starting material IIIa) of Δ^{11}-pregnene-3,20-dione (V), m.p. 124–127° (total yield after two chromatograms 85.5%).

Δ^{11}-Pregnene-3,20-dione (V) *from pregnane-12α-ol-3,20-dione-12α-(2-naphthalenesulfonate)* (IIIb). The diketonaphthalenesulfonate IIIb used in this experiment was prepared as follows: A solution of 1.2 g. of 3,20-bisethylenedioxypregnane-12α-ol (II), m.p. 78–80°, and 1.56 g. of 2-naphthalenesulfonyl chloride in 6.3 cc. of pyridine was kept for 6 days at 50°. The product was extracted with ether and the organic solution was washed with iced dilute hydrochloric acid, iced sodium bicarbonate solution and with water and was dried over sodium sulfate. Evaporation of the solvent gave 1.63 g. of amorphous product, $\lambda_{max}^{C_2H_5OH}$ 227–228 mμ (log ε 4.8), representing crude *12α-hydroxy-3,20-bisethylenedioxypregnane-12α-(2-naphthalenesulfonate)* (IVb). In another run, 2 g. of diketal II gave 2.5 g. of IVb, $\lambda_{max}^{C_2H_5OH}$ 226 mμ (log ε 4.5). This product was chromatographed on 100 g. of silica gel. Benzene–ethyl acetate (84:16) eluted 1.5 g. of a clear oil, $\lambda_{max}^{C_2H_5OH}$ 227–228 mμ (log ε 4.9), which was dissolved in 141 cc. of absolute acetone and treated for 36 hr. with 197 mg. of *p*-toluenesulfonic acid. The usual working up gave an amorphous reaction product (1.25 g.) which was chromatographed on 50 g. of silica gel. Benzene–ethyl acetate fractions eluted 694 mg. of a clear, amorphous product, representing *pregnane-12α-ol-3,20-dione-12α-(2-naphthalenesulfonate)* (IIIb), $\lambda_{max}^{C_2H_5OH}$ 227–228 mμ (log ε 5.0), ν_{max}^{smear} 1700 and 1695 cm.$^{-1}$ (3,20-diketone).

A quantity of 655 mg. of this purified diketonaphthalenesulfonate IIIb (equivalent to 610 mg. of tosylate IIIa) was chromatographed on 20 g. of aluminum oxide (*p*H 8.5, activity II) under conditions identical to those employed for the reaction of tosylate IIIa with this reagent. Benzene-ether (4:1) eluted 300 mg. (76% yield) of *Δ^{11}-pregnene-3,20-dione* (V), m.p. 124–127°. The rest of the chromatogram fractions (355 mg.) was rechromatographed, as described in the case of the tosylate IIIa. Thus, another 50 mg. (13% from 655 mg. of naphthalenesulfonate IIIb) of Δ^{11}-pregnene-3,20-dione, m.p. 124–127°, was obtained (total yield after two chromatograms 89%).

Rapid chromatography of naphthalenesulfonate IVb *on acidic aluminum oxide.* A quantity of 500 mg. of 12α-hydroxy-3,20-bisethylenedioxypregnane-12α-(2-naphthalenesulfonate) (IVb) was dissolved in a small amount of benzene and absorbed on 15 g. of acidic aluminum oxide (*p*H 6, activity III). The product was rapidly chromatographed, the first elutions being made with petroleum ether (b.p. 30–60°)–benzene (1:4) mixtures. Thus, there was obtained 268 mg. (77%) of crude 11-unsaturated product which was subjected to the usual exchange reaction with acetone and *p*-toluenesulfonic acid. From the reaction mixture, 116 mg. of crystalline *Δ^{11}-pregnene-3,20-dione* (V) was obtained; m.p. 126–127.5°, not depressed upon admixture of an authentic sample; the mother liquors amounted to 84 mg.

Acknowledgment. We extend sincere thanks to Mr. R. W. White, of the Science Service Laboratory, London, Ontario, for the infrared analyses; to Dr. H. Rosatzin, of our laboratory, for the measurements of the ultraviolet spectra, and to Mrs. J. Capitaine for expert assistance in some of the experiments. We are greatly indebted to the Federal-Provincial Departments of National Health and Welfare, Ottawa and Toronto, to Ayerst, McKenna and Harrison Limited, Montreal, and to the Canadian Life Insurance Officers Association, for financial support. One of us (S.F.P.) wishes to express his gratitude to the Departments of Medical Research and Chemistry of this University for financial assistance. The constant encouragement of Dean J. B. Collip and the kind interest of Professor J. A. Gunton were highly appreciated.

LONDON, ONTARIO, CAN.

