It was found advantageous to carry the 16-dehydroacetate II to the above bromohydrin acetate without purification of intermediates. In a typical example, 11.6 g. (0.03 mole) of II yielded 11.3 g. (78% over-all) of good quality bromohydrin acetate.

Bromohydrin acetate (6.1 g., 0.013 mole) in 75 ml. o 95% ethanol was hydrogenated over 5 g. of 5% palladium-on-calcium carbonate. Hydrogen uptake stopped after 36 hours. The filtrate after removal of the catalyst was treated with 5 g. of potassium hydroxide in 35 ml. of water and allowed to stand for 3 hours at room temperature. The solution was neutralized with acetic acid, diluted with water, extracted with chloroform and the residue from chloroform distillation crystallized from aqueous methanol to give XI, thick needles, 3.4 g. (74%), m.p. 260–261°, $[\alpha]_D$ −6° (MeOH); λ_{max}^{KBr} 2.89 (m), 2.96 (shoulder), 3.01 (s), 5.83 (s), 6.04 (s) μ.

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.09; H, 9.57; N, 3.99.

The acetate XII, clusters of needles from aqueous methanol, had m.p. 231–233°, $[\alpha]_D$ −14°, λ_{max}^{KBr} 2.96 (w), 3.00 (w), 5.75 (s), 5.83 (shoulder), 6.05 (s) μ.

Anal. Calcd. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70; N, 3.46. Found: C, 67.90; H, 8.83; N, 3.65.

17α-Hydroxy-12a-aza-C-homo-5α-pregnane-3,12,20-trione (XIII).—Alcohol XI (1.6 g., 0.0044 mole) was dissolved in 50 ml. of *t*-butyl alcohol and 2.1 g. of *t*-butyl hypochlorite added. After 2 hours in the dark at room temperature, the solution was diluted with 25 ml. of water, stirred in an ice–water-bath and sodium bisulfite added until the yellow color had disappeared. The mixture was diluted with water, extracted with chloroform, the chloroform washed well with water and distilled. The residue was crystallized from aqueous ethanol to give the desired ketone XIII, small needles, 1.2 g. (75%), m.p. 274–277°, $[\alpha]_D$ +8° (MeOH); λ_{max}^{KBr} 2.99 (w), 3.16 (w, broad), 5.82 (s), 6.09 (s) μ.

Anal. Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.59; H, 9.04; N, 3.60.

SKOKIE, ILL.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

The Partial Synthesis of 12α-Methyl-11-dehydrocorticosterone

BY B. G. CHRISTENSEN, R. G. STRACHAN, N. R. TRENNER, B. H. ARISON, RALPH HIRSCHMANN AND J. M. CHEMERDA

RECEIVED NOVEMBER 21, 1959

The partial synthesis of 12α-methyl-11-dehydrocorticosterone is described. The addition of methylmagnesium iodide to a steroidal 11β,12β-oxide resulted in rearrangement to a C-nor-11ξ-(α-hydroxy-α-ethyl)-pregnane derivative while the action of dimethylmagnesium resulted in the desired 12α-methyl-11β-hydroxy functionality. The chemistry of the latter reaction derives strong support from the use of n.m.r. spectroscopy. The influence of 12-oxygenated functions upon the positions of the C-18 and C-19 proton resonances is discussed in detail. A reproducible procedure for the preparation of dimethylmagnesium is also described.

The quest for anti-inflammatory steroids possessing increased activity or lacking side-effects has included several modifications[1] of the hydrocortisone molecule. Of these, the introduction of 6α- or 16-methyl substituents[2] has been particularly rewarding. Also the demonstrated enhancement of activity[3,4] due to the 12α-halogen substituent provided further impetus to the synthesis of a steroidal derivative methylated at position 12.

Although several procedures for the insertion of the 12α-methyl functionality might be envisioned, the addition of a methyl organometallic to an 11β,-12β-epoxide appeared to be the method of choice. The known diaxial opening of 5,6-epoxides with methyl Grignard reagents[5] suggested that the desired 11β-hydroxy-12α-methyl grouping would be the expected product of such an addition. Furthermore, the anticipated conversion *via* the 11-ketone to the equatorial 12β-epimer, which was expected to be the thermodynamically more stable isomer, also would make the 12β-methyl derivatives readily available. Accordingly, 11β,12β-epoxypregnane-3,20-dione 3,20-bis-(ethylene ketal) was prepared by the following route.

12α-Bromopregnane-3,11,20-trione[6] was converted to the corresponding 3,20-bis-(ethylene ketal) with ethylene glycol and *p*-toluenesulfonic acid.[7] Because of the loss of bromine during reduction of steroidal bromo-ketones with certain other hydrides,[4,8] lithium borohydride was the reagent of choice[4] in the preparation of the bromohydrin. This compound was not isolated as a crystalline intermediate, but was transformed immediately to the desired 11β,12β-epoxide IV.

The action of methyl Grignard reagents in opening 5,6-epoxides has been the subject of several investigations,[5] but their action upon other steroidal epoxides has remained largely unexplored. When IV was treated with methylmagnesium iodide in refluxing benzene, a crystalline product was obtained which gave the correct analysis for the desired bisketal VIII. However, since this product formed an acetate under conditions which do not normally effect acetylation of an 11β-hydroxyl group and

(1) For an excellent recent summary see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 682.

