185°. Further purification was effected by two crystallizations from water and one from ethanol–petroleum ether (b.p. 30–60°); m.p. 185–187°, $[\alpha]_D^{28}$ +62° (*c* 1.5, ethanol).

Anal. Calcd. for $C_{10}H_{18}O_3N_2S_2$: C, 40.94; H, 6.52; N, 14.32; S, 21.86. Found: C, 41.35; H, 6.69; N, 14.60; S, 22.16.

Ethyl 3-O-acetyl-2-S-ethyl-1,2-dithio-5-aldehydo-α-D-xylo-(lyxo)-pentodialdofuranoside (dimeric) (VI). The dried sirup (V) resulting from the periodate oxidation of 0.5 g. of ethyl 2-*S*-ethyl-1,2-dithio-α-D-gluco(manno)furanoside, as described above, was aged for 24 hr. and was then acetylated for 8 hr. at room temperature with 10 ml. of pyridine and 2 ml. of acetic anhydride. The solid obtained by decantation after pouring into 200 ml. of ice and water, was crystallized by trituration with methanol. Pure material was obtained by recrystallization from ether–petroleum ether; m.p. 133–134°, $[\alpha]_D^{27}$ +128.5° (*c* 1.2, chloroform).

Anal. Calcd. for $C_{11}H_{18}O_4S_2$: C, 47.43; H, 6.52; S, 23.03; mol. wt. dimer, 556. Found: C, 47.36; H, 6.72; S, 23.07; mol. wt. (Rast), 501.

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The Synthesis of 21-*O*-Alkylhydrocortisone Derivatives and of 11β-Hydroxy-17α,21-methylenedioxy-4-pregnene-3,20-dione[1a]

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The observation[2] that treatment of a polyhydroxylated steroid derivative with potassium *t*-butoxide and methyl iodide results in preferential *O*-methylation of a 21-hydroxy group in the presence of 11β- and 17α-hydroxy groups,[3] prompted us to use this convenient procedure for the preparation of certain 21-*O*-alkyl derivatives of hydrocortisone. We now wish to communicate the results of our investigation.

Several 21-*O*-methyl derivatives have already been reported. Cortisone 21-*O*-methyl ether has been obtained[4] *via* the reaction of 20-cyano-3α,21-dihydroxy-17-pregnene-11-one with methanolic alkali followed by elaboration of the 17α-hydroxy 20-ketone moiety and the ring A Δ⁴-3-one, a relatively complex procedure. More recently, Zorbach and Tamorria described[5] the synthesis of 21-O-methyldeoxycorticosterone by treatment of 21-diazoprogesterone with methanol in the presence of boron trifluoride etherate. Finally, during the course of our study, Neeman and coworkers reported the convenient preparation[6] of 21-O-methyldeoxycorticosterone and 17-*O*-methyltestosterone from the respective free steroids by treatment with diazomethane in the presence of fluoboric acid. No testing results for any of these compounds were reported.

As *t*-butoxide-alkyl halide treatment of a Δ⁴-3-ketone will result in C-4 alkylation,[3,7] and presumably a 17α-hydroxy 20-ketone will undergo D-homoannulation, it was necessary to carry out the *O*-alkylation with a compound having the 3- and 20-carbonyl functions blocked. A suitably blocked starting material for the synthesis of 21-*O*-alkyl derivatives in the glucocorticoid series was therefore, the conveniently available hydrocortisone 3,20-bisethylene ketal (I).[8]

Treatment of bisketal I with potassium *t*-butoxide (3 molar equivalents) and methyl iodide (6 molar equivalents) in hot *t*-butyl alcohol resulted in the anticipated preferential methylation of the 21-hydroxyl group, and afforded the 21-*O*-methyl 3,20-bisketal II. Ketal hydrolysis of II with 1% methanolic sulfuric acid then gave the desired 21-*O*-methylhydrocortisone (IV). By a similar procedure, 21-*O*-hexadecylhydrocortisone (V) was prepared. When bisketal I was treated with potassium *t*-butoxide and 2-bromopyridine, the desired 21-*O*-(2-pyridyl) derivative VI could not be isolated, and instead a low yield of the 17α,21-oxide VII[9] was obtained. Presumably, the initially formed VI underwent internal cyclization to give VII, a reaction facilitated by resonance stabilization of the departing pyridone anion. Preliminary attempts to effect condensation with ethyl bromoacetate and with 2-dimethylaminoethyl chloride were unsuccessful and were not pursued.

