tographed on acid-washed alumina. The material eluted with ether–petroleum ether (6:4) through ether was recrystallized from methylene chloride–ether and gave 481 mg. of product XIVb, m.p. 187–193°. A sample recrystallized for analysis from the same solvent pair melted at 190–196°. Upon admixture with a sample of 7α-methyl-17,20;20,21-bismethylenedioxypregnane-3,11-dione (IX), m.p. 205–210° (215°), the melting point was depressed to 170–190°; λ_{max}^{Nujol} 5.88, 9.0–9.3 μ.

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 69.20; H, 7.80.

Bromination and Dehydrobromination of 7β-Methyl-17,20;20,21-bismethylenedioxyallopregnane-3,11-dione (XIVb).—The diketone (50 mg.) was dissolved in 1.5 ml. of dimethylformamide and to this solution was added 22.5 mg. of bromine in 1.5 ml. of dimethylformamide and 11 mg. of *p*-toluenesulfonic acid. After 3 hours, the bromine color had disappeared and the reaction mixture was worked up in the usual manner to give 62 mg. of an oil which would not crystallize. Bromine analysis on the oil showed that it contained 14.94% bromine. The calculated value for $C_{24}H_{33}O_6Br$ is 16.07%. The crude oil was then treated with 14 mg. of semicarbazide hydrochloride, 26 mg. of semicarbazide and 2 ml. of dimethylformamide for two hours at room temperature. The product was then isolated in the usual manner but not purified. The crude semicarbazone mixture was then treated with 0.8 ml. of pyruvic acid, 0.8 ml. of acetic acid and 0.8 ml. of water at room temperature for 19 hours. The reaction was worked up in the usual manner and 60 mg. of crude product was obtained. Ultraviolet analysis on this crude product showed a λ_{max}^{MeOH} 233 mμ (*E*% 128), indicating a Δ^1-3-ketone. Attempts to separate the mixture were unsuccessful.

7β-Methylprednisone-BMD (XV).—To a solution of 100 mg. of 7β-methyl-17,20;20,21-bismethylenedioxyallopregnane-3,11-dione (XIVb) in 2 ml. of *t*-butyl alcohol and 0.1 ml. of acetic acid was added 100 mg. of mercury, 74 mg. of selenium dioxide and 3.3 ml. of *t*-butyl alcohol. The reaction mixture was stirred under reflux for 16 hours. The reaction mixture was filtered and the filtrate diluted with ethyl acetate. The ethyl acetate solution was then extracted with ammonium sulfide solution, sodium bicarbonate solution, dilute hydrochloric acid, dried and evaporated to dryness. The residue was then chromatographed on acid-washed alumina. The fractions eluted with ether–chloroform (4:1) through ether–chloroform (3:2) were combined and recrystallized from methylene chloride–ether resulting in 36 mg. of product XV, m.p. 245–253°. A sample recrystallized for analysis melted at 248–254°, λ_{max}^{MeOH} 238 mμ (ε 14,500); $\lambda_{max}^{H_2SO_4}$ 261 mμ (*E*% 362), 317 mμ (*E*% 276) (inflection), 338 mμ (*E*% 260); $\lambda_{max}^{CHCl_3}$ 5.80, 5.95, 6.10, 6.18, 8.8–9.2 μ.

Anal. Calcd. for $C_{24}H_{30}O_6$ (414.48): C, 69.54; H, 7.30. Found: C, 68.93; H, 7.15.

7α-Methylprednisone-BMD (XVI).—To 15 mg. of 7α-methylcortisone-BMD (X), 0.3 ml. of *t*-butyl alcohol, 0.02 ml. of glacial acetic acid and *ca.* 35 mg. of mercury was added 10 mg. of selenium dioxide in 0.5 ml. of *t*-butyl alcohol. The mixture was heated under reflux with stirring for 7 hours, an additional 10 mg. of selenium dioxide in 0.8 ml. of *t*-butyl alcohol was added and the reaction continued for 15 hours longer. The resultant mixture was filtered and the precipitate washed thoroughly with ethyl acetate. The ethyl acetate solution was washed with ammonium sulfide solution, dilute hydrochloric acid, aqueous sodium bicarbonate, dried and concentrated to 17 mg. of yellow oil. This was chromatographed on 1 g. of acid-washed alumina. The ether–chloroform (4:1) effluents yielded crystalline 7α-methylprednisone-BMD (XVI). Recrystallization from methylene chloride–ether resulted in 4 mg., m.p. 253–258°. Upon admixture with a sample of 7β-methylprednisone-BMD (XV) above, there was a marked depression, m.p. 220–250°, λ_{max}^{MeOH} 239 mμ (ε 15,500); $\lambda_{max}^{H_2SO_4}$ 260 mμ (*E*% 431), 314 mμ (*E*% 316) (inflection), 340 mμ (*E*% 245); λ_{max}^{Nujol} 5.82, 5.95, 6.10, 6.18, 8.8–9.2 μ. There was insufficient material for elemental analysis.