(2) For references demonstrating the effect of methyl substitution see R. E. Beyler, F. Hoffman and L. H. Sarett, *J. Org. Chem.*, **25**, *in press* (1960).

(3) J. E. Herz, J. Fried and E. F. Sabo, *ibid.*, **78**, 2017 (1956); J. Fried, J. E. Herz, E. F. Sabo and M. H. Morrison, *Chemistry & Industry*, 1232 (1956). See, however, J. Fried and A. Borman in "Vitamins and Hormones," Vol. XVI, Academic Press, Inc., New York, N. Y., 1959, p. 342.

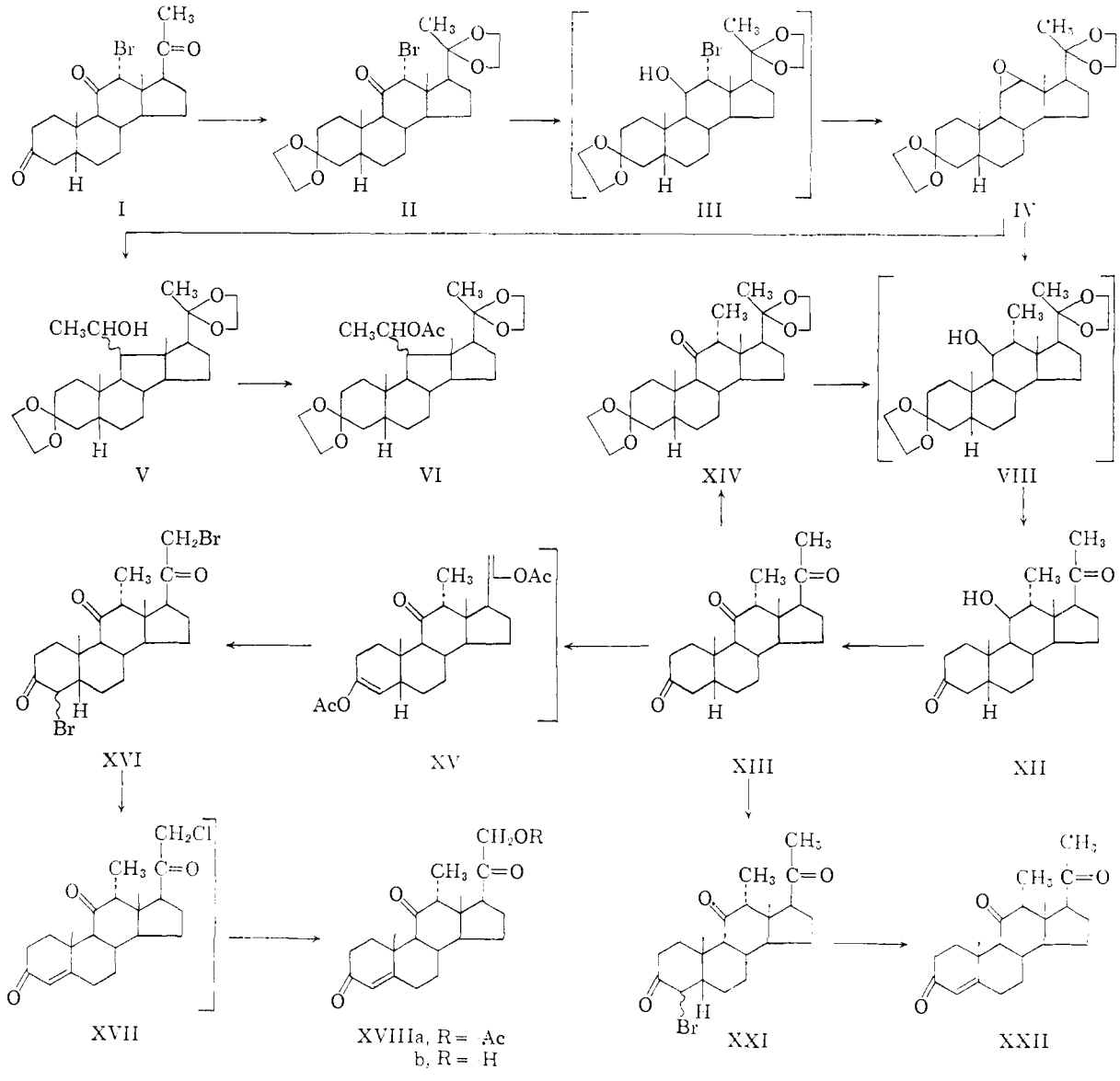
(4) D. Taub, R. D. Hoffsommer and N. L. Wendler, THIS JOURNAL, **78**, 2912 (1956); **79**, 452 (1957).

(5) See ref. 1, pp. 199 and 692.

(6) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 726 (1943).

(7) R. A. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1369 (1952).

(8) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **36**, 1241 (1953); J. N. Cornforth, J. M. Osbond and G. H. Phillips, *J. Chem. Soc.*, 970 (1954).