In view of the enhanced glucocorticoid activity reported[10] for the *O,O'*-alkylidene derivatives of 16α,17α-diols, it was of interest to prepare a 17,21-*O,O'*-alkylidene derivative[11] of hydrocortisone. Bisketal I was treated with potassium *t*-butoxide and methylene bromide to give the 17α,21-methylenedioxy derivative VIII, treatment of which with refluxing 1% methanolic sulfuric acid for one hour resulted in preferential hydrolysis of the ketal group at C-3 to give IX in 88% crude yield. It may be noted that these hydrolysis conditions

(1) (a) This paper is part of a continuing program of research in the steroid hormone field. For the previous paper in this series see R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, 26, 1223 (1961). (b) To whom inquiries concerning this paper should be addressed.

(2) W. S. Allen and M. J. Weiss, *J. Org. Chem., in press.*

(3) N. W. Atwater [*J. Am. Chem. Soc.*, 79, 5315 (1957)] reported no evidence of 17-*O*-alkylation when testosterone was treated with potassium *t*-butoxide and methyl iodide.

(4) Huang-Minlon, R. Tull, and J. Babcock, *J. Am. Chem. Soc.*, 76, 2396 (1954).

(5) W. W. Zorbach and C. R. Tamorria, *J. Org. Chem.* 22, 1127 (1957).

(6) M. Neeman, M. C. Caserio, J. D. Roberts, and W. S. Johnson, *Tetrahedron*, 6, 36 (1959).

(7) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Am. Chem. Soc.*, 76, 2852 (1954).

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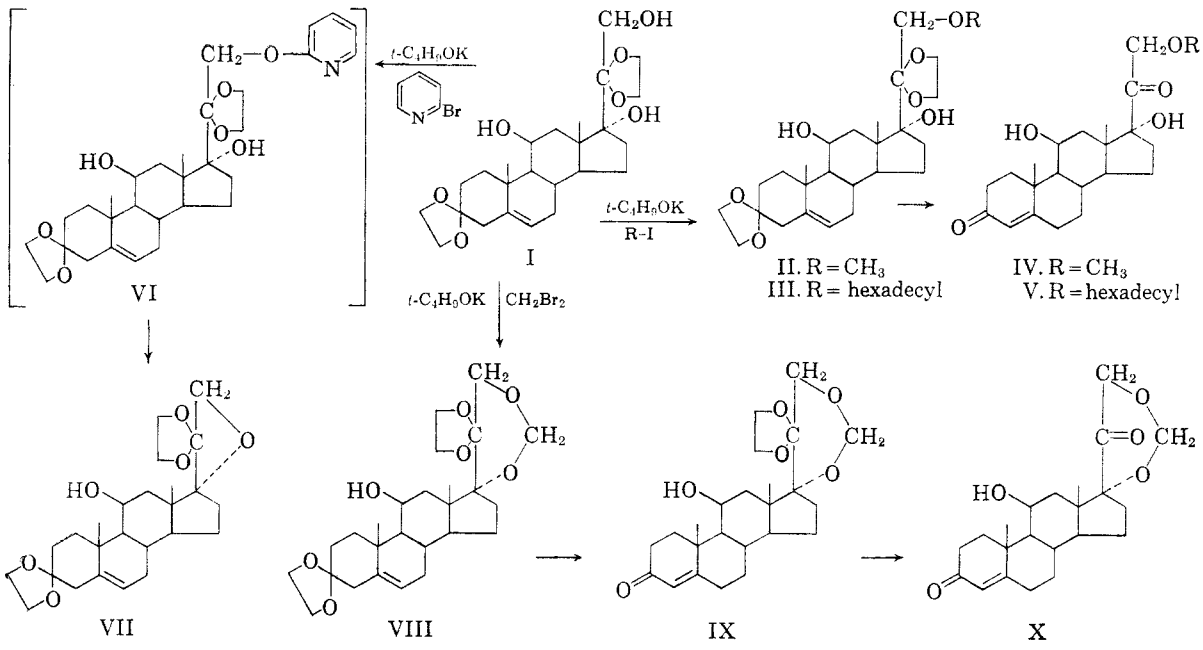
(11) 17α,21-Isopropylidenedioxy steroid derivatives have recently been reported [M. Tanabe and B. Bigley, *J. Am. Chem. Soc.*, 83, 756 (1961)].



