[CONTRIBUTION FROM MERCK SHARP AND DOHME RESEARCH LABORATORIES]

Bismethylenedioxy Steroids. III. The Synthesis of 7α- and 7β-Methylhydrocortisones[1]

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The synthesis of 7α- and 7β-methylhydrocortisones is reported. Catalytic reduction of a 5,7(7')-diene with an 11α-oxygenated substituent leads to the 7α-methyl series, whereas catalytic reduction of a 7-methyl-4,6-diene-3-one with an 11β-oxygenated substituent leads to the 7β-methyl series.

The introduction of methyl groups in the hydrocortisone molecule at positions 2,[2] 6[3] and 16[4] has led to an enhancement of antiinflammatory activity. The introduction of a methyl group at positions 4,[5] 9[1] and 11[6] has resulted in diminished antiinflammatory activity. It should be noted that these positions are all adjacent to a functional group and it was of interest to determine the effect of a methyl group at an isolated position (such as carbon 7) in hydrocortisone. On this and other grounds, we initiated a program to prepare 7α- and 7β-methylhydrocortisones.[7] Not only are these compounds of biological interest, but the numerous chemical transformations used illustrate further the utility of the bismethylenedioxy (BMD) blocking group.[8]

Several approaches to the synthesis of 7-methylhydrocortisone were attempted. Initial attempts involved the 1,6-addition of methylmagnesium bromide to Δ⁶-cortisone-BMD. These attempts in our hands were unsuccessful.[9]

The most feasible alternative approach to the 7-methyl derivatives appeared to be through a Δ⁵-unsaturated steroid since a point of attack is thus created at the allylic C-7 position. Reaction of a 7-ketone with methyl Grignard reagent seemed like the most reliable method of introducing a methyl group at C-7. Thus the problem of preparing the requisite 7-ketone was investigated. The starting material for the synthesis was the previously reported[8] 17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (I). This compound was converted to the 3-ketal derivative II[1] by known dioxolanation procedures. Compound II was then converted to the desired 7-ketone III by several methods. The first procedure involves the oxidation of II with *t*-butyl chromate.[10] The second method involves the direct oxidation of II with chromium trioxide in pyridine. The first method suffers from a low yield as well as the extreme care necessary in working with large amounts of alcohol-free *t*-butyl chromate. The second method resulted in an even lower yield of product. A third procedure involves a three-step sequence reported by Lenhard and Bernstein[11] for the preparation of 7-ketodesoxycorticosterone. This appears to be the method of choice and involves allylic bromination (C-7) of II with N-bromosuccinimide followed by reaction of the crude bromo compound with neutral alumina to produce the 7-alcohol which was then oxidized with chromium trioxide in pyridine to the 7-ketone III. Isolation of the intermediates in the sequence was not necessary; however, improved yields were obtained when the 7-alcohol was purified.

Reaction of the Δ⁵-7-one III with methylmagnesium iodide led to the two expected products,[12] the 7-methylcarbinol IV and the 7-exomethylene compound V. Compound IV can be converted to V by treatment with acetic anhydride in pyridine. The diene V was also synthesized by reaction of the 7-ketone III with the triphenylphosphine–methylene reagent of Wittig and Schöllkopf.[13] Compounds IV and V are both useful intermediates in our synthesis.

The differences in biological activity of α- and β-substituents in several positions of the steroid nucleus is well known and a stereospecific synthesis of both isomers would be desirable. It was hoped that a stereospecific synthesis of both isomers could be achieved by catalytic reduction of 11α- or 11β-oxygenated precursors. There are numerous reports in the literature[14] that the direction of reduction of the Δ⁴-bond in steroids is influenced by the oxygen substituent at C-11.

(1) Paper II in this series, Frances Hoffman, R. E. Beyler and M. Tishler, THIS JOURNAL, **80**, 5322 (1958).

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

(3) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sabek and J. A. Hogg, *ibid.*, **78**, 6213 (1956).

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

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

(6) R. E. Beyler, Frances Hoffman and L. H. Sarett, THIS JOURNAL, **82**, 178 (1960); G. S. Fonken and J. A. Hoff, *Tetrahedron*, **2**, 365 (1958).

(7) After this manuscript was written, the synthesis of 7β-methylhydrocortisone appeared; J. Zderic, H. Carpio and H. J. Ringold, THIS JOURNAL, **81**, 432 (1959); C. H. Robinson, O. Gnoj and E. P. Oliveto, *J. Org. Chem.*, **24**, 121 (1959).

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

(9) A recent patent, J. C. Babcock and J. Allan Campbell, U. S. Patent 2,838,534 (June 10, 1958), reports the addition of methylmagnesium bromide to 11β,21-dihydroxy-4,6,17(20)-[*cis*]-pregnatrien-3-one 21-acetate and conversion of the product to a mixture of 7α- and 7β-methylhydrocortisone.

(10) (a) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952); (b) R. V. Oppenauer and H. Oberrauch, *Anales. Asoc. Quim. Argentine*, **37**, 246 (1949); (c) P. N. Rao and P. Kurath, THIS JOURNAL, **78**, 5660 (1956).

(11) R. H. Lenhard and S. Bernstein, *ibid.*, **78**, 989 (1956).

(12) B. Bann, I. M. Heilbron and F. S. Spring, *J. Chem. Soc.*, 1274 (1936).

(13) G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954); F. Sondheimer and R. Mechoulam, THIS JOURNAL, **79**, 5029 (1957).

(14) (a) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3711 (1952); (b) C. Djerassi, R. Yashin and G. Rosenkranz, *ibid.*, **74**, 422 (1952); (c) C. Djerassi, G. Rosenkranz, J. Pataki and S. Kaufmann, *J. Biol. Chem.*, **194**, 115 (1952); (d) J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **195**, 751 (1952); (e) O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, 1286 (1953).

These reports show that an 11α-hydroxy group favors "top side reduction" leading predominantly to the 5β-isomer, whereas the 11-ketone or 11β-hydroxy groups favor "bottom side reduction" to give predominantly the 5α-isomer. If this directive influence would operate at the 7-position as well, the appropriate substituent at C-11 would provide a stereospecific synthesis of both epimers at C-7.

7α-Methylhydrocortisone (XII).—Our first objective was the synthesis of the 7α-methyl compound which, according to the above theory, would require an 11α-oxygenated substituent. An attempt to prepare the 11α-hydroxy derivative VI by reduction of V with sodium in boiling propanol[15] resulted not only in reduction of the 11-ketone to the 11α-ol but concomitant reduction of the diene system to a complex mixture of monoölefins and isomers at C-7. Removal of the dioxolane at C-3 gave a mixture of saturated and conjugated ketones which were separated with Girard T reagent. In this way, we were able to prepare 7Σ-methylcortisone-BMD, but the process did not appear practical and at best would result in a mixture of epimers at C-7. For this reason, the 7-methylcarbinol IV was then reduced to the 11α-hydroxy derivative VII with sodium in boiling propanol and this product was in turn acetylated with acetic anhydride in pyridine to give an 11α-monoacetate VIIa. Previous experiments on attempted acetylation and pyrolysis of the 7-methylcarbinol had indicated that this reaction was rather difficult (see Experimental conversion of IV to V). Results from other work in these laboratories[16] however, had indicated a rather smooth preparation of carbonate esters by reaction of hindered alcohols with dimethyl carbonate and sodium hydride in refluxing benzene. We planned to utilize this method to prepare the 7-carbonate ester which could then be pyrolyzed to the diene VIb. Somewhat to our surprise, the reaction of VIIa with dimethyl carbonate and sodium hydride in refluxing benzene gave the diene VIa. This results from ester interchange at C-11 as well as elimination at C-7. Compound VIa was more efficiently prepared by reaction of VII with dimethyl carbonate and sodium hydride. The diene VIa appeared to be a desirable compound on which to attempt hydrogenation experiments. Since the 7,7′-double bond appeared from models to be less hindered than the 5,6-double bond, it seemed possible that we might be able to hydrogenate it selectively. Numerous attempts at selective hydrogenation of VIa with a variety of catalysts were unsuccessful. However, by using a palladium oxide catalyst in glacial acetic acid–acetic anhydride, it was possible to hydrogenate the diene VIa to the saturated 3-ketone VIII (loss of the dioxolane at C-3 accompanied the reaction). The assignment of stereochemistry at C-5 and C-7 in VIII is based on subsequent reactions. Bromination of the saturated 3-ketone VIII in dimethylformamide[17] followed by dehydrobromination yielded a 3-keto-Δ^4-compound. These experiments indicate that the A:B ring juncture in VIII is *cis*[18] and the hydrogen at C-5 would thus be *beta*. Since catalytic hydrogenation *usually* gives products in which all the hydrogen atoms have approached the molecule from one side[19] and since hydrogenation at C-5 occurred from the top side, then hydrogenation at C-7 probably also occurred from the top side. This leads to the assigned 5β,7β-configuration for the hydrogens in VIII and the 7α-configuration for the methyl group.