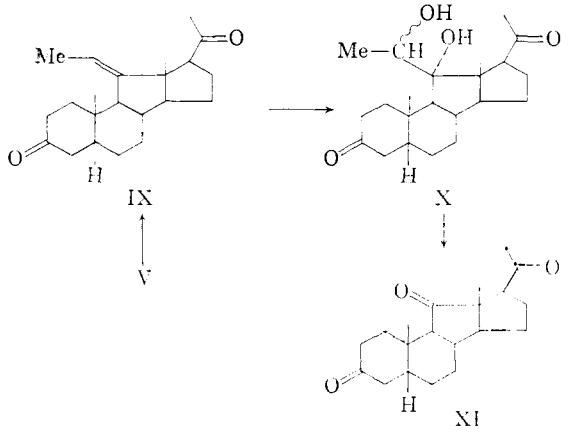
gave a positive iodoform test, its structure is formulated as V.[9] It is noteworthy that V was the major product of the Grignard reaction despite the fact that it contains two *trans*-fused cyclopentane rings, although this transformation is not without precedent.[10]

Chromatography of the mother liquors afforded additional amounts of crystalline V. Acid treatment of the non-crystalline residues yielded a further product which gave an analysis and showed spectral properties consistent with the desired 11β-hydroxy-12α-methylpregnane-3,20-dione (XII). As expected XII did not acetylate under the conditions which resulted in the esterification of V.

(9) Further support is given this formulation by the observation that removal of the ethylene ketal protecting groups resulted in dehydration presumably forming IX. Upon osmylation and lead tetraacetate oxidation of the latter, a product was obtained which had infrared maxima at 5.76 and 5.84 μ (no hydroxyl or acetate absorption was present).

(10) N. L. Wendler, R. F. Hirschmann, H. L. Slates and R. W. Walker, THIS JOURNAL, **77**, 1632 (1955).

Since Bartlett and Berry[11] had previously prevented ring-contraction in the opening of cyclic ox-

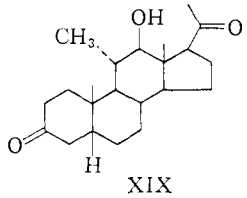


(11) P. D. Bartlett and C. M. Berry, *ibid.*, **56**, 2683 (1934).

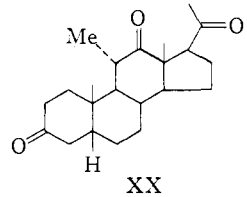
ides by the use of dimethylmagnesium, this reagent seemed the agent of choice. However, it was not possible to prepare the reagent in over 18% yield by any of several published modifications[12] of the Schlenk precipitation procedure.[13] Although the *in situ* preparation of dimethylmagnesium[12d] in the presence of the dioxane–magnesium halide precipitate was successful, the method was fraught with severe mechanical difficulties. Fortunately, a further modification of the Schlenk method, the addition of a *half-mole* of dioxane per *mole* of titratable ionic halide instead of the usual excess, afforded reproducible yields of halide-free dimethylmagnesium of the order of 70%. When only the specified amount of dioxane was added, only the magnesium halide was precipitated, and the loss of dimethylmagnesium was minimized.

The use of dimethylmagnesium smoothly effected the desired transformation, although the product was not isolated directly but was converted into the free diketone XII in 41% over-all yield. This product was identical with that isolated in small yield from the reaction of methylmagnesium iodide on the oxide IV after removal of the ketal groups. Subsequent oxidation of XII with chromium trioxide–acetic acid supplied 12α-methylpregnane-3,11,20-trione (XIII) in excellent yield.

While the principle of the diaxial opening[14] of steroid epoxides is well established, additional evidence that these products possess structures XII and XIII rather than XIX and XX was sought. The molecular rotation difference ($M_D^{11\text{-ketone}} - M_D^{11\beta\text{-OH}}$) between the former two products was −63°—compared to the average value of −17°.[15] Since an asymmetric center is present in XII and XIII at C-12, but not in the reference compounds, these results do not provide rigorous support for these structures. Nevertheless, the value of −63° differs markedly from the +220° value[15] observed in the oxidation of a 12β-hydroxyl to a 12-ketone.



XIX



XX

Furthermore, nuclear magnetic resonance studies made possible an unambiguous choice between the possible structures. It became necessary first to establish the influence of 12-oxygenated functions upon the positions of C-18 and C-19 methyl proton resonances in much the same manner as had been done by Shoolery and Rogers[16] for the 11-oxygenated functions. The results of these spectral findings, which are summarized in Table I, demonstrate that the 12-carbonyl function is *without appreciable effect* upon the position of the 19-methyl protons and that, moreover, it shifts to lower magnetic field the position of the 18-methyl protons by about 0.27 tau unit. Indeed this shift is so large that in the n.m.r. spectra of 2,5α,22β,25D-spirostene-12-one, hecogenin acetate and manogenin diacetate the usual positions of the 18- and 19-methyl proton resonances are reversed. These data also suggest[17] that the position of the 18-methyl protons is shifted by about −0.15 tau unit in the presence of the sapogenin sidechain of the stereochemistry under discussion. This conclusion is consistent with the value given for diosgenin.[18]

TABLE I

PROTON RESONANCE POSITIONS (IN TAU UNITS)

Substance	Observed 19-CH_3	Observed 18-CH_3	Δτ[(12-desoxy) − (12-oxygenated)] 19-CH_3	Δτ[(12-desoxy) − (12-oxygenated)] 18-CH_3
2,5α,22β,25D-Spirostene	9.08	9.08	....	....
2,5α,22β,25D-Spirostene-12-one	9.02	8.80	....	....
			+0.06	+0.28
Tigogenin acetate	9.05	9.12	....	....
Hecogenin acetate	9.05	8.93	....	....
			0	+0.19
Progesterone	8.75	9.28	....	....
12-Ketoprogesterone	8.65	8.93	....	....
			+0.10	+0.35
		Average	+0.05	+0.27
Rockogenin	9.06	9.14	−0.01	−0.02
12-Epirockogenin	9.09	9.09	−0.04	+0.03
Manogenin diacetate	9.13	8.89	....	....