Acknowledgment.—The authors wish to thank Mr. J. J. Wittick and his associates for ultraviolet absorption spectra, Mr. R. N. Boos and his associates for the microanalyses, Dr. N. R. Trenner and Mr. R. W. Walker for the infrared spectra and Dr. D. E. Williams for the rotatory dispersion curves.

RAHWAY, N. J.

[CONTRIBUTION FROM MERCK SHARP AND DOHME RESEARCH LABORATORIES]

Bismethylenedioxy Steroids. IV.[1] 11α-Methylhydrocortisone Acetate and 9α-Chloro-11α-Methylhydrocortisone Acetate

BY R. E. BEYLER, FRANCES HOFFMAN AND L. H. SARETT

RECEIVED MAY 21, 1959

Syntheses of 11α-methylhydrocortisone acetate (V) and 9α-chloro-11α-methylhydrocortisone acetate (XIII) are described. The former was prepared from cortisone-BMD by a five-step synthesis; the latter from an eight-step syntheses starting with 9α-fluorohydrocortisone-BMD. Both V and XIII are devoid of biological activity.

The synthesis of 11α-alkylated adrenocortical steroids is of considerable theoretical interest in view of the enhanced antiinflammatory activity exhibited by 2-,[3] 6-[3] and 16-[4] alkylated hydrocortisone and derived compounds.

Placement of an equatorial methyl group adjacent to the 3-keto-Δ^4-system (at C_2 or C_6) or a methyl group next to the side chain (16α or 16β), which are the sites of metabolic inactivation, has given enhanced biological activity. In contrast, a methyl group directly on the essential 3-keto Δ^4-system (at C_4) completely obliterated activity.[5] 7α- or 7β-methyl substitution, which is relatively remote from functional groups, gave moderately reduced activity.[1]

The substitution of methyl groups in the C-ring allows one to study the effect on the antiinflamma-

(1) Paper III, R. E. Beyler, A. E. Oberster, Frances Hoffman and L. H. Sarett, THIS JOURNAL, **82**, 170 (1960).

(2) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955).

(3) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956); (b) J. H. Fried, G. E. Arth and L. H. Sarett, *ibid.*, **81**, 1235 (1959).

(4) (a) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *ibid.*, **80**, 3160 (1958); (b) 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); (c) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4428 (1958); (d) 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, *ibid.*, **80**, 4431 (1958); (e) D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, *ibid.*, **80**, 4435 (1958); (f) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 6687 (1958).

(5) N. G. Steinberg, R. Hirschmann and J. M. Chemerda, *Chemistry & Industry*, 975 (1958).

tory-essential 11-oxygen function. 9α-Methyl-hydrocortisone had moderately reduced activity.[6] Bush[7] has suggested that the mode of action of these hormones at the molecular level may involve the oxidation of the 11-hydroxyl to an 11-oxo form. Thus it was of interest to synthesize an adrenocortical steroid with a methyl group attached directly to the critical carbon eleven of the steroid nucleus.

This paper describes the synthesis of 11α-methylhydrocortisone acetate (V) in five steps from the readily accessible 17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (I).[8] After this work was completed, a preliminary communication of Fonken and Hogg[9] appeared which described the synthesis of 11α-methylhydrocortisone acetate by a different route. The synthesis of 11α-methylandrostane derivatives[10] and other 11α-methylpregnane[11] derivatives has also been published recently.

The synthesis of 9α-chloro-11α-methylhydrocortisone acetate (XIII) from 9α-fluorohydrocortisone-BMD (VI)[8] constitutes the second portion of this communication.

11α-Methylhydrocortisone Acetate.—Reaction of cortisone-BMD (I)[8] with ethylene glycol–*p*-toluenesulfonic acid gave cortisone-BMD-3-dioxolane (II). When II was allowed to react with excess methyllithium[12] for four hours at room temperature, a 60% yield of 11α-methylhydrocortisone-BMD-3-dioxolane (III) was isolated by direct crystallization. Its structure was readily discernible from the fact that it contained a hydroxyl but no carbonyl absorption band in the infrared. The stereochemistry is assigned on the basis of known 11α-attack in the mechanistically similar reduction of an 11-ketone with lithium aluminum hydride.

Removal of the 3-dioxolane group of III with *p*-toluenesulfonic acid in acetone gave 11α-methylhydrocortisone-BMD (IV). The BMD protecting group was hydrolyzed with 50% acetic acid at 100° for 6.5 hours. Acetylation and chromatography gave the desired 11α-methylhydrocortisone acetate (V). The dioxolane and BMD hydrolysis can be combined into one step, but we have usually isolated the intermediate 3-keto Δ^4-compound.

