(*cf.* method A). Identity with XVIII was established also by comparison of the paper chromatogram.

8-Hydroxy-19-norcortexone 21-Acetate (XIX) from 8-Hydroxy-19-norcortexone (XVIII).—A solution of 24.3 mg. of XVIII, m.p. 192–197°, in 1.0 ml. of pyridine and 0.5 ml. of acetic anhydride was kept at room temperature for 17 hr. The excess acetic anhydride was decomposed with ice and, after the addition of water, the mixture was repeatedly extracted with ether. The extract was washed successively with 5% hydrochloric acid, water, 5% sodium carbonate, and water. After drying over sodium sulfate, evaporation of the ether yielded 23.8 mg. of a residue which crystallized on short standing, m.p. 164–172°. Recrystallization from acetone–hexane gave 18.6 mg. of prisms, m.p. 179–181°, $[\alpha]^{26}D$ +111.0°, $M^{26}D$ +415° (11.2 mg., α +1.24°), λ_{max}^{alc} 242 mμ (ϵ 17,000).[28]

The infrared spectrum showed (PE-21, 62 mg./ml., 0.1-mm. cell, Fig. 2) $\nu_{max}^{CHCl_3}$ 3620 (free –OH), 3500 (bonded –OH), 3030 (possibly solvent artifact), 2960 (CH stretch in alicyclic rings), 2890 (CH stretch in alicyclic rings), 1749 (21-acetoxy-20 ketone), 1724 (21-acetoxy-20 ketone), 1660 (Δ^4 3 ketone, C=O), 1616 (Δ^4-3 ketone, C=C), 1469.5, 1450, 1420 (C-2 methylene), 1413 (–CO–CH_2–OC, methylene in α position to carbonyl), 1380 (shoulder, angular methyl group), 1374 (acetate methyl group), 1263 (19-nor-Δ^4-3-keto-8-ol?), 1091 (as 1263?), 1066, 1044, 969, 938 (as 1263?), 879 (as 1263?), 660 (as 1263?) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_5$(374.48): C, 70.56; H, 8.08. Found[25]: C, 70.38; H, 8.00 (dried over P_2O_5 for 48 hr).

(28) Determination in 95% ethanol on a Cary Model 14 recording spectrophotometer by courtesy of Mr. Richard J. Warren, Smith Kline and French Laboratories, Philadelphia, Pa.

Investigations on Steroids. XXXVII. Conversion of Pseudostrophanthidin into 19-Hydroxy-8,19-epoxy-17α-progesterone and the C-17 Epimers of 8-Hydroxy-19-norprogesterone[1,2]

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5-Hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (I) which has been synthesized from pseudostrophanthidin was converted into 19-hydroxy-8,19-epoxy-17α-progesterone (VI). In this procedure, I first reacted with methylmagnesium bromide yielding the amorphous 3β,5,20,21-tetrahydroxy-19-methoxy-8,19-epoxy-bisnor-5β-cholane (II) which possibly represented a mixture of C-20 epimers. Oxidation of II with sodium periodate gave the crystalline 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (III) which was converted by several oxidation methods into 5-hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (IV). Unexpectedly, dehydration of IV by treatment with methanol in the presence of a small amount of hydrochloric acid was associated with inversion of the configuration at C-17, thus leading to 19-methoxy-8,19-epoxy-17α-progesterone (V) which was converted into 19-hydroxy-8,19-epoxy-17α-progesterone (VI) by demethylation. The α configuration of the side chain in V and VI follows from the fact that the oxidation of VI with chromic acid resulted in the formation of 19:8-lacto-17α-progesterone (VII) which had been described previously. Demethylation of IV gave the amorphous 5,19-dihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (IX) which was converted into 8-hydroxy-19-norprogesterone (X) by treatment with mild alkali. When VI was treated with mild alkali, a product (VIII) resulted which represents 8-hydroxy-19-nor-17α-progesterone. VI produced no significant progestational effects and was found to be inactive as a progesterone inhibitor. Both X and VIII produced no significant progestational effects. X, when tested as a progesterone inhibitor, was found to be inactive.

In the preceding publication from this laboratory,[4] the conversion of pseudostrophanthidin into 19-hydroxy-8,19-epoxycortexone and 8-hydroxy-19-norcortexone was described. As a continuation of this work, the preparation of analogous compounds of progesterone type appeared to be indicated.

The reaction of a ketol ester with methylmagnesium bromide, followed by oxidation of the resulting product with sodium bismuthate has been reported as a useful method for the conversion of a ketol side chain to the corresponding methyl ketone.[5] Hence, 5-hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (I)[4] was considered a suitable starting material for the synthetic work in mind. Treatment of I with tenfold the required amount of methylmagnesium bromide yielded the amorphous 3β,5,20,21-tetrahydroxy-19-methoxy-8,19-epoxy-bisnor-5β-cholane (II) which possibly represented a mixture of C-20 epimers. For the oxidation of II to the methyl ketone we preferred the use of sodium periodate[6] to that of sodium bismuthate. Hence, treatment of the amorphous II with sodium periodate gave the crystalline 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (III) which by oxidation was converted into 5-hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (IV). This oxidation was achieved in three different ways: (1) with N-bromoacetamide, (2) with chromic acid in an acetone solution, and (3) by means of the chromic acid–pyridine complex. The first two procedures resulted in incomplete reaction, and a small amount of the remaining starting material III could not be removed by recrystallization. The last procedure appears to be the most convenient one. When IV was treated with methanol in the presence of a small amount of hydrochloric acid, dehydration oc-

(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7, CY757-C8, and CA00757-10) from the National Cancer Institute of the National Institutes of Health.