[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

Investigations on Steroids. XXXIV. 8,19-Epoxyprogesterone and 8,19-Epoxycortexone[1,2]

KLAUS OTTO[3] AND MAXIMILIAN EHRENSTEIN

Received December 30, 1960

Ethyl 8,19-epoxy-3β,5-dihydroxy-5β-etianate (III), which is obtainable as a minor reaction product in the selective dehydration of 3β,5,14,19-tetrahydroxy-5β,14β-etianic acid (I) leading mainly to ethyl 3β,5,19-trihydroxy-Δ^{14}-5β-etienate (II), has been transformed by conventional methods into 8,19-epoxyprogesterone (X) and 8,19-epoxycortexone (XVII). A conspicuous feature of the 8,19-epoxy series is the pronounced, abnormal levorotatory shift which occurs when the 5β-hydroxy-3-oxo compounds are converted into the Δ^4-3-ketones. As the analogous 19:8-lactone compounds behave normally in this respect, no explanation for this phenomenon can be given at present.

The degradation of strophanthidol to 3β,5,14,19-tetrahydroxy-5β, 14β-etianic acid (I) was described from this laboratory some time ago.[4] Treatment of I with 0.1 *N* ethanolic hydrogen chloride resulted mainly in simultaneous esterification and selective

(1) This investigation was supported by research grants (CY757-C5 and CY757-C6) from the National Cancer Institute of the National Institutes of Health, Public Health Service. A part of the K-Strophanthin used in this investigation was kindly donated by S. B. Penick & Co., New York, N. Y.

(2) The findings of this paper were presented on Sept. 5, 1958, at the 4th International Congress of Biochemistry in Vienna (*cf.* Maximilian Ehrenstein: Biochemistry of the Corticoids, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 [Symposium: Biochemistry of Steroids], Pergamon Press, p. 259 (1959).

(3) Dr. Klaus Otto was the recipient of a Fulbright Travel Grant and was on leave of absence from the Physiologisch-chemisches Institut der Universität Bonn, West Germany.

(4) M. Ehrenstein and A. R. Johnson, *J. Org. Chem.*, 11, 823 (1946).

dehydration affording a fair yield of ethyl 3β,5,19-trihydroxy-Δ^{14}-5β-etienate (II).[4-8] A number of interesting by-products were obtained in this reaction,[9] such as ethyl 8,19-epoxy-3β,5-dihydroxy-5β-etianate (III).[10] This compound is probably formed by way of a $\Delta^{8,14}$-unsaturated intermediate, *viz.* ethyl 3β,5,19-trihydroxy-$\Delta^{8,14}$-5β-etienate, which, because of the presence at carbon atom 10 of a hydroxymethyl group instead of a methyl group, is unstable and immediately rearranges to the 8,19-epoxide (III).[6] One may assume that this involves the *trans*-addition of the hydroxyl group to the double bond and, consequently, the hydrogen atom at carbon atom 14 is denoted as having the α-configuration.

In the presence of a carboxyl—rather than a hydroxymethyl—group at carbon atom 10, a 19:8-lactone bridge is formed in analogous fashion. The formation of such 19:8-lactones has been studied in detail and they may now be prepared as sole reaction products in good yield. As a consequence, it has been possible to synthesize a number of 19:8-lactone analogs of progesterone and cortexone.[11,12] Although the optimal conditions for the formation of the 8,19-epoxides have not yet been established,[13] an appreciable amount of III accumulated as a by-product of the dehydration reaction mentioned above. It was decided to convert it into the 8,19-epoxy analogs of progesterone (X) and cortexone (XVII).

III was converted by saponification into 8,19-epoxy-3β,5-dihydroxy-5β-etianic acid (IV) which has been described earlier.[4] IV was reconverted into III by treatment with diazoethane, indicating that no change of configuration had taken place at carbon atom 17. Acetylation of IV gave 8,19-epoxy-3β-acetoxy-5-hydroxy-5β-etianic acid (V) whose acid chloride was reacted with diazomethane to yield 8,19-epoxy-21-diazo-3β-acetoxy-5-hydroxy-5β-pregnan-20-one (VI). On treating VI with concentrated hydriodic acid,[7,11,14-17] 8,19-epoxy-3β-acetoxy-5-hydroxy-5β-pregnan-20-one (VII) resulted. Saponification of VII furnished 8,19-epoxy-3β,5-dihydroxy-5β-pregnan-20-one (VIII) which by oxidation with chromium trioxide gave 8,19-epoxy - 5 - hydroxy - 5β - pregnane - 3,20 - dione (IX). Treatment of IX with Girard's reagent T yielded 8,19-epoxyprogesterone [8,19-epoxy-Δ^4-pregnene-3,20-dione] (X).