The 11α-methyl substituent was found to have a large effect on polarity as measured by paper strip running rate. The R_f of 11α-methylhydrocortisone acetate was 1.8 to 2.0 with respect to hydrocortisone acetate in a benzene–formamide system. The influence of an 11α-methyl group on molecular rotation was also quite large, namely −88° (M_D of hydrocortisone acetate +666; M_D of 11α-methylhydrocortisone acetate +578°) in methanol.

A by-product, obtained from the BMD hydrolysis, was eluted from alumina before 11α-methylhydrocortisone acetate. Analytical data indicated that its structure probably was 11-methyl-4,9-(11)-pregnadiene-17α,21-diol-3,20-dione-21-acetate, which would result from acid-catalyzed dehydration of V. Although we have not usually encountered dehydrations during BMD reversals in other instances, it has occurred occasionally, as for example with a saturated 3-ketone.

9α-Chloro-11α-Methylhydrocortisone Acetate.—The reaction of methyllithium with 9α-fluorocortisone-BMD-3-dioxolane (VIII) took a different course from that of its nonfluorinated companion described above. This finding led us to the preparation of hydrocortisone modified by chlorine and methyl substituents at the 9- and 11-positions, respectively.

9α-Fluorohydrocortisone-BMD (VI)[8] was readily oxidized with chromic acid in acetic acid to 9α-fluorocortisone-BMD (VII). Ketalization of VII with ethylene glycol and *p*-toluenesulfonic acid gave the corresponding dioxolane VIII.[13] When VIII was treated with methyllithium,[14] the product obtained in good yield was the 11α-methyl-9,11β-oxide IX. Although this product might have been predicted, it is perhaps surprising that this is the only product obtained. Its structure was readily assigned because it showed neither hydroxyl nor carbonyl bands in the infrared. Elemental analysis also revealed the absence of fluorine from the molecule and so the oxide structure was assured.

Chemical evidence for structure IX was provided: The 3-dioxolane was removed to give the corresponding 3-keto-Δ^4-compound X. Cleavage of the oxide with hydrogen chloride in chloroform according to the method of Fried and Sabo[15] gave 9α-chloro-11α-methylhydrocortisone-BMD (XI). The oxide X could be reformed by treatment of XI with potassium carbonate in aqueous methanol.

Although 9α-chloro-11α-methylhydrocortisone-BMD (XI) required only removal of the BMD protecting group to give the desired compound, we were unsuccessful in our attempts to convert it to 9α-chloro-11α-methylhydrocortisone acetate (XIII). However, the 11α-methyl-9,11β-oxide (IX)

(6) Frances Hoffman, R. E. Beyler and M. Tishler, THIS JOURNAL, **80**, 5322 (1958).

(7) I. E. Bush, *Experientia*, **12**, 325 (1958).

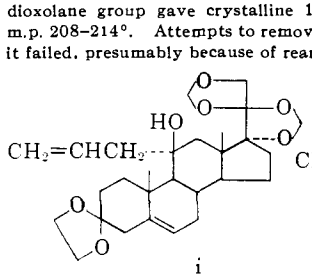
(8) R. E. Beyler, R. M. Moriarty, Frances Hoffman and L. H. Sarett, THIS JOURNAL, **80**, 1517 (1958).

(9) G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365 (1958).

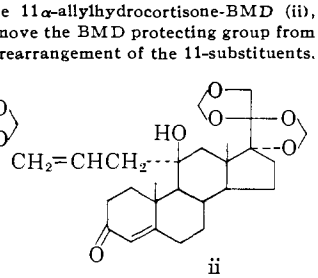
(10) J. C. Babcock, presented at the 129th Meeting of the American Chemical Society, Dallas, Tex., 1956; N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958), see footnote on p. 148; H. J. Ringold, E. Batres and J. A. Zderic, *ibid.*, **2**, 164 (1958).

(11) G. S. Fonken, Abstracts of the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, p. 99N; G. S. Fonken *J. Org. Chem.*, **23** 1075 (1958).

(12) Methylmagnesium iodide in refluxing xylene (2.25 hours) did not appreciably add to the 11-ketone as judged by the infrared spectrum of the crude product. However, allylmagnesium bromide did add to give the amorphous 11α-allyl adduct (i). Removal of the 3-dioxolane group gave crystalline 11α-allylhydrocortisone-BMD (ii), m.p. 208–214°. Attempts to remove the BMD protecting group from it failed, presumably because of rearrangement of the 11-substituents.