Two procedures were used for the conversion of VIII to 7α-methylhydrocortisone (XII). The first route involved the bromination[17] of VIII followed by semicarbazone formation. The 11α-methyl carbonate ester was then hydrolyzed and the reversal of the semicarbazone gave the 11α-hydroxy compound Xb. This compound was then oxidized to 7α-methylcortisone-BMD (X). Reduction of X with lithium aluminum hydride followed by oxidation with manganese dioxide[20] yielded 7α-methylhydrocortisone-BMD (Xa). The alternate method for the conversion of VIII to Xa involved the bromination of IX followed by semicarbazone formation to yield XI. Sodium borohydride reduction of the semicarbazone XI gave the 11β-ol XIa and pyruvic acid reversal of the semicarbazone yielded Xa. Removal of the BMD protecting group with aqueous acetic acid or aqueous formic acid yielded 7α-methylhydrocortisone (XII) also characterized as the 21-acetate XIIa.

7β-Methylhydrocortisone (XX).—In order to favor "bottom side reduction" and thus the 7β-methyl configuration, we turned to the 11β-ol series. Compound IV upon reduction with lithium aluminum hydride yielded the 11β-ol derivative XVII. Treatment of XVII with *p*-toluenesulfonic acid in acetone led to the dienone XVIII. Compound XVIII was also prepared by lithium aluminum hydride reduction of V followed by treatment with *p*-toluenesulfonic acid. Selective hydrogenation of the 6,7-double bond in XVIII with 5% palladium-on-Darco in methanol with added base[21] resulted in 7β-methylhydrocortisone-BMD (XIX) which was isomeric with Xa. The two compounds were shown to be different by mixed melting point and infrared data. Removal of the BMD protecting group by reaction with aqueous acetic acid yielded 7β-methylhydrocortisone (XX) which again was shown to be different from XII by mixed melting point and infrared data (see Figs. 1 and 2).

We attempted to substantiate further our assignment of stereochemistry at C-7 by rotatory dispersion. The rotatory dispersion curve of 7β-methyltestosterone (*equatorial* methyl) is reported[22]

(15) H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **74**, 4470 (1952); H. L. Herzog, M. A. Jevnik and E. B. Hershberg, *ibid.*, **75**, 269 (1953); H. Heusser, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952).

(16) D. R. Hoff, *et al.*, to be published.

(17) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).

(18) C. Djerassi, *ibid.*, **71**, 1003 (1949), and references cited therein.

(19) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. Whetstone, *ibid.*, **64**, 1985 (1942); C. Mannich, *Arch. Pharm.*, **254**, 349 (1946); von Pl. A. Plattner, H. Heusser and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

(20) F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953), and references cited therein.

(21) E. R. Garrett, R. H. Donia, B. A. Johnson and L. Scholten, *ibid.*, **78**, 3340 (1956); D. A. Shepherd, J. A. Campbell and B. A. Johnson, U. S. Patent 2,679,106 (December 14, 1954).

(22) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958).

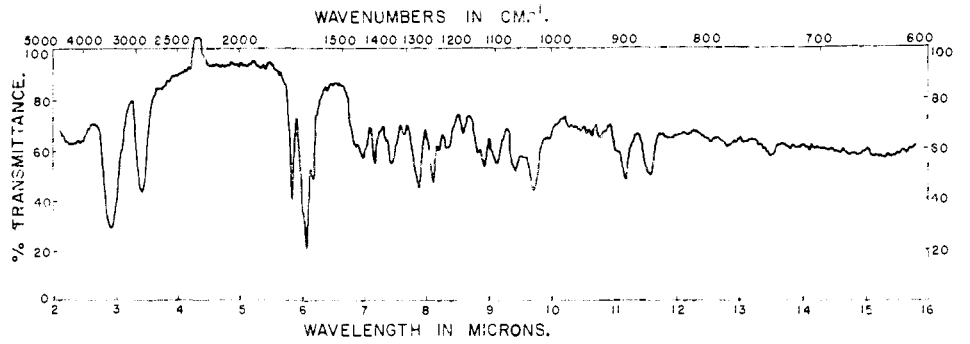


Fig. 1.—Infrared spectrum (KBr) of 7α-methylhydrocortisone (XII).

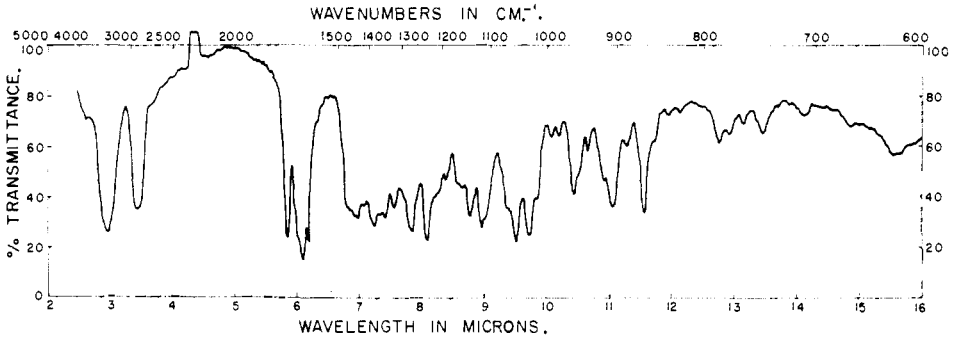


Fig. 2.—Infrared spectrum (KBr) of 7β-methylhydrocortisone (XX).

