81.6°; infrared carbonyl absorption, 5.70 (strong), 5.62 μ (weak); ultraviolet absorption, $\lambda_{max}^{ethanol}$ 287 mμ (ε 32)].

Anal. Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.40; H, 9.36.

A 2,4-dinitrophenylhydrazone derivative (VII) was prepared from 0.21 g. (0.0019 mole) of VI to give 0.50 g. (90%) of orange needles, m.p. 157.2–157.5°.

Hydrogenation of Bicyclo[2.2.1]hept-2-en-7-one (I).—In a hydrogenation flask 0.119 g. (0.00184 mole) of I with *ca.* 5 ml. of 95% ethanol and 50 mg. of 5% palladium on carbon was stirred under hydrogen at room temperature and atmospheric pressure. After 40 min. the ketone had taken up 98% of the theoretical volume of hydrogen. The catalyst was removed by filtration and the resulting filtrate was treated with 2,4-dinitrophenylhydrazone reagent to give 0.480 g. (92%) of the 2,4-dinitrophenylhydrazone of bicyclo[2.2.1]heptan-7-one, m.p. 152–154°. After recrystallization from ethanol, the orange needles melted at 156–157.5°.

Bicyclo[2.2.1]heptan-7-ol (VIII).—To a solution of 0.1029 g. (0.00093 mole) of bicyclo[2.2.1]heptan-7-one in 10 ml. of anhydrous ether was added dropwise with stirring a solution of 0.7412 g. (0.019 mole) of lithium aluminum hydride in 4 ml. of ether at 0°. After addition was complete the solution was stirred for 2 hr. whereupon 2.96 ml. of water was added dropwise to the stirring solution. The resulting slurry was stirred for 0.5 hr., filtered, and the precipitate washed with ether. The filtrate was dried over anhydrous magnesium sulfate, and the drying agent was removed by filtration. The ether was removed by flash evaporation to give 0.0897 g. (86%) of VIII, m.p. 151.5–153°. The white crystalline solid was recrystallized twice from petroleum ether (b.p. 65–75°) to give pure VIII, m.p. 152.4–153.6° (lit.[20] m.p. 152–153°).

Sarett Oxidation of Bicyclo[2.2.1]heptan-7-ol (VIII).—A solution of 0.73 g. of VIII in 20 ml. of pyridine was added to the complex formed from 2.0 g. of chromium trioxide and 20 ml. of pyridine.[21] After standing for 24 hr. the reaction mixture was poured into water and extracted with three portions of benzene-e her. The combined extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated. Treatment of the concentrate with 2,4-dinitrophenylhydrazine reagent gave 0.70 g. (37%) of VII, m.p. 155–157°, without purification.

***exo*-2,3-Epoxybicyclo[2.2.1]heptan-7-one (XI).**—Bicyclo-[2.2.1]hept-2-en-7-one (1.50 g., 0.0139 mole) was added to 44.5 ml. of benzene containing 2.35 g. (0.0170 mole) of perbenzoic acid. The reaction mixture was kept at 2° for 64 hr. at which time iodometric titration indicated the reaction of 0.0129 mole of perbenzoic acid. The reaction mixture was extracted with two 25-ml. portions of a 10% sodium hydroxide solution followed by 25 ml. of water, and dried over anhydrous magnesium sulfate. Removal of the drying agent, followed by concentration of the solvent and dilution with pentane gave 0.99 g. (0.008 mole, 62%) of white crystalline XI. A combination of recrystallization from petroleum ether (b.p. 60–70°) and sublimation gave an analytical sample, m.p. 144–145°.

Anal. Calcd. for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.45; H, 6.46.

Bicyclo[2.2.1]hept-2-en-*anti*-7-ol (IX).—Bicyclo[2.2.1]hept-2-en-7-one (2.16 g.) was treated with excess lithium aluminum hydride in anhydrous ether at 0°. Hydrolysis with water, followed by filtration and removal of the solvent, gave an oily solid, which, after recrystallization from hexane and sublimation, yielded 1.20 g. (52%) of pure IX, m.p. 117.5–119.5° (lit. m.p. 117–118°).[7,22]

***exo*-2,3-Epoxybicyclo[2.2.1]heptan-*anti*-7-ol (XII).**—Bicyclo-[2.2.1]hept-2-en-7-ol (0.55 g.) was added to a solution of 0.975 g. of perbenzoic acid in 25 ml. of methylene chloride. The reaction mixture was allowed to stand for 72 hr. at 2°, washed twice with 25 ml. of saturated sodium carbonate solution, washed once with 10 ml. of water, and dried over anhydrous magnesium sulfate. The solvent was stripped to yield 0.51 g. (82%) of white crystalline product, m.p. 150–155°. Two recrystallizations from hexane–benzene followed by sublimation gave an analytical sample of XII, m.p. 195.6–196.4°.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 67.00; H, 8.19.

***exo*-2,3-Epoxybicyclo[2.2.1]heptan-7-one (XI) *via* Oxidation of XII.**—A solution of 0.50 g. of pure XII in 15 ml. of pyridine was added to a stirred solution of the complex formed from 1.50 g. of chromium trioxide in 15 ml. of pyridine.[21] The reaction was stirred overnight, diluted with water, and extracted with ether. The ethereal solution was washed thoroughly with water, dried over anhydrous magnesium sulfate, filtered, and the ether evaporated to give 0.15 g. of semicrystalline keto epoxide. One recrystallization from petroleum ether (b.p. 60–70°) followed by sublimation gave pure XI, m.p. 142.5–143.5°. The infrared spectrum of this product was identical with XI obtained from the reaction of I with perbenzoic acid.

(20) S. Winstein and E. T. Stafford, *J. Am. Chem. Soc.*, **79**, 505 (1957).

(21) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(22) (a) S. Winstein and M. Shatavsky, *ibid.*, **78**, 592 (1956); (b) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).

The Synthesis of 1α-Methylhydrocortisone and 1α-Methylcortisone Acetate[1]

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The synthesis of 1α-methylhydrocortisone, 1α-methylcortisone, and 1-methylprednisolone are described. The 1-methyl substituent is introduced by conjugate addition of methyl Grignard to the Δ^1-3-keto steroid (I). The configuration of the 1-methyl is assigned by optical rotatory dispersion.

The introduction of methyl groups into the hydrocortisone molecule at positions 2,[2a] 6,[2b] 15,[3] and 16[4] has led to an enhancement of anti-inflammatory activity of the parent corticoid. Methylation at virtually all other positions in the hydrocortisone molecule, to give 4-,[5] 5-,[6] 7-,[7] 9-,[8,10] 11-,[9] 12-,[10] 14-, and 21-[11]methylhydrocortisones, has been reported to lead to diminution of anti-inflammatory activity. For the cases of enhanced cortical activity in which the substituent clearly can be designated as axial or equatorial (*i.e.*, exclusive of 15- and 16-methyl), methyl group orientation has been both α and equatorial. In order to

(1) Presented at the 145th National Meeting of the American Chemical Society, New York, N.Y., September, 1963.