(2) The essential findings of this paper were presented by M. Ehrenstein on May 15, 1962, at the International Congress on Hormonal Steroids in Milano, Italy (*cf.* Tokuo Kubota and Maximilian Ehrenstein, "Synthesis of a Structural Isomer of Aldosterone and of Related Compounds," in "Hormonal Steroids," Biochemistry, Pharmacology and Therapeutics, Proceedings of the First International Congress on Hormonal Steroids, Vol. 2, Academic Press, New York, N. Y., 1964, in press). In addition, this paper was presented by M. Ehrenstein at the following places: Universität Bonn, Organisch-Chemisches Kolloquium (July 22, 1963); Universität Hamburg, Universitätskrankenhaus Eppendorf (July 23, 1963); Freie Universität Berlin, Pharmazeutisches Institut (July 26, 1963, a.m.); and Dahlemer wissenschaftliches Colloquium, Pharmakologisches Institut (July 26, 1963, p.m.).

(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 345 (1964).

(5) M. Uskokovic, R. I. Dorfman, and M. Gut, *ibid.*, **23**, 1947 (1958).

(6) *Cf., e.g.*, P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).

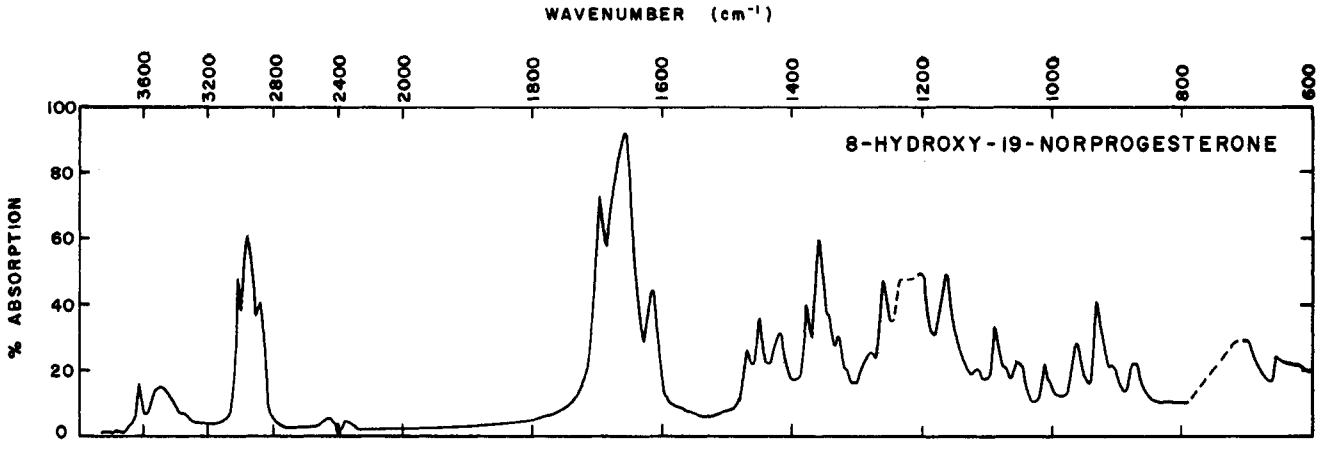


Fig. 1.—Infrared spectrum of 8-hydroxy-19-norprogesterone (X). The dotted lines in Fig. 1 and 2 indicate that chloroform distorts the region 3020–3000 cm.$^{-1}$ and obliterates the regions 1250–1200 cm.$^{-1}$ and 800–700 cm.$^{-1}$.

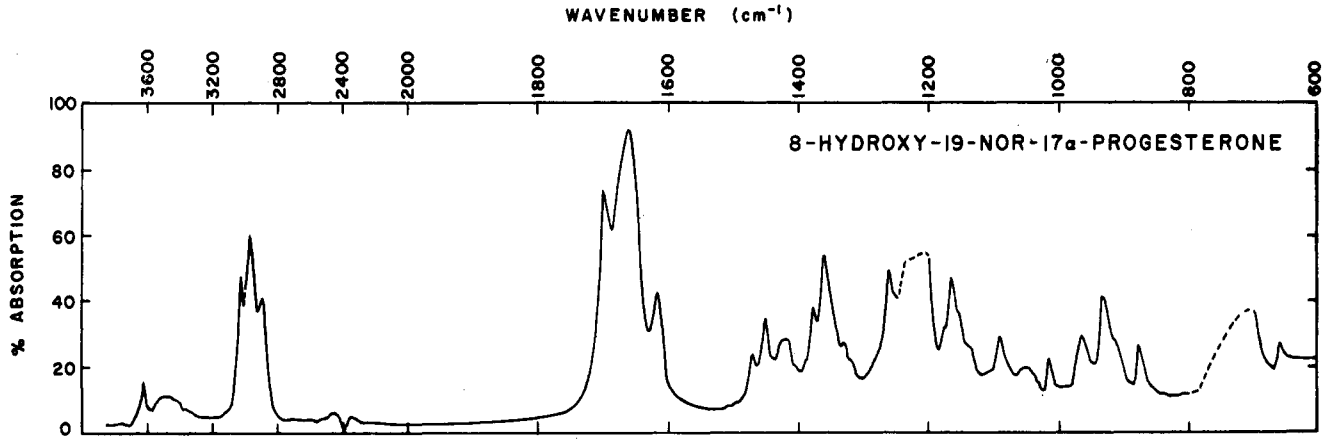


Fig. 2.—Infrared spectrum of 8-hydroxy-19-nor-17α-progesterone (VIII).

curred. The levorotatory change in the molecular rotation associated with the conversion of the 5β-hydroxy 3-ketone (IV) to the Δ^4-3-ketone (V) (ΔM_D −499°) was found to be considerably greater than that observed in the analogous case of the C-17 ketol[4] (ΔM_D −320°). It was surmised, therefore, that in the present instance (C-17 methyl ketone) the reaction was connected with inversion of the configuration at C-17[7,8] resulting in the formation of 19-methoxy-8,19-epoxy-17α-progesterone (V). This interpretation was substantiated by the subsequent reactions, namely the demethylation of V to 19-hydroxy-8,19-epoxy-17α-progesterone (VI) which on oxidation with chromic acid was converted into a 19:8-lactone that is not identical with an authentic sample of 19:8-lacto-progesterone [8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone] prepared in our laboratory previously,[9] but identical with 19:8-lacto-17α-progesterone [8-hydroxy-3,20-dioxo-Δ^4-17α-pregnen-19-oic acid 19:8-lactone] (VII).[9] It may be noted that the infrared spectra of the Δ^4-3-ketones of this group appear to be normal (*cf.* Experimental section, compounds V and VI).