when applied to bisketal I result in complete ketal hydrolysis.[9] Heating the 20-monoketal IX with 1% methanolic sulfuric acid for four hours at reflux, also did not cause substantial 20-ketal hydrolysis, and IX was recovered in 63% yield. However, a twenty-four hour refluxing period with this reagent, or treatment with refluxing 60% aqueous formic acid for two hours converted IX to the desired 17α,21-methylenedioxy-3,20-dione X. Several attempts to effect the hydrolysis of X to hydrocortisone were unsuccessful.

Compounds IV, V, and X when assayed in adrenalectomized rats by the liver glycogen and thymus involution procedure[12] at a 500 γ daily dose for five days were found to be inactive.

EXPERIMENTAL[13]

11β,17α-Dihydroxy-21-methoxy-5-pregnene 3,20-bisethylene ketal (II). To a solution of potassium (1.7 g.) in *t*-butyl alcohol (100 ml.) under nitrogen was added a slurry of 11β,17α,-21-trihydroxy-5-pregnene 3,20-bisethylene ketal[8] (I, 6.0 g.) in *t*-butyl alcohol (100 ml.) followed by methyl iodide (5.5 ml.). The mixture was stirred and refluxed for 3 hr. After cooling, chloroform (800 ml.) was added and the mixture washed to neutrality with water. The extract was dried and evaporated to give a solid residue which was crystallized from acetone–petroleum ether. This gave 4.3 g., m.p. 176–177° (70%). Recrystallization from the same solvent pair did not change the melting point; $[\alpha]_D^{25}$ −34° (chloroform); ν_{max} 3470, 1106, and 1058 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{40}O_7$ (464.58): C, 67.21; H, 8.68. Found: C, 67.12; H, 9.00.

11β,17α-Dihydroxy-21-methoxy-4-pregnene-3,20-dione (IV). A solution of 11β,17α-dihydroxy-21-methoxy-5-pregnene 3,20-bisethylene ketal (II, 1.0 g.) in methanol (100 ml.) containing aqueous sulfuric acid (10 ml., 8%) was refluxed for 1 hr. Water was added and the mixture concentrated *in vacuo* until crystallization was effected. The product was filtered, washed with water, and dried. This gave 0.72 g., m.p. 251–254° (81%). Recrystallization from acetone raised the melting point to 254–256°; $[\alpha]_D^{25}$ +145° (dioxane); λ_{max} 241 mμ (ϵ 16,500). The infrared spectrum was identical to that of an authentic sample.[2]

21-Hexadecyloxy-11β,17α-dihydroxy-5-pregnene 3,20-bisethylene ketal (III). In a manner similar to that used for the preparation of II (above), treatment of I (10.0 g., 22.2 mmoles) in *t*-butyl alcohol (100 ml.) with a solution of potassium (3.0 g., 0.72 mmole) in *t*-butyl alcohol (100 ml.) and 1-bromohexadecane (16.7 g., 55 mmoles) gave an oily residue after the usual workup. Trituration with acetone yielded 10.2 g., m.p. 73–78.5°. An additional 6 g., m.p. 72–78°, was obtained by concentration of the mother liquor (combined yield 91%). Recrystallization of the combined fractions raised the melting point to 84.5–85.0°; $[\alpha]_D^{25}$ −19° (chloroform); ν_{max} 3422, 1106, 1056, and 1032 cm.$^{-1}$

Anal. Calcd. for $C_{41}H_{70}O_7$ (674.97): C, 72.95; H, 10.45. Found: C, 72.73; H, 10.51.