(2) (a) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955); (b) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *ibid.*, **78**, 5213 (1956).

(3) P. F. Beal and R. W. Jackson, private communication.

(4) S. L. Steelman, E. R. Morgan, and R. H. Silver, *Steroids*, **1**, 163 (1963).

(5) N. G. Steinberg, R. H. Hirschmann, and J. M. Chemerda, *Chem. Ind.* (London), 975 (1958).

(6) J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 1684 (1960).

(7) R. E. Beyler, A. E. Oberster, F. Hoffmann, and L. H. Sarett, *ibid.*, **82**, 170 (1960).

(8) F. Hoffman, R. E. Beyler, and M. Tishler, *ibid.*, **80**, 5322 (1958).

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

(10) J. Fried, private communication.

(11) H. J. Hess, S. K. Figdor, G. M. K. Huges, R. Pinson, Jr., and W. T. Moreland, 138th National Meeting of the American Chemical Society, New York, N.Y., September, 1960, p. 39P.

evaluate further this influence of α-methyl substitution and to provide steric protection from metabolism of ring A[12] we undertook the preparation of 1α-methylhydrocortisone (α and axial) and 1-methylprednisolone.

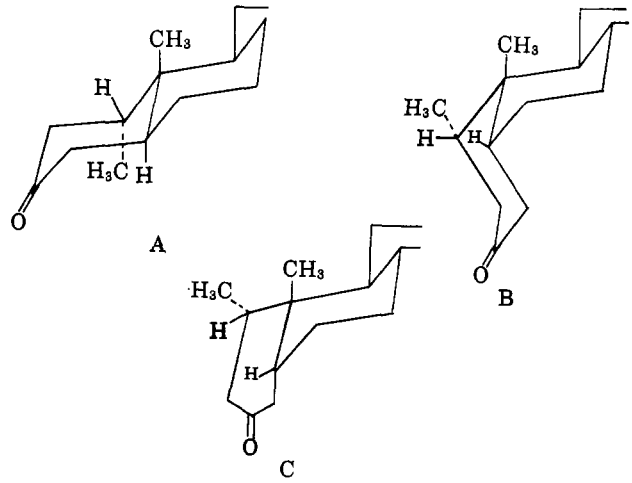
Earlier approaches to 1-methyl steroids have involved principally the dienone phenol rearrangement of $\Delta^{1,4}$-3-ketones followed by Birch reduction to give compounds which are probably 1β-methyl-19-nor steroids, although evidence for the conformation of the methyl group was not available. In this manner 1-methyl-19-nortestosterone,[13] 1-methyl-19-norprogesterone,[14] 1-methyl-17α-ethinyl-19-nortestosterone, and 1-methyl-19-norhydrocortisone[13] were synthesized. One might anticipate, however, that a 1-methyl-19-norcorticoid would be an unlikely prospect for enhanced cortical activity since 19-norhydrocortisone[15] itself is less active than hydrocortisone.

Weichert and Kaspar[16] have embarked on 1-methyl steroid syntheses by taking advantage of the Michael addition of diazomethane to a 5α-Δ^1-3-ketone, which gave a pyrazoline which was in turn pyrolyzed giving the 1-methyl-Δ^1 system. Reduction afforded principally 1β-methyl steroids which lack the desired α configuration needed to test the previous structural hypothesis. Until Djerassi recently published the short wave-length optical rotatory dispersion[17] curve of 1α- and 1β-methyl-19-norprogesterones, the configuration of the methyl group had been obscure.

The most attractive route to 1α-methyl corticoids appeared to be *via* the 5β-Δ^1-ketone (I) which can be obtained from the incubation of 5β-pregnane-3,11,20-trione cyclic 20-(ethylene acetal) with *Septomixia affinis*.[18] Inverse addition of methyl Grignard to the α,β-unsaturated ketone (I) afforded the 1-methyl derivative (II) which gave, on ketal hydrolysis, 1-methylpregnanetrione (IX). Stereochemical considerations based on a study of molecular models suggested that alkylation need not take place preferentially from one side of the molecule. In this particular case, however, α attack might appear to be favored since the added substituent would be in the thermodynamically favorable equatorial configuration. Alkylations similar to this one have been reported[19] to yield exclusively the kinetic product; we found that the copper-catalyzed Grignard alkylation of I yielded stereoselectively the equatorial isomer. An explanation of the stereoselectivity and stereochemistry of our alkylation product has been sought. Subsequent to the completion of this work Mori[20] carried out the conjugate addition of methyl Grignard to Δ^1-dihydrotestosterone (A/B *trans*) and obtained 1α-methyltestosterone after introduction of the Δ^4-bond. Similarly 1α-methylcoprostan-3-one, 1α-methylcholest-4-en-3-one and its reduction product 1α-methylcholestan-3-one were prepared.