As in the cortexone series,[4] refluxing of VI with 0.1 *N* methanolic sodium hydroxide gave the corresponding 19-nor compound, 8-hydroxy-19-nor-17α-progesterone (VIII), m.p. 155–156°, $[\alpha]_D$ +38.9°, and a by-product which probably represents the 17β epimer (X).

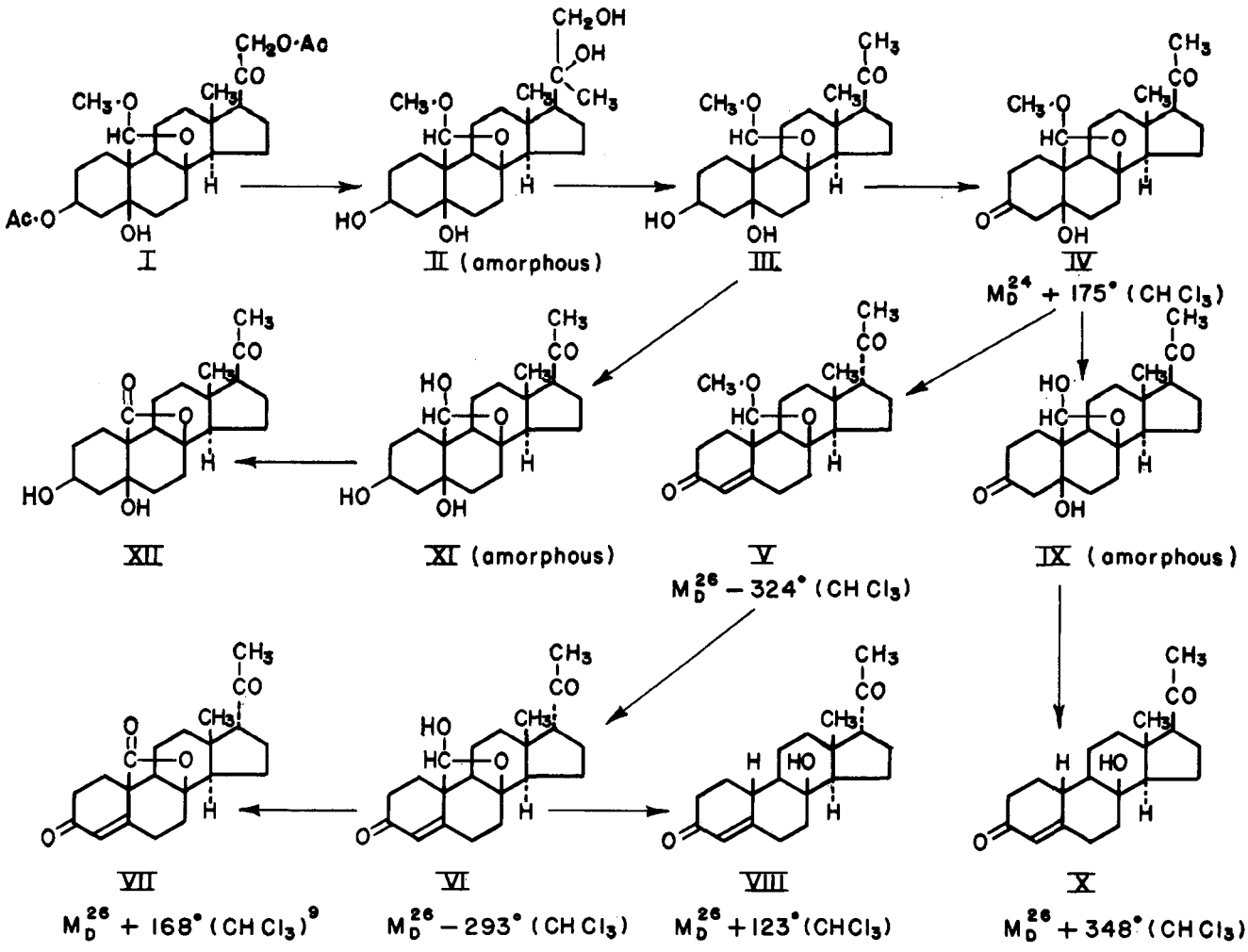
In another approach to obtaining 19-nor compounds, we followed an alternative procedure which had been applied in the cortexone series.[4] IV was first demethylated by treatment with 70% acetic acid. This yielded amorphous material considered to be 5,19-dihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (IX). Subsequent refluxing with 0.1 *N* methanolic sodium hydroxide gave as main product a compound, m.p. 178–180°, $[\alpha]_D$ +110°, that is clearly different from VIII. On the other hand, the analytical values and the ultraviolet and infrared findings satisfy the structure of an 8-hydroxy-19-norprogesterone. One must conclude, therefore, that this compound is a stereoisomer of VIII. Because of its more pronounced dextrorotation[7] it may be assigned the structure of the 17β isomer, *i.e.*, 8-hydroxy-19-norprogesterone (X). In this reaction a small amount of a by-product was isolated which probably represents the 17α isomer (VIII). It is noteworthy that the infrared absorption spectra of X (Fig. 1) and VIII (Fig. 2) are remarkably similar. The only significant qualitative difference is the extra band near 1118 cm.$^{-1}$ in X (Fig. 1).

From the foregoing findings it must be concluded that IV still contains the original 17β-CO·CH$_3$ grouping. On subjecting IV to dehydration by refluxing with methanol containing hydrochloric acid, simul-

(7) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co, New York, N. Y., 1959, p. 566.

(8) *Cf.* also W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961).