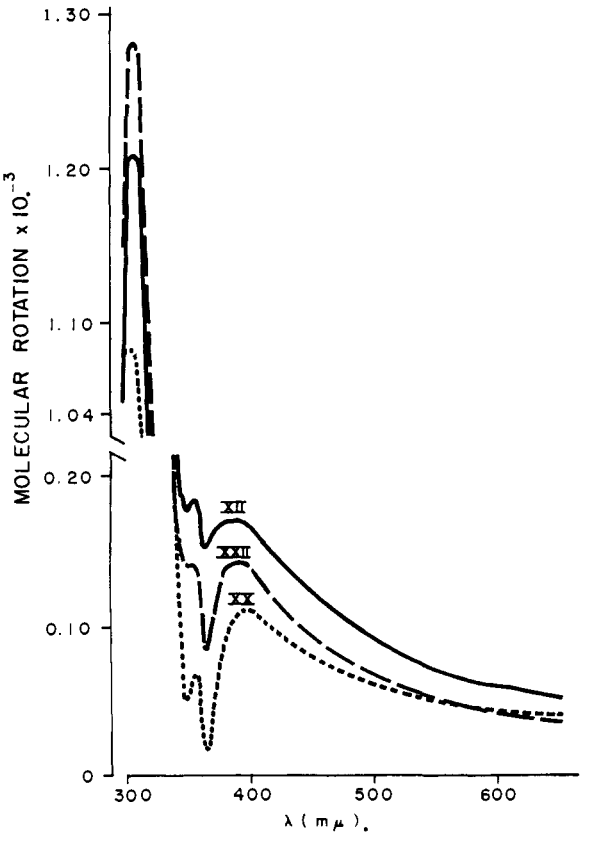


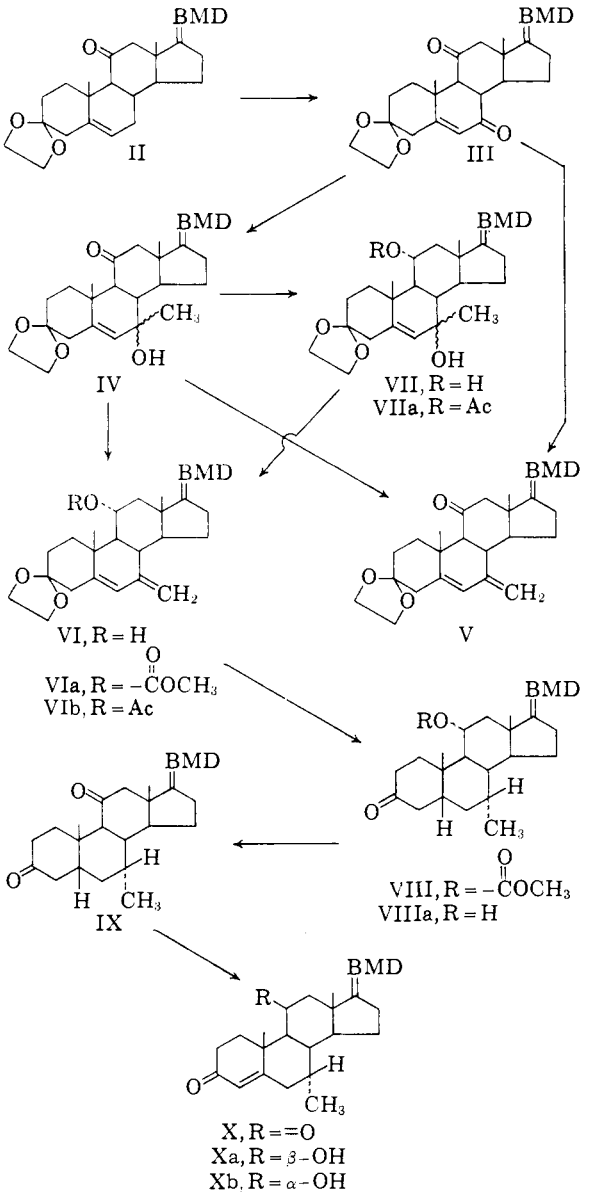
Fig. 3.—Rotatory dispersion curves for 7α-methylhydrocortisone (XII), hydrocortisone (XXII) and 7β-methylhydrocortisone (XX).

to be identical with that of testosterone, whereas the *axial* epimer 7α-methyltestosterone exhibited a slightly altered dispersion curve.[22] Rotatory dispersion curves on our 7α- and 7β-methylhydrocortisones showed that both compounds had curves which were generally of similar shape to that for hydrocortisone (see Fig. 3).

Preparation of 7α- and 7β-methylprednisone-BMD was also carried out in the course of this investigation. Treatment of the 11α-acetate derivative VIIa with *p*-toluenesulfonic acid in acetone yielded the dienone XIII. Reduction of this dienone with palladium oxide in acetic anhydride–acetic acid yielded a single product, the A:B *trans*-7β-methyl-3-ketone XIV. The assignment of configuration at C-5 was again based on bromination–dehydrobromination experiments which yielded a Δ^1-3-ketone indicating that the configuration of the hydrogen at C-5 was *alpha*. This result appears to be in disagreement with the findings of Djerassi, *et al.*,[14] in that with an 11α-substituent, reduction apparently led to predominantly the 5α-isomer. However, the reduction 5β- is greatly favored by addition of base to the hydrogenation medium[14e] and since our work was done under acid conditions, the result may not be at all unexpected. The configuration at C-7 in XIV was inferred to be 7β-methyl for the same reasons given above.[19] In order to substantiate the 7β-methyl configuration for XIV, it was hydrolyzed to the 11α-ol XIVa, oxidized to the 11-ketone XIVb and this in turn oxidized with SeO_2[23] to 7β-methylprednisone-BMD (XV).

Treatment of 7α-methylcortisone-BMD (X) with SeO_2 yielded 7α-methylprednisone-BMD

(23) von Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthumus, M. S. DeWinter and D. A. Van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).



(XVI) which was shown to be different from XV by mixed melting point and infrared data.

Biological testing[24] showed that 7α-methylhydrocortisone (XII) had about 0.1 the activity of hydrocortisone in liver glycogen and less than 0.25 in systemic granuloma. 7β-Methylhydrocortisone (XX) exhibits about 0.1 the activity of hydrocortisone in liver glycogen assay and about 0.4 the activity in systemic granuloma. Neither compound exhibits any mineralcorticoid activity in adrenalectomized rats. The above data show that the 7α- and 7β-methyl are activity-diminishing groups in adrenocortical steroids. Further, the effect on activity is about the same in either the 7α- or 7β-methyl series.

Experimental

3-Ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (II).—One hundred seventy-five grams of 17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (I) was dissolved in 3.2 l. of benzene. To this solution was added 330 ml. of ethylene glycol and 2.6 g. of *p*-toluenesulfonic acid. The reaction mixture was heated under reflux for 48 hours with a water separator. The reaction mixture was then cooled, diluted with water and the layers separated. The benzene layer was washed with saturated sodium bicarbonate solution, dried and evaporated *in vacuo*. The resulting 188 g. of crude product was chromatographed on 3 kg. of acid-washed alumina. Elution of the column with petroleum ether–ether (1:1) yielded 76 g. (39%) of 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (II), m.p. 200–205°. Recrystallization from methanol and ether gave an analytical sample, m.p. 210–212°; λ_{max}^{Nujol} 5.88, 9.0–9.3 μ.

Anal. Calcd. for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68. Found: C, 67.46; H, 7.73.

Using the exchange dioxolanation procedure,[25] the product, m.p. 205–210°, was 41%.

3-Ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11-dione (III). A. *t*-Butyl Chromate Method.[10c]—Five grams of 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (II) was dissolved in 40 ml. of carbon tetrachloride and heated under reflux. To this solution was added a mixture of 52 ml. of *t*-butyl chromate in carbon tetrachloride,[10a] 6 ml. of glacial acetic acid and 18 ml. of acetic anhydride over a 15-minute period. The reaction mixture was then heated under reflux with stirring for 8 hours, then left at room temperature overnight. The reaction mixture was cooled in an ice-bath and a solution of 12 g. of oxalic acid in 100 ml. of water was added slowly to decompose the excess *t*-butyl chromate. This was followed by the addition of 5 g. of solid oxalic acid. The reaction mixture was then allowed to warm to room temperature and the layers were separated. The organic layer was washed with water, dried and evaporated to dryness under vacuum. The resulting 5.1 g. of material was chromatographed on 150 g. of acid-washed alumina. Elution with chloroform yielded 850 mg. of 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11-dione (III). Recrystallization from methylene chloride–ether afforded an analytical sample, m.p. 195–200 (215)°; λ_{max}^{MeOH} 238 mμ (ε 11,100); λ_{max}^{Nujol} 5.85, 5.96, 6.1, 9.0 μ.

