^1-derivatives to the corresponding C-21 alcohols then could be accomplished readily by our recently described C-21 hydroxyl introduction,[14] a reaction involving direct base-catalyzed C-21-iodination of a Δ^4-3-ketone or a $\Delta^{1,4}$-3-ketone. Furthermore it was of interest to prepare these hitherto undescribed 21-desoxy compounds for biological evaluation.

We have indeed found that 21-desoxycortisone (II) may be converted readily to 6α-methyl-21-desoxycortisone (VIII) and finally to 6α-methylcortisone acetate (IX).

While 21-desoxycortisone (II)[15a-e] itself is not at present a commercially available steroid intermediate, a number of attractive chemical and combined chemical–biological routes to II may be envisioned. For our purposes the compound was prepared most readily in over 80% yield by removal of the C-21-hydroxyl function of cortisone.

Treatment of cortisone in pyridine solution at 0° with *p*-toluenesulfonyl chloride is known to lead to a mixture of products,[16-19] but under the conditions we employed the major product was probably the C-21 chloride with smaller amounts of the C-21 pyridinium salt.[16-18] However, the total product without purification was reduced with sodium iodide in acetic acid to afford 21-desoxycortisone (II) in 83% yield.[20] Ketalization of this compound by the benzene–ethylene glycol–*p*-toluenesulfonic acid[21] method gave the bisketal III thereby protecting the C-3 and C-20 keto groups from attack by Grignard reagent[22] and introducing a C-5,6-double bond.[23] Subsequent epoxidation of

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(2) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956).

(3) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

(4) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).

(5) M. Ackroyd, W. J. Adams, B. Ellis, V. Petrow and I. A. Stuart-Webb, *ibid.*, 4099 (1957).

(6) V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *ibid.*, 4105 (1957).

(7) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *ibid.*, 4112 (1957).

(8) J. A. Camphell, J. C. Babcock and J. A. Hogg, Abs. 132nd Meeting Amer. Chem. Soc., New York, 1957, p. 24-P.

(9) See, however, references 4 and 6 where the authors describe alternative routes through a 6-keto-3,5-cyclo-steroid or a 6-keto-5α-bromo-3β-acetate system.

(10) M. I. Ushakov and O. S. Madaeva, *J. Gen. Chem. (U.S.S.R.)*, **9**, 436 (1939).

(11) L. F. Fieser and J. Rigaudy, THIS JOURNAL, **73**, 4660 (1951).

(12) R. B. Turner, *ibid.*, **74**, 5362 (1952).

(13) (a) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littel and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953); (b) private communication from Dr. J. A. Zderic of these laboratories.

(14) H. J. Ringold and G. Stork, THIS JOURNAL, **80**, 250 (1958).

(15) (a) L. H. Sarett, *ibid.*, **70**, 1454 (1948); (b) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952); (c) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952); (d) P. D. Meister, D. H. Peterson, H. C. Murray, G. B. Spero, S. H. Epstein, A. Weintraub, L. M. Reineke and H. M. Leigh, *ibid.*, **75**, 416 (1953); (e) R. H. Levin, B. J. Magerlein, A. V. McIntosh, A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scheri and E. S. Gutsell, *ibid.*, **76**, 546 (1954).

(16) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(17) C. Djerassi and A. L. Nussbaum, THIS JOURNAL, **75**, 3700 (1953).

(18) W. J. Leanza, J. P. Conbere, E. F. Rogers and K. Pfister, *ibid.*, **76**, 1691 (1954).

