and extracted with four 10-ml. portions of ethyl acetate. The extract was washed successively with water, 5% sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over sodium sulfate and evaporating the solvent, 19.7 mg. of crystalline material resulted. Recrystallization from methanol gave 14.9 mg. of needles, m.p. 266–268° dec. There was no depression of the melting point when mixed with the analytical sample, m.p. 265–267° dec., obtained by acetylation of X.

Investigations on Steroids. XXXVI. Conversion of Pseudostrophanthidin into 19-Hydroxy-8,19-epoxycortexone and 8-Hydroxy-19-norcortexone[1,2]

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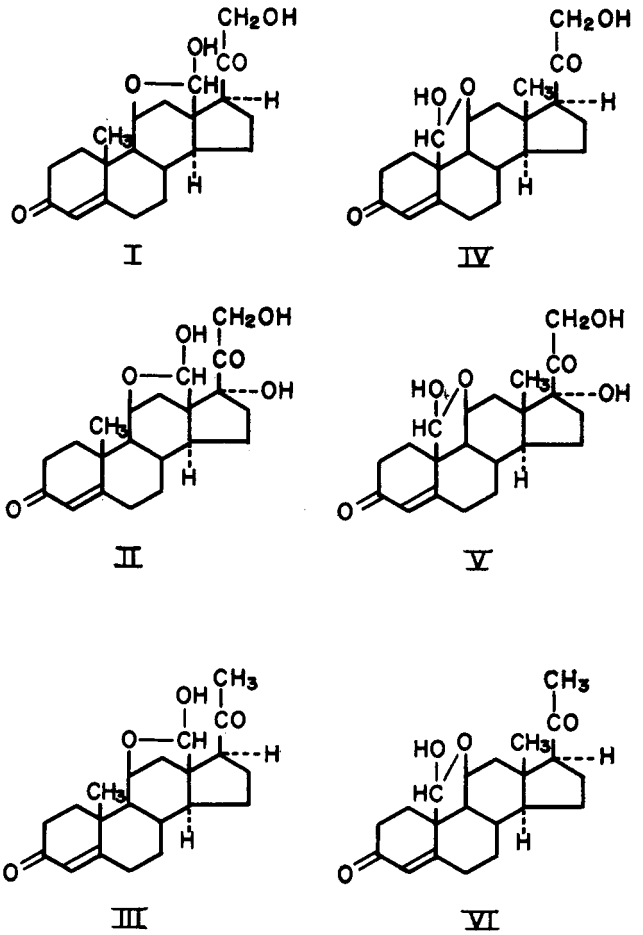
The conversion of pseudostrophanthidin (VII) into a structural isomer of aldosterone, *viz.*, 19-hydroxy-8,19-epoxycortexone (XV), is reported. In this procedure VII was first subjected to ozonization, yielding the amorphous 3β,5,19,21-tetrahydroxy-8,19-epoxy-5β-pregnan-20-one (VIII); this was converted into the crystalline methylal (IX) which was characterized as the 3,21-diacetate (X). Selective oxidation of IX with N-bromoacetamide gave 5,21-dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (XI) which by demethylation was converted into 5,19,21-trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (XII). Dehydration of XI yielded 19-methoxy-8,19-epoxycortexone (XIII) which was transformed into XV by demethylation. Acetylation of XIII gave 19-methoxy-8,19-epoxycortexone 21-acetate (XIV) which was demethylated to yield 19-hydroxy-8,19-epoxycortexone 21-monoacetate (XVI). Oxidation of XVI with chromic acid gave 19:8-lactocortexone acetate (XVII) which had been described previously. This conversion lends support, especially, to the structures proposed for XIII, XIV, XV, and XVI. The conversion of XI into XIII was associated with an abnormal levorotatory shift, and the products derived from XIII, *i.e.*, XIV, XV, and XVI, show this unexpected feature of optical rotation. On treating either XII or XV with mild alkali, conversion occurred into 8-hydroxy-19-norcortexone (XVIII) which was characterized as the 21-acetate (XIX). Compound XVIII appears to be the first 8-hydroxy analog of a steroid hormone ever prepared.[15c] 19-Hydroxy-8,19-epoxycortexone (XV) produced no mineralocorticoid effects and was found to be inactive as a cortexone inhibitor. 8-Hydroxy-19-norcortexone (XVIII) caused sodium retention of a low order.

Recent investigations in a number of laboratories have opened pathways for the introduction of a functional group at the angular carbon atom 18. Outstanding in this respect is the photolytic approach of Barton and co-workers which resulted in a partial synthesis of aldosterone and of a number of structurally related 3-oxo-Δ^4 steroids. In these synthetic products, we find the C-18:C-11β oxygen bridge present as a lactone, hemiacetal, or ether grouping. By variation of the side chain at carbon atom 17, steroids with the ketol, dihydroxyacetone, and methyl ketone groupings have been prepared. Among the compounds of especial interest may be listed aldosterone (I),[4,5] 17α-hydroxyaldosterone (II),[5] and 21-desoxyaldosterone (III).[6,7]

The photolytic procedure of Barton, as it is applied to an 11β nitrite, not only permits the functionalization of the angular carbon atom 18, but it also results in a functionalization of carbon atom 19. Hence a number of steroids have become available which have a C-19:C-11β, rather than a C-18:C-11β oxygen



(1) This investigation was supported in whole by Public Health Service Research Grants (CY757-C7 and CY757-C8) 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. For abstract see, "Excerpta Medica," International Congress Series, No. 51, International Congress on Hormonal Steroids, Round Table Discussions, p. 57). In addition, this paper was reported 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.).

