16β-METHYL CORTICAL STEROIDS

Sir:

We wish to report the preparation of 16β-methyl homologs of cortisone and its congeners. These substances are the first β-substituted cortical steroid derivatives to be reported which are more potent anti-inflammatory agents than the corresponding parent steroids. Previously described potentiating substituents have been attached to the α-face of the steroid nucleus.[1]

Addition of diazomethane[2] to 3α-acetoxy-16-pregnene-11,20-dione[3] gave the corresponding pyrazoline derivative, m.p. 186–190° dec., *Anal.* Found: C, 69.37; H, 8.01, which was converted by pyrolysis to 3α-acetoxy-16-methyl-16-pregnene-11,-20-dione (I), m.p. 165–167°, $[\alpha]_D^{Chf.}$ +75°, $\lambda_{max.}^{MeOH}$ 249 mμ (9,300). *Anal.* Found: C, 74.30; H, 8.80. Hydrogenation of I in methanol over palladium on calcium carbonate led smoothly to 3α-acetoxy-16β-methylpregnane-11,20-dione (II), m.p. 160–163°; $[\alpha]_D^{Chf.}$ +96°. *Anal.* Found: C, 74.15; H, 9.15. Reaction of II with acetic anhydride–perchloric acid[4] in chloroform-carbon tetrachloride led to the corresponding 17(20)-enol acetate, which with perbenzoic acid[5] in benzene followed by alkaline hydrolysis afforded 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione (III), m.p. 192–197°, $[\alpha]_D^{Chf.}$ +67°. *Anal.* Found: C, 72.97; H, 9.25. Confirmation of the structure of III was obtained by acetylation of III at C-3 followed by cleavage oxidation[6] to the known 3α-acetoxy-16β-methyletiocholane-11,17-dione.[7] Bromination of III yielded the corresponding 21-bromide, m.p. 165–175° dec. *Anal.* Found: C, 59.34; H, 7.55; Br, 18.14, which on treatment with potassium iodide and potassium acetate in refluxing acetone gave 3α,17α,21-trihydroxy-16β-methylpregnane-11,20-dione 21-acetate, m.p. 222–228°, $[\alpha]_D^{Chf.}$ +124.5°. *Anal.* Found: C, 68.79; H, 8.44. Oxidation of the latter compound with N-bromosuccinimide in aqueous *t*-butanol afforded 17α,21-dihydroxy-16β-methylpregnane-3,11,20-trione 21-acetate, m.p. 210–212°, $[\alpha]_D^{Chf.}$ +130°. *Anal.* Found: C, 68.81; H, 7.91, which on monobromination at C-4 followed by dehydrobromination *via* the 3-semicarbazone produced **16β-methylcortisone acetate** (IVa), m.p. 230–236°, $[\alpha]_D^{Chf.}$ +252°, $\lambda_{max.}^{MeOH}$ 238 mμ (15,800). *Anal.* Found: C, 69.24; H, 7.58. Hydrolysis of IVa by means of potassium bicarbonate in aqueous methanol yielded **16β-methylcortisone** (IV), m.p. 205–210°, $[\alpha]_D^{Chf.}$ +237°, $\lambda_{max.}^{MeOH}$ 238 mμ (16,200), *Anal.* Found: C, 70.84; H, 8.40. IV was converted *via* its 3,20-disemicarbazone[8] by hydride reduction, reversal and acetylation to **16β-methylhydrocortisone acetate** (V), m.p. 220–225°; $[\alpha]_D^{Chf.}$ +187, $\lambda_{max.}^{MeOH}$ 242 mμ (15,800). *Anal.* Found: C, 69.10; H, 7.89.

Dehydrobromination of the 2,4-dibromide of 17α,21-dihydroxy-16β-methylpregnane-3,11,20-trione 21-acetate led to **16β-methylprednisone acetate** (VIa), m.p. 230–233°, $[\alpha]_D^{Chf.}$ +216°, $\lambda_{max.}^{MeOH}$ 238 mμ (15,100). *Anal.* Found: C, 69.25; H, 7.25. Potassium bicarbonate–aqueous methanol hydrolysis of VIa afforded **16β-methylprednisone** (VI), m.p. 195–200°, $[\alpha]_D^{Chf.}$ +205, $\lambda_{max.}^{MeOH}$ 238 mμ (14,900). *Anal.* Found: C, 70.91; H, 7.57. 16β-Methylhydrocortisone 21-acetate (Va) was dehydrogenated by reaction with selenium dioxide[9] to **16β-methylprednisolone acetate** VIIa, m.p. 209–214°, $\lambda_{max.}^{MeOH}$ 243 mμ (15.000). *Anal.* Found: C, 68.76; H, 7.55, which on treatment with potassium bicarbonate in aqueous methanol was converted to **16β-methylprednisolone** VII, m.p. 205–210°, $[\alpha]_D^{Chf.}$ +145°, $\lambda_{max.}^{MeOH}$ 243 mμ (14,600). *Anal.* Found: C, 70.57, H, 8.08.

16β-Methyl-9α-fluoroprednisolone acetate, m.p. 205–208°, 16β-methyl-9α-fluoroprednisolone, m.p. 225–227°, and related compounds have been prepared and will be described in a forthcoming publication.

This series of compounds exhibited unusually high anti-inflammatory activity comparable to that observed with the corresponding 16α-methyl cortical steroids.[1] Details of the biological findings will appear elsewhere.

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(1) *Cf.* G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, L. H. Sarett, THIS JOURNAL, **80**, 3160 (1958); G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk and C. A. Winter, *ibid.*, **80**, 3161 (1958), and references cited therein.

(2) *Cf.* A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

(3) H. L. Slates and N. L. Wendler, *J. Org. Chem.*, **22**, 498 (1957).

(4) *Cf.* D. H. R. Barton, R. M. Evans, J. C. Hamlett, P. G. Jones and T. Walker, *J. Chem. Soc.*, 747 (1954).

(5) *Cf.* T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

(6) *Cf.* N. L. Wendler, D. Taub and H. L. Slates, *ibid.*, **77**, 3559 (1955).

(7) N. L. Wendler and D. Taub, *Chemistry and Industry*, 415 (1958).

(8) *Cf.* N. L. Wendler, Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951). See also R. E. Jones and S. A. Robinson, *J. Org. Chem.*, **21**, 586 (1956).

(9) *Cf.* Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).