The magnitude of the shifts to lower magnetic fields of the 19-methyl protons under the influence of 11-oxygenated functions is well established[16] and usually amounts to 0.2 tau unit for an 11-carbonyl and 0.25 tau unit for an 11β-hydroxyl, whereas for the 18-methyl protons the respective shifts are 0 and 0.25 tau unit. The n.m.r. spectra of the steroid products which are the subject of this paper are given in Table II.

Since there is good agreement between the observed and calculated positions of the 18- and 19-methyl protons based upon the assigned structures but very poor agreement if the substituents at C-11 and C-12 be reversed, there appears to be little room for doubt that these steroids are 11-oxygenated compounds and that the new methyl protons observed as typical spin–spin coupled doublets in the regions of 8.5 and 8.6 tau units are at the 12-position.

To demonstrate that the oxidation of the 11β-hydroxyl functionality of XII to the 11-ketone of XIII under the acidic reaction conditions employed had not effected a concomitant epimerization of the C-12 methyl group, 12α-methylpregnane-3,11,20-trione was converted to its 3,20-bis-(ethylene ketal) which was reduced at C-11. After removal of the protecting groups, a product was obtained which was identical with the 11β-hydroxy-12α-methylpregnane-3,20-dione obtained from the 11β,12β-

(12) (a) A. C. Cope, THIS JOURNAL, **57**, 2238 (1935); (b) G. F. Wright, *ibid.*, **61**, 1155 (1939); (c) C. A. Guthrie, E. Y. Spencer and G. F. Wright, *Can. J. Chem.*, **35**, 875 (1957); (d) T. S. Reid, Master's Dissertation, 1938, Rutgers University.

(13) W. Schlenk and W. Schlenk, Jr., *Ber.*, **62**, 920 (1929).

(14) A. Fürst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(15) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948).

(16) J. N. Shoolery and M. T. Rogers, THIS JOURNAL, **80**, 5121 (1958).

(17) The method of computing these positions is based upon the empirical rules of Shoolery and Rogers.[16] The actual values used here for the 18- and 19-methyl shift computation, however, were derived from our own extensive n.m.r. steroid data.

(18) W. E. Rosen, J. B. Ziegler, A. C. Shabica and J. N. Shoolery, *ibid.*, **81**, 1687 (1959).

TABLE II

11β-HYDROXY-12α-METHYLPREGNANE-3,20-DIONE

τ	Rel. area	Assignment	Calculated based on above structure
5.87[19]	1	11β-OH	..
6.52, 6.60	1	11α-H	..
7.77	3	17β-CH_3	..
8.61	3	10-CH_3	8.63 (8.89)[20]
8.68, 8.85	1.5, 1.5	12-CH_3	..
8.88	3	13-CH_3	8.95 (9.17)[20]

12α-METHYLPREGNANE 3,11,20-TRIONE

7.79	3	17β-CH_3CO	..
8.65	4.5	10-CH_3	8.68 (8.83)[20]
8.48, 8.65	1.5, 1.5	12-CH_3	..
9.22	3	13-CH_3	9.20 (8.94)[20]

3,20-DIHYDROXY-12α-METHYL-3,20-PREGNADIENE-11-ONE 3,20-DIACETATE

4.85	1	4-H	..
5.00	2	$=CH_2$	..
7.79	6	3,20-CH_3CO	..
8.73	3	10-CH_3	8.70 (8.93)[20]
8.64, 8.83	1.5, 1.5	12-CH_3	..
9.26	3	13-CH_3	9.25 (8.94)[20]

epoxide IV as previously described. Indeed, epimerization at C-12 did not occur to any appreciable extent even when XIII was heated with potassium *t*-butoxide in *t*-butyl alcohol for several days.[21]

Several attempts were made toward the elaboration of the adrenocortical side-chain. Efforts to form a 3-dimethyl ketal,[23] selectively dehydrogenate the A-ring by means of selenium dioxide[24] or to reduce the 3-carbonyl selectively with sodium borohydride[25] were unrewarding in this series.[26]

Two attempts to introduce the dienone A-ring microbially also were fruitless. When 12α-methylpregnane-3,11,20-trione (XIII) was subjected to the action of *Nocardia sp.*, no change was observed. Indeed 12α-bromopregnane-3,11,20-trione also was unaffected under these conditions which readily transformed pregnane-3,11,20-trione. However, 12α-methyl-4-pregnene-3,11,20-trione (XXII),[26a] obtained by monobromination of XIII and dehydrohalogenation of that product, was converted into an unknown substance with *Bacillus sphaericus*. This transformation product contained the dienone chromophore, but the polarity was inconsistent with the desired product.

The conversion of XIII into its corresponding 3,20-bis-enolacetate by the action of isopropenyl acetate[27] is evidenced by the n.m.r. spectrum, which has been summarized in Table II. Dibromination,[28] followed by dehydrobromination[29] with LiCl–DMF afforded 21-chloro-12α-methyl-4-pregnene-3,20-dione (XVII). Displacement of the halogen atom with acetate and hydrolysis to the alcohol gave 12α-methyl-11-dehydrocorticosterone (XVIIIb) which was purified by partitioning between formamide and benzene.