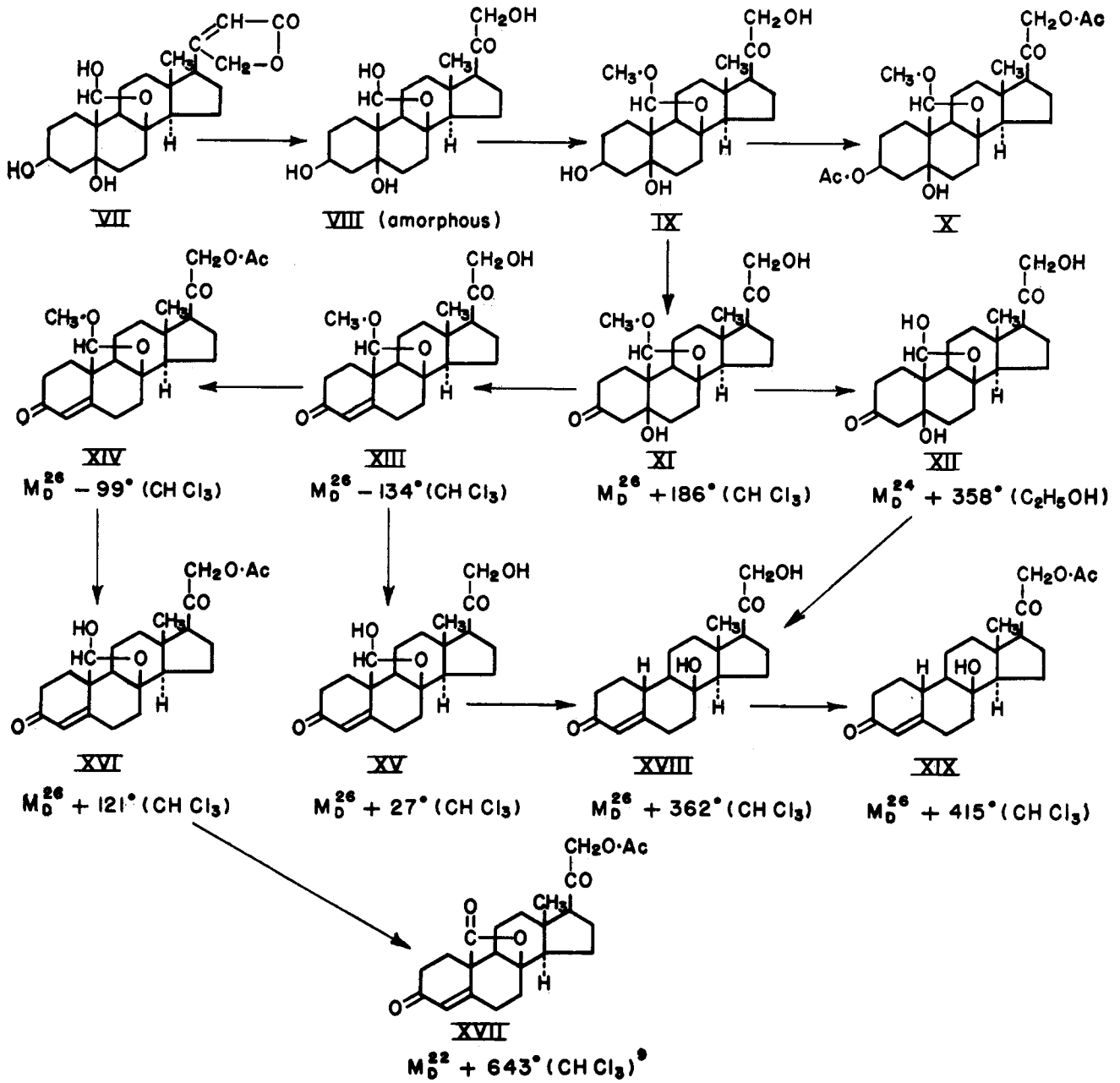
(3) On leave of absence from the Shionogi Research Laboratory, Osaka, Japan, 1961–1963.

(4) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961).

(5) D. H. R. Barton and J. M. Beaton, *ibid.*, **84**, 199 (1962).

(6) R. H. Hesse, H. Kohler, and M. M. Pechet, Abstracts, Division of Biological Chemistry, 141st National Meeting of the American Chemical Society, Washington, D. C., 1962, pp. 22C–23C.

(7) *Cf.* also, K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **45**, 347 (1962).



bridge. Among others, the compounds analogous in structure to I, II, and III, have been reported, *viz.*, 19-oxocorticosterone 19:11-hemiacetal (IV),[5] 19-oxocortisol 19:11-hemiacetal (V),[5] and 19-oxo-11β-hydroxyprogesterone 19:11-hemiacetal (VI),[6] respectively.

It is to be noted that compound IV is a structural isomer of aldosterone (I). It contains the same functional groups and differs from I only regarding the location of the hemiacetal bridge which extends from C-19 to C-11β. Among the aims of our laboratory has been the preparation of a related structural isomer of aldosterone, namely the one in which the hemiacetal bridge extends from C-19 to C-8, *viz.*, 19-hydroxy-8,19-epoxycortexone (19-oxo-8-hydroxycortexone 19:8-hemiacetal) (XV).[8] We previously have reported other compounds belonging to this series. These products contain a C-19:C-8 lactone[9] or a C-19:C-8 ether bridge.[10]

For the preparation of XV, pseudostrophanthidin (VII)[11] served as starting material. VII was subjected to ozonolysis and, after reductive cleavage of the ozonide and hydrolysis of the 21-glycolate, 3β,5,19,21-tetrahydroxy-8,19-epoxy-5β-pregnan-20-one (VIII) was obtained in an amorphous state. Subsequent treatment of VIII with methanol in the presence of a trace of hydrochloric acid gave the crystalline methylal, namely 3β,5,21-trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (IX).[12] IX was characterized as the 3,21-diacetate, *i.e.*, 5-hydroxy-3β,21-diacetoxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one (X). On treating the methylal (IX) with N-bromoacetamide, selective oxidation occurred in the 3-position yielding 5,21-dihydroxy-

(8) In agreement with the proposals of Fieser, the trivial name cortexone is preferred to 11-desoxycorticosterone (*cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, pp. 602 and 706).