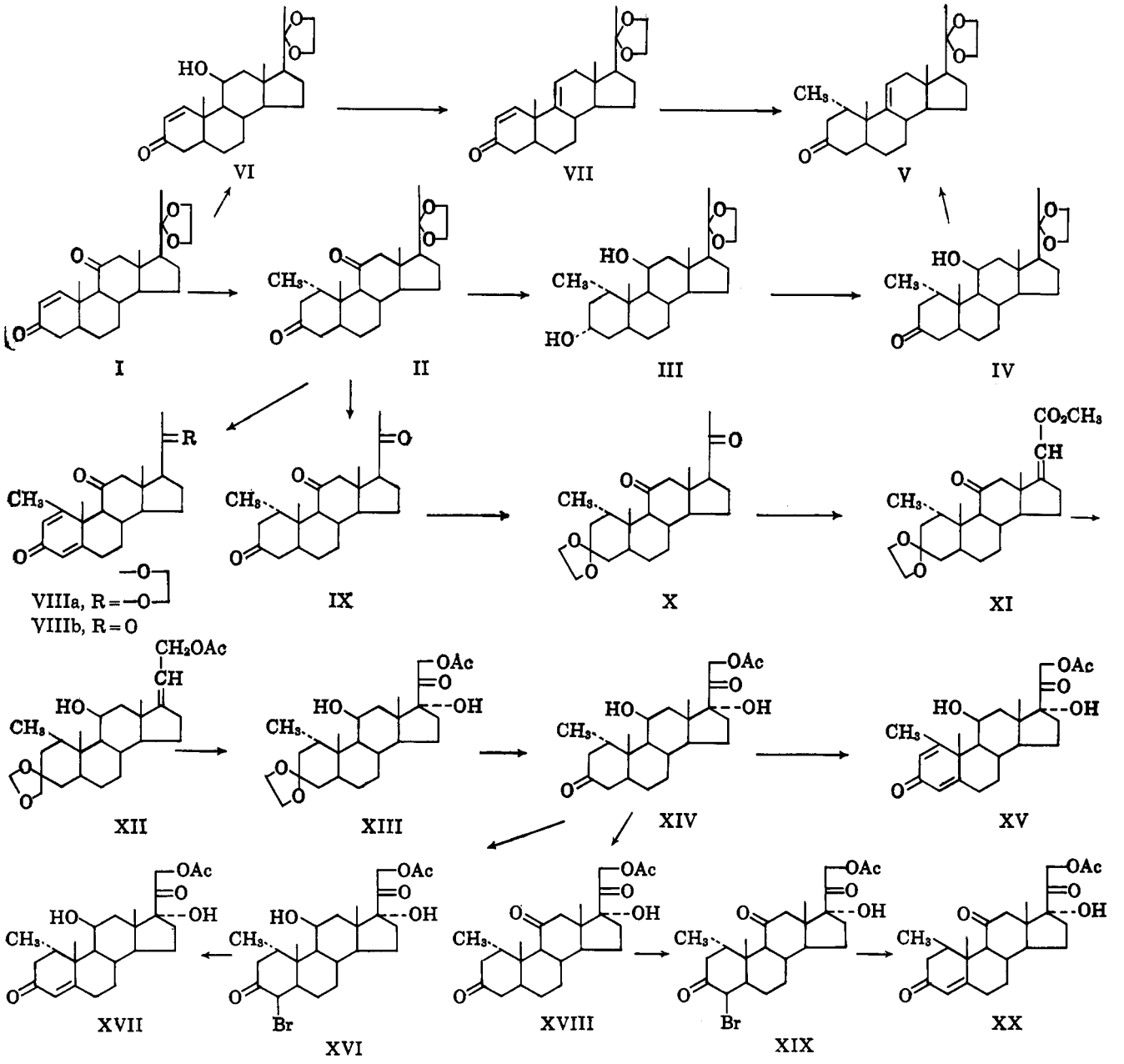
(12) W. E. Dulin, L. E. Barnes, E. M. Glenn, S. C. Lyster, and E. J Collins, *Metab. Clin. Exptl.*, **7**, 398 (1958).
(13) H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 2477 (1956).
(14) C. Djerassi, A. E. Lippman, and J. Grossman, *ibid.*, **78**, 2479 (1956).
(15) L. Sarett, "International Congress on Steroid Hormones," Milano, 1962.
(16) R. Weichert and E. Kaspar, *Ber.*, **93**, 1710 (1960).
(17) C. Djerassi, R. Records, E. Bummenberg, K. Mislow, and A. Moscovitz, *J. Am. Chem. Soc.*, **84**, 871 (1962).
(18) G. S. Fonken and H. C. Murray, *J. Org. Chem.*, **27**, 1102 (1962).
(19) H. D. House and H. W. Thompson, *ibid.*, **28**, 360 (1963).
(20) H. Mori, *Chem. Pharm. Bull.* (Tokyo), **10**, 386 (1962).

Mori[20] found that the 1α-methyl A/B-*trans* system (A) showed a typical positive Cotton effect curve whereas the 1α-methyl A/B *cis* system exhibited an abnormal weak positive Cotton curve. He observed from examination of molecular models of the 1α-methyl A/B *cis* system (abnormal Cotton curve) that in conformation B the 1α-methyl group violates the van der Waals radius of the 11-methylene. Since this appeared energetically unfavorable, he concluded that the A-ring actually existed in conformation C, which he suspected would give an abnormal O.R.D. curve. Subsequent publications by Djerassi[21] confirmed the hypothesis that such a boat or twist conformation might exhibit an abnormal exhalted O.R.D. curve. Similarly the 1-methyl-3-keto 20-ketals (IV and V) exhibited abnormal exhalted negative Cotton effect curves (molecular amplitudes $a = -55°$ and $-70°$, respectively) with respect to the normal negative Cotton curve of a closely related 3-keto 5β-steroid [calculated molecular amplitude = ($-8°$ for compound A, Fig. 1) − ($25°$, for contribution for the β-equatorial methyl group) = $-33°$]. Consequently, we have concluded that our A/B *cis* 1-methyl steroid (II) possessed a 1α-methyl substituent and that A-ring exists in a boat or twist conformation.



In order to examine the possibility that the stereoselectivity of the 1-methylation might be directed *via* initial complexing of the Grignard reagent with the 11-ketone followed by alkylation internally at C-1,[22] the following experiments were carried out. The dione I was reduced with lithium aluminum hydride to the 3,11-diol and then oxidized selectively by means of the Oppenauer oxidation to the 11β-hydroxy 3-ketone (VI). This compound was in turn dehydrated to the diene VII. Upon alkylation the diene VII gave a single 1,4-addition product which was established to be the 1α-methyl steroid (V). The structure of V was related unequivocally to the original alkylation product (II) by reduction to the diol III, Oppenauer oxidation to the ketone IV, and finally dehydration which afforded the 1α-methyl $\Delta^{9(11)}$-steroid (V) identical in all regards with that obtained from the alkylation of the diene VII. Thus the stereochemical course of the 1,4-

(21) (a) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962); (b) C. Djerassi, E. Lund, and A. A. Akhrem, *J. Am. Chem. Soc.*, **84** 1249 (1962).
(22) J. A. Campbell and J. C. Babcock, *ibid.*, **81**, 4069 (1959).



Grignard step was the same whether a double bond or a ketone was present at C-11.

Selective halogenation at C-4 of the trione IX was unsuccessful under conditions[23] where 4-halo-5β-pregnane-3,11,20-triones are prepared in high yield from 5β-pregnane-3,11,20-trione.[24] Since selective halogenation at C-4 was not possible at this juncture, it was decided first to construct the dihydroxyacetone side chain and introduce the Δ^4-bond late in the synthesis. In order to establish that the A-ring would accommodate a Δ^4-bond a sample of the ketal II was dehydrogenated with selenium dioxide to the diene VIIIa, and the ketal hydrolyzed to yield the 1-methyl-$\Delta^{1,4}$-3,11,20-trione (VIIIb). Its structure was confirmed both by its infrared and ultraviolet spectra.