For preparing 8,19-epoxycortexone (XVII), IV served as starting material. Oxidation with chromium trioxide gave 8,19-epoxy-5-hydroxy-3-oxo-5β-etianic acid (XIII) which by treatment with Girard's reagent T underwent dehydration, yielding 8,19-epoxy-3-oxo-Δ^4-etienic acid (XIV). By the action of diazoethane, XIV was converted into the corresponding ethyl ester, *viz.* ethyl 8,19-epoxy-3-oxo-Δ^4-etienate (XII) which was identical with a product prepared earlier[6] in analogous fashion from III by way of ethyl 8,19-epoxy-5-hydroxy-3-oxo-5β-etianate (XI). Treatment of the acid chloride of XIV with diazomethane gave 8,19-epoxy-21-diazo-Δ^4-pregnene-3,20-dione (XV). On heating XV with acetic acid, 8,19-epoxycortexone acetate [8,19 - epoxy-21 - acetoxy - Δ^4 - pregnene-3,20-dione] (XVI) resulted which by saponification was converted into 8,19-epoxycortexone [8,19-epoxy-21-hydroxy-Δ^4-pregnene-3,20-dione] (XVII).

In considering the optical rotations in the 8,19-epoxy series, one is struck by the unexpected, very pronounced, levorotatory shift which is associated with the conversion of a 5β-hydroxy-3-ketone into a Δ^4-3-ketone (IX → X, XI → XII, XIII → XIV). In each instance, this reaction was achieved under mild conditions, i.e. by the action of Girard's reagent T. Because of this observation it appeared desirable to study the rotatory dispersion curves[18] of some of these compounds which were determined through the courtesy of Professor Carl Djerassi at Wayne State University (now at Stanford University). The curve obtained with the 5β-hydroxy-3-ketone XIII (Fig. 1) is typical of a 5β-3-oxo steroid.[19,20] On the other hand, the Δ^4-3-ketones XIV (Fig. 2) and XII (Fig. 3) gave virtually identical, *positive* multiple Cotton effect curves. They are enantiomorphic in type with those of ordinary Δ^4-3-oxo-steroids[21] including the 19-hydroxy[20] and 19:8-lactone[11] series. This must be due to either (a) a change in configuration (which seems impossible since the saturated ketone XIII

(5) M. Ehrenstein, A. R. Johnson, P. C. Olmsted, V. I. Vivian, and M. A. Wagner, *J. Org. Chem.*, 15, 264 (1950).

(6) M. Ehrenstein and H. C. Neumann, *J. Org. Chem.*, 16, 335 (1951).

(7) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, 21, 774 (1956).

(8) M. Ehrenstein and K. Otto, *J. Org. Chem.*, 24, 2006 (1959).

(9) For a discussion of these by-products *cf.* ref. 7.

(10) This product was originally assigned the structure of ethyl 3β,5,19-trihydroxy-$\Delta^{8,14}$-5β-etienate; *cf.* refs. 4, 5.

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

(12) In agreement with the proposals of Fieser, the trivial name cortexone is preferred to 11-desoxycorticosterone. *Cf.* "Steroids" by Louis F. Fieser and Mary Fieser, Reinhold Publishing Corp., New York, 1959; v. pp. 602, 706.

(13) *Cf.* G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, 16, 1615 (1951); see p. 1615, footnote 2.

(14) R. D. H. Heard and P. Ziegler, *J. Am. Chem. Soc.*, 72, 4328 (1950).

(15) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, 19, 1758 (1954).

(16) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, 21, 783 (1956).

(17) G. W. Barber and M. Ehrenstein, Liebig's *Ann. Chem.*, 603, 89 (1957).

(18) For general literature *cf.* "Optical Rotatory Dispersion. Applications to Organic Chemistry" by Carl Djerassi, McGraw-Hill Book Co., Inc., New York, 1960.

(19) *Cf.*, *e.g.*, ref. 18, pp. 50, 75.

(20) E. J. Becker and M. Ehrenstein, *J. Org. Chem.*, 26, 510 (1961).

(21) *Cf.*, *e.g.*, ref. 18, pp. 17, 61, 65.