(9) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961).

(10) K. Otto and M. Ehrenstein, *ibid.*, **26**, 2871 (1961).

(11) T. Kubota and M. Ehrenstein, *ibid.*, **29**, 342 (1964).

(12) From a theoretical point of view, one may consider the existence of two epimeric forms in the series of the C-19 methylals. Only one form was isolated in the present instance.

TABLE I

THE SODIUM-RETAINING EFFECT OF 8-HYDROXY-19-NORCORTEXONE (XVIII) IN THE SALINE-TREATED ADRENALECTOMIZED RAT

Experiment designation	Compound	Total dose, μg.	No. of rats	Sodium excretion, mg./2 hr. ± S.E.	Potassium excretion, mg./2 hr. ± S.E.
I	0	0	5	3.17 ± 0.57	2.42 ± 0.21
	Cortexone	3	5	1.23 ± 0.16	3.46 ± 0.27
		9	5	0.19 ± 0.07	3.40 ± 0.06
	8-Hydroxy-19-norcortexone (XVIII)	1	5	2.49 ± 0.31	3.23 ± 0.16
		5	5	2.57 ± 0.35	2.77 ± 0.28
		25	5	2.27 ± 0.39	2.65 ± 0.24
II	0	0	7	2.42 ± 0.24	2.03 ± 0.18
	8-Hydroxy-19-norcortexone (XVIII)	200	7	1.57 ± 0.13	1.83 ± 0.07

19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione (XI). Demethylation of XI, by heating with 70% acetic acid, gave 5,19,21-trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione (XII). Dehydration of XI furnished 19-methoxy-8,19-epoxycortexone (XIII). In order to forestall simultaneous demethylation, this reaction was carried out by refluxing in a solution of methanol in the presence of a small amount of concentrated hydrochloric acid. XIII was characterized as the acetate, namely, 19-methoxy-8,19-epoxycortexone 21-acetate (XIV). The demethylation of XIII and XIV was achieved by heating with 70% acetic acid leading to 19-hydroxy-8,19-epoxycortexone (XV) and 19-hydroxy-8,19-epoxycortexone 21-monoacetate (XVI), respectively. Oxidation of XVI with chromic acid gave a product which was identical with 19:8-lactocortexone acetate (21-acetoxy-8-hydroxy-3,20-dioxo-Δ^4-pregnen-19-oic acid 19:8-lactone) (XVII) reported previously from this laboratory.[9] This proves in particular that the dehydration of XI to XIII was not connected with inversion of the configuration at C-17.[13]

An interesting phenomenon in the series of 19:8-hemiacetal compounds is the abnormal levorotatory shift which occurs on converting the 5β-hydroxy 3-ketone (XI) into the Δ^4-3-ketone (XIII). The infrared spectra of the Δ^4-3-ketones of this group appear to be normal (*cf.* Experimental section, compounds XIV, XV, XVI). The abnormal levoratatory shift has been previously observed in the series of the 8,19-ethers[10] where the infrared spectra of the Δ^4-3-ketones are likewise normal. Conversely, in the series of the 19:8-lactones, no levorotatory shift was observed on dehydrating the 5β-hydroxy 3-ketones to the Δ^4-3-ketones, and yet the infrared spectra of the latter show abnormalities.[9] The optical rotatory dispersion curves of some 19:8-hemiacetal compounds will be recorded in a subsequent paper.[14]

To the best of our knowledge, no 8-hydroxy analogs of steroid hormones have been described definitely. In a sense, the 8β-position is analogous to that of the 11β-position, because it is "axial" and, in the same relative location between the angular carbon atoms 18 and 19. Therefore, it was of interest to prepare 8β-hydroxy steroids and to study their physiological activities. For the synthesis of such compounds, the microbiological approach has to be ruled out because so far no enzyme has been found capable of hydroxylating in the 8-position.[15] Some of the compounds of the 19:8-hemiacetal series appear eminently suitable for the preparation of the desired products. Cleavage of the 19:8-hemiacetal bridge under appropriate conditions should lead to 8β-hydroxy analogs of steroid hormones including those of the 19-nor series. Various possibilities will be investigated in this laboratory. As a first step in this direction, the facile preparation of 8β-hydroxy-19-nor compounds has been achieved.[13]

Barton recently[5] reported the smooth conversion of 19-oxocorticosterone 19:11-hemiacetal (IV) into 19-norcorticosterone by treatment with mild base at room temperature. In similar fashion, refluxing of XV[16] with 0.1 *N* methanolic sodium hydroxide gave a satisfactory yield of 8-hydroxy-19-norcortexone (XVIII). By the same procedure, XVIII also can be obtained from XII. Acetylation of XVIII yielded 8-hydroxy-19-norcortexone 21-acetate (XIX).

Biological Activity.—The bioassays were conducted at the Endocrine Laboratories (Director, Dr. Elva G. Shipley) in Madison, Wis.[17] 19-Hydroxy-8,19-epoxycortexone (XV), in doses of 1.0 and 25.0 μg., produced no sodium retention or potassium excretion in salt (sodium chloride) loaded adrenalectomized male rats. This means that, if XV has sodium-retaining activity, it is less than 1/250th as active as aldosterone. When tested in similar fashion as a cortexone inhibitor (6 μg. of cortexone plus 1000 μg. of XV), it was found to be inactive.

8-Hydroxy-19-norcortexone (XVIII) exhibited sodium retention of a low order and the dose–response curve was more shallow than that of cortexone. The 25-μg. dose caused a 28% decrease in sodium excretion (experiment I), but increasing the dose eight times (experiment II) did not significantly increase the response (*cf.* Table I).