In order to protect the 3-ketone, the trione IX was selectively ketalized employing selenium dioxide and ethylene glycol in chloroform[25] to give the 3-monoketal (X). Employing the sequence of Hogg, *et al.*,[26] the side chain was glyoxylated, brominated, and the Favorskiĭ rearrangement carried out to give the ester XI in *ca.* 50% yield. Reduction with lithium aluminum hydride followed by acetylation in pyridine afforded the allylic ester (XII). Oxidation with N-methylmorpholine peroxide–hydrogen peroxide complex in the presence of osmium tetroxide gave the desired side-chain elaborated steroid (XIII). Acid hydrolysis of the ketal XIII afforded 1α-methyldihydrohydrocortisone acetate (XIV). Bromination with one mole of bromine in acetic acid containing a trace of hydrogen bromide followed by dehydrohalogenation *via* semicarbazone formation and pyruvate cleavage afforded 1α-methylhydrocortisone acetate (XVII). The structure of compound XIV and XVII were confirmed by their n.m.r. spectra which are summarized in Table I. The ultraviolet spectrum of the hydrocortisone derivative XVII was abnormal [λ_{max} 247 mμ (ε 13,150)].

(23) For summary of selective halogenations, see H. J. E. Lowenthal, *Tetrahedron*, **6**, 286 (1959).

(24) This fact lends further credence to the assumption that the A-rings of the 5β-3-ketones II–V possess a boat or twist conformation.

(25) E. P. Oliveto, H. I. Smith, C. Gerold, R. Rausser, E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1414 (1956).

(26) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *ibid.*, **77**, 4436 (1955).

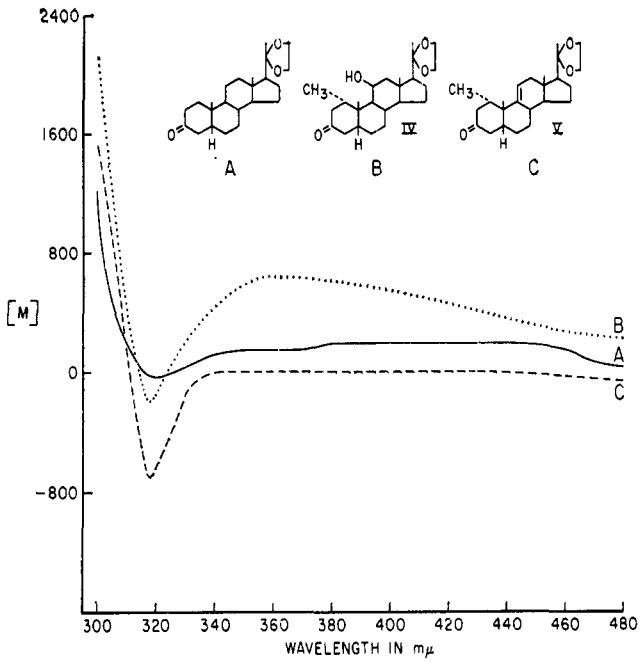


Figure 1.

A possible explanation of this fact may lie in the distortion of the A-ring by the 1α-methyl group which manifests itself also in the abnormal exalted O.R.D. curves (Fig. 1). Dreiding models do suggest, owing to the 11α-H–1α-methyl interaction, that the A-ring distortion in XVII is greater than in the 11-keto compound (XX) which has a normal ultraviolet spectrum.

If an excess of bromine is employed for the bromination of XIV, then the 11β-hydroxyl is oxidized to a ketone and 1α-methylcortisone acetate (XX) is the sole product isolated after dehydrohalogenation. 1α-Methylcortisone (XX) was prepared alternately by chromium trioxide oxidation of dihydrohydrocortisone acetate (XIV) to 1α-methyldihydrocortisone acetate (XVIII) followed by the bromination–dehydrohalogenation sequence. 1-Methylprednisolone acetate (XV) was prepared by selenium dioxide oxidation of the dihydrohydrocortisone (XIV). The structure of this product was confirmed by its infrared and ultraviolet spectra.

Compounds XVIII and XX exhibited very weak, if any, glucocorticoid activity.[27]

Experimental[28]

1α-Methyl-5β-pregnane-3,11,20-trione Cyclic 20-(Ethylene Acetal) (II).—To the Δ^1-5β-pregnene-3,11,20-trione 20-ketal (2.5 g., 6.7 mmoles) dissolved in 50 ml. of purified tetrahydrofuran containing 200 mg. of copper(I) bromide, chilled in an ice bath, was added dropwise a solution of 5 ml. of 3 *M* methylmagnesium bromide (15 mmoles) and 200 mg. of copper(I) bromide dissolved in 10 ml. of purified tetrahydrofuran with stirring. The stirred solution was allowed to come to room temperature during 2 hr. The reaction mixture was again chilled, treated with saturated ammonium chloride, and diluted with 150 ml. of ether. The organic layer was separated, washed with saturated ammonium chloride, twice with saturated sodium chloride solution, then dried over sodium sulfate. The solvent was removed on the rotary vacuum evaporator then absorbed onto a short Florisil[29] column (50 g.) and the product eluted with 5% acetone–Skellysolve B. This crystalline material was recrystallized from Skellysolve B–acetone giving 1.73 g. (69%) of a crystalline solid, m.p. 163–167°. A sample was recrystallized twice for analysis, m.p. 165.5–169°. Physical constants were ν_{max} 1700, 1330, 1070 and 1047 cm.$^{-1}$; O.R.D. (*c* 1.005, dioxane, 25°), $[M]_{290}$ +3130°, $[M]_{300}$ + 2320°, $[M]_{320}$ +1180°, $[M]_{355}$ +1005°, $[M]_{380}$ + 1080°, and $[M]_{589}$ + 595°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.46; H, 9.75.

1α-Methyl-5β-pregnane-3,11,20-trione (IX).—The 1α-methyl 20-ketal from the previous experiment (1.50 g., 3.88 mmoles) was dissolved in 25 ml. of alcohol (warm) and treated with 10 ml. of 3 *N* hydrochloric acid, then warmed on a steam bath for 3 hr. followed by dilution with hot water to the point of incipient crystallization. The product separated as white crystalline bars, 870 mg. (65%), m.p. 142–165°. Recrystallization twice from acetone–Skellysolve B afforded 510 mg. of product, m.p. 169–173°. A sample was recrystallized twice for analysis, m.p. 172–174°; ν_{max} 1697 and 1690 cm.$^{-1}$; O.R.D. (*c* 1.004, dioxane, 25°), $[M]_{302}$ +6210°, $[M]_{312.5}$ +7050°, $[M]_{340}$ +3815°, $[M]_{400}$ +1785°, $[M]_{480}$ 823°, and $[M]_{589}$ 377°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.79; H, 9.52.

