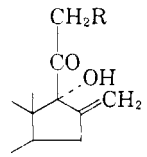
Communications TO THE EDITOR

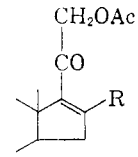
16-Methylene and Δ^{15}-16-Methyl Cortical Steroids

Sir:

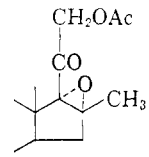
The enhanced antiinflammatory activity and elimination of sodium retention brought about by introduction of a 16α-methyl[1] or 16β-methyl[2,5] substituent (but not a 16,16-dimethyl substituent[3]) into cortical steroids have been reported. In the present communication we report syntheses of the versatile related systems: 16-methyleneprednisone 21-acetate (VI), 16-methylene-9α-fluoroprednisolone 21-acetate (VII), and Δ^{15}-16-methyl-9α-fluoroprednisolone 21-acetate (VIII).



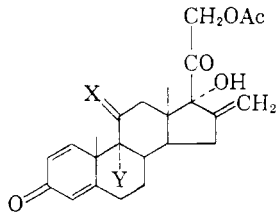
I, R = H
II, R = OAc



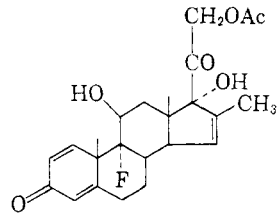
III, R = H
IV, R = CH_3
IX, R = CH_3, Δ^{14}
X, R = CH_3, 15α-Cl



V



VI, X = O, Y = H
VII, X = , Y = F



VIII

Reaction of 3α,17α-dihydroxy-16-methylenepregnane-11,20-dione (I)[4,5] with bromine in chloroform occurred exclusively by substitution at C-21 to give 21-bromo-16-methylenepregnane-3α-17α-diol-11,20-dione, m.p. 200–204°; $[\alpha]_D^{CHCl_3}$ +34°. *Anal.* Found: C, 60.31; H, 7.38. The 21-bromo compound on treatment with potassium iodide and potassium acetate in refluxing acetone was converted into 21-acetoxy-16-methylenepregnane-3α,17α-diol-11,20-dione (II), m.p. 172–175°; $[\alpha]_D^{CHCl_3}$ +44°. *Anal.* Found: C, 68.47; H, 8.24. Oxidation of II at C-3 with sodium dichromate in acetic acid led to 21-acetoxy-16-methylenepregnane-17α-ol-3,11,20-trione, double m.p. 175–185°, 205–215°; $[\alpha]_D^{CHCl_3}$ +38°. *Anal.* Found: C, 68.85; H, 7.72. Dibromination of the latter followed by dehydrobromination in dimethylformamide-dimethylaniline led to 16-methyleneprednisone 21-acetate (VI), m.p. 214–217°; $[\alpha]_D^{CHCl_3}$ +123°; $\lambda_{max}^{CH_3OH}$ 238 mμ (14,100); $\lambda_{max}^{CHCl_3}$ 2.74, 2.86–3.00, 5.73 sh., 5.76, 5.84, 6.00, 6.14, 6.20, 11.19 μ. *Anal.* Found: C, 69.96; H, 6.94. The 16-methylene hydrogens in VI as well as in other 16-methylene steroids exhibited a characteristic NMR doublet near 44 and 51 c.p.s. relative to benzene.