For comparison, it should be stated that the mineralocorticoid activity of 19-norcortexone is approximately twice that of cortexone.[18] Apparently no data have

(13) *Cf.* the pertinent discussion in the subsequent paper: T. Kubota and M. Ehrenstein, *J. Org. Chem.*, **29**, 351 (1964).

(14) T. Kubota and M. Ehrenstein, *ibid.*, **29**, 357 (1964).

(15) (a) Ch. Tamm, *Angew. Chem.*, **74**, 225 (1962), p. 227. (b) S. H. Eppstein, P. D. Meister, H. C. Murray, and D. H. Peterson [*Vitamins Hormones*, **14**, 389 (1956)] have discussed the possible 8-hydroxylation of cortexone and progesterone. Although no definite conclusions were reached, the authors discussed the possibility that a compound prepared microbiologically by Fried may well be 8β-hydroxyprogesterone. (c) NOTE ADDED IN PROOF, DECEMBER 30, 1963.—The 8β-hydroxylation of Reichstein's compound S by a microorganism recently has been reported. *Cf.* K. Tori and E. Kondo, *Tetrahedron Letters*, **No. 10**, 645 (1963).

(16) Treatment at room temperature yielded a fair amount of unchanged starting material (XV).

(17) The authors are indebted to Dr. Ralph I. Dorfman, Worcester Foundation for Experimental Biology, for the interpretation of these bioassays.

(18) A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 148 (1955).

been recorded on the mineralocorticoid and glucocorticoid activities of 19-norcorticosterone (11β-hydroxy-19-norcortexone).[19] The glucocorticoid activity is assumed to be negligible because, in this respect, 19-norhydrocortisone and 19-norcortisone are considerably less active than hydrocortisone.[19]

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.—Unless otherwise stated, the 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 otherwise stated, 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 otherwise stated, 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,5,19,21-Tetrahydroxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal] (VIII) and 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IX) from Pseudostrophanthidin (VII).—A solution of 5.178 g. (12 mmoles of $C_{23}H_{32}O_6 \cdot 1^1/_2H_2O$) of VII, m.p. 155–158°, in 420 ml. of ethyl acetate was divided equally between two reaction bottles. Each part was cooled in Dry Ice–acetone, and oxygen containing approximately 3% ozone was passed in for 15 min. The lilac colored solution was allowed to remain in the cold bath for 15 min. After this time the color had faded and the ozonization was resumed for 15 more min. The mixture was then kept in the cold for 1 hr. (retention of color) and, after removing the excess ozone by passing oxygen through, the solvent was evaporated *in vacuo* at room temperature. The combined residues were dissolved in 60 ml. of glacial acetic acid and 3 g. of zinc dust was added gradually. The mixture was kept at room temperature for 30 min. and, after subsequently heating it at 70–90° for 45 min., the potassium iodide–starch reaction was negative. The precipitate was filtered and washed with acetic acid. The filtrate was evaporated *in vacuo*, leaving an oily residue which was taken up in 50 ml. of methanol and 550 ml. of chloroform. The solution was successively washed with 100 ml. of water, 100 ml. of *N* sodium carbonate, and two 100-ml. portions of water. After drying over sodium sulfate, evaporation of the solvent yielded 4.240 g. of neutral material (foam), representing the crude 21-glycolate of VIII. From the carbonate phase there was isolated, in the usual fashion, 0.516 g. of acidic material as a foam.

To the neutral fraction, dissolved in 100 ml. of methanol, a solution of 3.0 g. of potassium carbonate in 50 ml. of water was added under an atmosphere of nitrogen. The mixture was allowed to stand at room temperature for 2 hr. and, after the addition of 300 ml. of saturated aqueous sodium chloride, it was repeatedly extracted with a total of 600 ml. of chloroform. The extract was washed with two 100-ml. portions of saturated aqueous sodium chloride and, after drying over sodium sulfate, the solvent was evaporated, yielding 2.878 g. of a foam representing crude VIII.[20] From the aqueous phase there was isolated, after acidification, 0.360 g. of acidic material as a foam.

A solution of the crude VIII (2.878 g.) in 60 ml. of methanol containing 0.6 ml. of concentrated hydrochloric acid was refluxed for 20 min. and, after diluting with 250 ml. of water, it was repeatedly extracted with a total of 550 ml. of chloroform. The extract was washed with 100 ml. of 0.2 *N* sodium carbonate and two 100-ml. portions of water, and was then dried over sodium sulfate and evaporated to dryness, leaving 2.853 g. of a foam, representing crude IX. This was chromatographed over 90 g. of Florisil (30 × 270 mm.). Chloroform and chloroform–acetone, 19:1, eluted a total of 0.381 g. of material which did not crystallize. Chloroform–acetone, range 19:1 to 4:1, eluted a total of 1.7134 g. of fractions which could be crystallized from acetone–hexane. This material was combined and recrystallized from acetone–hexane yielding 1.3177 g. of prisms, m.p. 175–178°. Repeated recrystallization gave 1.0830 g. of pure IX, m.p. 190–193°. The mixture melting point with the analytical sample[20] was not depressed. The terminal eluates of the chromatogram gave a total of 0.387 g. of material which could not be crystallized.

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] (X) from 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (IX).—A solution of 500 mg. of IX, m.p. 187–189°, in 5 ml. of pyridine and 5 ml. of acetic anhydride was kept at room temperature for 16 hr. After the addition of ice, the mixture was extracted with ether and the extract was washed successively with 5% hydrochloric acid, water, 1 *N* sodium carbonate, and water. After drying over sodium sulfate and evaporating the solvent, 591.0 mg. of a foamy residue resulted. Crystallization from aqueous methanol gave 550.5 mg. of prisms, m.p. 93–97°. By further recrystallization from aqueous methanol the melting point was not altered, $[\alpha]^{26}D$ +77.4°, $M^{26}D$ +370° (18.7 mg., α +1.45°).