(9) G. W. Barber and M. Ehrenstein, *ibid.*, **26**, 1230 (1961).



taneously epimerization of the 17β-CO·CH₃ side chain occurred. This probably proceeded by way of the 17,20-enol, and resulted in the formation of the 17α-CO·CH₃ grouping (V). Although normally in steroids having the C/D *trans* fusion, the 17β-CO·CH₃ side chain is relatively stable,[7] there are known exceptions, for instance, in the 18:11β-lactones the 17α-CO·CH₃ side chain represents the most stable configuration.[10a] Nevertheless, it was surprising that treatment of IV with methanol containing a small amount of concentrated hydrochloric acid gave predominantly the epimeric 17α compound (V). It may be assumed that this epimerization is the result of a long-range effect caused by the deformation of the steroid ring system owing to the 19:8-bridged structure. In future work, attempts will be made to prepare the C-17 epimer of V, *i.e.*, 19-methoxy-8,19-epoxyprogesterone, and to demonstrate its epimerization to V by the action of hydrochloric acid.

As stated earlier, IX was treated with 0.1 *N* methanolic sodium hydroxide which is a well-known reagent for the epimerization of unstable substituents in the α-position to ketone groups. The reaction proceeded predominantly with retention of the original 17β side chain, yielding as main product 8-hydroxy-19-norprogesterone (X). In this reaction, the 8-hydroxy-19-oxo grouping was possibly present in the unbridged form which shows less strain than the hemiacetal structure.

It is interesting to note that in our work in the 19-hydroxy-8,19-epoxycortexone series,[4] the 21-hydroxy analog of compound IV did not undergo epimerization of the 17β-ketol side chain on refluxing with methanol containing hydrochloric acid. One might reason that, in the cortexone series, the 20-ketone grouping is stabilized by hydrogen bonding with the vicinal 21-hydroxyl group, thus preventing the formation of the 17,20-enol.

Although compound VIII has been assigned the structure of 8-hydroxy-19-nor-17α-progesterone, it should be mentioned that the available data on molecular rotations (Table I, examples 1–4) support the alternate structure of 8-hydroxy-19-nor-14β,17α-progesterone. However, epimerization at C-14 on alkaline treatment of VI appears unlikely. Inversion at carbon atoms 10 and 8 also would not be anticipated in view of analogous experiments with 19:11β-bridged compounds.[10b]

With the intention of exploring an alternative route for the preparation of IX, III was first demethylated to the amorphous 3β,5,19-trihydroxy-8,19-epoxy-5β-pregnan-20-one (XI). By subsequent selective oxidation with N-bromoacetamide, we then expected to arrive at IX which had been obtained in amorphous form by the earlier approach. The product resulting from the oxidation of XI with N-bromoacetamide was crystalline and, furthermore, on heating in a solution

(10) (a) J. Schmidilin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **40**, 2291 (1957); *cf.* also P. Wieland, K. Heusler, H. Ueberwasser, and A. Wettstein, *ibid.*, **41**, 416 (1958), p. 420; P. Wieland, K. Heusler, and A. Wettstein, *ibid.*, **44**, 2121 (1961), p. 2122. (b) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962).

TABLE I

COMPARISON OF MOLECULAR ROTATIONS

Compound	Ref.	M_D, deg.	ΔM_D (b − a)
1. (a) Compound X	*a*	+348	−225
(b) Compound VII	*a*	+123	
2. (a) Progesterone	*b*	+641	−204
(b) 14β,17α-Progesterone	*c*	+437	
3. (a) 19-Hydroxyprogesterone	*d*	+611	−243
(b) 19-Hydroxy-14β,17α-progesterone	*e*	+368	
4. (a) 19-Norprogesterone	*f*	+441	−270
(b) 19-Nor-14α,17α-progesterone	*g*	+171	
5.*(a) Progesterone	*h*	+459 (dioxane)	−585
(b) 17α-Progesterone	*h*	−126 (dioxane)	

[a] This paper. [b] F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953). [c] Pl. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948). [d] G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **19**, 1758 (1954). [e] M. Ehrenstein and M. Dünnenberger, *ibid.*, **21**, 783 (1956). [f] C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4440 (1953). [g] G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957). [h] W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961).

* NOTE ADDED IN PROOF, DECEMBER 30, 1963.—For detailed discussion of the differences of the molecular rotations of 17β-20-ketopregnanes and 17α-20-ketopregnanes, including additional pairs of examples, *cf.* "17α-20-Ketopregnanes. A Review," by Mordecai B. Rubin, *Steroids*, **2**, 561 (1963).

of dioxane in the presence of a trace of hydrochloric acid, did not yield an α,β-unsaturated ketone. This permits the conclusion that the oxidation product is 3β,5,8-trihydroxy-20-oxo-5β-pregnan-19-oic acid 19:8-lactone (XII), although the infrared spectrum shows a slight abnormality (*cf.* Experimental section). In other words, the hemiacetal grouping underwent selective oxidation and the resulting lactone (XII) is resistant to further oxidation. It was reported earlier that a compound of the structural type of XII may be resistant to oxidation by N-bromoacetamide.[11]

Biological Activity.—Bioassays for progestational and antiprogestational activity were carried out by Dr. Roy Hertz, Chief of the Endocrinology Branch of the National Cancer Institute. 19-Hydroxy-8,19-epoxy-17α-progesterone (VI) was tested in each of three Clauberg rabbits at a total dose per rabbit of 5.0 mg. No evidence of progestational or estrogenic activity was apparent at this dose, whereas control animals simultaneously injected with 0.5 mg. of progesterone showed the expected response. In bioassays for possible antagonism of progestational activity, a mixture of 0.1 mg. of progesterone and 1.0 mg. of VI was given daily for 5 days to each of three Clauberg rabbits. This failed to have any effect upon the expected response to the administered progesterone.

8-Hydroxy-19-norprogesterone (X) and 8-hydroxy-19-nor-17α-progesterone (VIII) were both subjected to the Clauberg test in each of three rabbits at a total dose of 1.0 mg. The results were negative, whereas in this test 0.25 mg. of progesterone gives a moderate effect. Hence X and VIII are less than one-fourth as active as progesterone, if at all. X also was tested for antiprogestational activity and was found to be inactive at a total dose of 5.0 mg. when assayed against a total dose of 0.5 mg. of progesterone in each of three Clauberg rabbits.

For comparison, it should be noted that both 19-norprogesterone[12] and 19-nor-14β,17α-progesterone[13] were found to be four to eight times as active as progesterone with regard to progestational potency.