1α-Methyl-3α,11β-dihydroxy-5β-pregnan-20-one Cyclic (Ethylene Acetal) (III) and 1α-Methyl-11β-hydroxy-5β-pregnane-3,20-dione Cyclic 20-(Ethylene Acetal) (IV).—A 5.6-g. sample of the dione II was dissolved in 100 ml. of isopropyl alcohol and 2.5 g. of sodium borohydride dissolved in 50 ml. of water containing 0.5 ml. of 3 *M* sodium hydroxide solution was added. The mixture was heated at reflux for about 20 hr. After 7 hr. an additional 5 g. of sodium borohydride was added. The alcohol was then removed under reduced pressure and the solid isolated, washed with water, and dried (*in vacuo*, 60°). The infrared spectrum of this product was consistent with the expected structure, m.p. 171–186°; yield, 5.6 g. The crude diol was dissolved in 100 ml. of hot toluene containing 5.0 ml. of cyclohexanone and a small quantity of the solvent distilled so as to dry the reaction mixture. Aluminum tri-*t*-butoxide (5.6 g.) was then added and the suspension heated at reflux for 2 hr. The cooled suspension was extracted consecutively with *N* hydrochloric acid, water, saturated sodium chloride solution, dried with sodium sulfate, and evaporated to a small volume under reduced pressure. The residue was adsorbed onto 250 g. of Florisil and eluted over a gradient of from 2 to 15% acetone–Skellysolve B during twenty-five 400-ml. fractions. **Fractions 7–11** (2.67 g.) were combined and recrystallized from acetone to give 2.07 g. of the ketone (IV), m.p. 176–179°; ν_{max} 3400, 1690, and 1223 cm.$^{-1}$. A sample was recrystallized four times for analysis, m.p. 178.0–179.5°; O.R.D. (*c* 1.67, dioxane), $[M]_{48}$ +224°, $[M]^{max}_{360}$ +640°, $[M]^{min}_{317.5}$ −192°, and $[M]_{300}$ +2116°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.96; H, 9.95.

Fractions 14–19 (1.61 g.) were combined and recrystallized from acetone to give 1.2 g. of the diol III, m.p. 188–194.5°. A sample was recrystallized four times for analysis, m.p. 197.0–199.5°; ν_{max} 3480, 1218 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.43; H, 10.41.

11β-Hydroxy-5β-pregn-1-ene-3,20-dione Cyclic 20-(Ethylene Acetal) (VI).—5β-Pregn-1-ene-3,11,20-trione cyclic 20-(ethylene acetal) (10 g.) was treated as described previously. With removal of the toluene after oxidation a solid was isolated and recrystallized from ethyl acetate to give 3.48 g. of crude product, m.p. 202–208.5°. A sample was recrystallized four times from acetone, m.p. 217.5–218.5°; ν_{max} 3400, 1656, and 1613 cm.$^{-1}$; λ_{max} 227 mμ (ε 9300).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.99; H, 9.21.

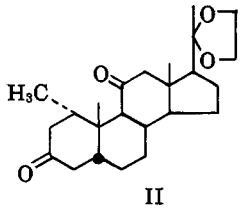
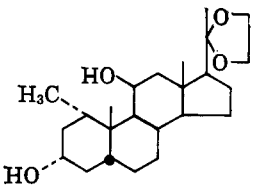
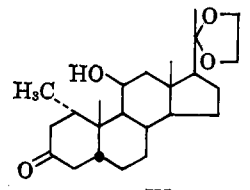
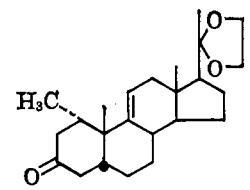
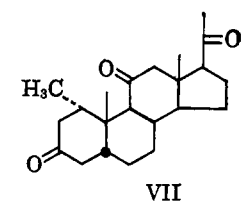
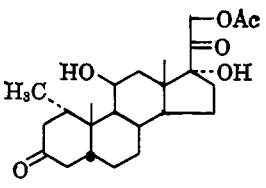
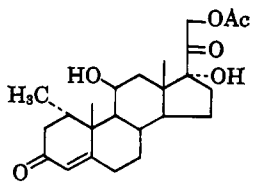
1α-Methyl-5β-pregn-9(11)-ene-3,20-dione Cyclic 20-(Ethylene Acetal) (V).—The alcohol (IV, 500 mg., 1.28 mmoles) was dissolved in 5 ml. of dry pyridine and treated under nitrogen with 193 mg. (1.4 moles) of N-bromoacetamide at room temperature for 15 min. The solution was then chilled in an ice bath and

(27) R. Stafford, L. Barnes, B. Bowman, and M. Meinzinger, *Proc. Soc. Exptl. Biol. Med.*, **89**, 371 (1955).

(28) Melting points were taken by capillary (except where noted) and are uncorrected. Infrared spectra were recorded as mineral oil mulls employing a *Perkin-Elmer Model 21 spectrometer*. N.m.r. spectra were determined on 5–10% solutions in deuteriochloroform (except where noted) at 60 Mc. with a Varian 4320/2 spectrometer, employing tetramethylsilane as an internal reference. Frequencies are reported in cycles per second relative to tetramethylsilane as 0 c.p.s. Skellysolve B is a petroleum ether fraction, b.p. 50–70°.

(29) A synthetic magnesium silicate manufactured by the Floridin Co., Warren, Pa.

TABLE I

Compound	Function	Frequency, c.p.s.[a]	Multiplet	J	No. of H
 II	Ketal	234	m		4
	19-H[b]	74	s		3
	18-H	45	s		3
	21-H	75	s		3
	1α-CH_3[c]	54.7	d	6.5	3
 III	11α-H	258	m		1
	Ketal	241	m		4
	3β-H	*ca.* 240	m		1
	21-H	79	s		3
	19-H	70	s		3
	18-H	60	s		3
	1α-CH_3	61.5	d	8	3
 IV	11α-H	264	m		1
	Ketal	241	m		4
	21-H	79	s		3
	19-H	76	s		3
	18-H	63	s		3
	1α-CH_3	57.5	d	7	3
 V	Ketal	240	m		4
	11-H	338	m		1
	21-H	80	s		3
	19-H	69	s		3
	1α-CH_3	63.5	d	7	3
	18-H	44	s		3
 VII	21-H	125	s		3
	19-H	74	s		3
	18-H	34.5	s		3
	1α-CH_3	52.5	d	7	3
 XII	21-H[d]	296.5	AB	17	2
	11α-H	266	m		1
	19-H	72	s		3
	18-H	56	s		3
	1α-CH_3	56	d	6	3
 XVII	4-H	338	m		1
	21-H	292	AB	17	2
	11α-H	269	m		1
	19-H	82	s		3
	18-H	55.5	s		3
	1α-CH_3	63	d	6.5	3