The infrared spectrum showed (PE-421, 60 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3566 (lightly bonded –OH), 3004 (probably solvent artifact), 2950 and 2925 (doublet only partially resolved, C–H stretch), 2875 (C–H stretch), 1740[21] (acetate, C=O stretch), ~1727[21] (shoulder, 20-keto-21-acetoxy, C=O stretch), 1453 (shoulder), 1441, 1408 (C-21 methylene, C-H scissor), 1374 (CH_3 groups), 1303, 1148, 1087, 1043, ~1016, 975, 955, 918, 843, 835 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{38}O_8$ (478.59): C, 65.25; H, 8.00. Found: C, 65.00, 65.21[22]; H, 7.51, 8.13.[22]

5,21-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (XI) from 3β,5,21-Trihydroxy-19-methoxy-8,19-epoxy-5β-pregnan-20-one [3β,5,8,21-Tetrahydroxy-19,20-dioxo-5-β-pregnane 19:8-Hemiacetal 19-Methylal] (IX).—To a solution of 700 mg. of IX, m.p. 190–193°, in 24.5 ml. of *t*-butyl alcohol and 10.5 ml. of water, was added 500 mg. of N-bromoacetamide[23] in an atmosphere of nitrogen. After keeping the mixture in the dark at room temperature for 22 hr., 60 ml. of water was added

(19) A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6110 (1958).

(20) In a similar preliminary experiment the crude reaction product VIII (442.6 mg.) was chromatographed over 13 g. of Florisil. The early and late eluates gave a weak blue tetrazolium reaction and were discarded. The other fractions gave a very strong blue tetrazolium reaction, but none could be crystallized. They were combined (404.4 mg.) and converted into the 19-methylal (IX) by refluxing for 30 min. with 10 ml. of methanol containing 0.1 ml. of concentrated hydrochloric acid. After adding 40 ml. of water, the mixture was repeatedly extracted with a total of 100 ml. of chloroform. The extract was washed with 20 cc. of 0.5 *N* sodium carbonate and 20 ml. of water, and after drying over sodium sulfate, the solvent was removed *in vacuo*, yielding 402.4 mg. of crude IX as a foam. Crystallization from acetone–hexane, followed by standing in a refrigerator overnight, yielded 202.1 mg. of clusters of needles, m.p. 168–173°. Recrystallization from acetone–hexane and ethyl acetate raised the melting point to 188–191° (after drying the product over calcium chloride *in vacuo*), $[\alpha]^{26}D$ +55.4°, $M^{26}D$ +219° (19.4 mg., α +1.07°). *Anal.* Calcd. for $C_{22}H_{34}O_6$ (396.49): C, 66.98; H, 8.69. Found: C, 67.26; H, 8.61.

(21) There is a slight anomaly in the shape of the C=O band envelope. Normally in the spectra of 3,21-diacetoxy-20 ketones the peak at the lower wave number is the more intense. *Cf.* Charts No. 183, 184, 186, 191, 504, 510, and 511 in the Atlas of "Infrared Absorption Spectra of Steroids," Vol. I and II, Interscience Publishers, Inc., New York, N. Y., 1953 and 1958.

(22) Analysis by Dr. Alfred Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim (Ruhr), West Germany.

(23) 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)].

and an amount of solid sodium thiosulfate sufficient to remove the free bromine. The mixture was then repeatedly extracted with a total of 150 ml. of chloroform. After washing the extract with water and drying over sodium sulfate, evaporation of the solvent yielded 735 mg. of a foam. Crystallization from acetone–hexane gave 538.3 mg. of needles, m.p. 211–213°. Further recrystallization from acetone–hexane furnished plates, m.p. 211.5–213.5°, $[\alpha]^{26}D$ +47.5°, $M^{26}D$ +186° (22.80 mg., α +1.08°).

Anal. Calcd. for $C_{22}H_{32}O_5$ (392.48): C, 67.32; H, 8.22; CH_3O, 7.91. Found: C, 66.97; H, 8.03; CH_3O, 5.10.

5,19,21-Trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal] (XII) from 5,21-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (XI).—A solution of 100 mg. of XI, m.p. 208–211°, in 10 ml. of 70% acetic acid was heated at 85–95° for 40 min. and was then evaporated to dryness *in vacuo*. By adding a little benzene to the residue and again evaporating the solvent, crystalline material resulted which by recrystallization from acetone gave 65.6 mg. of small prisms, constant m.p. 231–235° dec., $[\alpha]^{24}D$ +94.6°, $M^{24}D$ +358° (13.0 mg. in 2 ml. of 95% ethanol).[24]

Anal. Calcd. for $C_{21}H_{30}O_5$ (378.47): C, 66.65; H, 7.99. Found[25]: C, 66.94; H, 7.95 (dried over P_2O_5 for 48 hr.).

19-Methoxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal] (XIII) from 5,21-Dihydroxy-19-methoxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,29-trioxo-5β-pregnane 19:8-Hemiacetal 19-Methylal] (XI).—A solution of 200 mg. of XI, m.p. 212–214°, in 10 ml. of methanol and 0.1 ml. of concentrated hydrochloric acid was refluxed for 30 min. After the addition of 50 ml. of water the mixture was extracted with one 40-ml. and three 20-ml. portions of chloroform. The extract was washed with water, and after drying over sodium sulfate, it was evaporated to dryness leaving 191.4 mg. of a foam. Crystallization from acetone–hexane gave 119.3 mg. of prisms, m.p. 185–193°. By repeated recrystallization the melting point was raised to 190–193°, $[\alpha]^{26}D$ −35.8°, $M^{26}D$ −134° (17.50 mg., α −0.63°), λ_{max}^{alc} 241.5 mμ (ϵ 17,000).

Anal. Calcd. for $C_{22}H_{30}O_5$ (374.48): C, 70.56; H, 8.08. Found: C, 70.36; H, 8.08.

