NOTES

The Biological Activity of Certain 17α,20; 20,21-Bismethylenedioxy Corticoid Derivatives

MARTIN J. WEISS, ROBERT E. SCHAUB, AND SIDNEY MAUER

Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

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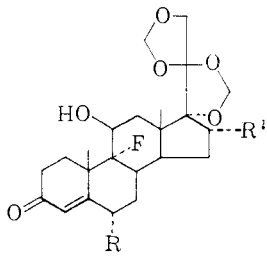
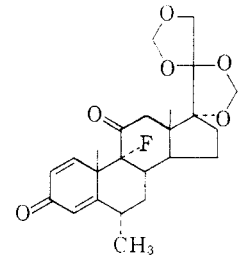
The significant glucocorticoid activity displayed by the 20-ketal derivatives of a variety of 11-oxygenated corticoids[1] prompted us to investigate the possibility that other side-chain derivatives would behave similarly. In this paper we wish to report the thymolytic and mineralocorticoid activity of certain 17α,20;20,21-bismethylenedioxy (BMD) derivatives, namely, those (I–IV) of 9α-fluorohydrocortisone,[2] 6α,9α-difluorohydrocortisone,[3] 9α-fluoro-6α-methylprednisone,[1] and 9α-fluoro-16α-methylprednisolone.[4,5] All four parent compounds are potent glucocorticoids. The desired BMD derivatives were conveniently prepared by treatment of the parent 17α,21-





III

I, R = H, R^1 = H
II, R = F, R^1 = H
IV, R = H, R^1 = CH_3,Δ^1

(1) W. S. Allen, H. M. Kissman, S. Mauer, I. Ringler, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 133 (1962).

(2) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **79**, 1130 (1957).

(3) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chem. and Ind.*, 1002 (1958).

(4) 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, *J. Am. Chem. Soc.*, **80**, 3161 (1958). E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *J. Amer. Chem. Soc.*, **80**, 4431 (1958).

(5) After the completion of our studies glucocorticoid activity was reported for a number of bismethylenedioxy derivatives including compound I.[6] The preparation of compound IV was also reported.[6]

dihydroxy-20-ketones with formalin and hydrochloric acid according to the reported procedure.[6]

The thymolytic and mineralocorticoid assay results obtained with the several BMD derivatives are listed in Table I. Also given in this Table are the activities of certain related 20-ketals and of certain of the parent 20-ketones. All four BMD derivatives (I–IV) showed a substantial degree of thymolytic activity, although each was less potent than the parent 20-ketone. In the one instance (compound III), where a comparison was possible, the BMD derivative had essentially the same activity as the corresponding 20-ketal. Also, the BMD derivative of 9α-fluorohydrocortisone was about as active as the 20-ketal of 9α-fluorocortisone. Of greatest interest is the observation that conversion of 9α-fluoro-6α-methylprednisone to the BMD derivative III results in the reversal of the salt-retaining properties of the parent compound. This BMD derivative (III) has considerable promise since its relative potency is 14.5 and, thus it is apparently three to four times as active as triamcinolone. It is

TABLE I

CORTICOID ACTIVITY OF VARIOUS BMD DERIVATIVES AND CERTAIN RELATED COMPOUNDS

Compound	Relative potency (hydrocortisone) as measured by thymus involution[a]	Mineralocorticoid[b]
9α-Fluorohydrocortisone BMD (I)	2.4(1.4–4.2)	Retainer
6α,9α-Difluorohydrocortisone BMD (II)	13.9(10.5–18.5)	Retainer
9α-Fluoro-6α-methylprednisone BMD (III)	14.5(10.0–21.1)	No effect
9α-Fluoro-16α-methylprednisolone BMD (IV)	5.3(3.9–7.2)	No effect
9α-Fluorohydrocortisone	5.8(4.1–8.3)	Retainer
9α-Fluorocortisone 20-ethylene ketal[c]	2.2(1.5–3.1)[d]	Retainer
9α-Fluoro-6α-methylprednisone	32(22–47)	Retainer
9α-Fluoro-6α-methylprednisone 20-ethylene ketal 21-acetate[c]	15(10–22)	Retainer
9α-Fluoro-16α-methylprednisolone (dexamethasone)	53(45–62)	Excretor
9α-Fluoro-16α-hydroxyprednisolone (triamcinolone)	3.7(3.3–4.2)	Excretor

[a] Unless otherwise noted these assays (subcutaneous) were carried out by the procedure described by I. Ringler and R. Brownfield, *Endocrinology*, **66**, 900 (1960). [b] This assay is based on the response of adrenalectomized male rats to a single subcutaneous 16 mcg. dose of compound as measured after a 5-hr. urine collection. [c] See ref. 1. [d] Assay (subcutaneous) carried out by the procedure described by S. Bernstein, R. Littell, J. J. Brown and I. Ringler, *J. Am. Chem. Soc.*, **81**, 4573 (1959).

(6) R. E. Beyler, F. Hoffman, R. M. Moriarty and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

worth noting that 20-ketalization does not reverse the salt-retaining properties of 9α-fluoro-6α-methylprednisone.[1] Reversal of salt-retention was not observed on the conversion of 9α-fluorohydrocortisone or 6α,9α-difluorohydrocortisone to the corresponding BMD derivatives I and II, respectively. However, it is probable that 9α-fluoro-6α-methylprednisone is a significantly weaker salt-retainer than either of these two compounds.[7,10]

Experimental[11]

9α-Fluoro-6α-methyl-17α,20;20,21-bismethylenedioxypregna-1,4-diene-3,11-dione (9α-Fluoro-6α-methylprednisone BMD, III).—To a solution of 9α-fluoro-17α,21-dihydroxy-6α-methylpregna-1,4-diene-3,11,20-trione[1] (465 mg.) in chloroform (20 ml.) was added 37% aqueous formaldehyde (5 ml.) and concd. hydrochloric acid (5 ml.). The two-phase system was stirred vigorously at room temperature for 48 hr. The chloroform layer was separated and washed with saturated sodium bicarbonate solution and then with water. After drying over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo* and the residue was triturated with absolute ethanol. The solids were then filtered to give 231 mg. (42%) of III, m.p. 264–265° dec. Recrystallization from methanol of material obtained in a pilot experiment (20% yield) gave white crystals, m.p. 263–264° dec.; $[\alpha]^{25}D$ +54.4° (0.87% in $CHCl_3$); $\lambda_{max.}^{CH_3OH}$ 238 mμ (ε = 16,400); $\lambda_{max.}^{KBr}$ 5.79, 5.99, 6.13, 6.19, 9.15 μ.