The 16-methylene group was introduced into 16-unsubstituted cortical steroids by an alternate procedure capable of general application. 9α-Fluoroprednisolone 21-acetate was converted by dehydration of its 3,20-disemicarbazone[6] into 21-acetoxy-9α-fluoro-1,4,16-pregnatriene-11β-ol-3,20 dione (III), m.p. 220–223°; $[\alpha]_D^{CHCl_3}$ +148°; $\lambda_{max}^{CH_3OH}$ 239 mμ (25,100); *Anal.* Found: C, 68.34; H, 7.10. The 1,4,16-pregnatriene (III) on treatment with diazomethane followed by pyrolysis gave 21-acetoxy-9α-fluoro-16-methyl-1,4,16-pregnatriene-11β,17α-diol-3,20-dione (IV), m.p. 232–235°; $[\alpha]_D^{CHCl_3}$ +92°; $\lambda_{max}^{CH_3OH}$ 243 mμ, (22,700); *Anal.* Found: C, 69.18; H, 7.05. Oxidation of IV with organic peracids at the 16,17-double bond proceeded essentially without involvement of the ring A dieneone system to give 16α,17α-oxido-21-acetoxy-9α-fluoro-16β-methyl-1,4-pregnadiene-11β-ol-3,20-dione (V), m.p. 227–230°; $[\alpha]_D^{CHCl_3}$ +146°; $\lambda_{max}^{CH_3OH}$ 237 mμ (15,100); *negative* tetrazolium test[7]; *Anal.* Found: C, 66.58; H, 6.74. Brief treatment of V with hydrogen chloride in acetic acid gave a mixture of 16-methylene-9α-fluoroprednisolone 21-acetate (VII), m.p. 231–234°; $[\alpha]_D^{CHCl_3}$ +43°; $\lambda_{max}^{CH_3OH}$ 238 mμ (15,700); $\lambda_{max}^{CHCl_3}$ 2.73, 2.85–2.90, 5.73, 5.76,

(1) 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); (b) 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. Am. Chem. Soc.*, **80**, 4431 (1958).

(2) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); (b) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958); (c) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6627 (1958).

(3) R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **24**, 1617 (1959).

(4) G. Nominé, D. Bertin, and A. Pierdet, *Tetrahedron*, 8, 217 (1960).

(5) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

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

(7) *Cf.* R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

5.99, 6.10, 6.18, 11.2 μ. *Anal.* Found: C, 66.74; H, 6.71, and 16-methyl-9α-fluoro-1,4,15-pregnatriene-11β,17α,21-triol-3,20-dione 21-acetate (VIII), m.p. 242–247°; $[\alpha]_D^{C_5H_5O}$ +45°; $\lambda_{max}^{CH_3OH}$ 238 mμ (15,100); λ_{max}^{Nujol} 2.91, 3.05, 5.75, 5.81, 6.01, 6.15, 6.19, 11.25 μ. *Anal.* Found: C, 66.72; H, 7.08. Extended reaction of the 16β-methyl-16α,17α-oxide (V) with hydrogen chloride in acetic acid led to the 16-methylene compound (VII) and two substances evidently derived from the Δ^{15}-16, methyl compound (VIII).[8] These are, respectively-9α-fluoro-16-methyl-1,4,14,16-pregnatetraene-11,21-diol-3,20-dione 21-acetate (IX), m.p. 282–285° dec. $[\alpha]_D^{CHCl_3}$ +531°; $\lambda_{max}^{CH_3OH}$ 307 mμ (12,400), 236 mμ (16,200). *Anal.* Found: C, 69.48; H, 6.88, and 9α-fluoro-15α-chloro-16-methyl-1,4,16-pregnatriene-11,21-diol-3,20-dione 21-acetate (X), m.p. 272–275° dec. $\lambda_{max}^{CH_3OH}$ 241 mμ (20,800); $\lambda_{max}^{CHCl_3}$ 2.77, 2.90–2.95 (11β-OH), 5.74 μ (21-OAc), 6.00 μ (3,20-C=O), 6.12, 6.18, 11.16 μ.

The biological properties of the pertinent new compounds are currently being evaluated.

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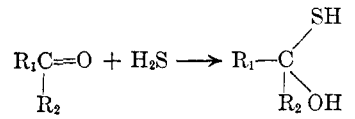
(8) Compare (5).