19-Methoxy-8,19-epoxycortexone 21-Acetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal 21-Acetate] (XIV) from 19-Methoxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal] (XIII).—A solution of 160 mg. of XIII, m.p. 189–192°, in 2 ml. of pyridine and 2 ml. of acetic anhydride was kept at room temperature for 16 hr. The addition of ice and water produced a white crystalline precipitate. After extracting with three 20-ml. portions of ether, the extract was washed successively with 5% hydrochloric acid, 1 *N* sodium carbonate, and water. After drying over sodium sulfate, evaporation of the solvent yielded 177.2 mg. of a crystalline residue, m.p. 160–172°. Repeated recrystallization from acetone–hexane gave 130.4 mg. of prisms, constant m.p. 183.5–185°, $[\alpha]^{26}D$ −23.8°, $M^{26}D$ −99° (14.05 mg., α −0.33°), λ_{max}^{alc} 241 mμ (ϵ 15,600).

The infrared spectrum showed (PE-421, 50 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 2978 (probably solvent artifact), 2949 (C–H stretch), 2915 (C–H stretch), 1748 (20-keto-21-acetoxy), 1725 (20-keto-21-acetoxy), 1665 (Δ^4-3-ketone), 1621 (Δ^4-3-ketone), 1448, 1410 (C-21 methylene), 1372 ($-CH_3$ groups), 1340, 1323 (19-methoxy-8,19-epoxy Δ^4-3-ketone ring system), 1267, 1161, 1111 (as 1323), 1096 (as 1323), 1078 (as 1323), 1050, 1012, 997 (as 1323), 974 (as 1323), 948 (as 1323), 904 (as 1323), 869 (as 1323), 839 (as 1323) $cm.^{-1}$.

Anal. Calcd. for $C_{24}H_{32}O_6$ (416.52): C, 69.21; H, 7.74. Found: C, 69.64; H, 7.79.

19-Hydroxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal] (XV) from 19-Methoxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal] (XIII).—A solution of 191.5 mg. of XIII, m.p. 189–192°, in 20 ml.of 70% acetic acid was heated at 100° for 1.5 hr. in a stream of nitrogen[26] and was then evaporated to dryness *in vacuo*. A small amount of acetic acid was removed by adding benzene to the residue and evaporating once more. The crude reaction product was chromatographed over 6 g. of Florisil. Elution with chloroform (40 ml.) and with chloroform–acetone, 49:1 (60 ml.) and 19:1 (60 ml.), gave a total of 72.0 mg. of material which could not be crystallized. Chloroform–acetone, 19:1 (40 ml.), 9:1 (60 ml.), and 4:1 (100 ml.), eluted a total of 111.0 mg. of fractions which crystallized from acetone–hexane. Recrystallization of the combined fractions gave 98.2 mg. of needles, m.p. 185–188°, $[\alpha]^{26}D$ +7.6°, $M^{26}D$ +27° (18.80 mg., α +0.14°), λ_{max}^{alc} 243 mμ (ϵ 15,100).

The infrared spectrum showed (PE-421, 45 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3603 (free –OH), ~3440 (very broad, bonded –OH), 3000 (probably solvent artifact), 2950 (C–H stretch), 2917 (C–H stretch), 2872 (C–H stretch), 1709 (20-ketone, C=O stretch), 1665 (Δ^4-3-ketone, C=O stretch), 1622 (Δ^4-3-ketone, C=C stretch), 1450, 1383 (angular methyl C–H bend), 1360, 1325 (19-hydroxy-8,19-epoxy Δ^4-3-ketone ring system), 1269 (not too well-resolved), 1163 (as 1325), 1115, 1079, 1050, 1011 (as 1325), 977 (as 1325), 922, 901 (as 1325), 875 $cm.^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_5$ (360.46): C, 69.98; H, 7.83. Found: C, 69.97; H, 7.72; wt. loss, 0.24.

19-Hydroxy-8,19-epoxycortexone 21-Monoacetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 21-Acetate] (XVI) from 19-Methoxy-8,19-epoxycortexone 21-Acetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 19-Methylal 21-Acetate] (XIV).—To 100 mg. of XIV, m.p. 183.5–185°, was added 10 ml. of 70% acetic acid and the solution was heated at 100° for 1.5 hr. whereby it turned dark red.[27] The solvent was evaporated *in vacuo* and, for the removal of small amounts of acetic acid, the evaporation was repeated after the addition of some benzene. The product was chromatographed over 3 g. of Florisil and each fraction was examined by paper chromatography (system: formamide–benzene; reagent: blue tetrazolium). The first 12 eluates, obtained with benzene and benzene–chloroform (range 9:1 to 1:1), were practically empty. Fractions 13 to 18, eluted with a total of 60 ml. of chloroform (total wt., 15.3 mg.), consisted essentially of starting material XIV. Fractions 19 to 33, obtained by elution with chloroform–acetone, ratios 49:1 (60 ml.), 19:1 (50 ml.), and 9:1 (40 ml.) (combined wt., 73.0 mg.), all gave the same single spot in the paper chromatogram, indicating the reaction product XVI. Fractions 34 to 39 eluted with chloroform–acetone (range 4:1 to 1:1) and with acetone yielded a total of 16.6 mg. of yellow oil. The reaction product XVI (73.0 mg.) was crystallized from acetone–hexane yielding 44.3 mg. of prisms, m.p. 180–182°. Further recrystallization from acetone–hexane gave plates, m.p. 181–182°, $[\alpha]^{26}D$ +30.0°, $M^{26}D$ +121° (10.00 mg., α +0.30°), λ_{max}^{alc} 243 mμ (ϵ 14,100).