Compound XVIIIb was significantly less active than 11-dehydrocorticosterone in the liver glycogen deposition assay. No sodium retention was observed in the adrenalectomized rat.[30] It has been suggested[31] that the 12α-bromo function of 12α-bromo-11-ketoprogesterone interferes with the reduction of the 11-ketone *in vivo*. Similarly, the 12α-methyl group may sterically inhibit this enzymatic reduction *in vivo*.

Experimental[32]

12α-Bromopregnane-3,11,20-trione 3,20-Bis-(ethylene Ketal) (II).—A solution of 39.98 g. (0.098 mole) of 12α-bromopregnane-3,11,20-trione[6] ($[\alpha]^{24}D$ −3.74°), 1.075 g. (0.005 mole) of *p*-toluenesulfonic acid monohydrate, 24.6 ml. (0.44 mole) of freshly distilled ethylene glycol and 924 ml. of benzene (previously dried over sodium) was slowly distilled through a Vigreux column for 5 hours, while keeping the volume constant by adding dry benzene. The reaction mixture was extracted twice with 5% sodium bicarbonate solution, washed with water, dried and concentrated *in vacuo*. The product was crystallized from methanol and had a m.p. 173–175°, yield 34.87 g. (72%). A sample was prepared for analysis by recrystallization from acetone–methanol; m.p. 179–181°, $[\alpha]^{24}D$ −19.65°.

(19) Position concentration variable.

(20) The values in parentheses were calculated assuming that the C-11 and C-12 functions are reversed and that the 11α-methyl group in the resulting structures is without effect.

(21) This failure to isomerize is particularly interesting in view of the observation that the rotation in methanol is 7.6° lower than that in chloroform since Mazur and Sondheimer [THIS JOURNAL, **80**, 5221 (1958)] have reported that this difference is "considerably" lower in the case of epimerizable α-methyl ketones. This difference in their examples of epimerizable methyl groups is of the order of −19 to −26° so that the shift in question might be viewed as borderline. The usual shift due to change of solvent from chloroform to methanol is +8 to +10°.[22]

(22) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 209.

(23) E. P. Oliveto, C. Gerold and E. B. Hershberg, THIS JOURNAL, **76**, 6116 (1954).

(24) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(25) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3711 (1952).

(26) For examples of interaction of the side-chain and the 12α-position see N. Danieli, Y. Mazur and F. Sondheimer, *Chemistry & Industry*, 1724 (1958); S. Bernstein and R. Littell, *J. Org. Chem.*, **24**, 871 (1959); P. L. Julian in "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, p. 198.

(26a) This compound has also been prepared by a different route by Dr. Gordon Thomas at the Squibb Institute for Medical Research; Dr. J. Fried, who described this work at the Gordon Conference on Steroids and Related Natural Products (July, 1958), has authorized this reference. The two specimens were identical.

(27) R. B. Moffett and D. F. Weisblatt, THIS JOURNAL, **74**, 2183 (1956); H. Vanderhaeghe, F. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *ibid.*, **74**, 2810 (1952).

(28) H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan and J. A. Hogg, *ibid.*, **76**, 743 (1954).

(29) R. P. Holysz, *ibid.*, **75**, 4432 (1953).

(30) We are indebted to Drs. S. L. Steelman and H. C. Stoerk and their associates for these evaluations.

(31) I. E. Bush and V. B. Mahesh, *Biochem. J.*, **71**, 718 (1959).

(32) Melting points are uncorrected. Rotations were determined in chloroform unless noted otherwise.

The n.m.r. spectra were obtained in part through the use of a Varian V-4300B high resolution spectrometer operating at 40 megacycles and in part from a V-4300C model at 60 megacycles.

The spectra were obtained by using in all cases 15% solutions in deuteriochloroform. The positions of the proton resonances were determined relative to benzene as an external standard and by use of a Hewlett-Packard model 200CD wide range oscillator with which "side bands" were put on each recording usually at −60 and +260 c.p.s. from benzene. The side band oscillator was calibrated by a frequency counter and all τ-values given were calculated on the basis of corrected peak positions. The tau (τ) values of the chemical shifts were calculated using the equation: $\tau = (\nu_0/40.00) + 3.50$ (G. V. P. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)) when the ν_0-values represent 40 megacycle spectra. For 60 megacycle data, 40.00 should be replaced with 60.00. The ν_0-values are precise to ±0.50 c.p.s.

Anal. Calcd. for $C_{25}H_{37}O_5Br$: C, 60.36; H, 7.49; Br, 16.04. Found: C, 60.38; H, 7.70; Br, 15.71.

11β,12β-Epoxypregnane-3,20-dione 3,20-Bis-(ethylene Ketal) (IV).—Twenty grams of 12α-bromopregnane-3,11,20-trione 3,20-bis-(ethylene ketal) (II), (0.0402 mole) was dissolved in 1200 ml. of tetrahydrofuran and the solution was cooled in an ice-bath. A filtered solution of 16 g. of lithium borohydride (0.734 mole) in tetrahydrofuran was added with stirring over a period of 45 minutes. The reaction was stirred for 3 hours at room temperature and the excess lithium borohydride was decomposed by the addition of dilute acetic acid. The tetrahydrofuran was removed *in vacuo* after the addition of 200 ml. of water. The reduction product was extracted into chloroform, washed with a 5% bicarbonate solution and with water before concentration *in vacuo* to a clear oil.