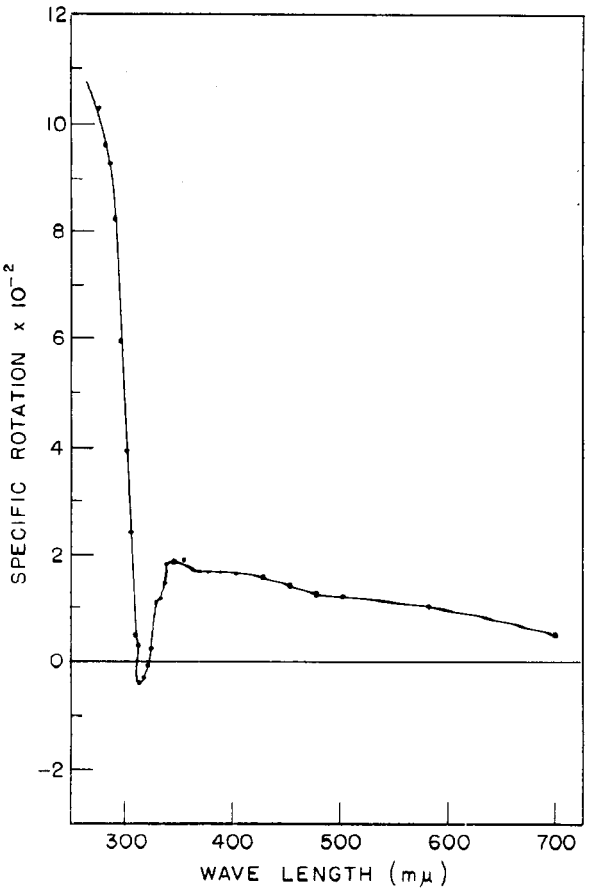


Fig. 1. Rotatory dispersion curve of 8,19-epoxy-5-hydroxy-3-oxo-5β-etianic acid (XIII) (m.p. 226–230° dec.) in dioxane (c = 0.056; t = 27°).

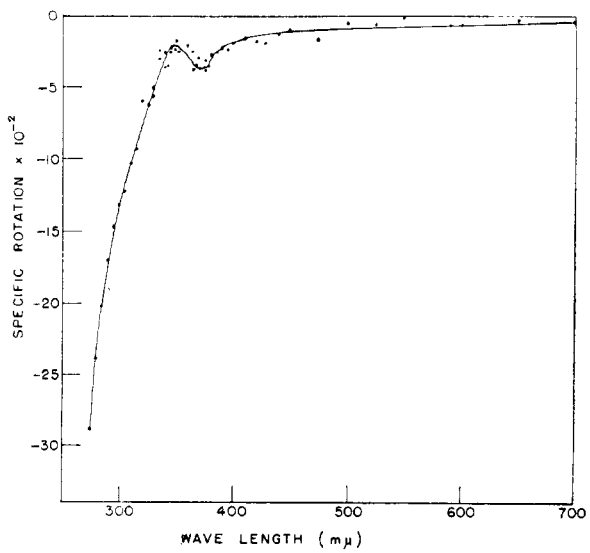


Fig. 2. Rotatory dispersion curve of 8,19-epoxy-3-oxo-Δ⁴-etienic acid (XIV) (m.p. 235–240° dec.) in dioxane (c = 0.044; t = 29.5°).

is normal) or (b) some obscure conformational effect.[22]

(22) The authors had the privilege of discussing these aspects with Dr. W. Klyne (Postgraduate Medical School of London) on his visit to their laboratory on January 15, 1960.

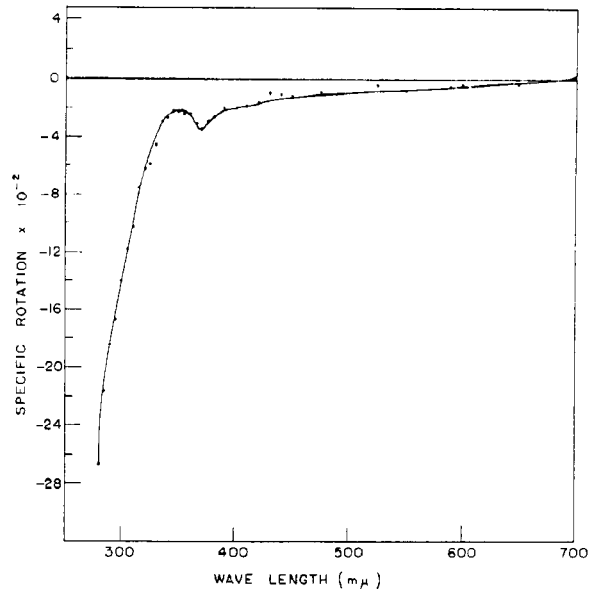
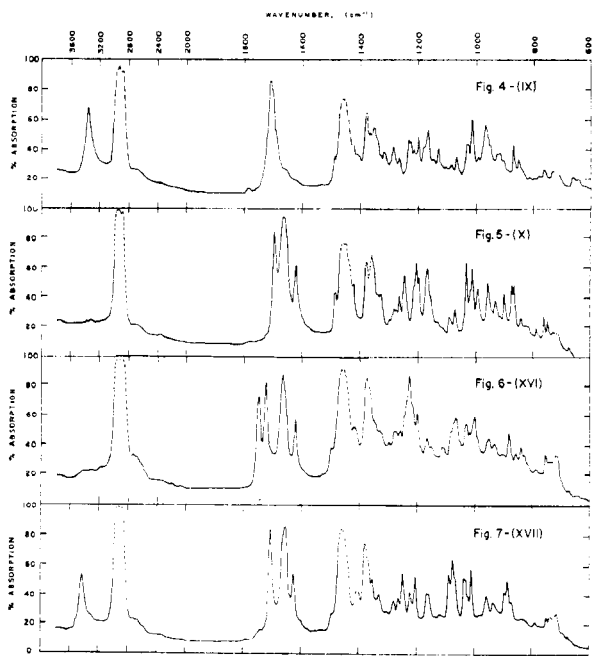