(11) *Cf.* ref. 9, p. 1232.

Experimental

Melting Points.—The melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The true melting points are approximately 3° lower than those reported.

Absorption Spectra.—Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer. The infrared studies including the tentative assignment of bands were carried out in the Division of Pure Chemistry of the National Research Council of Canada in Ottawa, Ontario, through the courtesy of Dr. R. Norman Jones. The spectra were measured in chloroform solution on the Perkin-Elmer 421 grating instrument (PE-421) or on the Perkin-Elmer 21 instrument with a sodium chloride prism (PE-21). The values of the reported frequencies are corrected.

Analyses.—Unless stated otherwise, the microanalyses were performed by Dr. E. W. D. Huffman, Wheatridge, Colo., on samples which were dried to constant weight *in vacuo* (phosphorus pentoxide, 80°). The per cent loss of weight on drying is recorded.

Optical Rotation.—No correction for crystal solvent has been made. Unless stated otherwise, the sample was dissolved in chloroform to make 2 ml. of solution and the rotation was determined in a 2-dm. semimicrotube.

Nomenclature.—In the headings alternative names are given, the one in brackets expressing the true character of the functional groups.

3β,5,20,21-Tetrahydroxy-19-methoxy-8,19-epoxybisnor-5β-cholane [3β,5,8,20,21-Pentahydroxy-19-oxobisnor-5β-cholane 19:8-Hemiacetal 19-Methylal] (II) from 5-Hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [5,8-Dihydroxy-3β,21-diacetoxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (I).—Through a mixture of 2.440 g. of magnesium[14] and 40 ml. of ether, methyl bromide was passed until the metal was completely dissolved. The mixture was refluxed with stirring for 15 min. to remove the excess methyl bromide. A solution of 800 mg. of I, m.p. 92–96°, in 120 ml. of tetrahydrofuran[15] was added dropwise to the Grignard reagent at 15–20° over a period of 20 min. This produced a small amount of a precipitate which went into solution on heating.[16] The heating was continued until the boiling point of the mixture had been raised to 55° (after approximately 30 min., water of condenser turned off). The reaction mixture was then refluxed at this temperature for 5 hr.[17] and, after cooling, it was poured into a mixture of 24 g. of ammonium chloride and crushed ice. The product was then extracted with one 200-ml. and two 150-ml. portions of ethyl ether. The extract was washed with saturated aqueous sodium chloride and, after drying over sodium sulfate, evaporation of the solvent yielded 727 mg. (calcd., 686 mg.) of crude II as a foam. The product gave a slightly positive reaction with blue tetrazolium. By paper chromatography, only a small amount of the deacetylated starting material, *i.e.*, 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one, could be detected as contaminant.

(12) (a) C. Djerassi, L. Miramontes, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4440 (1953); (b) W. W. Tullner and R. Hertz, *Endocrinology*, **52**, 359 (1953).

(13) (a) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944); (b) W. M. Allen and M. Ehrenstein, *Science*, **100**, 251 (1944); (c) G. W. Barber and M. Ehrenstein, *Ann.*, **603**, 89 (1957); (d) M. Ehrenstein, G. W. Barber, and R. Hertz, *Endocrinology*, **60**, 681 (1957); (e) C. Djerassi, M. Ehrenstein, and G. W. Barber, *Ann.*, **612**, 93 (1958).

(14) Fisher magnesium metal, turnings for Grignard reaction.

(15) Fisher certified reagent, treated with solid potassum hydroxide, followed by distillation over lithium aluminum hydride.

(16) In preliminary experiments carried out under essentially the same conditions, benzene was used as a solvent instead of tetrahydrofuran. A copious precipitate separated from the reaction mixture during the period of heating. It probably consisted of an incompletely reacted Grignard complex which prevented the reaction from going to completion.

(17) In a repeat experiment refluxing at 58° for 2.5 hr. proved sufficient.

3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (III) from 3β,5,20,21-Tetrahydroxy-19-methoxy-8,19-epoxy-bisnor-5β-cholane [3β,5,8,20,21-Pentahydroxy-19-oxo-bisnor-5β-cholane 19:8-Hemiacetal 19-Methylal] (II).—To 1.469 g. of crude II (containing a trace of solvent, resulting from 1.600 g. of I, m.p. 92–96°) in 80 ml. of methanol was added a solution of 2.160 g. of sodium periodate in 60 ml. of water. The mixture was allowed to stand at room temperature for 18 hr. and, after the addition of 250 ml. of water, it was extracted with one 250-ml. and three 100-ml. portions of ethyl acetate. The extract was washed successively with water, two 100-ml. portions of 1 *N* sodium carbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate, the solvent was evaporated yielding 1.088 g. of a foam. Crystallization from acetone–hexane gave 762 mg. of plates, m.p. 220–223°. By concentrating the mother liquor, an additional yield of 149 mg. of crystalline material, m.p. 213–218°, was obtained (total yield, 911 mg.; 72% from I). Recrystallization gave the analytical sample, m.p. 220–223°, $[\alpha]^{26}D$ +49.9°, $M^{26}D$ +189° (18.2 mg., α +0.91°).

The infrared spectrum showed (PE-421, 53 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3600 (free –OH), 3458 (broad, bonded –OH), 2997 (probably solvent artifact), 2942 (C–H stretch), 2922 (C–H stretch), 1700 (C-20 ketone), 1453, 1444, ~1413 (broad), 1381, 1358, 1188 (weak), 1173 (weak), 1151, 1128 (weak), 1090, 999, 978, 965, 947, 915, 899, 855, 821 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_5$ (378.51): C, 69.81; H, 9.05. Found: C, 70.02; H, 9.07; wt. loss, 0.49.

The carbonate phase was acidified by the addition of 10% hydrochloric acid and was then extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride and, after drying over sodium sulfate, the solvent was evaporated, leaving 100.5 mg. of a foam. Crystallization from acetone–hexane gave 32.2 mg. of needles, m.p. 209–212°. In a repeat experiment the melting point was 220–223°. There was no depression of the melting point upon admixture with an authentic sample of 3β,5-dihydroxy-19-methoxy-8,19-epoxy-5β-etianic acid (m.p. 223–226°).[18] This product has obviously originated from 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (*cf.* the preparation of II).