Anal. Calcd. for $C_{25}H_{32}O_8$ (460.51): C, 65.20; H, 7.00. Found: C, 65.21; H, 6.99.

B. **Chromic Anhydride–Pyridine Method.**—Five hundred milligrams of II was dissolved in 5 ml. of pyridine. This solution was added to the complex formed from 500 mg. of chromium trioxide in 5 ml. of pyridine. The reaction mixture was heated under reflux for 10 minutes, and allowed to stand at room temperature overnight. The reaction mixture was then poured into water and extracted with ether. The extracts were washed, dried and evaporated to dryness. Chromatography of the residue gave a very low yield of product III, m.p. 200–210°, λ_{max}^{MeOH} 239 mμ (ε 10,900).

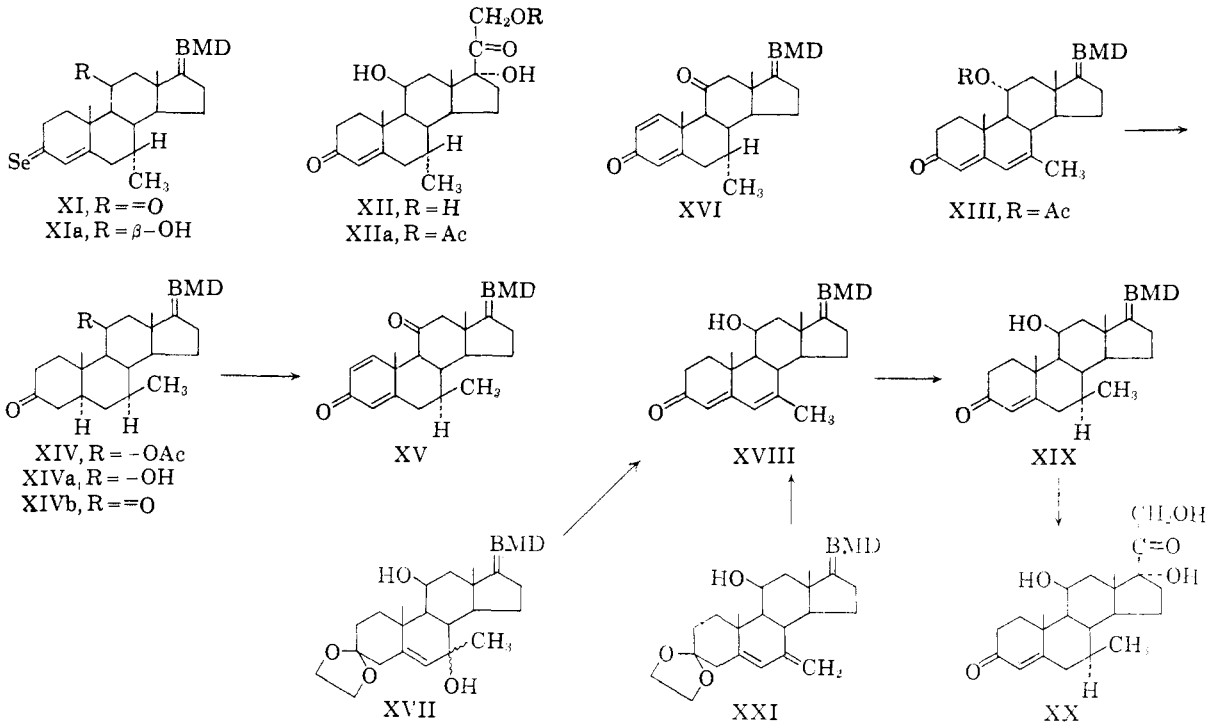
C. **Three-step Procedure.**—Fifty grams of 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (II) was dissolved in 800 ml. of carbon tetrachloride and to this stirred solution was added 50 g. of potassium acetate. The reaction mixture was heated to reflux and 22 g. of *N*-bromosuccinimide was rapidly added along with a few crystals of benzoyl peroxide. The reaction mixture was then heated and irradiated for 3 minutes with a photospot lamp. The reaction mixture was then rapidly cooled, filtered and washed with saturated sodium bicarbonate solution and dried over potassium carbonate. This solution, containing the crude 7-bromo compound, was filtered from the drying agent and then stirred with 350 g. of ethyl acetate-washed alumina for 4 hours. The reaction mixture was filtered and evaporated to dryness yielding 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7ε-ol-11-one. An analytical sample prepared by recrystallization from methylene chloride–ether melted at 247–253°; λ_{max}^{Nujol} 2.88, 5.92, 9–9.4 μ.

Anal. Calcd. for $C_{25}H_{34}O_8$ (462.52): C, 64.92; H, 7.41. Found: C, 64.70; H, 7.39.

Thirty-eight grams of the crude product from above was dissolved in 380 ml. of pyridine and added to a slurry of 38 g.

(24) We wish to thank Dr. R. H. Silber and Dr. H. C. Stoerk of the Merck Institute for Therapeutic Research for the biological testing of these compounds.

(25) H. J. Dauben, Jr., B. Laken and H. J. Ringold, THIS JOURNAL, **76**, 1359 (1954).



of chromium trioxide in 380 ml. of pyridine. The reaction mixture was left at room temperature overnight and then poured into water and extracted with ether. The ethereal extracts were washed, dried and evaporated to dryness. The resulting residue was chromatographed on 1200 g. of acid-washed alumina. Elution with chloroform yielded 7.5 g. of product III, m.p. 214–217°, λ_{max}^{MeOH} 239 mμ (ε 11,000). This sample melted higher than the analytical sample prepared by method A. Mixed melting point and infrared data showed it to be identical with that prepared by method A.

Reaction of 3-Ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11-dione (III) with Methylmagnesium Iodide.—Five grams of III in 100 ml. of dry tetrahydrofuran was added to methylmagnesium iodide (prepared from 2.5 g. of magnesium, excess methyl iodide and 200 ml. of ether). The reaction mixture was stirred at room temperature for 2.5 hours, cooled in ice and decomposed with water. The reaction mixture was extracted with ethyl acetate, the extracts dried and evaporated resulting in 5 g. of an oil which upon trituration with ether partially crystallized. The crystalline material was separated and recrystallized from methylene chloride–ether resulting in 1.75 g. of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7-ol-11-one (IV), m.p. 265–280°; λ_{max}^{Nujol} 2.85, 5.90, 9.0–9.2 μ.

Anal. Calcd. for $C_{26}H_{36}O_8$ (476.55): C, 65.53; H, 7.61. Found: C, 65.37; H, 7.75.

The mother liquors from above were chromatographed on 110 g. of acid-washed alumina. The material eluted from the column with ether was recrystallized from methylene chloride–ether and resulted in 1.0 g. of 7-methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (V), m.p. 203–208°, λ_{max}^{MeOH} 236 mμ (ε 17,900); λ_{max}^{Nujol} 5.89, 6.05, 9.0, 11.2 μ.

Anal. Calcd. for $C_{26}H_{34}O_7$ (458.53): C, 68.10; H, 7.47. Found: C, 68.35; H, 7.73.

In addition to V, another 100 mg. of IV was eluted from the column with ether–chloroform (3:2).