The infrared spectrum showed (PE-421, 50 mg./ml., 0.1-mm. cell) $\nu_{max}^{CHCl_3}$ 3600 (free–OH), 3405 (very broad, bonded –OH), 3000 (probably solvent artifact), 2965 (C–H stretch), 2915 (C–H stretch), 2865 (C–H stretch,) 1747 (20-keto-21-acetoxy), 1727 (20-keto-21-acetoxy), 1659 (Δ^4-3-ketone), 1623 (Δ^4-3-ketone), 1450 ($-CH_2-C{=}C-$), 1413 (C-21 methylene), 1374 (CH_3 groups), 1341, 1326 (19-hydroxy-8,19-epoxy Δ^4-3-ketone ring system), 1163 (as 1326), 1100, 1065, 1051, 1013 (as 1326), 977 (as 1326), 924 (as 1326), 903 (as 1326) $cm.^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.49): C, 68.64; H, 7.51. Found: C, 68.66; H, 7.38.

19:8-Lactocortexone Acetate [21-Acetoxy-8-hydroxy-3,20-dioxo-Δ^4-pregnene-19-oic Acid 19:8-Lactone] (XVII) from 19-Hydroxy-8,19-epoxycortexone 21-Monoacetate [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal 21-Acetate] (XVI).—To 8.0 mg. of XVI, m.p. 181–182°, in 5 ml. of acetone was added 0.015 ml. of a solution of 4.00 mg. of chromium trioxide (approximately 200% excess) in 2 *N* sulfuric acid. The mixture was kept at room temperature (28°) for 15 min. and, after the addition of 15 ml. of water, it was repeatedly extracted with chloroform. The extract was washed with water and, after drying over sodium sulfate, the solvent was evaporated. leaving 8.3 mg. of an oil which did not crystallize. Tested in a paper chromatogram (system: formamide–benzene; 2.5 hr.; reagent: blue tetrazolium), the product showed a spot corresponding to that of 19:8-lactocortex-

(24) Determination by Dr. Hiroyuki Ageta.

(25) 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.

(26) In preliminary experiments it was shown that heating at 80° for 1 hr. and chromatography of the reaction product resulted in the isolation of a substantial amount of starting material (XIII). Under more vigorous conditions a red discoloration occurs (*cf.* preparation of XVI), unless one operates in an atmosphere of nitrogen. It has generally been found that the cleavage of the C-19 methoxy group in the Δ^4-3 ketones of this series is more difficult to achieve than in the saturated compounds.

(27) For explanation, see ref. 26.

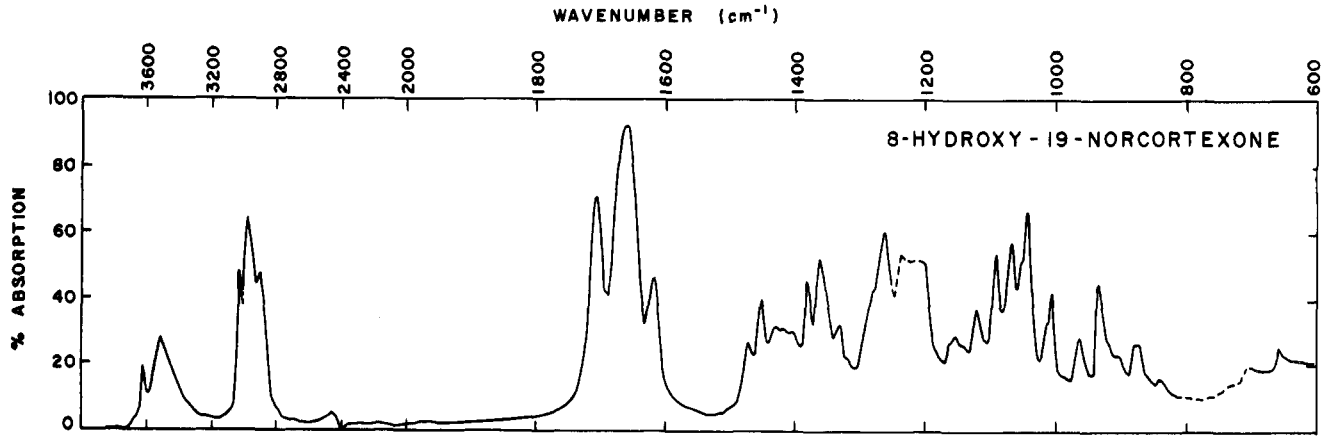


Fig. 1.—Infrared spectrum of 8-hydroxy-19-norcortexone (XVIII). The dotted lines in Fig. 1 and 2 indicate that chloroform distorts the region 3020–3000 cm.$^{-1}$ and obliterates the regions 1250–1200 cm.$^{-1}$ and 800–700 cm.$^{-1}$.

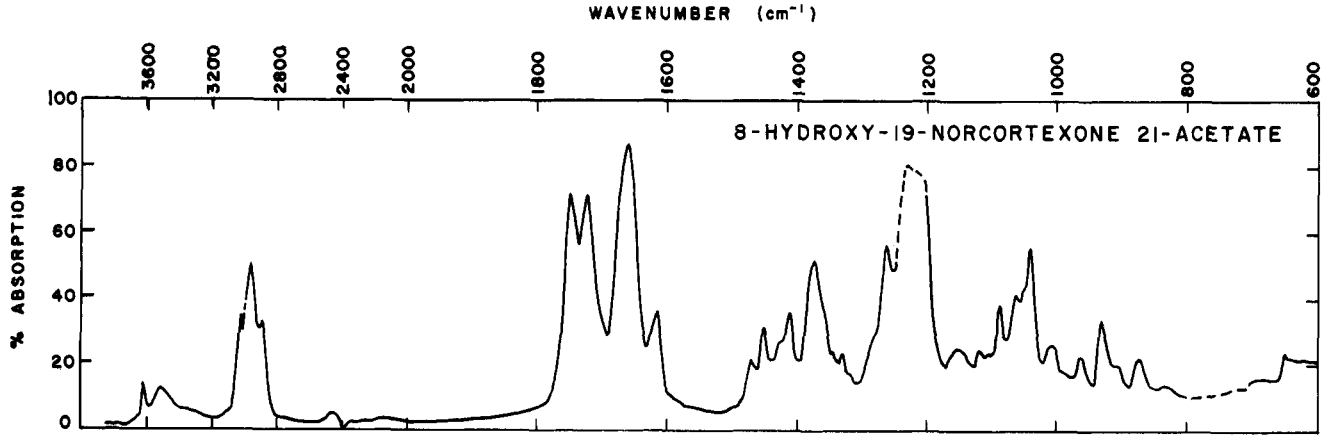


Fig. 2.—Infrared spectrum of 8-hydroxy-19-norcortexone 21-acetate (XIX).