i

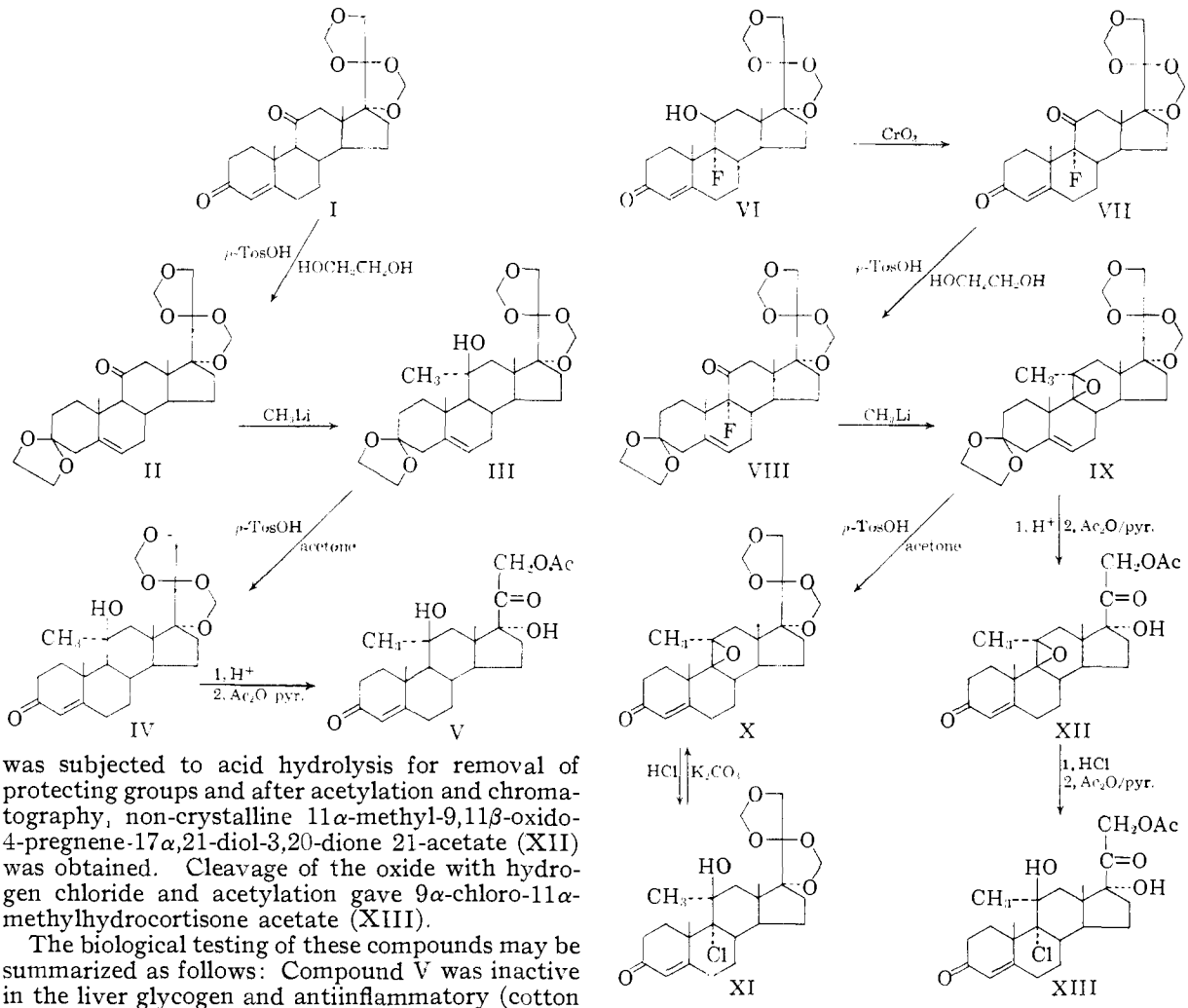


ii

(13) When an attempt was made to reverse the order of these two steps, it was found that the dioxolane of VI could not be successfully prepared directly. The exact nature of the mixture obtained was not thoroughly investigated, but considerable conjugated ketone survived and transformation in ring C had also occurred in part of the product. The only satisfactory way to prepare 9α-fluorohydrocortisone-BMD-3-dioxolane is by reduction of VIII with sodium borohydride.

(14) The use of methylmagnesium iodide in this reaction did not give any of the oxide, even when the reaction was carried out in refluxing xylene for 2.25 hours.

(15) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).



was subjected to acid hydrolysis for removal of protecting groups and after acetylation and chromatography, non-crystalline 11α-methyl-9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione 21-acetate (XII) was obtained. Cleavage of the oxide with hydrogen chloride and acetylation gave 9α-chloro-11α-methylhydrocortisone acetate (XIII).