Reaction of 3-Ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11-dione (III) with Triphenylphosphine–Methylene Reagent.—To 55 mg. of triphenylmethylphosphonium bromide in 10 ml. of dry ether was added 1.36 ml. of 1.1 *M* butyllithium in a pressure bottle. An immediate orange color appeared and all the solid disappeared from the flask within 15 minutes. The pressure bottle was then opened and 500 mg. of 3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11-dione (III) in 6 ml. of dry tetrahydrofuran was added. The reaction flask was sealed and the reaction mixture stirred at room temperature for one hour, heated at 65–70° for 3 hours, and then left at room temperature overnight. The reaction mixture was decomposed with moist ether and filtered through Super-cel. The filtrate was dried and evaporated. Chromatography of the resulting oil on alumina gave 7-methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (V) which was eluted with ether. Recrystallization from methylene chloride–ether resulted in 75 mg., m.p. 200–205°. There was no depression in melting point upon admixture with V resulting from the methyl Grignard reaction above.

Conversion of 7-Methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7-ol-11-one (IV) to 7-Methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (V).—To 100 mg. of 3-ethylenedioxy-7-methyl-17,20;20,21-bismethylenedioxy-5-pregnene-7-ol-11-one (IV) in 1.0 ml. of pyridine was added 1.0 ml. of acetic anhydride. The reaction mixture was heated at 100° for 16 hours, poured into water and extracted with ether. The latter was washed with dilute hydrochloric acid, sodium bicarbonate solution, dried and concentrated to 101 mg. of an oil. Chromatography on alumina provided 47 mg. of V, m.p. 218–220°.

Reduction of V with Sodium in Boiling Propanol.—A solution of 100 mg. of 7-methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (V) in 10 ml. of propanol was heated to reflux and 700 mg. of sodium metal (cut in small pieces) was added. After all the sodium was added, the reaction was heated at reflux for one hour. Then 5 ml. of methanol was added followed by the addition of 10 ml. of water. The reaction mixture was concentrated by distillation under vacuum, the residue dissolved in ethyl acetate, washed with water, dried and evaporated resulting in 90 mg. of crude product. This crude product was transparent in the ultraviolet indicating that the diene system had also been attacked. Removal of the dioxolane with *p*-toluenesulfonic acid in acetone gave crude material which exhibited λ_{max}^{MeOH} 242 mμ (*E*% 230). Oxidation with chromium trioxide in pyridine and separation with Girard T reagent afforded a low yield of crystalline 7ξ-methylcortisone-BMD, m.p. 195–202°, λ_{max}^{MeOH} 240 mμ (ε 15,300).

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.5): C, 69.21; H, 7.74. Found: C, 68.98; H, 8.00.

7-Methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11α-diol (VII).—To a solution of 100 mg.

of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7-ol-11-one (IV) in 10 ml. of boiling propanol was added 700 mg. of sodium metal in small portions over a 30-minute period. After all the sodium had been added, the solution was heated under reflux an additional 90 minutes. Methanol was then added to destroy any excess sodium. The solution was cooled and diluted with 20 ml. of water. The resulting solution was concentrated *in vacuo* to about 5 ml. and then extracted with ethyl acetate. The extracts were washed with water, dried over sodium sulfate and evaporated to dryness resulting in 90 mg. of crude product VII which was of suitable purity for subsequent reactions. A sample purified for analysis by recrystallization from methylene chloride–ether melted at 225–233°; λ_{max}^{Nujol} 3.12, 9.1–9.2 μ.

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.58): C, 65.25; H, 8.00. Found: C, 65.60; H, 7.78.

The 11α-monoacetate VIIa was prepared by treatment of VII with acetic anhydride in pyridine at 100° for 10 minutes. An 82% yield of VIIa, m.p. 240–247°, resulted by crystallization from ether. The analytical sample melted at 245–250°; λ_{max}^{Nujol} 2.9, 5.83, 7.9, 9.0–9.18 μ.

Anal. Calcd. for $C_{28}H_{40}O_9$ (520.6): C, 64.59; H, 7.74. Found: C, 65.13; H, 7.50.

7-Methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11α-ol 11α-Methyl Carbonate Ester (VIa).—To a stirred solution of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11α-diol 11α-monoacetate (VIIa) (110 mg.) in 5 ml. of dry benzene was added 200 mg. of finely powdered sodium hydride and 4 ml. of dry dimethyl carbonate. The stirred solution was then heated to reflux and one drop of dry methanol was added. The reaction mixture was heated under reflux for 3 hours, cooled and filtered through Super-cel. The resulting filtrate was taken to dryness under vacuum, the residue redissolved in ether and again filtered through Super-cel. Removal of the ether resulted in 110 mg. of an oil; λ_{max}^{MeOH} 292 mμ (*E*% 53.2), 236 mμ (*E*% 231). The oil was chromatographed on 3 g. of acid-washed alumina. Elution with petroleum ether–ether (4:6) resulted in 56 mg. (51%) of product VIa which melted at 218–222° after recrystallization from methylene chloride–ether. The product showed λ_{max}^{MeOH} 236 mμ (ε 19,200); λ_{max}^{Nujol} 5.78, 7.78 and 9.1 μ.

Anal. Calcd. for $C_{28}H_{38}O_9$ (518.58): C, 64.85; H, 7.39. Found: C, 64.70, 65.00; H, 7.35, 7.55.

Alternate Procedure.—To 4.07 g. of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11α-diol (VII) in 125 ml. of dry benzene was added 60 ml. of dimethyl carbonate and 3.5 g. of sodium hydride in mineral oil (50% by weight). After addition of 5 drops of methanol, the mixture was refluxed with stirring for 40 hours. The reaction mixture was worked up in the manner used above and 2.55 g. (58%) of product VIa, m.p. 212–220°, was obtained. This product was identical with that prepared above.

7α-Methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one 11α-Methyl Carbonate Ester (VIII).—7-Methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnane-11α-ol 11α-methylcarbonate ester (VIIa), 1.99 g., was dissolved in 180 ml. of glacial acetic acid and 20 ml. of acetic anhydride. To this solution was added 2.0 g. of palladium oxide and the mixture was hydrogenated with shaking at 40 pounds initial pressure for 30 hours. (Additional hydrogen was added to the vessel several times since the solvent consumed considerable hydrogen.) The solvent was filtered from catalyst and concentrated under vacuum to dryness. The residue was dissolved in methylene chloride, washed with 5% sodium hydroxide solution, dried and concentrated to a residue of 1.91 g. Several recrystallizations from ether resulted in 994 mg. of product VIII, m.p. 185–193°, suitable for further transformations. Chromatography of the mother liquors on acid-washed alumina gave an additional 371 mg. of product with effluents including ether to ether-chloroform (7:3). Analytically pure material, m.p. 193–195°, was obtained by recrystallization from methylene chloride–ether; λ_{max}^{Nujol} 2.8–3.2, 5.75, 5.85, 7.85, 9.07–9.22 μ.

Anal. Calcd. for $C_{26}H_{35}O_8$ (478.56): C, 65.25; H, 8.00. Found: C, 65.79; H, 8.19.

Conversion of 7α-Methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one 11α-Methyl Carbonate Ester (VIII) to 7α-Methylhydrocortisone 21-Acetate (XIIa). Procedure A. 4-Bromo-7α-methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one 11α-Methyl Carbonate Ester.—To a solution of 128 mg. of VII in 4 ml. of dimethylformamide was added 60 mg. of bromine in 4 ml. of dimethylformamide and 2 mg. of *p*-toluenesulfonic acid. The reaction mixture was left at room temperature until the bromine color disappeared. The reaction mixture was then diluted with 40 ml. of ether, washed with water and dried over sodium sulfate. Evaporation of the solvent resulted in 140 mg. of crude product which crystallized upon trituration with ether. Recrystallization from methylene chloride–ether gave 106 mg. (70%) of 4-bromo-7α-methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one 11α-methylcarbonate ester, m.p. 203–210° dec.