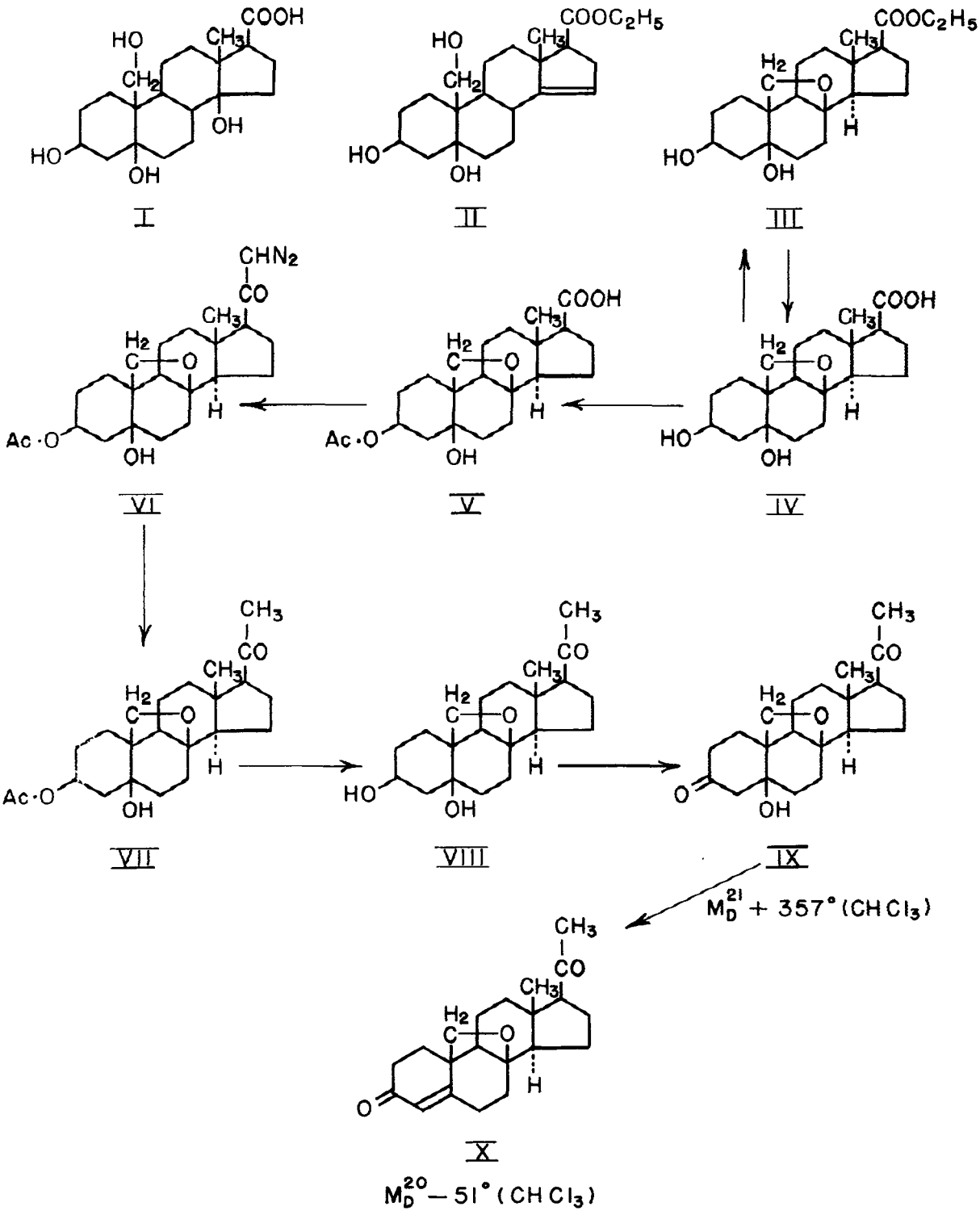
Fig. 3. Rotatory dispersion curve of ethyl 8,19-epoxy-3-oxo-Δ⁴-etienate (XII) (m.p. 125.5–127.5°) in dioxane (c = 0.070; t = 28°).