5-Hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IV) from 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19-8 Hemiacetal 19-Methylal] (III). A. By Oxidation with N-Bromoacetamide.—To 100 mg. of III, m.p. 210–213°, in 4.9 ml. of *t*-butyl alcohol and 2.1 ml. of water was added 73 mg. of N-bromoacetamide.[19] The mixture was kept at room temperature for 21 hr., diluted with 20 ml. of water, and decolorized by the addition of a sufficient amount of solid sodium thiosulfate. After extracting with four 15-ml. portions of chloroform, the extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave 97.9 mg. of a foam which was crystallized from acetone–hexane, yielding 66.9 mg. of prisms, m.p. 185–188°. Repeated recrystallization from acetone–hexane gave 28.6 mg. of prisms, m.p. 192–195°. The mixture melting point with the starting material was depressed (182–192°). In a paper chromatogram (system: formamide–benzene; reagent: 70% phosphoric acid) the product, unexpectedly, gave a spot less mobile than that of the starting material, $[\alpha]^{26}D$ +47.1°, $M^{26}D$ +177° (12.7 mg., α +0.60°).

The infrared spectrum showed (PE-421, 52 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3593 (free –OH), ~3455 (very broad, bonded –OH), 2997 (probably solvent artifact), 2945 and 2921 (doublet, not too well resolved, C–H stretch), 2870, 2816 (very weak), 1703 (C-3 ketone and C-20 ketone), 1453, 1418 (C-2 and C-4 methylenes), 1381 (angular methyl group), 1357 (C-21 methyl), 1315 (very weak), 1160, 1088, 1044 (very weak), 1004, 964, 920, 901 (weak), 854 (very weak) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_5$ (376.50): C, 70.18; H, 8.57. Found: C, 70.37; H, 8.61; wt. loss, 0.73.

B. By Oxidation with Chromic Acid in a Solution of Acetone.—To 95 mg. of III, m.p. 220–223°, in 25 ml. of acetone kept at 2° was added by drops 0.07 ml. of an aqueous solution containing 18.69 mg. of chromium trioxide and 0.016 ml. of sulfuric acid. The mixture was kept at 2–6° for 25 min. and, after the addition of 75 ml. of water, was extracted with three 25-ml. portions of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, leaving 93.1 mg. of a foam which was crystallized from acetone–hexane, yielding 61.0 mg. of prisms, m.p. 191–194°. Concentration of the mother liquor gave an additional 11.8 mg. of crystals, m.p. 191–193°; total yield, 72.8 mg. The mixture melting point with the product obtained by method A was not depressed. As became evident in a subsequent reaction (dehydration to V), the isolated product still contained a substantial amount of the starting material III.

C. By Oxidation with the Chromic Acid–Pyridine Complex.—To a complex prepared from 12 ml. of pyridine and 1.2 g. of chromium trioxide was added a solution of 1.208 g. of III, m.p. 222–224°, in 18 ml. of pyridine. After keeping the mixture at room temperature for 18 hr., it was diluted with 400 ml. of water and extracted with one 300-ml. and three 100-ml. portions of chloroform–ether, 1:4. The extract was washed successively with 10% hydrochloric acid, 5% hydrochloric acid, water, 0.5 *N* sodium carbonate, and water. After drying over sodium sulfate, evaporation of the solvent gave 1.125 g. of a foam, which was crystallized from acetone–hexane, yielding 869.7 mg. of crystals m.p. 188–192°. Recrystallization from acetone–hexane gave 735.9 mg. of crystals, m.p. 195–196°, $[\alpha]^{24}D$ +46.6°, $M^{24}D$ +175° (19.3 mg., α +0.90°).[20]

Anal. Calcd. for $C_{22}H_{32}O_5$ (376.50): C, 70.18; H, 8.59. Found[21]: C, 70.31; H, 9.02.

19-Methoxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal 19-Methylal] (V) from 5-Hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IV).—To 200.0 mg. of IV, m.p. 195–196° (obtained by oxidation method C), in 20 ml. of methanol was added 0.2 ml. of concentrated hydrochloric acid. The mixture was refluxed for 20 min. and was then diluted with 100 ml. of water and extracted with one 60-ml. and three 30-ml. portions of chloroform. The extract was washed with 2% sodium bicarbonate and with water. After drying over sodium sulfate and evaporating the solvent, 194.8 mg. of a residue resulted which was chromatographed over 6 g. of Florisil. Elution with benzene–chloroform, ratios 4:1 (20 ml.) and 1:1 (120 ml.), and with chloroform (80 ml.) gave a total of 143.9 mg. of fractions which could be crystallized. The combined material was crystallized from acetone–hexane yielding 132.0 mg. of prisms, m.p. 134–140°. By repeated recrystallization from acetone–hexane the melting point was raised to 142–145°, $[\alpha]^{26}D$ −90.3°, $M^{26}D$ −324° (18.65 mg., α −1.68°), λ_{max}^{alc} 241.5 mμ (ε 14,200).

The infrared spectrum showed (PE-421, 51 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3005 (probably solvent artifact), 2955, 2925, 2875, 1700 (C-20 ketone), 1665 (Δ⁴-3-ketone), 1623 (Δ⁴-3-ketone), 1448, 1419, 1382 (angular methyl group), 1357 (C-21 methyl), 1325 (19-methoxy-8,19-epoxy Δ⁴-3-ketone ring system), 1272, 1171, 1160, 1112 (as 1325), 1097 (as 1325), 1081 (as 1325), 1011 (shoulder, as 1325), 995 (as 1325), ~975 (as 1325), 949 (as 1325), 905 (as 1325), 870 (as 1325), 840 (as 1325) cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_4$ (358.48): C, 73.71; H, 8.44. Found: C, 73.49; H, 8.15; residue, 0.5.