The biological testing of these compounds may be summarized as follows: Compound V was inactive in the liver glycogen and antiinflammatory (cotton pellet) tests. Compound XIII was inactive in the liver glycogen test and did not cause sodium retention in adrenalectomized rats.[16]

Experimental[17]

17α,20;20,21-Bismethylenedioxy-4-pregnene-3,11-dione (I).—Fifty grams of cortisone was suspended in 2000 ml. of chloroform. To this mixture was added a solution of 500 ml. of formalin (37% aqueous formaldehyde) and 500 ml. of concentrated hydrochloric acid and the two-phase reaction mixture was stirred at room temperature for 48 hours. The chloroform layer was separated and washed with water and a saturated solution of sodium bicarbonate, dried over magnesium sulfate and evaporated to dryness *in vacuo*. Methanol was then added and evaporated to dryness. The resulting crystals were triturated with methanol, cooled, filtered and washed well with cold methanol; 39.5 g. of 17α,-20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (I) was obtained, m.p. 242–250°. A sample was recrystallized from methanol and acetone for analysis, m.p. 258–262°; λ_{max}^{MeOH} 238 mμ, E 15,600; λ_{max}^{Nujol} 5.85, 5.98, 6.12, 9.0–9.3 (BMD) μ; $[\alpha]^{27}D$ +82 ± 2° (c 1, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; HCHO, 14.9. Found: C, 68.70; H, 7.38; HCHO, 14.2.

17α,20;20,21-Bismethylenedioxy-3-ethylenedioxy-5-pregnene-11-one (II).—Five grams of 17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (I) was suspended in 250 ml. of benzene. To this suspension was added 25 ml. of ethylene glycol and 500 mg. of *p*-toluenesulfonic acid. The reaction mixture was heated under reflux for 18 hours with a water separator. It was cooled and the layers separated. The benzene layer was washed with water and a saturated solution of sodium bicarbonate, dried over magnesium sulfate and evaporated *in vacuo*. The residue was triturated with ether and the resulting crystals filtered to yield 2.1 g. of 17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene-11-one (II), m.p. 180–190°. The analytical sample was prepared by recrystallization from ether, m.p. 207–210°; λ_{max}^{Nujol} 5.87, 9.0–9.2 μ; $[\alpha]^{27}D$ −87 ± 4° (*c* 0.5, $CHCl_3$). *Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.05; H, 7.55.

Similarly, reaction of I with 2-methyl-2-ethyl-1,3-dioxolane and *p*-toluenesulfonic acid in benzene gave approximately 50% of II, whose identity was proved by infrared and melting point comparison with the above-prepared sample.

17α,20;20,21-Bismethylenedioxy-3-ethylenedioxy-11α-methyl-5-pregnene-11β-ol (III).—Three grams of cortisone-BMD-3-dioxolane (II) was stirred in 75 ml. of dry ether in an ice-bath as 25 ml. of 1.5 *M* methyllithium in ether was rapidly added. The mixture was then stirred at room temperature for four hours. During this time the coarse crystalline steroid, which was only partly in solution at the beginning, dissolved and a fine precipitate of the lithium salt replaced it. The mixture was poured into 100 ml. of ice-water, separated and the aqueous phase extracted with two more portions of ether. The ether was dried and concentrated to *ca.* 10 ml., cooled and filtered to give 1.90 g. of the 11α-methyl adduct III, m.p. 157–160°. The analytical sample was prepared by recrystallization twice from ether, m.p. 162–163.5°; λ_{max}^{Nujol} 2.83, 9.0–9.3 μ. *Anal.* Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.82. Found: C, 67.83; H, 8.50.

(16) The authors are indebted to Dr. R. H. Silber for the liver glycogen and antiinflammatory tests and to Dr. H. C. Stoerk for the sodium retention test.

(17) All melting points were determined on a Kofler micro hot-stage.

17α,20;20,21-Bismethylenedioxy-11α-methyl-4-pregnene-11β-ol-3-one (IV).—To 1.70 g. of III in 20 ml. of acetone was added 200 mg. of *p*-toluenesulfonic acid. This mixture was kept at room temperature for 17 hours and concentrated *in vacuo* to near dryness. The residue was taken up in methylene chloride, washed with aqueous sodium bicarbonate and concentrated to a crystalline residue, 1.52 g. This was slurried in *ca.* 5 ml. of hot methanol, cooled and filtered to give 1.10 g. of 11α-methylhydrocortisone-BMD (IV), m.p. 202–212°. Recrystallization from methanol and ether gave an analytical sample, m.p. 210–214°; λ_{max}^{MeOH} 243 mμ, *E* 15,800; λ_{max}^{Nujol} 3.00, 6.04, 6.15, 9.0–9.4 μ. *Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.06; H, 8.39.

17α,20;20,21-Bismethylenedioxy-11α-allyl-4-pregnene-11β-ol-3-one.—To 434 mg. of cortisone-BMD-3-dioxolane (II) in 10 ml. of dry ether was added allylmagnesium bromide, prepared from 0.87 ml. of allyl bromide and 0.72 g. of magnesium in 10 ml. of ether. The mixture was stirred at room temperature, suitably protected from air and moisture, for 3 hours. The mixture was then poured into ice-water, separated and the aqueous phase extracted again with ether. The ether was dried and evaporated to give 464 mg. of residue. Chromatography on alumina yielded 406 mg. of oil in the effluents from ether–petroleum ether (1:1) to ether.