Infrared Spectra

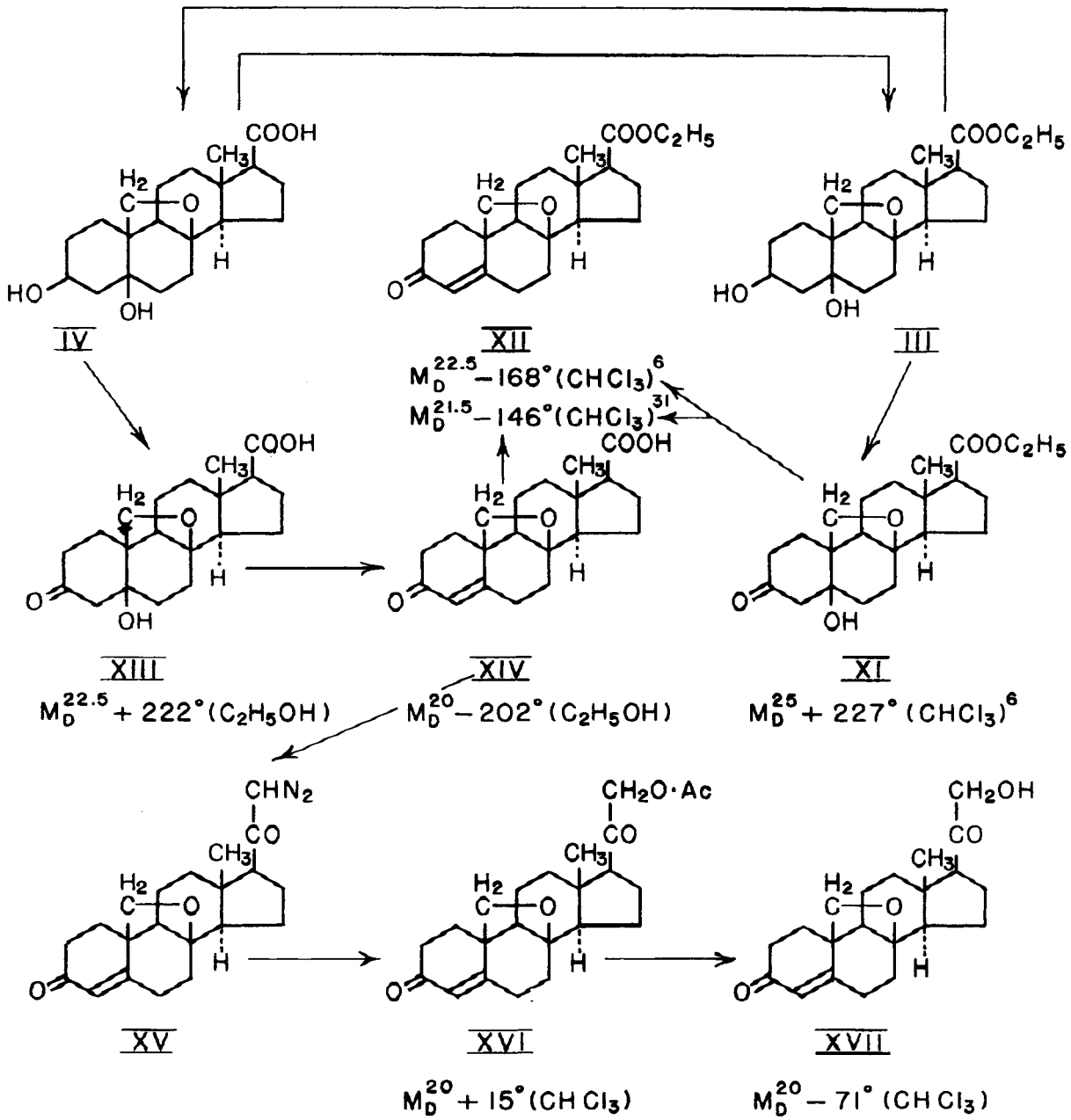
Fig. 4. 8,19-Epoxy-5-hydroxy-5β-pregnane-3,20-dione (IX). Fig. 5. 8,19-Epoxyprogesterone (X). Fig. 6. 8,19-Epoxycortexone acetate (XVI). Fig. 7. 8,19-Epoxycortexone (XVII)

In view of the abnormal rotatory dispersion curves of the Δ⁴-3-ketones of this series (Fig. 2 and 3), it was hoped that a study of the infrared absorption curves of these compounds would shed some light on this matter. The pertinent spectra were determined through the courtesy of Dr. R. Norman Jones in the Division of Pure Chemistry of the National Research Council of



Canada in Ottawa, Ont.[23] They were obtained with a Perkin-Elmer Model 21 spectrometer (sodium chloride prism). "The infrared spectra of compounds IX, X, XVI, and XVII have been measured as Nujol mulls (Fig. 4, 5, 6, and 7, respectively). In addition, IX has been measured in chloroform solution and X in carbon disulfide. The spectra all exhibit the typical hydroxyl and carbonyl bands expected for the proposed structures and there are no significant displacements of the C=O and C=C stretching bands of the Δ^4-3-ketone-group of X, XVI and XVII such as were observed