[a] Downfield from tetramethylsilane. [b] R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1380 (1961); G. Slomp and F. A. MacKellar, *J. Am. Chem. Soc.*, in press. [c] G. Slomp and R. B. McGarvey, *ibid.*, **81**, 2200 (1959). [d] N. R. Trenner, B. H. Arinson, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).

the excess oxidant destroyed with sulfur dioxide gas. The reaction mixture was then diluted with 25 ml. of water and refrigerated. The white crystalline product was filtered, washed thorough y with water, and dried (*in vacuo*, 60°); yield, 400 mg. The solid was adsorbed onto 30 g. of Florisil and eluted over a gradient of from 2 to 7.5% acetone–Skellysolve B during twenty 50-ml. fractions. **Fractions 10–18** contained 131 mg. of material whose infrared spectrum was identical with that of the starting material. **Fractions 2–5** (276 mg.) were crystalline olefin, m.p. 159.0–159.5°. A sample was recrystallized for analysis, m.p. 159.0–159.5°; ν_{max} 3030, 1706, and 1600 cm.$^{-1}$; O.R.D. (*c* 1.09, dioxane), $[M]_{480}$ −67°, $[M]_{370}$ 00°, $[M]_{340}$ 00°, $[M]^{min.}_{317.5}$ −707°, and $[M]_{305}$ +875°.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.42; H 9.83.

5β-Pregna-1,9(11)-diene-3,20-dione Cyclic 20-(Ethylene Ace-

tal (VII).—The alcohol (VI, 3.1 g.) was treated as described previously with 1.0 g. of N-bromoacetamide in 20 ml. of pyridine. The crude product weighed 1.4 g., m.p. 110–144°. This material was adsorbed onto 75 g. of Florisil and eluted with twenty-four 100-ml. portions of acetone–Skellysolve B over a gradient of from 2 to 10% acetone. **Fraction 8–11** (365 mg.) proved to be the 11-ketone. **Fraction 4–5** (143 mg.) were combined and recrystallized from acetone two times, m.p. 164.5–166.5°; ν_{max} 3040, 1675, and 1612 cm.$^{-1}$; λ_{max}^{EtOH} 226 mμ (ε 20,200).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.32; H, 9.43.

Grignard Alkylation of 5β,Pregna-1,9(11)-diene-3,20-dione Cyclic 20-(Ethylene Acetal).—The olefin (VII, 375 mg.) dissolved in 10 ml. of freshly purified tetrahydrofuran was chilled to 0° under nitrogen and 10 mg. of copper(I) bromide added. To this cold stirred solution was added, dropwise, 1 ml. of 3 *N* methylmagnesium bromide (in ether) and 10 ml. of copper(I) bromide in 5 ml. of tetrahydrofuran after which the reaction mixture was allowed to warm to room temperature during 1 hr. The suspension was again chilled and 5 ml. of saturated ammonium chloride solution added dropwise. The organic layer was separated and the aqueous phase extracted three times with ether. The combined extracts were washed consecutively with saturated ammonium chloride solution, saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness. The residue was adsorbed onto 50 g. of Florisil and eluted over a gradient of from 0–5% acetone–Skellysolve B. Fraction 10 was the 1α-methyl olefin (V). One spot was observed by t.l.c. (silica gel G, 35% ethyl acetate–65% cyclohexane). The structure was confirmed by the infrared spectrum of this fraction, m.p. 158.8–159.5°. **Fractions 11–16** (mixture of three components) were recombined and rechromatographed on 32 g. of Florisil taking twenty-five 50-ml. fractions over a gradient of from 0.5 to 2% acetone–Skellysolve B, plus ten fractions of 5% acetone. **Fractions 13–24** were combined and recrystallized to give 127 mg. of 1α-methyl-5β-pregn-9(11)-ene-3,20-dione 20-cyclic (ethylene acetal) (V), m.p. 156.5–157.5°, identical by infrared with an authentic sample, admixture with an authentic sample exhibited no melting point depression. **Fractions 26–27** contained a gum whose infrared spectrum was consistent with 1,2-addition to give 3ξ-hydroxy-5β-pregna-1,9(11)-dien-20-one cyclic (ethylene acetal). The mother liquor solids (29 mg.) from the crystallization of combined fractions 13–24 by t.l.c. (*vide infra*) are a mixture of the 1α-methyl product (V) and a second slower moving substance. These solids dissolved in acetone were applied to a preparative t.l.c. (silica gel G, 20 cm. × 20 cm. × 1 mm.) and the chromatogram developed with ethyl acetate–cyclohexane (1:1). The position of the products was determined by strip spraying with 50% aqueous sulfuric acid followed by heat. The slower moving product was isolated in the usual manner[30] (extracted into acetone), but there was insufficient material for characterization.

1-Methyl-1,4-pregnadiene-3,11,20-trione Cyclic 20-(Ethylene Acetal) (VIIIa).—A stirred mixture of 1α-methyl-5β-pregnane-3,11,20-trione cyclic 20-(ethylene acetal) (3.0 g.), selenium dioxide (1.8 g., Fairmount Chemical Co.), pyridine (0.6 ml.), and *t*-butyl alcohol (200 ml.) was heated to reflux under nitrogen for about 30 hr. The cooled solution was filtered (Super-Cel filter aid) then taken to dryness under reduced pressure. The residue was taken up in ethyl acetate (100 ml.), treated with Norit, and washed consecutively with water, freshly prepared ammonium sulfide, cold 17% ammonium hydroxide, water, dilute hydrochloric acid, water, saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness under reduced pressure giving a brown gum. The gum was dissolved in methylene chloride and adsorbed onto 125 g. of Florisil. The product was eluted over a gradient of from 7 to 18% acetone in Skellysolve B. Fractions 7–10 were combined and recrystallized from Skellysolve B–acetone to give 410 mg. of light yellow crystals, m.p. 165.0–172.5°. A sample was recrystallized once for analysis, m.p. 176.0–177.8°; ν_{max} 3020, 2990, 1710, 1668, 1662 and 1603 cm.$^{-1}$; λ_{max} 244 mμ (ε 16,950), *R* (244 mμ/264 mμ) = 2.01 ($\Delta^{1,4}$).

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.77; H, 8.33.

1-Methyl-1,4-pregnadiene-3,11,20-trione (VIIIb).—The dione (VIIIa, 340 mg.) dissolved in acetone (20 ml.) was treated with 3 *N* hydrochloric acid (1 ml.) overnight. The solution was diluted with an equal volume of water and the acetone removed under reduced pressure to give a partially crystalline solid. The solid was adsorbed onto a short Florisil column (10 g.) and eluted with 10% acetone–Skellysolve B to give 170 mg. of crystalline material, m.p. 194.0–195.5°. A sample of this material was recrystallized for analysis, m.p. 194.5–195.2°; ν_{max} 3060, 3020, 2990, 1710, 1668, 1622, and 1603 cm.$^{-1}$; λ_{max} 244 mμ (ε 17,650).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.22; H, 8.38.