To 379 mg. of the above oil in 3.0 ml. of acetone was added 50 mg. of *p*-toluenesulfonic acid. This mixture was kept at room temperature for 18 hours and worked up as in preparation of IV above, yielding 331 mg. of the crude 11α-allylhydrocortisone-BMD. Recrystallization from ether and methanol gave an analytical sample, m.p. 208–214°; λ_{max}^{MeOH} 243 mμ, *E* 14,700; λ_{max}^{Nujol} 3.0, 6.00, 6.08 (C=CH_2), 6.18, 9.0–9.2 μ. *Anal.* Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.20; H, 7.76.

11α-Methylhydrocortisone Acetate (V).—Six hundred and ninety milligrams of IV and 50 ml. of 50% acetic acid were heated on the steam-bath under nitrogen for 6.5 hours. The resultant mixture was concentrated *in vacuo*, dissolved in 2.0 ml. of pyridine and 1.8 ml. of acetic anhydride, and kept at room temperature for 16 hours. The usual work-up provided 742 mg. of oil; λ_{max}^{MeOH} 242 mμ, *E*% 364; BT assay, 78% of hydrocortisone acetate. This product was chromatographed on 25 g. of acetone-activated acid-washed alumina. The fractions from ether–chloroform (3:7) to ether–chloroform (1:9) contained 339 mg. of crude crystalline V. Recrystallization from methylene chloride–ether gave 191 mg. of crystals, m.p. 194–201°. The analytical sample, recrystallized from methanol and methylene chloride–ether, melted at 196–200°. Fonken and Hogg[9] gave a melting point of 191–195°; λ_{max}^{EtOH} 243 mμ, *E* 16,350. Our physical properties were: λ_{max}^{MeOH} 243 mμ, *E* 15,900; λ_{max}^{Nujol} 2.95–3.2, 5.72(sh), 5.87, 6.03, 6.17, 8.10 μ; $[\alpha]_D$ +138 ± 4° (*c* 0.5, MeOH), M_D +578°; hydrocortisone acetate rotational data from these laboratories: $[\alpha]_D$ +163° (MeOH), M_D +666°. *Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.22; H, 8.12.

In the early ether–chloroform (3:1) region there was found 51 mg. of impure starting material IV, as evidenced by a negative BT test.

In the late ether–chloroform (3:1) and ether–chloroform (1:1) region, 99 mg. of another crystalline compound was found. It was recrystallized to give 56 mg., m.p. 194–203°. A sample recrystallized from methanol and methylene chloride–ether gave the presumed **11-methyl-4,9(11)-pregnadiene-17α,21-diol-3,20-dione 21-acetate**, m.p. 199–206°; λ_{max}^{MeOH} 240 mμ, *E* 16,400; λ_{max}^{Nujol} 3.0–3.2, 5.72, 5.78, 6.02, 6.20, 8.10 μ. *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.78; H, 8.09.

9α-Fluoro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (VI).—Twenty grams of 9α-fluorohydrocortisone was suspended in 1000 ml. of chloroform. To this mixture was added a solution of 400 ml. of formalin and 400 ml. of concentrated hydrochloric acid. The two-phase reaction mixture was stirred at room temperature for one hour. The layers were separated and the chloroform phase was washed with water and a saturated solution of sodium bicarbonate. After drying over magnesium sulfate, evaporation *in vacuo* and trituration with methanol, 14 g. of 9α-fluoro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (VI) was obtained, m.p. 250–260°. Recrystallization from methanol–methylene chloride provided an analytical sample, m.p. 255–262°; λ_{max}^{Nujol} 2.9, 5.99, 6.12, 9.15 μ; $[\alpha]_D$ +30 ± 2° (*c* 1, $CHCl_3$). *Anal.* Calcd. for $C_{23}H_{31}O_6F$: C, 65.38; H, 7.39. Found: C, 65.74; H, 6.89.

9α-Fluoro-17α,20;20,21-Bismethylenedioxy-4-pregnene-3,11-dione (VII).—One gram of 9α-fluoro-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (VI) was dissolved in 10 ml. of 90% glacial acetic acid and was then combined with 1 g. of chromium trioxide in 10 ml. of glacial acetic acid. The reaction mixture was allowed to stand at room temperature for 15 minutes. After the addition of water, the reaction mixture was extracted well with methylene chloride and washed with a saturated solution of sodium bicarbonate. The methylene chloride was dried and the solvent evaporated to yield 881 mg. of crude crystalline product which was of suitable quality for use in further transformations. Recrystallization from methylene chloride–methanol gave analytically pure 9α-fluoro-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (VII), m.p. 280–290°; λ_{max}^{Nujol} 5.80, 6.01, 6.12, 9.0 μ. *Anal.* Calcd. for $C_{23}H_{29}O_6F$: C, 65.79; H, 6.95. Found: C, 66.09; H, 6.64.