The yield of V depends on the purity of the starting material IV which sometimes contains appreciable amounts of the unoxidized compound III, especially when it is prepared by oxidation methods A or B. If this is the case, III is eluted in the chromatogram as a second, more polar compound.

19-Hydroxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal] (VI) from 19-Methoxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal 19-Methylal] (V).—A solution of 140 mg. of V, m.p. 142–145°, in 30 ml. of 70% acetic acid was heated at 100° for 80 min. and was then evaporated *in vacuo* yielding a reddish brown oil[22] which was chromatographed over 4.5 g. of Florisil (13 × 80 mm.). Elution with chloroform (90 ml.) and chloroform–acetone, 9:1 (45 ml.) yielded fractions which crystallized from acetone–hexane. Hence these fractions were combined (96.5 mg.) and the material was crystallized from acetone–hexane yielding 57.3 mg. of needles, m.p. 158–179°. Recrystallization

(18) T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 357 (1964).

(19) Freshly precipitated from a chloroform solution by the addition of hexane; 97.3% purity by titration [*cf.* R. S. Schreiber, *Org. Syn.*, **31**, 17 (1951)].

(20) Determination by Dr. Hiroyuki Ageta.

(21) Analysis by Mikrolaboratorium (Director, W. Manser), Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, Zürich, Switzerland. We wish to thank Professor V. Prelog for this courtesy.

(22) *Cf.* ref. 4, footnote 26.

gave 32.9 mg. of needles of constant m.p. 196.5–199.5°, $[\alpha]^{26}D$ −85.0°, $M^{26}D$ −293° (13.60 mg., α −1.16°), λ_{max}^{alc} 243 mμ (ε 12,900).

The infrared spectrum showed (PE-421, 45 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3603 (free –OH), ~3398 (broad, bonded –OH), 3002 (probably solvent artifact), 2957 (C–H stretch), 2919 (C–H stretch), 2875 (C–H stretch), 1699 (C-20 ketone), 1665 (Δ⁴-3-ketone), 1622 (Δ⁴-3-ketone), 1470, 1448, 1416, 1381, 1358 (C-21 methyl), 1325 (19-hydroxy-8,19-epoxy Δ⁴-3-ketone ring system), ~1165 (broad, as 1325), 1101, 1062, 1025, 1011 (as 1325), 975 (as 1325), 920 (as 1325), 898 (as 1325), 872, 825 cm.⁻¹.

Anal. Calcd. for $C_{21}H_{28}O_4$(344.45): C, 73.23; H, 8.19. Found: C, 73.01; H, 8.15; residue, 0.3.

19:8-Lacto-17α-progesterone [8-Hydroxy-3,20-dioxo-Δ⁴-17α-pregnen-19-oic Acid 19:8-Lactone] (VII) from 19-Hydroxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8-Hemiacetal] (VI).—To 5.0 mg. of VI, m.p. 196–199°, in 7 ml. of acetone was added 0.01 ml. of a solution of 1.33 mg. of chromium trioxide (approximately 33% excess) in 4 *N* sulfuric acid. The mixture was kept at 11–13° under nitrogen for 6 min. and, after the addition of 20 ml. of water, was extracted with two 25-ml. portions of chloroform–ether (4:1). The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, yielding 5.2 mg. of an oil. Crystallization from acetone–hexane gave 4.8 mg. of needles, m.p. 187–193°. Examination by paper chromatography (system: propylene glycol–toluene; reagent: phosphoric acid) showed, in addition to a faster moving spot, a strong spot corresponding to the starting material VI. Therefore, the crystals and mother liquors were combined and subjected to further oxidation. A solution of the product in 5 ml. of acetone was treated with 0.01 ml. of a solution of 1.33 mg. of chromium trioxide in 4 *N* sulfuric acid at 15° under nitrogen for 20 min. The mixture was worked up as described above, yielding 5.2 mg. of an oil which on crystallization from acetone–hexane gave 4.6 mg. of plates, m.p. 202–205°. There was no depression of the melting point on admixture with an authentic sample of 19:8-lacto-17α-progesterone (VII,[9] m.p. 203–206°). On admixture with 19:8-lactoprogesterone[9] (m.p. 161–163°) the melting point was depressed to 142–154°. Upon admixture with the starting material VI (m.p. 196–199°), the melting point was depressed to 177–181°. The reaction product was recrystallized once more from acetone–hexane giving 4.2 mg. of plates, m.p. 203–206°. Again there was no depression of the melting point upon admixture with VII.

8-Hydroxy-19-nor-17α-progesterone (VIII) from 19-Hydroxy-8,19-epoxy-17α-progesterone [19-Oxo-8-hydroxy-17α-progesterone 19:8 Hemiacetal] (VI).—A solution of 40.6 mg. of VI, m.p. 186–190°, in 5 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed for 30 min. under an atmosphere of nitrogen. The reaction mixture was neutralized with dilute acetic acid and, after the addition of 25 ml. of water, it was extracted with one 30-ml. and three 15-ml. portions of ether–chloroform (4:1). The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, leaving 36.4 mg. of an oil which was chromatographed over 1.5 g. of Florisil. Elution with benzene–chloroform, 1:1 (5 ml.), chloroform (15 ml.), and chloroform–acetone, ratios 49:1 (15 ml.) and 19:1 (15 ml.), gave a total of 31.9 mg. of material which was crystallized from acetone–hexane yielding 23.1 mg. of VIII as prisms, m.p. 148–151°. This was contaminated by a small amount of felt-like needles, m.p. 100–140°, probably representing, although in an impure state, 8-hydroxy-19-norprogesterone (X). Repeated recrystallization of the major product (VIII) from acetone–hexane gave an analytical sample as plates, m.p. 155–156°, $[\alpha]^{26}D$ +38.9°, $M^{26}D$ +123° (11.80 mg., α +0.46°), λ_{max}^{alc} 242.5 mμ (ε 15,700).