Epoxide formation was effected by the addition of a solution of 39 g. (0.695 mole) of potassium hydroxide in 650 ml. of isopropyl alcohol and heating at 55° for 1.25 hours. A copious precipitate of potassium bromide separated during this period. The reaction mixture was poured into water and extracted with ether. After washing the ethereal solution with water and drying, the solution was concentrated to about 100 ml. *in vacuo* and the product (m.p. 132–134°) was filtered off; wt. 9.05 g. (54%), $[\alpha]^{22}D$ +45.55°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 72.02; H, 8.95.

C-Nor-11ξ-(α-hydroxy-α-ethyl)-pregnane-3,20-dione 3,20 Bis-(ethylene Ketal)[33] (V) and 11β-Hydroxy-12α-methylpregnane-3,20-dione (XII).—A 2 molar solution (216 ml., 0.432 mole) of methylmagnesium iodide in ether was added to a solution of 15.0 g. (0.0358 mole) of 11β,12β-oxidopregnane-3,20-dione 3,20-bis-(ethylene ketal) in 300 ml. of anhydrous benzene. The mixture was heated under reflux in a nitrogen atmosphere for 3.25 hours. The excess Grignard reagent was decomposed by the dropwise addition of a saturated ammonium chloride solution. The layers were separated and the aqueous layer was extracted twice with chloroform. The combined organic extracts were washed with water, dried and concentrated *in vacuo*. Direct crystallization from ether afforded 6.025 g. (m.p. 170–172°) of V. Chromatography on 500 g. of Merck alumina of the mother liquors from the crystallization yielded an additional 3.36 g. of V (total 9.39 g. or 60%) with 9:1 benzene–chloroform as the eluent.

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.82; H, 9.87.

The mother liquors from this last crystallization were dissolved in 1.62 l. of methanol and refluxed for 1.25 hours after adding 64.9 ml. of 8.5% sulfuric acid. Solid sodium bicarbonate was added to neutralize the acid and the mixture was filtered. The solvent was removed *in vacuo* and the aqueous suspension was extracted three times with chloroform. The organic extracts were washed with water, dried and concentrated *in vacuo* to give an oil. This oil was crystallized from ether–petroleum ether to give 590 mg. (4.75%) of 11β-hydroxy-12α-methylpregnane-3,20-dione (XII), m.p. 240–242°, $[\alpha]D$ +111.2°.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.32; H, 10.06.

C-Nor-11ξ-(α-hydroxy-α-ethyl)-pregnane-3,20-dione 11-Acetate 3,20-Bis-(ethylene Ketal) (VI).—A solution of 0.475 g. (0.00109 mole) of V in 0.97 ml. (0.00497 mole) of acetic anhydride and 2.37 ml. of pyridine was heated at 55° for 4 hours before adding 9 ml. of water. The reaction mixture was extracted with chloroform and the extracts were washed with 1.2 *N* hydrochloric acid, with 5% sodium bicarbonate solution and with water. Drying, concentrating *in vacuo* and crystallizing from methanol gave 0.275 g. (53%) of VI, m.p. 154–154.6°.

Anal. Calcd. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.30. Found: C, 70.69; H, 9.52.

Dimethylmagnesium.—A solution of methylmagnesium chloride was prepared by passing dry, gaseous methyl chloride into a mixture of 145 g. (5.96 moles) of magnesium turnings and 4.75 l. of anhydrous ether until a substantial part of the metal had reacted. A precipitate, presumably magnesium chloride, found after standing overnight was removed by filtration through a Super-cel cake in a dry-box under a dry nitrogen atmosphere. Dioxane (82.00 ml., 0.959 mole) was added from a dropping funnel with stirring to 3.63 l. (2.48 moles) of the 0.683 *M* solution of magnesium chloride (containing 0.532 in meq./ml. of chloride ≅ 0.966 mole of $MgCl_2$). The mixture was again allowed to stand overnight before filtering through a Super-cel cake as before. *Note: Dimethylmagnesium is extremely pyrophoric when dry. The appropriate measures should be taken to guard against this hazard.*[34] *The inside of the bottom portion of the funnel below the filter-cake tended to become dry during the long filtration and was especially dangerous.* The filtrate (2.0 l.) was 0.438 molar (0.876 mole, 71% of theoretical) in dimethylmagnesium and contained 0.0056 to 0.0171 meq. chloride/ml. when this procedure was followed.

11β-Hydroxy-12α-methylpregnane-3,20-dione (XII).—A solution of dimethylmagnesium (1.1 l. of a 0.960 molar solution, 1.06 moles) was placed in a dry 2-l. round-bottomed flask equipped for downward distillation. Dry dioxane (800 ml.) was added from a dropping funnel at such a rate while the ether was being distilled that the volume remained approximately constant. 3,20-Bis-(ethylenedioxy)-11β,12β-epoxypregnane (50 g., 0.119 mole) in 334 ml. of dry dioxane was added and the reaction mixture was heated under reflux for 24 hours. The excess dimethylmagnesium was decomposed with saturated ammonium chloride solution. After the addition of water, the solution was extracted three times with ether. The ethereal extracts were washed with water, dried and concentrated *in vacuo* to give 50.69 g. of a yellow oil.

A benzene solution of this oil was adsorbed on 1.15 kg. of Merck alumina. Some starting material (IV, 11.24 g.) was eluted with benzene–chloroform (9:1) and the desired material (31.48 g.), an oil (crude VIII) with benzene–chloroform (3:2).