21-Hexadecyloxy-11β-hydroxy-4-pregnene-3,20-dione (V). A solution of 21-hexadecyloxy-11β-hydroxy-5-pregnene 3,20-bisethylene ketal (III, 1.6 g.) in methanol (160 ml.) containing sulfuric acid (8% v/v) (16 ml.) was refluxed for 1 hr. Water was added and the crystalline product collected by filtration. This gave material melting at 85–94°. Recrystallization from acetone–petroleum ether raised the melting point to 111–112°; $[\alpha]_D^{25}$ +92° (chloroform); λ_{max} 242 mμ (ϵ 15,000); ν_{max} 3510, 1728, 1662, 1627, 1140, and 1114 cm.$^{-1}$

Anal. Calcd. for $C_{37}H_{62}O_5$ (586.87): C, 75.75; H, 10.64. Found: C, 75.39; H, 10.88.

Treatment of bisketal I with potassium t-butoxide and 2-bromopyridine. Formation of 11β-hydroxy-17α,21-epoxy-5-pregnene 3,20-bisethylene ketal (VII). In a manner similar to that used for the preparation of II, treatment of bisketal I (10 g., 22.2 mmoles) in *t*-butyl alcohol (100 ml.) with a solu-

(12) See S. Bernstein, R. Littell, J. J. Brown, and I. Ringler [*J. Am. Chem. Soc.*, **81**, 4523 (1959), footnote a to Table I] for a description of this assay.

(13) All melting points were determined in a capillary tube and are uncorrected. The ultraviolet spectra were determined in methanol solution on a Cary recording spectrophotometer unless otherwise specified. The infrared spectra (pressed potassium bromide disc) were determined with a Perkin-Elmer spectrophotometer (Model 21). Optical rotations were determined in a 1-dm. semi-micro tube at wave length 5893 Å (D). All evaporations were carried out under reduced pressure. Except where otherwise noted, the petroleum ether used was that fraction boiling at 60–70°.

tion of potassium (3 g., 72 mmoles) in *t*-butyl alcohol (100 ml.) and 2-bromopyridine (4 g., 25 mmoles) gave an oily residue after the usual work up. This residue was crystallized from acetone to give 1 g., m.p. 218–231° (10%). Recrystallization from acetone raised the m.p. to 251.5–252.5°; $[\alpha]_D$ −28° (chloroform). The infrared spectrum was identical to that of an authentic sample.[9]

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.26; H, 8.45.

Treatment of the above product (VII) with 1% methanolic sulfuric acid (1 hr. reflux) gave a 77% yield (m.p. 204–205°) of 13α,21-epoxy-11β-hydroxy-17β-methyl-18-nor-17α-Δ^4-pregnene-3,20-dione. Recrystallization from acetone–petroleum ether raised the m.p. to 206–208°; $[\alpha]_D^{25}$ +52° (chloroform); λ_{max} 242 mμ (ϵ 16,900). The infrared spectrum was identical to that of an authentic sample.[9,14]

11β-Hydroxy-17α,21-methylenedioxy-5-pregnene 3,20-bisethylene ketal (VIII). To a solution of potassium (1.7 g.) in *t*-butyl alcohol (100 ml.) under nitrogen was added a slurry of 11β,17α,21-trihydroxy-5-pregnene 3,20-bisethylene ketal (I, 6.0 g.) in *t*-butyl alcohol (100 ml.) followed by the addition of methylene bromide (5.0 ml.). The mixture was stirred and refluxed for 3 hr. After cooling, chloroform (800 ml.) was added and the mixture washed to neutrality with water. The extract was dried and evaporated to give a solid residue which was crystallized from acetone–petroleum ether; yield 3.85 g., m.p. 220–240°. Several recrystallizations from the same solvent pair raised the melting point to 252–255°; $[\alpha]_D^{25}$ −42° (chloroform); ν_{max} 3448, 1092, 1052, and 956 cm.$^{-1}$

Anal. Calcd. for $C_{26}H_{39}O_7$ (462.56): C, 67.51; H, 8.28. Found: C, 67.56, 67.09, 67.42; H, 8.52, 8.59, 8.36.

11β-Hydroxy-17α,21-methylenedioxy-4-pregnene-3-one 20-ethylene ketal (IX). A solution of 11β-hydroxy-17α,21-methylenedioxy-5-pregnene 3,20-bisethylene ketal (VIII) (250 mg.) in methanol (50 ml.) containing sulfuric acid (8%, 5 ml.) was refluxed for 1 hr. It was poured into water and the mixture neutralized with solid sodium bicarbonate. The resulting crystalline product was collected by filtration. This gave 200 mg., m.p. 195–197° (88%). Recrystallization from acetone–petroleum ether raised the melting point to 235–237°; $[\alpha]_D^{25}$ +97° (chloroform); $\lambda_{max}^{CH_3OH}$ 241 mμ (ϵ 16,900); ν_{max} 3436, 1664, 1612, 1046, and 956 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 68.35; H, 8.20.