The infrared spectrum showed (PE-21, 55 mg./ml., 0.1-mm. cell, Fig. 2) $\nu_{max}^{CHCl_3}$ 3622 (free –OH), 3475 (very broad, bonded –OH), 3030 (possibly solvent artifact), 2970 (CH stretch in alicyclic rings), 2890 (CH stretch in alicyclic rings), 1701 (C-20 ketone), 1663 (Δ⁴-3-ketone, C=O), 1617 (Δ⁴-3-ketone, C=C), 1472, 1452, 1420 (C-2 methylene), 1381 (angular methyl group), 1361 (methyl group in CH_3–CO–), 1263 (19-nor-Δ⁴-3-keto-8-ol?), 1165 (CH_3–CO–?), 1093 (as 1263?), 1017, 967, 937 (as 1263?), 882 (as 1263?), 661 (as 1263?) cm.⁻¹.

Anal. Calcd. for $C_{20}H_{28}O_3$ (316.44): C, 75.91; H, 8.92. Found[21]: C, 76.20; H, 8.90 (dried over P_2O_5 for 48 hr.).

5,19-Dihydroxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal] (IX) and 8-Hydroxy-19-norprogesterone (X) from 5-Hydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8-Dihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IV).—A solution of 200 mg. of IV, m.p. 195–196°, in 20 ml. of 70% acetic acid was heated at 90° for 40 min. in a stream of nitrogen. Evaporation to dryness *in vacuo*, treatment of the residue with benzene, and renewed evaporation yielded the crude product IX which resisted attempts at crystallization. A solution of this material in 20 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed in a stream of nitrogen for 30 min. The reaction mixture was neutralized with dilute acetic acid, and, after the addition of 80 ml. of water, it was extracted with one 75-ml. and three 30-ml. portions of chloroform–ether (1:4). After washing the extract with water and drying over sodium sulfate, evaporation of the solvent gave 168.9 mg. of a foam which was chromatographed over 6.0 g. of Florisil. Elution with benzene–chloroform, 1:1 (40 ml.), chloroform (60 ml.), and chloroform–acetone, ratios 49:1 (60 ml.) and 19:1 (40 ml.), gave ten individual fractions, of which eight could be made to crystallize. No one fraction depressed the melting point of any other. Therefore, this material, including the two amorphous residues, was combined (157.3 mg.) and crystallized from acetone–hexane, giving 114.1 mg. of needles, m.p. 167–175°. Repeated recrystallization from acetone–hexane yielded 84.7 mg. of needles, constant m.p. 178–180°. The mixture melting points with VIII and VI showed pronounced depressions, $[\alpha]^{26}D$ +110°, $M^{26}D$ +348° (19.7 mg., α + 2.17°), λ_{max}^{alc} 242.5 mμ (ε 17,300).

The infrared spectrum showed (PE-21, 55 mg./ml., 0.1-mm. cell, Fig. 1) $\nu_{max}^{CHCl_3}$ 3622 (free –OH), 3490 (broad, bonded –OH), 3030 (possibly solvent artifact), 2965 (CH stretch in alicyclic rings), 2885 (CH stretch in alicyclic rings), 1699 (C-20 ketone), 1661 (Δ⁴-3-ketone, C=O), 1617 (Δ⁴-3-ketone, C=C), 1471, 1451, 1420 (C-2 methylene), 1380 (angular methyl group), 1361 (methyl group in CH_3–CO–), 1333, 1263 (19-nor-Δ⁴-3-keto-8-ol?), 1167 (CH_3–CO–?), 1118, 1089.5 (as 1263?), 1058, 1015.5, 970, 937 (as 1263?), 880 (as 1263?), 659 (as 1263?) cm.⁻¹.

Anal. Calcd. for $C_{20}H_{28}O_3$ (316.44): C, 75.91; H, 8.92. Found[21]: C, 76.00; H, 8.91 (dried over P_2O_5 for 48 hr).

From the mother liquors of the recrystallizations 9.9 mg. of prisms, m.p. 138–145°, was isolated. The mixture melting point with VIII was not depressed.

3β,5,19-Trihydroxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal] (XI) and 3β,5,8-Trihydroxy-20-oxo-5β-pregnan-19-oic Acid 19:8-Lactone (XII) from 3β,5-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8-Trihydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (III).—A solution of 50 mg. of III, m.p. 210–213°, in 5 ml. of 70% acetic acid was heated at 75–85° for 1 hr. and was then evaporated to dryness *in vacuo*. The residue was treated with benzene and the solvent was removed again, leaving 47.9 mg. of a foam representing crude XI. Attempts at crystallization failed.

To the crude XI (47.9 mg.) in 3.5 ml. of *t*-butyl alcohol and 1.5 ml. of water was added 36 mg. of N-bromoacetamide.[19] The mixture was kept at room temperature overnight, then diluted with 20 ml. of water, decolorized by the addition of sodium thiosulfate, and extracted with chloroform. Evaporation of the solvent gave 43.9 mg. of a foam. Crystallization and recrystallization from acetone–hexane gave 18.0 mg. of XII as prisms, m.p. 228–232° dec. In the original belief that this was a 3-oxo compound as represented by structure IX, the product was subjected to the conditions of dehydration[23] with the result that no α,β-unsaturated ketone was obtained. The recovered material (XII) was repeatedly recrystallized, yielding plates of m.p. 242–246°.

The infrared spectrum showed (PE-21, ~10 mg./ml., 1-mm. cell) $\nu_{max}^{CHCl_3}$ 3710, 3610 (shoulder, free –OH), 3510 (broad), 2970, 2890 (shoulder), 1759[24] (19:8 lactone[24]), 1704 (C-20 ketone), 1387 (angular methyl), 1359 (C-21 methyl), 1158, 1129, 1102, 1083, ~1016 (broad), 987, ~942 and ~923 (unresolved doublet) cm.⁻¹.

Anal. Calcd. for $C_{21}H_{30}O_5$(362.47): C, 69.59; H, 8.34. Found[21]: C, 69.23; H, 7.76.

(23) The product was dissolved in 5 ml. of dioxane and, after the addition of 0.05 ml. of concentrated hydrochloric acid, the solution was kept at 70–75° for 20 min.

(24) This band is exceptionally low and is significantly displaced from other 19:8-lactenes which have been examined.[9] The band is still within the low acceptable range for a γ-lactone.