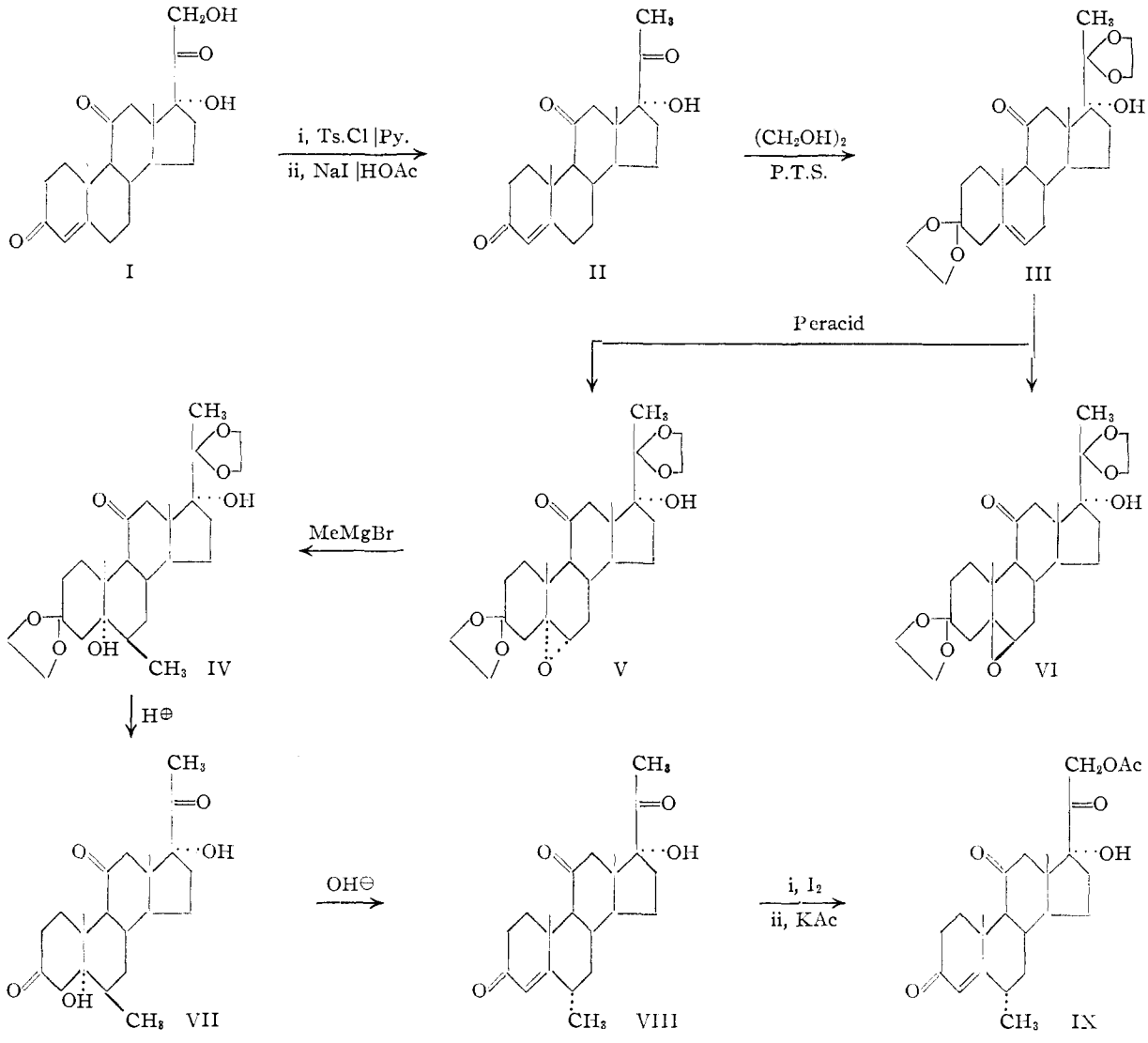
(19) For the preparation of cortisone 21-tosylate by a modified procedure of this reaction see P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955).

(20) This reaction was first carried out in these laboratories by Dr. O. Mancera to whom we offer our best thanks.

(21) See for example ref. 13.

(22) Under the reaction conditions employed the C-11 ketone is known to be stable to Grignard reagent; see for example H. J. Ringold, E. Batres and J. A. Zderic, *Tetrahedron*, **2**, 164 (1958).