9α-Fluoro-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene-11-one (VIII).—Eight hundred milligrams of 9α-fluoro-17α,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (VII) in 100 ml. of benzene was heated at reflux overnight with 5 ml. of ethylene glycol and 100 mg. of *p*-toluenesulfonic acid using a water separator to collect the water formed during the course of the reaction.

After cooling and diluting with water, the benzene layer was separated and washed with a saturated solution of sodium bicarbonate. It was dried and evaporated *in vacuo* to yield after recrystallization from ether–methylene chloride 319 mg. of analytically pure 9α-fluoro-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene-11-one (VIII), m.p. 250–257°; λ_{max}^{Nujol} 5.8, 9–9.2 μ. *Anal.* Calcd. for $C_{25}H_{33}O_7F$: C, 64.64; H, 7.16. Found: C, 64.50; H, 7.18.

11α-Methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene (IX).—Twelve grams of 9α-fluoro-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene-11-one (VIII) was dissolved in 240 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) and combined with 200 ml. of 0.85 *M* methyllithium in ether at 0° under nitrogen. The reaction mixture was stirred at ice-bath temperature for one hour. It was then poured into a saturated solution of sodium bicarbonate, extracted well with methylene chloride, dried and evaporated *in vacuo*. Chromatography of the crude crystalline product obtained (12 g.) on 240 g. of acid-washed alumina yielded, upon elution of the column with petroleum ether–ether (4:1), 4 g. of 11α-methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene (IX), m.p. 178–180°. An analytically pure sample was obtained by further recrystallization from ether–methylene chloride, m.p. 188–192°, λ_{max}^{Nujol} 9.0–9.2 μ, $[\alpha]_D$ +36 ± 2° (*c* 1, acetone). *Anal.* Calcd. for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.71; H, 7.86.

11α-Methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one (X).—Two hundred forty-five milligrams of 11α-methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene (IX) was dissolved in 25 ml. of acetone, combined with 25 mg. of *p*-toluenesulfonic acid and allowed to stand at room temperature for 6 hours. The reaction mixture was then evaporated *in vacuo* at room temperature. Water was added and the product was extracted with methylene chloride. The methylene chloride layer was washed with a saturated solution of sodium bicarbonate, dried and evaporated to yield 230 mg. of oil which crystallized when triturated with methanol. One hundred forty-three milligrams of 11α-methyl-9,11β-oxido-17α,20;-20,21-bismethylenedioxy-4-pregnene-3-one (X) was obtained, m.p. 225–230°. An analytical sample was prepared by recrystallization from methylene chloride–methanol, m.p. 232–236°; λ_{max}^{Nujol} 6.0, 6.2, 9.1–9.2 μ; $[\alpha]_D$ −74° (c 1, $CHCl_3$). *Anal.* Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.55; H, 7.67.

9α-Chloro-11α-methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (XI).—One hundred milligrams of 11α-methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one (X) was dissolved in 10 ml. of chloroform and cooled to ice-bath temperature. Five milliliters of 0.45 *N* hydrogen chloride in chloroform was added and the reaction mixture was stirred at ice-bath temperature for 30 minutes. The ice-bath was then removed and the reaction mixture was allowed to warm to room temperature for 1.5 hours. A slight reddish color was noted at the end of

this time. After dilution with water, extraction with chloroform, washing the chloroform with a saturated solution of sodium bicarbonate, drying and evaporation, an oil was obtained which, when triturated with ether, gave crystals. Subsequent recrystallization from methylene chloride–ether yielded 30 mg. of analytically pure 9α-chloro-11α-methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (XI), m.p. 260–265° dec.; λ_{max}^{Nujol} 2.8, 6.05, 6.2(sh), 9.2–9.4 μ. *Anal.* Calcd. for $C_{24}H_{32}O_6Cl$: C, 63.77; H, 7.13; Cl, 7.84. Found: C, 63.94; H, 7.34; Cl, 7.94.

11α-Methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-4-pregnene-3-one (X) from **9α-Chloro-11α-methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (XI).**—Twenty milligrams of 9α-chloro-11α-methyl-17α,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (XI) was heated at reflux for two hours in 5 ml. of methanol with 20 mg. of potassium carbonate in 2 ml. of water. After evaporation to dryness *in vacuo*, the product was extracted with methylene chloride, dried and evaporated to yield crystals which gave a negative Beilstein test. Recrystallization from methanol yielded 10 mg. of 11α-methyl-9,11β-oxido-17α,-20;20,21-bismethylenedioxy-4-pregnene-3-one (X), m.p. 235–240°. Admixture with an authentic sample of the oxide did not depress the melting point and the infrared spectra of the two compounds were identical.