(23) The sentences in quotation marks are comments supplied by Dr. R. Norman Jones. The transposition of the original recordings for publication was done in the Eastern Regional Research Laboratory in Philadelphia through the courtesy of Dr. C. Roland Eddy.



for the analogous 19:8-lactones.[11,24] One would expect to see absorption associated with the C—O bonds of the epoxide group somewhere in the range 1200–900 cm.$^{-1}$ If the spectrum of X is compared with that of progesterone [Δ^4-pregnene-3,20-dione],[25] three bands of X at 1033, 1012, and 992 cm.$^{-1}$ stand out prominently, while bands near 1033 and 1012 cm.$^{-1}$ are also present in the spectra of IX, XVI, and XVII. From this one might infer that these characteristics are probably associated with the presence of the 8,19-epoxide ring. However, this identification is speculative and there are no significant differences between the spectrum of IX and those of the other three compounds which could be correlated with the abnormal change in the rotatory dispersion.

The details of the characteristic band positions are as follows[26]:

(a) Compound IX (Nujol; Fig. 4)
3350 cm.$^{-1}$ Bonded C-5 hydroxyl
(1710) 1710 cm.$^{-1}$ C-20 and C-3 superimposed carbonyl bands
(1423) 1425 cm.$^{-1}$ C-2 and C-4 methylene of 3-ketone
(1352) 1352 cm.$^{-1}$ C-21 methyl of 20-ketone
(1035–1029) 1033–1027 cm.$^{-1}$ (doublet). 8,19-epoxide?
(1017) 1015 cm.$^{-1}$ 8,19-epoxide?

(24) R. N. Jones and B. S. Gallagher, *J. Am. Chem. Soc.*, **81**, 5242 (1959).

(25) *Cf.* chart 119 in: Infrared Absorption Spectra of Steroids. An Atlas. By Konrad Dobriner, E. R. Katzenellenbogen, and R. Norman Jones, Interscience Publishers, Inc., New York, 1953.

(26) The figures in parentheses are corrected for scale error. They are correct to ±1 cm.$^{-1}$

The spectrum of IX for the chloroform solution shows no significant differences, except for anticipated solvent effects.

(b) Compound X (Nujol; Fig. 5). No hydroxyl absorption
(1697) 1697 cm.$^{-1}$ C-20 ketone
(1664) 1665 cm.$^{-1}$ Δ^4-3-ketone
(1620) 1622 cm.$^{-1}$ C=C of Δ^4-3-ketone
(1421) 1423 cm.$^{-1}$ C-2 methylene of Δ^4-3-ketone
(1360) 1360 cm.$^{-1}$ C-21 methyl of 20-ketone
(1033) 1033 cm.$^{-1}$ 8,19-epoxide?
(1014) 1012 cm.$^{-1}$ 8,19-epoxide?

The spectrum of X for the carbon disulfide solution shows no significant differences to which structural importance can be attached. The contour of the band at 1012 cm.$^{-1}$ is changed.

(c) Compound XVI (Nujol; Fig. 6). No hydroxyl absorption
(1747) 1747 cm.$^{-1}$ C-21 acetate of 21-acetoxy-20-ketone
(1723) 1723 cm.$^{-1}$ C-20 ketone of 21-acetoxy-20-ketone
(1664) 1665 cm.$^{-1}$ Δ^4-3-ketone
(1620) 1622 cm.$^{-1}$ C=C of Δ^4-3-ketone
(1422) 1423 cm.$^{-1}$ C-2 methylene of Δ^4-3-ketone
(1413) 1415 cm.$^{-1}$ C-21 methylene of 21-acetoxy-20-ketone
(1228) 1228 cm.$^{-1}$ C-21 acetate
(1032) 1030 cm.$^{-1}$ 8,19-epoxide?
(1007) 1004 cm.$^{-1}$ 8,19-epoxide?

(d) Compound XVII (Nujol; Fig. 7)
3420 cm.$^{-1}$ Bonded C-21 hydroxyl
(1708) 1708 cm.$^{-1}$ C-20 ketone
(1656) 1657 cm.$^{-1}$ Δ^4-3-ketone
(1625) 1627 cm.$^{-1}$ C=C of Δ^4-3-ketone
(1408) 1410 cm.$^{-1}$ C-21 methylene of 21-hydroxy-20-ketone
(1037–1032) 1035–1030 cm.$^{-1}$ (doublet). 8,19-epoxide?
(1012) 1010 cm.$^{-1}$ 8,19-epoxide?

The only unusual feature here is the absence of the small band at 1420–1425 cm.$^{-1}$ which one would expect for the C-2 methylene group."