1α-Methyl-5β-pregnane-3,11,20-trione Cyclic 3-(Ethylene Acetal) (X).—1α-Methyl-5β-pregnane-3,11,20-trione (10.5 g.), selenium dioxide (10.5 g., Fairmount Chemical Co.), ethylene glycol (150 ml.), and alcohol-free chloroform (100 ml.) was stirred for 4 days at room temperature. The reaction mixture was then poured into water (1.25 l.) containing potassium carbonate (17 g.). The chloroform layer was separated and the aqueous extracted twice with methylene chloride. The combined extracts were dried with sodium sulfate, taken to a small volume under reduced pressure, then adsorbed onto 200 g. of Florisil. The product was eluted with eight 400-ml. fractions of 10% acetone–Skellysolve B and the combined solids were crystallized from acetone–Skellysolve B to give 4.42 g. of colorless cubes, m.p. 161.0–164.5°. A sample was recrystallized for analysis, m.p. 163.0–164.0°; ν_{max} 1700, 1225, 1185, 1150, 1060, and 1030 cm.$^{-1}$; O.R.D. (*c* 1.022, dioxane, 25°), $[M]_{295}$ +6600°, $[M]_{302.5}$ +6700°, $[M]_{335}$ +2955°, $[M]_{500}$ +428°, and $[M]_{589}$ +326°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.28; H, 9.26.

Methyl 3,11-diketo-5β-pregn-17(20)-en-21-oate Cyclic 3-(Ethylene Acetal) (XI).—A sample of the dione (X, 4.42 g., 11.86 mmoles) dissolved in *t*-butyl alcohol (75 ml.) and warmed to 55° under a cover of nitrogen was treated with ethyl oxalate (5.1 g., 35 mmoles, 4.7 ml.), heating was stopped and 25% sodium methoxide in methanol (23.72 mmoles, 5.06 g.) was added rapidly, then the solution allowed to come to room temperature during 1 hr. Glacial acetic acid (1.42 g., 23.72 mmoles) was added followed by sodium acetate (23.72 mmoles, 1.95 g.) in methanol (50 ml.). The solution was chilled to −2° and treated with bromine (24 mmoles, 3.04 g. in 40 ml. of cold methanol) dropwise over 10 min. Stirring was continued and after 5 min. 25% sodium methoxide (64 mmoles, 13.65 g., 14.0 ml.) added and the solution stirred at room temperature overnight. A small amount of insoluble material (*ca.* 10–100 mg.) was removed by filtration, the solution diluted with water (200 ml.), and the solvent distilled under reduced pressure. The product was extracted into methylene chloride, washed with water, dried with sodium sulfate, and adsorbed onto 125 g. of Florisil. The product was eluted in twenty 250-ml. fractions over a gradient of from one to 10% acetone in Skellysolve B. Fractions 2–7 contained 4.1 g. of crystalline material. These fractions were combined and crystallized from Skellysolve B to give 2.43 g., m.p. 137.0–143.0°. Two recrystallizations from Skellysolve B afforded an analytical sample, m.p. 148.5–150.0°; ν_{max} 1718, 1703, and 1655 cm.$^{-1}$; λ_{max} 233 mμ (ε 11,750).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.03; H, 8.89.

1α-Methyl-11β,21-dihydroxy-5β-preg-17(20)-en-3-one Cyclic 3-(Ethylene Acetal) 21-Acetate (XII).—The Favorskiĭ ester (XI) (2.3 g., 5.5 mmoles) dissolved in ether (25 ml.) was added to a suspension of lithium aluminum hydride (760 mg., 20 mmoles) in ether (25 ml.) at room temperature and stirred for 1 hr. The excess hydride was decomposed with ethyl acetate (0.5 ml.) followed by water (1.5 ml., 80 mmoles) with stirring. The ether solution was decanted, washed with saturated sodium chloride solution, dried with sodium sulfate, and evaporated to dryness under reduced pressure. The residue was taken up in a mixture of pyridine (10 ml.) and acetic anhydride (2 ml.) and allowed to stand at room temperature overnight. The solution was diluted to 100 ml. of water and the gummy precipitate washed with water by decantation. The residue was partitioned between ether–water and the ether solution washed twice with water, once with sodium chloride solution, dried with sodium sulfate, and evaporated to dryness. The residual pyridine was distilled azeotropically (*in vacuo*) by the addition of toluene to give a crystalline solid. This material was taken up in acetone and crystallized from Skellysolve B to give short colorless needles, m.p. 141.2–143.0°; yield, 1.04 g. (45%). A sample was recrystallized from Skellysolve B for analysis, m.p. 144.0–145.0°; ν_{max} 3560, 1725, 1673, and 1265 cm.$^{-1}$

(30) C. G. Honegger, *Helv. Chim. Acta*, **45**, 1409 (1962).

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.86; H, 9.18.

1α-Methyl-11β,17α,21-trihydroxy-5β-pregnane-3,20-dione Cyclic 3-(Ethylene Acetal) 21-Acetate (XIII).—The ketal (XII, 880 mg., 20 mmoles) dissolved in *t*-butyl alcohol (40 ml.) was treated with pyridine (1 drop), N-methylmorpholine oxide peroxide (2.4 ml.), and osmium tetroxide (4.8 mg. in 1.9 ml. of *t*-butyl alcohol). The resulting solution was allowed to stand under nitrogen overnight, after which sodium hydrosulfite (80 mg.) in water was added, and the solution stirred for 0.5 hr. The solution was then taken to dryness *in vacuo* and the residue taken up in methylene chloride. After washing (water) the methylene chloride solution was dried with sodium sulfate, and adsorbed onto 50 g. of Florisil. The product was eluted during fifteen 100-ml. fractions over a gradient of from 10 to 25% acetone–Skellysolve B. Fractions 3–5 contained 673 mg. of crystalline material which was recrystallized to give 430 mg. of colorless prisms, m.p. 192.5–204°, infrared consistent with structure; ν_{max} 3420, 1735, 1720 cm.$^{-1}$. A sample was recrystallized three times from acetone–Skellysolve B for analysis, m.p. 202.5–205.0°, ν_{max} 3640, 1736, 1715, and 1265 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{40}O_7$: C, 67.21; H, 8.68. Found: C, 67.01; H, 8.70.