Anal. Calcd. for $C_{24}H_{29}FO_6$: C, 66.65; H, 6.76; F, 4.39; Found: C, 66.35; H, 6.90; F, 4.60.

6α,9α-Difluoro-11β-hydroxy-17α,20;20,21-bismethylenedioxy-pregn-4-en-3-one (6α,9α-Difluorohydrocortisone BMD, II).—From 455 mg. of 6α,9α-difluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione[3] there was obtained, as described above for III, 230 mg. (46%) of II, m.p. 280° dec. Recrystallization from methanol afforded white crystals, m.p. 283° dec.; $[\alpha]^{25}D$ +3.5° (0.56% in $CHCl_3$); $\lambda_{max.}^{CH_3OH}$ 232 mμ (ε = 18,000); $\lambda_{max.}^{KBr}$ 5.91, 6.08, 9.10 μ.

Anal. Calcd. for $C_{23}H_{30}F_2O_6$: C, 62.71; H, 6.86; F, 8.63. Found: C, 63.26; H, 6.96; F, 8.66.

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(7) Our mineralocorticoid assay is not quantitative and therefore direct comparisons are not available. However, the following data taken from the literature certainly support our supposition: 6α-methyl-9α-fluoroprednisolone acetate (and free 21-ol) is reported to have a sodium retention activity about 0.1 times deoxycorticosterone acetate (DCA),[8,9] whereas 9α-fluorohydrocortisone acetate is five times DCA[8] and 6α,9α-difluoroprednisolone is reported to be equal to deoxycorticosterone.[9]

(8) J. Fried and A. Borman, *Vitamins and Hormones*, *XVI*, 350 (1958).

(9) J. Hogg, Sixth National Medicinal Chemistry Symposium, Amer. Chem. Soc., University of Wisconsin, Madison, Wisconsin, June 23–25, 1958.

(10) NOTE ADDED IN PROOF.—Subsequent electrolyte activity studies indicate that oral administration (doses up to 128 mcg. per animal) of III produces a diuresis and kaliuresis with

no effect on sodium excretion in adrenalectomized male rats. These effects are indicative of a sodium retainer.

(11) Melting points were taken in open capillary tubes and are uncorrected.

Synthesis of Sydnones and Sydnone Imines[1]

CLAUDE V. GRECO, WAYNE H. NYBERG, AND C. C. CHENG[2]

Midwest Research Institute, Kansas City, Missouri

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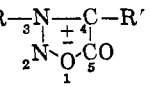
The interesting meso-ionic character[3] and the biological activity[4] exhibited by sydnones (I) have, in recent years, inspired the investigation of this type of compound by many workers. Daeniker and



I

Druey[5] reported that some polymethylene-bis-sydnones and polymethylene-bis-hydrazines showed slight tumor inhibitory activity *in vivo*. These facts, together with the information that 3-phenylsydnone (I, R = C_6H_5, R′ = H) possesses antitumor properties,[6] directed our attention to the preparation and evaluation of some 3-benzylsydnones, 3-alkylsydnones and sydnone imines for the general program of cancer chemotherapeutic studies.

The 3-substituted sydnones (IV, see Table III) have been prepared by the nitrosation of the appropriate N-substituted glycine (II, see Table I) and treatment of the N-nitroso derivative (III, see Table II) with acetic anhydride, by the procedure of Fugger, Tien, and Hunsberger.[3b] The sydnone imines (IX, see Table IV) were obtained as follows: condensation of glycolonitrile (VI) with the appropriate amine (V) yielded the corresponding N-substituted glycine nitrile

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) To whom all inquiries should be sent.

(3) For a general review of sydnones and related compounds see, for example, (a) W. Baker and W. D. Ollis, *Quart. Revs.*, **11**, 15 (1957); (b) J. Fugger, J. M. Tien, and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 1843 (1955); (c) J. M. Tien and I. M. Hunsberger, *J. Am. Chem. Soc.*, **77**, 6604 (1955); **83**, 178 (1961); (d) A. R. Katritzky, *Chem. Ind.*, 521 (1955); (e) A. Lawson and D. H. Miles, *J. Chem. Soc.*, 2865 (1959); (f) J. Ogilvie, V. K. Miyamoto, and T. C. Bruice, *J. Am. Chem. Soc.*, **83**, 2493 (1961).

(4) (a) P. Brooks and J. Walker, *J. Chem. Soc.*, 4409 (1957); (b) R. W. Putter and G. Wolfrum, German Patent 1,057,124 (Oct. 22, 1959), German Patent 1,069,633 (Nov. 26, 1959), Brit. Patent 823,001 (Nov. 4, 1959); (c) W. H. Edgerton, U. S. Patent 2,916,495 (Dec. 8, 1959).

(5) H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **40**, 918 (1957).

(6) Dr. Ronald B. Ross, National Cancer Institute, private communication. 3-Phenylsydnone had been submitted by Dr. D. J. Brown of the Australian National University.