(23) The corresponding 11β-alcohol may be obtained by $LiAlH_4$ reduction of III and can be converted to 6α-methylhydrocortisone by an identical sequence to that described for the 11-ketone; H. J. Ringold and A. Bowers, Mexican Patent Application No. 48360.



III with permonophthalic acid afforded the 5α,6α-epoxide V in 60% yield by direct crystallization of the reaction mixture. Chromatography of the mother liquors afforded an additional 17% of the α-epoxide and 15% of the β-epoxide VI. The structure proof and configurations assigned to these two epoxides followed from their mode of preparation, elemental analysis, the ratio of the two epoxides formed, their relative polarities toward alumina and a comparison of their molecular rotations.[24]

As was mentioned above it has now been well established[10-12] that 5α,6α-epoxides cleave to afford the corresponding 5α-hydroxy-6β-methyl compound with Grignard reagent. Accordingly, treatment of V with methylmagnesium bromide gave the 6β-methyl-5α-hydroxybis-ketal IV in good yield. Hydrolysis of the ketal groups with dilute aqueous methanolic sulfuric acid[25] afforded the diketone VII. Higher yields of VII were obtained if the intermediate 6β-methylbis-ketal IV was hydrolyzed without prior purification. Dehydration of the β-hydroxy-ketone VII with 0.25% methanolic potassium hydroxide under reflux afforded 6α-methyl-21-desoxycortisone (VIII). Proof that this dehydration was attended with concomitant inversion of the C-6 methyl group followed from the molecular rotation of the product[26] and the proven instability of a 6β-methyl-Δ^4-3-ketone to dilute alkali.[2,3]

The over-all yield of VIII from cortisone by the six-stage synthetic sequence outlined above was 30%. Finally 6α-methyl-21-desoxycortisone was converted directly into 6α-methylcortisone by the recent C-21 hydroxylation technique developed in these laboratories,[14] thus completing a new synthesis to the biologically highly active 6α-methylcortisone.

(24) Epoxidation of Δ^5-3-ketals or Δ^5-3β-acetates always leads to a mixture of α- and β-epoxides with the α-epoxide usually predominating, the ratio of the α-epimer being even higher in compounds containing a keto or β-substituted hydroxyl group at C-11. The α-epimer is in addition more polar toward alumina and more levorotatory than the β-epoxide. See for example ref. 2 and A. Bowers and H. J. Ringold, forthcoming publications.

(25) W. S. Allen, S. Bernstein and R. Littell, THIS JOURNAL, **76**, 6116 (1954).

(26) The contribution to the rotation of a 6α-methyl group is known to be very small, whereas a 6β-methyl group would exert a strong levorotatory effect; see for example reference 11.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Mr. E. Avila for these measurements and for the infrared spectra which were obtained with a Perkin-Elmer model 21 spectrophotometer with a sodium chloride prism. We are indebted to Miss M. E. Barba for skilled technical assistance. The elemental analyses were carried out by A. Bernhardt, Mülheim, Ruhr, Germany.

17α-Hydroxy-Δ⁴-pregnene-3,11,20-trione (II) (21-Desoxycortisone).—*p*-Toluenesulfonyl chloride (12.2 g., 1.15 *M*) was added to a solution of cortisone (20 g.) in pyridine (100 cc.) at 0°. After 16 hours at 0° water was added and the product isolated with methylene dichloride. The combined extracts were washed with dilute hydrochloric acid (2 *N*) water, sodium carbonate solution (5%) and finally water. After drying (Na_2SO_4) and removal of the solvent, the residue in acetic acid (1 l.) containing sodium iodide (70 g.) was heated under reflux for 1 hour[27] when it was poured into water and extracted with methylene dichloride. After washing this solution with water, sodium carbonate solution (5%), water, sodium thiosulfate solution (3%) and finally water it was dried (Na_2SO_4) and evaporated to afford 21-desoxycortisone (II) (16.6 g.) as needles from acetone–hexane, m.p. 225–230°, raised by crystallization from acetone–hexane to 234–236°, $[\alpha]_D$ +180°; lit.[15e] m.p. 233–237°, $[\alpha]_D$ +184°.