This oil was dissolved in 3.5 l. of methanol and heated under reflux with 468 ml. of 8.5% sulfuric acid for 1.25 hours. Solid sodium bicarbonate was added to neutralize the acid. After filtration, the methanol was removed *in vacuo*. The product was filtered and recrystallized from methanol to give a product identical with XII prepared above; wt. 13.24 g. (41% corrected yield), m.p. 240–242°.

12α-Methylpregnane-3,11,20-trione (XIII).—A slurry of 15.85 g. (0.0457 mole) of 11β-hydroxy-12α-methylpregnane-3,20-dione (XII) in 277 ml. of glacial acetic acid was cooled in an ice–water-bath before adding 42.0 ml. (0.033 mole) of a 0.785 molar solution of chromic oxide in acetic acid. The mixture was stirred at room temperature for 2.25 hours.

(33) **C-Norpregnane-3,11,20-trione (XI).**—A solution of 750 mg. (0.00174 mole) of V in 200 ml. of methyl alcohol containing 8.0 ml. of a 8.5% sulfuric acid solution was heated under reflux for 75 minutes. Solid sodium bicarbonate was added until the mixture was neutral. It then was filtered and the filtrate was concentrated *in vacuo* after adding water. The aqueous mixture was extracted with chloroform. The extracts were washed, dried and concentrated to give a clear oil which crystallized. After recrystallization from methyl alcohol, the sample (IX) melted at 173–178°, 340 mg. (60%).

An excess (100 mg. in 1.0 ml. of pyridine) of an osmium tetroxide solution was added to 150 ml. (0.000457 mole) of IX in 6.0 ml. of pyridine. The solution was allowed to stand at room temperature for 2 days. After adding 100 ml. of Skellysolve B, the osmate ester was filtered; wt. 280 mg. This ester was suspended in 30 ml. of dioxane and gaseous hydrogen sulfide was passed through for 5 minutes. The mixture was filtered and the precipitate washed with dioxane. The filtrate was concentrated to a dark oil, which was triturated with ether. The residue was decolorized with Nuchar C-1000N, before being concentrated and triturated with ether again; m.p. 192.5–194.5°, yield 42 mg. (25%).

A suspension of 14 mg. (0.0000386 mole) of the above X in 1 ml. of benzene was dissolved by adding 2 ml. of methyl alcohol. An excess (45 mg.) of lead tetraacetate was added and the solution was allowed to stand overnight. After adding 11 ml. of ether and 10 ml. of H_2O the layers were separated. The organic layer was washed with 5% sodium bicarbonate solution and water before drying and concentrated to yield 9 mg. of an oil (XI), which showed maxima at 5.76 and 5.85 μ—neither hydroxyl nor acetate absorption was indicated.

(34) The cautious addition of a saturated ammonium chloride solution seemed to be the most effective method of decomposing the excess dimethylmagnesium. The use of flammable organic solvents which react with this reagent, *e.g.*, acetone and ethyl acetate, or of solid carbon dioxide resulted in particularly violent reactions.

After adding 10 ml. of methanol to decompose the excess oxidizing agent, 465 ml. of water was added and the mixture was maintained at ice-bath temperature for 1 hour. The product was filtered and washed well with water before drying to constant weight; m.p. 179–181°, 13.78 g. (87%), $[\alpha]^{21}D$ +93.7°, $[\alpha]^{22}D$ +86.1° (MeOH).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.67; H, 9.36. Found: C, 76.48; H, 9.40.

12α-Methylpregnane-3,11,20-trione 3,20-Bis-(ethylene Ketal) (XIV).—A mixture of 1.00 g. (0.00290 mole) of 12α-methylpregnane-3,11,20-trione (XIII), 8.90 ml. (0.160 mole) of redistilled ethylene glycol, 39 mg. of *p*-toluenesulfonic acid monohydrate and 33.5 ml. of anhydrous benzene was heated for 5 hours at such a rate that the water formed during the reaction was removed slowly as an azeotrope. The residue was washed with bicarbonate solution and with water, dried and concentrated *in vacuo*. The product was crystallized from cyclohexane; wt. 700 mg. (56%), m.p. 127.5–128.5°, $[\alpha]^{20}D$ +42.4°.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.18; H, 9.32. Found: C, 71.83; H, 9.25.

11β-Hydroxy-12α-methylpregnane-3,20-dione 3,20-Bis-(ethylene Ketal) (VIII) and 11β-Hydroxy-12α-methylpregnane-3,20-dione (XII).—A solution of 200 mg. (0.000462 mole) of 12α - methylpregnane - 3,11,20 - trione 3,20 - bis-(ethylene ketal) (XIV) in 6.0 ml. of tetrahydrofuran was cooled to ice-bath temperature. A filtered solution of 180 mg. (0.0083 mole) of lithium borohydride in tetrahydrofuran was added over a 45-minute period with stirring and then the solution was stirred at room temperature for an additional 3 hours. A solution of 1.0 ml. of glacial acetic acid in 50 ml. of water was added to decompose the excess reducing agent before extracting with chloroform. The chloroform extracts were combined, washed with water, dried and concentrated *in vacuo* to give 185 mg. of VIII as a white foam.

A mixture of 2.80 ml. of 8.5% dilute sulfuric acid in 27.0 ml. of methanol was added to the above foam and the entire mixture was heated under reflux for 1.25 hours. Solid sodium bicarbonate was added to decompose the excess acid. The mixture was filtered and the methanol removed *in vacuo*. The product was filtered and crystallized from methanol; 85 mg. (53%), m.p. 238–240°. The melting point was undepressed upon admixture with authentic XII.