1α-Methyl-11β,17α,21-trihydroxy-5β-pregnane-3,20-dione 21-Acetate (XIV).—To the ketal (XIII) (2.05 g.) in acetone (15 ml.) was added *N* hydrochloric acid (1 ml.) and the solution allowed to stand overnight at room temperature. Water (15 ml.) was added and the acetone removed under reduced pressure to give a white solid. This material was washed, dried (*in vacuo*, 60°), and crystallized from acetone to give two crops: crop 1, 980 mg., m.p. 196.5–198°; crop 2, 430 mg., m.p. 192.5–196.5°. A sample was recrystallized for analysis, m.p. 194.5–195.5°; ν_{max} 3460, 3400, 1743, 1626, 1683, and 1272 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.63; H, 8.55.

1α-Methyl-17α,21-dihydroxy-5β-pregnane-3,11,20-trione 21-Acetate (XVIII).—A sample of the dione (XIV, 250 mg.) was dissolved in acetone (5 ml.) and oxidized with Jones reagent[31] (0.125 ml. of 2.67 *N* reagent, 1.5 mmoles) at room temperature for 10 min. The reaction mixture was then diluted with water to a volume of 20 ml. and refrigerated. The product was isolated by filtration, washed, and dried giving 210 mg. of solid. Recrystallization from acetone afforded 150 mg., m.p. 239.5–242°. The infrared of this material was consistent with the expected structure. A second crop was isolated, 31 mg., m.p. 237.0–240.5°. A sample of crop 1 material was submitted for analysis.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.03; H, 8.65.

1α-Methylhydrocortisone Acetate (XVII).—1α-Methyl-5β-dihydro F acetate (XIV, 420 mg., 1.0 mmoles) was dissolved with stirring in glacial acetic acid (10 ml.), a microdrop of 33% HBr–HOAc added followed by the dropwise addition of 4.72 ml. of freshly prepared 0.212 *M* bromine in acetic acid (1.1 mmoles) at such a rate that the bromine was consumed between the addition of each drop. The reaction was then poured into saturated sodium chloride solution (200 ml.) and refrigerated (bromination time *ca.* 3–4 min.). The product was filtered, washed with water, and dried giving 390 mg. of a yellow gum. The product was then taken up in dimethylformamide (5 ml.) and treated under nitrogen at 60° with 400 mg. of semicarbazide hydrochloride and 300 mg. of sodium acetate in 2 ml. of water for >2 hr. The solution was then treated with 1 ml. of 50% aqueous pyruvic acid at 60° for 2 hr. The resulting solution was poured into 50 ml. of saturated sodium chloride solution and the product filtered after refrigeration to give a light tan solid; it was dried at 60° *in vacuo;* yield, 210 mg. This material was chromatographed on 25 g. of Florisil taking 50-ml. fractions (twenty-five) over a gradient of from 5 to 25% acetone–Skellysolve B. Fractions 12–18 containing 115 mg. of crystalline material were combined and recrystallized for analysis from acetone–Skellysolve B to give colorless needles (crop 1) and cubes crop 2 (at 4°). Crop 1 exhibited m.p. 210.8–212° (Kofler); yield, 51 mg. Crop 2 exhibited m.p. 203–210.5° (Kofler); yield, 35 mg. The yield was 20.5% over-all from 5β-dihydro derivative, λ_{max} 247 mμ (ε 13,150).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.59; H, 7.89.

1α-Methylcortisone Acetate (XX).—1α-Methyl-5β-dihydrocortisone acetate (XI) (180 mg., 0.43 mmole) was dissolved with stirring in 20 ml. of glacial acetic acid and treated with a microdrop of 33% HBr–HOAc followed by 0.45 mole of bromine in acetic acid (2.14 ml. of 0.21 *M* solution). The reaction was allowed to proceed for *ca.* 3 min., after which the solution was poured into *ca.* 200 ml. of saturated sodium chloride solution and refrigerated. The white solid precipitate was filtered, washed with water, and dried briefly at 60° in the vacuum oven, then crystallized from acetone–Skellysolve B. The crystalline solid was taken up in dimethylformamide (5 ml.) and treated under nitrogen with 400 mg. of semicarbazide hydrochloride and 300 ml. of sodium acetate in 2 ml. of water for about 1 hr. at 60°. The solution was then treated with 1.5 ml. of 50% aqueous pyruvic acid at 60° for 2 hr. The solution was then poured into 50 ml. of saturated sodium chloride solution and the product recovered, after refrigeration, by filtration. The solid was then adsorbed onto 10 g. of Florisil (in methylene chloride) and eluted with 20-ml. fractions of 15% acetone–Skellysolve B. Fractions 7–10 were combined and crystallized for analysis from acetone–Skellysolve B to give 24.7 mg., m.p. 208.5–217.5° dec. (Kofler, subl. 199°); λ_{max}^{EtOH} 242.0 mμ (ε 14,100), essentially a single spot by benzene–formamide paper chromatogram. The infrared of this material was consistent with that of the expected structure as an acetone solvate. A sample was recrystallized for analysis, m.p. 212.5–214.5° (Kofler).

Anal. Calcd. for $C_{24}H_{32}O_6 \cdot CH_3COCH_3$: C, 68.33; H, 7.74. Found: C, 68.40; H, 7.59.

1-Methylprednisolone Acetate (XV).—1α-Methyl-5β-dihydrocortisone acetate (XIV, 780 mg.) and selenium dioxide (600 mg.) in 50 cc. of *t*-butyl alcohol containing 0.5 ml. of acetic acid was heated at reflux for 7 hr., an additional 600 mg. of selenium dioxide was added, and reflux continued 2 days under a cover of nitrogen. The solvent was removed under reduced pressure and the residue taken up in ethyl acetate (100 ml.) and treated with Norit. The ethyl acetate solution was washed consecutively with water, freshly prepared cold ammonium sulfide solution (three times with one back wash), dilute cold ammonium hydroxide solution (twice), water, dilute hydrochloric acid, water, saturated sodium chloride solution and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was taken up in methylene chloride and chromatographed on Florisil (50 g.) taking 100-ml. fractions over a gradient of from 10 to 25% acetone–Skellysolve B (20 fractions). Semisolid fractions 9–19 contained 88 mg. and were combined. Paper chromatogram on the benzene–formamide system indicated a mixture of seven substances. These materials were separated by preparative paper chromatography employing the benzene–formamide system. The products were eluted with methanol from the paper and the product (fraction group 2) separated from high-boiling solvents by chromatography over a short Florisil column and eluting with 20% acetone–Skellysolve B to give a small amount of a white crystalline solid. Recrystallization from ethanol–water afforded *ca.* 8 mg. of crystalline material, m.p. 231–239°, remelting at 248° (Kofler); λ_{max}^{EtOH} 253 mμ (ε 16,800), *R* (*a*253 mμ/*a*273 mμ) = 2.20 ($\Delta^{1,4}$); ν_{max} 3425, 1750, 1725, 1659, 1619 and 1265, and 1230 cm.$^{-1}$.

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(31) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).