17α-Hydroxy-Δ⁵-pregnene-3,11,20-trione-3,20-bis-ethyleneketal (III).—A solution of 21-desoxycortisone (II) (11.8 g.) and *p*-toluenesulfonic acid (0.5 g.) in benzene (750 cc.) was added to ethylene glycol (80 cc.) and the two-phase system distilled at such a rate that 300 cc. of distillate was collected in 3 hours. Benzene (300 cc.) then was added and the distillation continued at the same rate for a further 3 hours. After the addition of benzene (300 cc.) the system was heated under reflux for 24 hours with a water separator and then distilled slowly for a further 3 hours. Addition of sodium bicarbonate solution (200 cc. of 5%) and isolation with benzene gave a product m.p. 200–205°, λ_{max} 238 mμ, log ε 2.93. Crystallization from ethyl acetate containing a few drops of pyridine afforded the bis-ketal III (8.9 g.), m.p. 222–225° (no maximal absorption in the ultraviolet) raised by crystallization from ethyl acetate containing a trace of pyridine to 235–237° $[\alpha]_D$ −19°.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.37; H, 8.50.

Epoxidation of the Bis-ketal III with Permonophthalic Acid.—A solution of permonophthalic acid (6.75 g. in ether, 250 cc.) was added over 10 minutes to a solution of the bis-ketal III (6.2 g.) in chloroform (300 cc.) at 0°. After keeping at 0–5° for 18 hours, the solution was washed several times with cold sodium carbonate solution (5%) and then water. After drying (Na_2SO_4) and removing the solvent, crystallization from ethyl acetate–chloroform afforded the α-epoxide V (4.1 g.), m.p. 265–268°, raised by crystallization from ethyl acetate to 270–272°, $[\alpha]_D$ −35°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; O, 24.97. Found: C, 66.71; H, 8.43; O, 25.00.

The mother liquors upon evaporation afforded 2.47 g. of a mixture of α- and β-epoxides, a solution of which in benzene (200 cc.) was absorbed on alumina (Alcoa F-20, 150 g.). Elution with ether–acetone (90:10, 700 cc.) afforded the β-epoxide (1.06 g.) (15%), m.p. 216–219°, raised by crystallization from ethyl acetate to 222–224°, $[\alpha]_D$ −4°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.20; H, 8.15.

Further elution with ether–acetone (70:30, 900 cc.) afforded an additional 1.12 g. of the α-epoxide, m.p. 269–271°, total yield of α-epoxide 77%.

5α,17α-Dihydroxy-6β-methylpregnane-3,11,20-trione-3,20-bis-ethyleneketal (IV).—A solution of methylmagnesium bromide in ether (100 cc., 3 *N*) was added to a solution of α-epoxide V (940 mg.) in dry benzene (250 cc.) and the mixture heated under reflux for four hours. To the cooled solution ammonium chloride (20 g.) in water (200 cc.) was added and the product isolated with benzene. After drying (Na_2SO_4) and evaporating to 100 cc. the benzene solution was adsorbed onto alumina (Alcoa F-20) (50 g.). Elution with benzene–ether (50:50, 600 cc.) afforded 5α,17α-dihydroxy-6β-methylpregnane-3,11,20-trione-3,20-bis-ethylene-ketal (IV) (410 mg.), m.p. 208–210°, raised by crystallization from methanol to 217–219°, $[\alpha]_D$ −16° ($CHCl_3$ + 1 drop of pyridine), $\lambda_{max}^{CHCl_3}$ 1710 cm.$^{-1}$; no maximal absorption in the ultraviolet.