Anal. Calcd. for $C_{26}H_{37}O_6Br$ (557.57): Br, 14.67. Found: Br, 13.99.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11α-ol-3-one 11α-Methyl Carbonate Ester 3-Semicarbazone.—To a mixture of 22 mg. of semicarbazide hydrochloride, 38 mg. of semicarbazide free base and 100 mg. of 4-bromo-7α-methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one 11α-methyl carbonate ester was added 3.0 ml. of dimethylformamide. The system was purged thoroughly with nitrogen and the mixture stirred at room temperature for 2 hours. The reaction mixture was then cooled to 0°, diluted with 20 ml. of water and extracted with ethyl acetate. The extracts were washed with water, dried and evaporated to dryness leaving 106 mg. of crude product. Recrystallization from methylene chloride–methanol resulted in 73 mg. (76%) of product, m.p. 255–262° dec., λ_{max}^{MeOH} 269 mμ (ε 29,900).

Anal. Calcd. for $C_{27}H_{39}O_8N_3$ (533.61): N, 7.88. Found: N, 8.20.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11α-ol-3-one 3-Semicarbazone.—A mixture of 100 mg. of the above ester, 7.5 ml. of methanol and 1.5 ml. of 20% aqueous potassium hydroxide was heated under reflux for 2 hours. The reaction mixture was then concentrated *in vacuo* and extracted with ethyl acetate. The extracts were washed with water, dried and evaporated to dryness leaving 92 mg. (103%) of product which was not further purified, λ_{max}^{MeOH} 270 mμ (ε 29,650).

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11α-ol-3-one (Xb).—Two hundred mg. of the crude semicarbazone from above was dissolved in 2.5 ml. of pyruvic acid, 2.5 ml. of acetic acid and 2.5 ml. of water and left at room temperature for 19 hours. The reaction mixture was then diluted with water (20 ml.) and extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate solution, water and dried over sodium sulfate. Evaporation of the solvent left 145 mg. of crude product. Recrystallization from methylene chloride–ether gave 105 mg. (62%) of 7α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11α-ol-3-one (Xb) which melted at 240–248°, λ_{max}^{MeOH} 243 mμ (ε 12,800). A sample prepared for analysis melted at 245–250°; $\lambda_{max}^{CHCl_3}$ 2.8–2.9, 6.0, 6.2, 9.0–9.2 μ.

Anal. Calcd. for $C_{28}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 68.97; H, 8.08.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione (7α-Methylcortisone-BMD) (X).—To a mixture of 100 mg. of chromium trioxide and 1.0 ml. of pyridine was added a solution of 100 mg. of 7α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11α-ol-3-one in 1.0 ml. of pyridine. The reaction mixture was left at room temperature overnight, then poured into 20 ml. of water and extracted with ether. The extracts were washed, dried and evaporated to dryness. The resulting product was crystallized from methylene chloride–ether to yield 90 mg. (90%) of product X, m.p. 225–230°. A sample recrystallized for analysis melted at 229–234°, λ_{max}^{MeOH} 239 mμ (ε 15,200); λ_{max}^{KBr} 5.85, 6.0, 6.16, 9.0–9.3 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.50): C, 69.21; H, 7.74. Found: C, 69.12; H, 7.60.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (7α-Methylhydrocortisone-BMD) (Xa).—7α-Methylcortisone-BMD (X) (120 mg.) was reduced with 70 mg. of lithium aluminum hydride in 5 ml. of tetrahydrofuran for 2 hours at room temperature. The excess lithium aluminum hydride was destroyed with ethyl acetate and finally with water. The reaction mixture was then extracted with ethyl acetate, the extracts washed with water,

dried and evaporated to dryness resulting in 105 mg. of crude 3,11-diol which showed no carbonyl in its infrared spectrum. This crude diol was dissolved in 10 ml. of methylene chloride and 1.0 g. of activated manganese dioxide was added. The reaction mixture was stirred at room temperature overnight then filtered through Super-cel. The filtrate was taken to dryness. The crude residue was chromatographed on acid-washed alumina. Elution with chloroform–ether (3:2) resulted in 47 mg. (40%) of product Xa, m.p. 187–193°. A sample recrystallized from ether for analysis melted at 190–195°, λ_{max}^{MeOH} 242 mμ (ε 15,800); λ_{max}^{KBr} 2.86, 6.01, 6.18, 9.2 μ.

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 68.66; H, 8.07.

7α-Methylhydrocortisone 21-Acetate (XIIa).—A mixture of 40 mg. of 7α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (Xa) and 3.5 ml. of 60% aqueous formic acid was heated at 100° for 35 minutes. The solution was then taken to dryness under vacuum, the residue dissolved in ethyl acetate, washed with sodium bicarbonate solution, water and dried over sodium sulfate. Removal of the ethyl acetate resulted in 37 mg. of an oil which was acetylated with 0.3 ml. of pyridine and 0.3 ml. of acetic anhydride at 100° for 10 minutes. The reaction was worked up in the usual manner and 37 mg. of crude product XIIa was obtained. Several recrystallizations from methanol and acetone gave 9 mg. (36%) of product XIIa, m.p. 230–234°; λ_{max}^{KBr} 2.99, 5.75, 5.79, 6.07, 6.18, 8.08 μ; λ_{max}^{MeOH} 242 mμ (ε 16,400); 96.7% of hydrocortisone 21-acetate by quantitative blue tetrazolium assay.

Procedure B. 7α-Methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one (VIIIa).—To 1.36 g. of 7α-methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one 11α-methylcarbonate ester (VIII) in 100 ml. of methanol was added 20 ml. of 20% aqueous potassium hydroxide. This mixture was heated under reflux for two hours and then concentrated under reduced pressure to about 25 ml. The resultant suspension was extracted into methylene chloride, dried and concentrated to 1.2 g. of a gum. Trituration with ether gave crystalline 7α-methyl-17,20;20,21-bismethylenedioxypregnane-11α-ol-3-one (VIIIa). Recrystallization from ether provided an analytical sample, m.p. 204–208°, λ_{max}^{Nujol} 2.81, 5.85, 9.0–9.2 μ.

Anal. Calcd. for $C_{24}H_{36}O_6$ (420.53): C, 68.54; H, 8.63. Found: C, 68.77; H, 8.39.

7α-Methyl-17,20;20,21-bismethylenedioxypregnane-3,11-dione (IX).—A solution of 1.20 g. of VIIIa in 12 ml. of pyridine was added to the complex prepared from 1.2 g. of chromium trioxide and 12 ml. of pyridine. The reaction mixture was kept at room temperature for 18 hours, poured into water and extracted with ether. The ether extracts were washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, dried and concentrated to 1.02 g. of oil. Crystallization from ether gave 780 mg. of product IX, m.p. 200–210° (215°). An analytical sample, m.p. 205–210° (215°), was prepared by recrystallization from methanol and methylene chloride–ether; λ_{max}^{Nujol} 5.8, 8.9–9.6 μ.

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 69.50; H, 8.21.

4-Bromo-7α-methyl-17,20;20,21-bismethylenedioxypregnane-3,11-dione.—To 736 mg. of 7α-methyl-17,20;20,21-bismethylenedioxypregnane-3,11-dione (IX) and 10 mg. of *p*-toluenesulfonic acid in 21 ml. of dimethylformamide was added 22.5 ml. of bromine in dimethylformamide (15 mg./ml. or 338 mg. of bromine). After disappearance of the bromine color (about 3 hours), the reaction mixture was poured into about 200 ml. of water and extracted with ether. Concentration of the ether left 910 mg. of gum. Trituration with ether gave crystalline 4-bromo-7α-methyl-17,20;20,21-bismethylenedioxypregnane-3,11-dione. A sample recrystallized from ether for analysis melted at 177–179° dec.; λ_{max}^{Nujol} 5.75, 5.84, 9.0 μ.