11α-Methyl-9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione 21-Acetate (XII).—One hundred milligrams of 11α-methyl-9,11β-oxido-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5-pregnene (IX) was heated at steam-bath temperature for 5 minutes with 12 ml. of glacial acetic acid, 12 ml. of water and 2 ml. of concentrated hydrochloric acid. It was cooled, poured into 10% sodium hydroxide, extracted well with ethyl acetate, washed with water, dried and evaporated *in vacuo*. Acetylation of the total crude was accomplished by heating for 10 minutes on the steam-bath with 1 ml. of pyridine and 1 ml. of acetic anhydride. It was worked up in the usual manner and chromatographed on 4 g. of acid-washed alumina. Elution of the column with ether–chloroform (1:4) and chloroform gave 20 mg. of the desired 11α-methyl-9,11β-oxido-4-pregnene-17α,21-diol-3,-20-dione-21-acetate (XII) as a non-crystalline solid, suitable for use in subsequent transformations; $\lambda_{max}^{CHCl_3}$ 2.8, 5.70–5.79, 6.0, 6.15(sh), 7.90 μ.

9α-Chloro-11α-methyl-4-pregnene-11β,17α,21-triol-3,20-dione 21-Acetate (XIII).—One hundred twenty milligrams of 11α-methyl-9,11β-oxido-4-pregnene-17α,21-diol-3,20-dione 21-acetate (XII) was dissolved in 5 ml. of chloroform. It was cooled to ice-bath temperature and 5 ml. of 0.45 *N* hydrogen chloride in chloroform was added. The reaction mixture was allowed to stir at ice-bath temperature for a half-hour and at room temperature for a half-hour. Water and chloroform were added and the chloroform phase was washed with a saturated solution of sodium bicarbonate, dried, evaporated and the resulting oil chromatographed on 5 g. of acid-washed alumina. Elution of the column with ether–chloroform (1:4) and chloroform gave crystals which upon recrystallization from methylene chloride–ether gave 50 mg. of analytically pure 9α-chloro-11α-methyl-4-pregnene-11β,17α,21-triol-3,20-dione 21-acetate (XIII), m.p. 230–235° dec.; λ_{max}^{MeOH} 242 mμ, *E* 16,400; λ_{max}^{Nujol} 2.75, 3.0, 5.70, 5.80, 6.1, 6.2(sh), 8.1 μ. *Anal.* Calcd. for $C_{24}H_{33}O_6Cl$: C, 63.63; H, 7.34; Cl, 7.83. Found: C, 63.64; H, 7.40; Cl, 8.36.

Acknowledgment.—The authors wish to thank Dr. N. R. Trenner and Mr. R. W. Walker for certain of the infrared spectra, Mr. R. N. Boos and his associates for the elemental analyses and Mr. J. J. Wittick and associates for ultraviolet absorption spectra.

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[CONTRIBUTION FROM THE DEPARTMENT OF FOREST CHEMISTRY, COLLEGE OF FORESTRY, STATE UNIVERSITY OF NEW YORK, AND THE POLYMER RESEARCH LABORATORY, THE DOW CHEMICAL CO.]

Distribution of Methoxyl Groups in the Methylation of the Monosodio Derivatives of Methyl α-D-Glucopyranoside and Cellulose[1,2]

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RECEIVED JUNE 4, 1959

The monosodio derivatives of methyl α-D-glucopyranoside and cellulose were prepared and methylated, and the products were analyzed by hydrolysis and quantitative paper chromatography. The methylated derivatives of both contained unsubstituted, mono-, di- and tri-O-methylglucoses and the mono-O-methyl fraction contained the three principal isomers. In both cases, 2-O-methyl-D-glucose was the sugar present in the highest percentage of the hydrolyzate. Application of Spurlin's statistical treatment gave the relative rate constants: $k_2 = 5$, $k_3 = 1$, $k_6 = 2.5$, $k_a = 8$, $k_b = 6.7$.

The relative reactivities of the three hydroxyl groups in cellulose remains a fundamental problem in the chemistry of this polymer. This problem has gained an increasing amount of attention in recent years for a number of reasons. For one, a correlation appears to exist between the chemical and physical properties of cellulose derivatives and the relative distribution of the substituent groups on the primary and secondary hydroxyls.[3–6] For another, knowledge of the mode of distribution is important for elucidating the structure of addition compounds formed as intermediates[7–9] and in interpreting the mechanism of the substitution reactions used for the preparation of derived polymers of cellulose.[10–14]

Through the years a considerable weight of experimental evidence has been amassed which indicates that the C-2 hydroxyl group is the most acidic hydroxyl group of the three in the glucopyranoside repeating unit of cellulose. As a result, both equilibrium and rate-controlled reactions which involve the alkoxide anion appear to occur preferentially

(1) Based in part on a dissertation submitted by the author in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1956. The author was on a Research Fellowship sponsored by the American Viscose Corporation. Grateful acknowledgment is hereby expressed.

(2) Presented at the Symposium on Chemical Reactions of Polymers, Division of Polymer Chemistry, 136th Meeting of the American Chemical Society, Atlantic City, N. J., September 15, 1959.

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