Anal. Calcd. for $C_{26}H_{40}O_7 \cdot {}^1/_2CH_3OH$: C, 65.88; H, 8.71; O, 24.73. Found: C, 66.34; H, 8.90; O, 24.71.

5α,17α-Dihydroxy-6β-methylpregnane-3,11,20-trione (VII).—(a) Sulfuric acid (1.0 cc., 8%, v./v.) was added to a solution of the bis-ketal IV (250 mg.) in methanol (10 cc.) and the resulting solution heated under reflux. Almost immediately a white crystalline precipitate formed and after 35 minutes water (30 cc.) containing sodium carbonate (1.0 g.) was added and the product (190 mg.), m.p. 264–267°, isolated by filtration. After several crystallizations from ethanol–chloroform it had m.p. 263–266°, $[\alpha]_D$ +46° (pyridine) and exhibited no maximal absorption in the ultraviolet.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; O, 21.25. Found: C, 70.05; H, 8.60; O, 21.31.

(b) **Directly from α-Epoxide V.**—The α-epoxide V (1.60 g.) in benzene (400 cc.) was treated with a solution of methylmagnesium bromide (16 cc. of 3 *N*) exactly as described above. Isolation of the product with benzene afforded a crystalline product, m.p. 175–180°. The total product without purification was dissolved in methanol (70 cc.) containing sulfuric acid (6.0 cc. of 8% v./v.) and the ketal groups hydrolyzed as described in the previous experiment to afford 5α,17α-dihydroxy-6β-methylpregnane-3,11,20-trione (VII) (750 mg.), m.p. 257–265°, yield 62%.

6α-Methyl-21-desoxycortisone (VIII).—A solution of potassium hydroxide in methanol (0.5 cc. of 5%) was added to a suspension of 5α,17α-dihydroxy-6β-methyl-pregnane-3,11,20-trione (VII) (300 mg.) in methanol (10 cc.). After heating under reflux for 1 hour under nitrogen (complete solution after 30 minutes) the solution was acidified with acetic acid and evaporated to the point of crystallization. Addition of water and filtration afforded 6α-methyl-21-desoxycortisone (VIII) (280 mg.), m.p. 238–245°, raised by crystallization from methanol to 243–245°, $[\alpha]_D$ +165°, λ_{max} 238–240 mμ, log ε 4.16.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.52; H, 8.53.

6α-Methylcortisone Acetate (IX).—To a solution of 6α-methyl-21-desoxycortisone (VIII) (160 mg.) in a mixture of tetrahydrofuran (1.2 cc.) and methanol (0.7 cc.) was added iodine (240 mg.) and finely powdered calcium oxide (240 mg.). After stirring at room temperature for 3 hours, at which time the iodine color was discharged, the mixture was poured onto cold water (25 cc.) containing acetic acid (1.0 cc.). The product then was extracted with methylene dichloride, washed with water, dried (Na_2SO_4) and the solution evaporated to dryness. Acetone (25 cc.) and potassium acetate (1.0 g.) were added and the solution heated under reflux for 16 hours. Evaporation of the solvent, addition of water and isolation with methylene chloride gave a product which was dissolved in methanol (7.0 cc.) and water (3.0 cc.) containing sodium bisulfite (180 mg.) and heated under reflux for 1 hour. Evaporation of the bulk of the solvent and addition of ice-water gave a product which was removed by filtration, dried and adsorbed from benzene (20 cc.) onto neutral alumina (7.0 g.). Elution with benzene–ether (80:20, 200 cc.) afforded 6α-methylcortisone acetate, m.p. 208–213°, raised by crystallization to 225–227°, $[\alpha]_D$ +178° (dioxane), λ_{max} 238 mμ, log ε 4.19.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.13; H, 7.60.

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(27) It is pertinent to comment that these experiments were carried out at an altitude of 7800 ft. and that the boiling point of acetic acid is approximately 10° lower than at sea level.