12α-Methyl-11-dehydrocorticosterone (XVIII).—A mixture of 865 mg. (0.00251 mole) of 12α-methylpregnane-3,11,-20-trione (XIII), 10.5 ml. of redistilled isopropenyl acetate and 0.01 ml. of concentrated sulfuric acid was heated under reflux for 15 hours. The isopropenyl acetate was removed *in vacuo*. The product was dissolved in ether and washed with 5% bicarbonate solution and with water. The solution was dried and concentrated *in vacuo*. The product was dissolved in a minimum amount of formamide and partitioned with Skellysolve B several times. The Skellysolve B fractions were combined, washed well with water, dried and concentrated *in vacuo* to give 905 mg. of a light yellow oil. The product (XV) showed proton resonances at 4.85 and 5.00 tau units with a relative area ratio of 1:2, respectively, values in excellent agreement with the proposed structure.

The above oil was dissolved in 45.80 ml. of *t*-butyl alcohol. A solution of 799 mg. (0.0045 mole) of N-bromosuccinimide in 91.6 ml. of *t*-butyl alcohol and 50.4 ml. of 1 *N* sulfuric acid was added and the solution was allowed to stand at room temperature for 1.5 hours. After 4.26 g. of sodium sulfite was added, the solution was diluted with water and extracted with methylene chloride. The organic extracts were washed with water, dried and concentrated *in vacuo*. The crude product was crystallized from ether to give 465 mg. of a solid melting at 170–172.5°. The product (XVI) was used without further purification.

A mixture of 215 mg. of crude XVI, 64.5 mg. of anhydrous lithium chloride and 2.48 ml. of dimethylformamide was heated for 2 hours at 100° under a nitrogen atmosphere. Water was added dropwise with stirring to the reaction mixture. The product was filtered and dried to constant weight to give 160 mg. of crude XVII.

The above material was heated under reflux with 176 mg. of potassium acetate, 61 mg. of sodium iodide, 3.00 ml. of acetone and 0.046 ml. of glacial acetic acid. Excess water was added and the acetic acid removed *in vacuo* before extracting with chloroform. The chloroform layers were washed with a bicarbonate solution and with water before drying and concentrating *in vacuo* yielding 160 mg. of a white foam (XVIIIa).

The crude XVIIIa was hydrolyzed by dissolving in 4.50 ml. of methanol, adding 1.00 ml. of a 10% aqueous potassium bicarbonate solution and heating under reflux for 10 minutes. Acetic acid (1.13 mole) was added to neutralize the reaction mixture. After dilution with water, the mixture was extracted with ethyl acetate. The organic layers were washed with water, dried and concentrated *in vacuo* to yield 105 mg. of an oil (crude XVIIIb). This oil was dissolved in formamide and extracted six times with benzene–cyclohexane (1:1). The formamide solution was then extracted three times with benzene. The benzene solution was washed with water, dried and concentrated *in vacuo* to yield an oil which crystallized from ethyl acetate to yield 23.6 mg. (26% over-all from XIII) of 12α-methyl-11-dehydrocorticosterone (XVIIIb), m.p. 135–138.5°, λ_{max}^{MeOH} 238.0 mμ (15,800), $[\alpha]^{22}D$ +179°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.60; H, 8.66.

12α-Methyl-11-ketoprogesterone (XXII).—A solution of 1.00 g. (0.0029 mole) of 12α-methylpregnane-3,11,20-trione in 17.7 ml. of glacial acetic acid was cooled to −50 to −55° before adding 0.118 ml. of an acetic acid solution 0.1 *N* in HBr. A solution of 0.147 ml. (0.0029 mole) of bromine in 2.68 ml. of the above HBr–acetic acid solution was added dropwise over a 1-hour period. The reaction mixture was aged at this temperature for an additional hour before quenching by the addition of a solution of 0.475 g. of anhydrous sodium acetate in 3.53 ml. of water. A solid formed upon concentration of the chloroform *in vacuo*. Water (11.8 ml.) was added over a half-hour period and an equal volume was added rapidly at the end of this time. The precipitate was collected, washed with water and dried.

The 4ξ-bromo-12α-methylpregnane-3,11,20-trione was heated at 100° for 2 hours in a nitrogen atmosphere with 0.405 g. of anhydrous lithium chloride and 16.1 ml. of dimethylformamide. After cooling to room temperature, an excess of water was added and the solution was extracted three times with chloroform. The extracts were washed several times with water, dried over anhydrous sodium sulfate and concentrated. The yellow oil was crystallized from ethyl acetate to yield 0.380 g. (48%) of XXII, m.p. 151–153°.

The analytical sample was prepared by recrystallization from acetone–Skellysolve B; m.p. 152–154°, λ_{max}^{MeOH} 238.0 mμ (15,700), $[\alpha]^{22}D$ +229.8°.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.59; H, 8.68.

Acknowledgments.—The authors are indebted to Dr. L. H. Sarett for many stimulating discussions concerning this problem. We also wish to thank Mr. N. G. Steinberg for the preparation of several intermediates, Mr. Robert Walker for the interpretation of certain infrared absorption spectra and Mr. R. N. Boos and associates for microanalyses. The microbial studies were carried out by Dr. T. H. Stoudt.

RAHWAY, N. J.