Anal. Calcd. for $C_{24}H_{33}O_6Br$ (497.42): C, 57.95; H, 6.69; Br, 16.07. Found: C, 58.44; H, 6.84; Br, 16.27.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-3,11-dione 3-Semicarbazone (XI).—To the 900 mg. of 4-bromo-7α-methyl-17,20;20,21-bismethylenedioxypregnane-3,11-dione, described above, was added 340 mg. of semicarbazide hydrochloride, 200 mg. of semicarbazide free base and 27 ml. of dimethylformamide. The reaction mixture was purged with nitrogen and stirred at room temperature for one hour. The precipitate which had formed during the reaction was collected and washed with acetone to give 410 mg. of product XI, m.p. 287–289° dec. To the filtrate was added a large volume of water and the resulting suspension was extracted with ethyl acetate. The organic extract was washed, dried and concentrated to give 457 mg. of crystalline residue. The residue was washed with acetone and an additional 267 mg. of product XI, m.p. 280–282° dec., was obtained. The analytical sample, m.p. 288–290° dec., was prepared by recrystallization from methylene chloride–ethyl acetate and showed λ_{max}^{MeOH} 270 mμ (ε 29,100).

Anal. Calcd. for $C_{25}H_{35}O_6N_3$ (473.55): C, 63.40; H, 7.45; N, 8.87. Found: C, 62.69; H, 7.28; N, 9.97.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one 3-Semicarbazone (XIa).—Fifty milligrams of XI in 5 ml. of tetrahydrofuran and 1 ml. of water was stirred with 20 mg. of sodium borohydride at room temperature for 18 hours. The reaction mixture was heterogeneous during the entire reaction time. Four drops of glacial acetic acid was added followed by a large volume of water. The resulting suspension was extracted with ethyl acetate, the extracts were dried and concentrated to 46 mg. of product XIa. The product could not be recrystallized satisfactorily and was used directly in the next reaction.

7α-Methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (Xa).—Six hundred and eighty-eight milligrams of the above crude semicarbazone XIa was dissolved in 18 ml. of pyruvic acid–water–acetic acid (1:1:1) and kept at room temperature for 18 hours. The reaction was then worked up as above to give 480 mg. of residue. This crude product was acetylated in 4 ml. of acetic anhydride and 4 ml. of pyridine at 100° for 10 minutes. The acetylation product was worked up in the usual manner to give 490 mg. of gum which was chromatographed on 15 g. of acid-washed alumina. From the fractions eluted with ether–chloroform (3:1) to ether–chloroform (1:1), there was obtained 192 mg. of crystalline 7α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (Xa), m.p. 189–193°. Recrystallization from ether gave product, m.p. 190–195°, which was identical with Xa obtained in procedure A above.

From the fractions eluted with chloroform, there was obtained 43 mg. of 7α-methylhydrocortisone 21-acetate (XIIa) which was recrystallized from methanol to give 12 mg. of product, m.p. 238–245°. There was no depression upon admixture with the 7α-methylhydrocortisone 21-acetate (XIIa) obtained in procedure A above.

7α-Methylhydrocortisone (XII) and 7α-Methylhydrocortisone 21-Acetate (XIIa).—A mixture of 120 mg. of 7α-methyl-17,20;20,21-bismethylenedioxy-4-pregnene-11β-ol-3-one (Xa) in 10 ml. of 50% aqueous acetic acid was heated at 100° for 3 hours. The mixture was concentrated to near dryness under vacuum. The residue was dissolved in ethyl acetate, washed, dried and concentrated to give 118 mg. of gum. Crystallization from acetone gave 68 mg. of 7α-methylhydrocortisone (XII), m.p. 195–215°. A portion was recrystallized from acetone to give an analytical sample, m.p. 211–214° (219°), λ_{max}^{MeOH} 242 mμ (ε 16,400); $\lambda_{max}^{H_2SO_4}$ 241 mμ (*E*% 443), 365 mμ (*E*% 135); $[\alpha]_{max}^{MeOH}$ +170 ± 4° (*C* 0.5); infrared spectrum (Fig. 1); 84% F-alcohol by quantitative blue tetrazolium assay.

Anal. Calcd. for $C_{22}H_{32}O_5$ (376.48): C, 70.18; H, 8.57. Found: C, 70.56; H, 8.35.

Nineteen milligrams of the above product XII was acetylated with acetic anhydride and pyridine to yield the 21-acetate XIIa, m.p. 230–234°, which was identical with that produced by procedure A.

7-Methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11β-ol (XXI).—To a solution of 635 mg. of 7-methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11-one (V) in 30 ml. of dry tetrahydrofuran was added 250 mg. of lithium aluminum hydride. The reaction mixture was stirred at room temperature for 24 hours. Ethyl acetate was then added to the reaction mixture followed by the addition of water. The reaction mixture was then concentrated *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water, dried and evaporated to dryness. Recrystallization of the residue from methylene chloride–ether resulted in 550 mg. of product, m.p. 190–210°, suitable for subsequent reactions. A sample recrystallized for

analysis melted at 205–215°, λ_{max}^{MeOH} 242 mμ (ε 19,400); λ_{max}^{Nujol} 2.79, 6.05, 6.21, 8.9–9.3 μ.

Anal. Calcd. for $C_{26}H_{36}O_7$ (460.55): C, 67.80; H, 7.88. Found: C, 67.53; H, 8.43.

7-Methyl-17,20;20,21-bismethylenedioxypregna-4,6-diene-11β-ol-3-one (XVIII).—7-Methylene-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-11β-ol (550 mg.) was dissolved in 10 ml. of acetone and 20 mg. of *p*-toluenesulfonic acid was added. The reaction mixture was left at room temperature overnight. Sodium bicarbonate solution was then added to the reaction mixture and the acetone removed by distillation under vacuum. The residue was extracted with ethyl acetate, the extracts washed with water, dried and evaporated to dryness. The crude product was chromatographed on 15 g. of alumina. The material eluted with chloroform–ether (3:1) was recrystallized from methylene chloride–ether and resulted in 318 mg. of product XVIII, m.p. 265–290° dec. A sample recrystallized for analysis melted at 286–294°, λ_{max}^{MeOH} 296 mμ (ε 27,600); λ_{max}^{Nujol} 2.85–3.0, 6.02, 6.13, 6.26, 8.9–9.2 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.50): C, 69.21; H, 7.74. Found: C, 69.15; H, 7.50.

7-Methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11β-diol (XVII).—Twenty milligrams of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7-ol-11-one (IV) was dissolved in 3 ml. of dry tetrahydrofuran. To this solution was added 10 mg. of lithium aluminum hydride. The reaction mixture was heated at reflux for 24 hours, then decomposed with moist ether. The reaction mixture was then filtered through Super-cel, dried and evaporated to dryness. The crystalline residue was recrystallized from methylene chloride–ether and melted at 215–220°; λ_{max}^{Nujol} 2.9, 9.0–9.2 μ.

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.56): C, 65.25; H, 8.00. Found: C, 65.14; H, 7.95.

Later runs on larger amounts of material resulted in product in which the melting points were somewhat higher, m.p. 230–240°. However, admixture with the lower melting analytical sample above caused no depression and the infrared spectra were identical.