one acetate (XVII)[9] and differing from that of the somewhat faster moving 19:8-lacto-17α-cortexone.[9] Therefore, the crude product was chromatographed over 400 mg. of Florisil. Elution with chloroform (10 ml.), and chloroform–acetone, 9:1 (10 ml.) and 4:1 (10 ml.) gave residues weighing 3.0 mg., 3.2 mg., and 1.8 mg., respectively. In a paper chromatogram, the first fraction (3.0 mg.) gave a single spot indicating identity with XVII. Crystallization from acetone–hexane gave needles, m.p. 177–180°. The second (3.2 mg.) and third (1.8 mg.) fractions, when tested by paper chromatography, gave two spots, indicating the presence of XVII and of the starting material XVI. They were combined (5.0 mg.) and subjected to further oxidation by treatment in 2 ml. of acetone for 10 min. at room temperature (26°) with 0.02 ml. of a solution of 2.67 mg. of chromium trioxide in 4 *N* sulfuric acid. The reaction mixture was worked up as described above, and the crude product (4.5 mg.) was chromatographed over 150 mg. of Florisil. Elution with 20 ml. of chloroform and 10 ml. of chloroform-acetone (9:1) gave a total of 2.9 mg. of crystalline material, melting points between 177 and 182°. This was combined with the crystalline reaction product mentioned before (m.p. 177–180°). Recrystallization yielded 3.7 mg. of needles, m.p. 177–180°. There was no depression of the melting point upon admixture with an authentic sample of 19:8-lactocortexone acetate (XVII).[9]

8-Hydroxy-19-norcortexone (XVIII). A. From 19-Hydroxy-8,19-epoxycortexone [19-Oxo-8-hydroxycortexone 19:8-Hemiacetal] (XV).—A solution of 140 mg. of XV, m.p. 185–188°, in 14 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed for 30 min. under a stream of nitrogen. The reaction mixture was neutralized with dilute acetic acid and, after the addition of 70 ml. of water, extracted with one 50-ml. and three 25-ml. portions of chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to dryness, leaving 135.0 mg. of an oily residue which on paper chromatography (system: formamide–(benzene–chloroform) (7:5); reagent: blue tetrazolium) gave a spot indicating faster mobility than that of the starting material. The crude product was chromatographed over 4.5 g. of Florisil. Elution with chloroform–acetone, 49:1 (30 ml.), 19:1 (75 ml.), 9:1 (45 ml.), and 4:1 (60 ml.) yielded a total of 111.1 mg. of material which was crystallized from acetone–hexane to give 62.1 mg. of prisms, m.p. 178–189°. Repeated recrystallization from acetone–hexane raised the melting point to 196–199°, $[\alpha]^{26}D$ +109.0°, $M^{26}D$ + 362° (20.35 mg., α +2.22°), λ_{max}^{alc} 243 mμ (ϵ 18,400).

The infrared spectrum showed (PE-21, 57.5 mg./ml., 0.1-mm. cell, Fig. 1) $\nu_{max}^{CHCl_3}$ 3620 (free -OH), 3500 (bonded -OH), 3035 (possibly solvent artifact), 2965 (CH stretch in alicyclic rings), 2890 (CH stretch in alicyclic rings), 1709 (C-20 ketone), 1661 (not sharp, Δ^4-3-ketone, C=O), 1617 (Δ^4-3-ketone, C=C), 1471, 1452, 1420 (C-2 methylene), 1382 (angular methyl group), 1365, 1264 (19-nor-Δ^4-3-keto-8-ol?), 1121, 1091.5 (as 1264?), 1055, 1045, 1008, 962, 936 (as 1264?), 878 (as 1264?), 844, 660 (as 1264?) cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_4$ (332.44): C, 72.26; H, 8.49. Found[25]: C, 71.98; 8.36 (dried over P_2O_5 for 48 hr.).

B. From 5,19,21-Trihydroxy-8,19-epoxy-5β-pregnane-3,20-dione [5,8,21-Trihydroxy-3,19,20-trioxo-5β-pregnane 19:8-Hemiacetal] (XII).—A solution of 64.3 mg. of XII, m.p. 228–233° dec., in 7 ml. of 0.1 *N* methanolic sodium hydroxide was refluxed for 30 min. in an atmosphere of nitrogen. The reaction mixture was neutralized with dilute acetic acid and, after the addition of 35 ml. of water, extracted with one 30-ml. and three 15-ml. portions of chloroform. After washing the extract with water and drying over sodium sulfate, evaporation of the solvent left 53.4 mg. of an oily residue. Paper chromatography of this material indicated identity with the product obtained by method A (*vide supra*). The crude material was chromatographed over 2.0 g. of Florisil. Elution with chloroform–acetone, 49:1 (14 ml.), 19:1 (21 ml.), 9:1 (21 ml.), and 4:1 (14 ml.), yielded a total of 38.9 mg. of a product which on crystallization from acetone–hexane gave 21.1 mg. of prisms, m.p. 178–186°. There was no depression of the melting point upon admixture with an authentic sample of XVIII

(*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).