Hydrogen Sulfide Adducts of Halogenated Aldehydes and Ketones

Sir:

gem-Diols (aldehydes and ketone hydrates) derived from aldehydes and ketones with strong electron attracting groups—*e.g.*, chloral, bromal, glyoxylic acid, and highly fluorinated aldehydes and ketones—have been isolated and characterized. In recent years, a variety of *gem*-dithiols have been prepared and they appear to be a relatively stable class of compounds.[1,2] Apparently there is no previous report of the isolation of a compound with a hydroxyl and mercapto group on the same carbon.[3]

It has now been found that such compounds can be prepared by the reaction of hydrogen sulfide, without added catalyst, with fluorinated or chlorinated aldehydes and ketones:



R_1 = fluoroalkyl, fluorochloroalkyl chloroalkyl
R_2 = fluoroalkyl fluorochloroalkyl, H

For example, 1,3-dichloro-1,1,3,3-tetrafluoro-2-mercapto-2-propanol (b.p. 51°/15 mm., n_D^{24} 1.4208, $\lambda_{max}^{CHCl_3}$ 3.85 μ (sulfhydryl), 2.85 μ (hydroxyl), [*Anal.* Calcd. for $C_3H_2Cl_2F_4OS$: Cl, 30.4; F, 32.6; S, 13.8. Found: Cl, 30.5; F, 33.0; S, 14.0] was prepared in 91% yield by heating *sym*-dichlorotetrafluoroacetone with an excess (six-fold) of hydrogen sulfide in an autoclave at 80° for several hours. A lower yield was obtained from a comparable experiment at room temperature. The corresponding olthiols were also prepared from chloral, trifluoroacetaldehyde, pentafluoropropionaldehyde, heptafluorobutyraldehyde, 5-hydrooctafluorovaleraldehyde, decafluoro-3-pentanone, and tetradecafluoro-4-heptanone. The boiling points and refractive indices of these compounds are tabulated in Table I. All of these olthiols could be distilled *in vacuo*. The infrared spectra exhibited characteristic OH and SH frequencies. α-Hydroxy disulfides could be prepared by reaction of the olthiols with sulfenyl chlorides.

TABLE I

PROPERTIES OF OLTHIOLS, $R_1R_2C(OH)SH$

R_1	R_2	B.P./mm.	n_D^{25}
CCl_3	H	71–74/4	1.5533
CF_3	H	51/80	1.3879
C_2F_5	H	56/66	1.3611
C_3F_7	H	54/46	1.3507
$H(CF_2)_4$	H	69–71/17	1.3669
C_2F_5	C_2F_5	41/56	1.3251
C_3F_7	C_3F_7	38–39/10	—

A considerable variation in stability at room temperature was noted within this group of compounds. The olthiol derived from *sym*-dichlorotetrafluoroacetone appeared to be unchanged after several days at room temperature. The olthiol from decafluoro-3-pentanone, on the other hand, was completely decomposed, presumably to the ketone and hydrogen sulfide, after just a few hours at room temperature. Those derived from chloral and the fluorinated aldehydes are of intermediate stability.

Work is continuing to determine the scope of the H_2S— carbonyl addition reaction. A study is also being made of the chemistry of these new olthiols.

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(1) T. L. Cairns, G. L. Evans, A. W. Larchar, and B. C. McKusick, *J. Am. Chem. Soc.*, **74**, 3982 (1952).

(2) G. A. Berchtold, B. E. Edwards, E. Campaigne, and M. Carmack, *J. Am. Chem. Soc.*, **81**, 3148 (1959).

(3) Baumann, *Ber.*, **23**, 60 (1890), proposed the transient existence of 1,1-olthiols in the preparation of trithianes by the reaction of hydrogen sulfide with aldehydes. R. W. Borgeson and J. A. Wilkinson, *J. Am. Chem. Soc.*, **51**, 1453 (1929), also proposed a 1,1-olthiol as the intermediate in the conversion of furfural to thiofurfural by hydrogen sulfide.