Treatment of 100 mg. of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11β-diol (XVII) with 15 mg. of *p*-toluenesulfonic acid in 4 ml. of acetone at room temperature for 18 hours gave 96 mg. of 7-methyl-17,20;20,21-bismethylenedioxypregna-4,6-diene-11β-ol-3-one (XVIII), m.p. 280–290°. Recrystallization from acetone gave material, m.p. 286–294°, which was not depressed upon admixture with the sample prepared above.

7β-Methylhydrocortisone-BMD (XIX).—7-Methyl-17,20;20,21-bismethylenedioxy-pregna-4,6-diene-11β-ol-3-one (XVIII) (313 mg.) in 45 ml. of methanol to which had been added 3 mg. of potassium hydroxide and 150 mg. of 5% palladium-on-Darco was hydrogenated at one atmosphere. The hydrogenation was stopped after the uptake of one mole of hydrogen. The reaction mixture was filtered from the catalyst and evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried and evaporated to dryness resulting in 320 mg. of crude product which by ultraviolet analysis consisted of about 10% starting material and 60% desired product. The residue was chromatographed on 4 g. of acid-washed alumina. The material eluted with ether–chloroform (9:1) through ether–chloroform (8:2) was recrystallized several times from ether and resulted in 110 mg. of product XIX, m.p. 209–216°. A sample recrystallized for analysis melted at 214–216°, λ_{max}^{MeOH} 243 mμ (ε 16,000). The product upon admixture with a sample of Xa, m.p. 190–195°, melted at 170–195°.

Anal. Calcd. for $C_{24}H_{34}O_6$ (418.51): C, 68.87; H, 8.19. Found: C, 69.41; H, 8.53.

In addition to the product XIX, 65 mg. of starting material XVIII, m.p. 275–290°, was recovered by elution of the column with ether–chloroform (7:3).

7β-Methylhydrocortisone (XX).—Ninety-eight milligrams of 7β-methylhydrocortisone-BMD (XIX) was heated at 90° under nitrogen for 3 hours in 8 ml. of 50% aqueous acetic acid. The reaction mixture was then taken to dryness under vacuum. The residue was dissolved in ethyl acetate, washed with sodium bicarbonate solution, water, dried and evaporated to dryness leaving 84 mg. of residue. Recrystallization from acetone resulted in 34 mg. of product XX, m.p. 222–228°. The remainder of the material was chromatographed on Florisil and the product was eluted with chloroform–acetone (7:3). Recrystallization from acetone gave an additional 13 mg., m.p. 222–228°. A sample recrystallized for analysis melted at 224–228°; λ_{max}^{MeOH} 242 mμ (ε 15,900); $\lambda_{max}^{H_2SO_4}$ 242 mμ (*E*% 304), 285 mμ (*E*% 365), 375 mμ (*E*% 200), 388 mμ (*E*% 206); infrared spectrum (Fig. 2), $[\alpha]_D^{MeOH}$ +164 ± 4° (*c* 0.5), and 104.6% F-alcohol by quantitative blue tetrazolium assay. The product XX, m.p. 224–228°, upon admixture with a sample of XII, m.p. 211–214° (219°), melted at 195–210°.

Anal. Calcd. for $C_{22}H_{32}O_6$ (376.48): C, 70.18; H, 8.57. Found: C, 70.33; H, 8.76.

Zderic, *et al.*,[7] report the following properties for their 7β-methylhydrocortisone; m.p. 237–238°, $[\alpha]_D$ +30° (dioxane); λ_{max} 244, 292–294 mμ, log ε 4.22, 2.66.

7-Methyl-17,20;20,21-bismethylenedioxypregna-4,6-diene-11α-ol-3-one 11α-Acetate (XIII).—To a solution of 2 g. of 7-methyl-3-ethylenedioxy-17,20;20,21-bismethylenedioxy-5-pregnene-7,11α-diol (VII) in 20 ml. of acetone was added 120 mg. of *p*-toluenesulfonic acid. The reaction mixture was then left at room temperature. After about 3 hours, a thick mass of crystals separated in the flask. The reaction mixture was left for a total of six hours at room temperature, then diluted with water and extracted with ethyl acetate. The extracts were washed with sodium bicarbonate solution, dried and evaporated to dryness resulting in 1.78 g. of crude 7-methyl-17,20;20,21-bismethylenedioxypregna-4,6-diene-11α-ol-3-one which was used directly in the acetylation given below. A sample recrystallized for analysis from acetone melted at 255–260° dec., λ_{max}^{MeOH} 297 mμ (ε 27,900).

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.50): C, 69.21; H, 7.74. Found: C, 69.02; H, 7.50.

The total crude from above was acetylated with 7 ml. of acetic anhydride in 10 ml. of pyridine at room temperature overnight. The reaction was worked up in the usual manner and the crude product was chromatographed on acid-washed alumina. The material eluted with ether–chloroform (8:2) through ether–chloroform (7:3) was recrystallized from acetone–petroleum ether and gave 1.46 g. of product XIII, m.p. 220–230°. A sample recrystallized for analysis from the same solvent pair melted at 229–234°, λ_{max}^{MeOH} 295 mμ (ε 28,300); $\lambda_{max}^{CHCl_3}$ 5.8, 6.02, 6.15, 6.28, 7.98, 8.9–9.2 μ.

Anal. Calcd. for $C_{26}H_{34}O_7$ (458.53): C, 68.10; H, 7.47. Found: C, 68.13; H, 7.50.

7β-Methyl-17,20;20,21-bismethylenedioxyallopregnane-11α-ol-3-one 11α-Acetate (XIV).—The 11α-acetate XIII (1.46 g.) was dissolved in 126 ml. of glacial acetic acid and 14 ml. of acetic anhydride. To this solution was added 1.5 g. of palladium oxide catalyst. The reaction mixture was then hydrogenated at 40 lb. initial hydrogen pressure (more hydrogen was added as the pressure dropped) until the uptake of hydrogen ceased. The reaction mixture was then filtered and the filtrate taken to dryness under reduced pressure. The residue was taken up in ethyl acetate, washed with sodium bicarbonate solution, dried and evaporated to dryness. The total crude product was chromatographed on 45 g. of acid-washed alumina. The fractions eluted with ether–petroleum ether (7:3) through ether were combined and recrystallized from methylene chloride–ether and resulted in 900 mg. of product, XIV, m.p. 190–198°. The analytical sample melted at 193–200°; λ_{max}^{Nujol} 5.78–5.85, 7.9–8.0, 9.0–9.2 μ.

Anal. Calcd. for $C_{26}H_{38}O_7$ (462.56): C, 67.51; H, 8.28. Found: C, 67.79; H, 8.47.

7β-Methyl-17,20;20,21-bismethylenedioxyallopregnane-3,11-dione (XIVb).—A solution of 930 mg. of 7β-methyl-17,20;20,21-bismethylenedioxyallopregnane-11α-ol-3-one 11α-acetate (XIV) in 75 ml. of methanol and 15 ml. of 20% aqueous potassium hydroxide was heated at reflux for 2 hours. The reaction mixture was then concentrated under reduced pressure and extracted with ethyl acetate. The extracts were washed with water, dried and evaporated to dryness resulting in 870 mg. of an oil. Attempts to crystallize the oil were unsuccessful. The oil was then dissolved in 9 ml. of pyridine and added to the complex formed from 900 mg. of chromium trioxide in 9 ml. of pyridine. The reaction mixture was left at room temperature overnight, then worked up in the usual manner yielding 790 mg. of partially crystalline material. The total crude was chroma-

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.

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[CONTRIBUTION FROM MERCK SHARP AND DOHME RESEARCH LABORATORIES]

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

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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-

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