11β-Hydroxy-17α,21-methylenedioxy-4-pregnene-3,20-dione (X). *A. Hydrolysis with 1% sulfuric acid.* A solution of 11β-hydroxy-17α,21-methylenedioxy-4-pregnene-3-one 20-ethylene ketal (IX, 207 mg.) in methanol (50 ml.) containing sulfuric acid (8% v/v) (10 ml.) was refluxed for 24 hr. Water was added and the methanol evaporated to give a crystalline product which was collected by filtration; yield 139 mg. (75%), m.p. 180–185°. Recrystallization from acetone–petroleum ether raised the m.p. to 211–213°; $[\alpha]_D^{25}$ +185° (chloroform); λ_{max} 241 mμ (ϵ 16,500); ν_{max} 3460, 1714, 1667, 1618, 1118, and 1047 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_5$ (374.46): C, 70.56; H, 8.08. Found: C, 70.25; H, 8.15.

B. Hydrolysis with formic acid. A solution of IX in 60% formic acid was heated on a steam bath for 1 hr., and after the usual work-up and crystallization from acetone–petroleum ether, a 72% yield of 11β-hydroxy-17α,21-methylenedioxy-4-pregnene-3,20-dione (X) was obtained.

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4-Dibutylamino-2-methylpyrimidine-5-carboxaldehyde Semicarbazone

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The recent note by Wiley and Yamamoto[1] listing the various methods by which pyrimidine carboxaldehydes have been prepared prompts us to report on a further method with which we have had success, namely the reaction of hexamethylenetetramine on a 5-chloromethylpyrimidine.

EXPERIMENTAL

4-Dibutylamino-5-ethoxymethyl-2-methylpyrimidine. 4-Chloro-5-ethoxymethyl-2-methylpyrimidine[2] (110 g.) and 228 g. of dibutylamine were heated on the steam bath. An exothermic reaction ensued, the temperature of the reaction mixture rising to 145–150°. After 1 hr. the dibutylamine hydrochloride was removed by filtration, the filter cake was washed with ether, the combined filtrate and wash were concentrated, and the residue was distilled *in vacuo*. The product had b.p. 130° (0.23 mm.) and n_D^{24} 1.5022.

Anal. Calcd. for $C_{16}H_{29}N_3O$ (mol. wt. 279.41): C, 68.77; H, 10.46. Found: C, 68.32; H, 10.50.

The *picrate* had a m.p. of 87–88.5°, and is soluble in ether. The *chloroplatinate* crystallized with great difficulty.

5-Chloromethyl-4-dibutylamino-2-methylpyrimidine hydrochloride. A solution of 10 g. of the above dibutylaminopyrimidine in 50 ml. of glacial acetic acid was saturated with hydrogen chloride at 0°, and the solution heated in a sealed glass tube at 150–160° for 5 hr. The product,[3] a white waxy solid, was obtained by concentrating the solution. Yield, 13.8 g.

4-Dibutylamino-2-methyl-pyrimidin-5-carboxaldehyde semicarbazone. A 13.8-g. portion of the above material, which was soluble in water and alcohol, was recrystallized from glacial acetic acid, precipitated from ice cold aqueous solution with sodium bicarbonate, and the free base immediately extracted with ether. After drying the extract, the ether was removed and the residue dissolved in 140 ml. of 2-propanol. Water (3 ml.) and 4.8 g. of hexamethylenetetraamine were added and the solution refluxed for 6 hr. After removal of the 2-propanol, the resultant product was ex-

(1) R. M. Wiley and Y. Yamamoto, *J. Org. Chem.*, **25**, 1906 (1960).

(2) A generous sample of this material was supplied by Merck and Co.

(3) This was reconverted to 4-dibutylamino-5-ethoxymethyl-2-methylpyrimidine with sodium ethoxide. The product had n_D^{24} 1.5032. The picrate had a m.p. of 87–89.5°, showing no depression on admixture with authentic material.