In view of the decidedly abnormal rotatory dispersion curves, it is most remarkable that in the 8,19-epoxide spectra there are no abnormalities in the Δ^4-3-ketone absorption. Conversely, in the series of the 19:8-lactones[11] one finds abnormalities in the Δ^4-3-ketone absorption which do not show up in rotatory dispersion measurements. Further studies will be necessary to explain these discrepancies.

Physiological activity. 8,19-Epoxyprogesterone (X) was bioassayed for progestational activity by Dr. Roy Hertz, Chief of the Endocrinology Branch of the National Cancer Institute. The Clauberg test was entirely negative in each of two rabbits with a total dose of 1.0 mg. per animal. Since in this assay a maximal effect is obtained with 0.25 mg. of progesterone, the activity of X, if any, is probably less than one-tenth that of progesterone.

In assays carried out at the Worcester Foundation for Experimental Biology through the courtesy of Dr. Ralph I. Dorfman, 8,19-epoxycortexone (XVII), in doses of 6, 25 and 50 μg. had no effect on the excretion of sodium or potassium in salt (sodium chloride) loaded adrenalectomized rats. It appears, therefore, that XVII is devoid of mineralocorticoid activity.

EXPERIMENTAL

Melting points. The melting points were determined with the Fisher-Johns melting point apparatus and are uncorrected.

Absorption spectra. Ultraviolet spectra were determined in 95% ethanol with a Beckman Model DU spectrophotometer.

Analyses. 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°) according to Milner and Sherman.[27] The percentage loss of weight on drying is recorded; there was in no instance a gain of weight on exposure of the dried sample to the atmosphere.

Optical rotation. No correction for crystal solvent has been made. The sample was dissolved in chloroform to make 2 cc. of solution, and the rotation was determined in a 2-dm. semimicro tube.

Chromatography. The alumina (activity II) and silica gel used as adsorbents for chromatography have been described.[15]

8,19-Epoxy-3β,5-dihydroxy-5β-etianic acid (IV) *from ethyl 8,19-epoxy-3β,5-dihydroxy-5β-etianate* (III).[28] A solution of 300 mg. of III, m.p. 219–223°, in 35 cc. of *N* absolute ethanolic potassium hydroxide was refluxed for 8 hr. and subsequently left at room temperature for 13 hr. It was then concentrated *in vacuo* to a volume of approximately 5 cc. and, after the addition of 30 cc. of water, the neutral material was removed by extraction with two 20-cc. portions of ether. The aqueous phase was acidified by adding 6 cc. of 18% hydrochloric acid. The resulting white precipitate was filtered, washed thoroughly with water, and dried; yield 252 mg. (91%) of IV; m.p. above 300°. By extracting the filtrate with ethyl acetate, 18 mg. of additional material was obtained which gave 6 mg. (2%) of IV, m.p. 295–300°, after recrystallization from ethanol-water. Repeated recrystallization from ethanol-water (1:2) gave the analytical sample; m.p. 309–312° dec. $[\alpha]_D^{22.5}$ +64.4°; $M_D^{22.5}$ +226° (18.61 mg. in 2.0 cc. of ethanol, α + 1.20°).

Anal. Calcd. for $C_{20}H_{30}O_5$ (350.44): C, 68.52; H, 8.63. Found: C, 68.70; H, 8.60. Weight loss, 5.30.

Ethyl 8,19-epoxy-3β,5-dihydroxy-5β-etianate (III) *from 8,19-epoxy-3β,5-dihydroxy-5β-etianic acid* (IV). To 50 mg. of IV, m.p. 313–317°, in 5 cc. of ethanol was added dropwise a slight excess of an ethereal solution of diazoethane.[29] After the addition of 2 drops of glacial acetic acid, the solution was evaporated to dryness, yielding 61.6 mg. of a colorless crystalline residue. Recrystallization from acetone-hexane gave 51.1 mg. (95%) of III, m.p. 220–221°. The mixture m.p. with authentic III[6], m.p. 214–215°, was 219–221°.

8,19-Epoxy-3β-acetoxy-5-hydroxy-5β-etianic acid (V) *from 8,19-epoxy-3β,5-dihydroxy-5β-etianic acid* (IV). To 2.000 g. of IV, m.p. 300–305°, in 20 cc. of pyridine was added 20 cc. of redistilled acetic anhydride and the mixture was kept at room temperature for 14 hr. On adding 400 cc. of *N* hydrochloric acid, a crystalline precipitate separated which then was extracted with several portions of ethyl acetate. The organic phase was washed successively with two 25-cc. portions of 10% sulfuric acid, 75 cc. of *N* sodium bicarbonate, and five 25-cc. portions of water. After drying over sodium sulfate, the solution was evaporated to dryness, yielding 2.305 g. of a crystalline residue which was taken up in 10 cc. of glacial acetic acid. Water (5 cc.) was added and the solution was heated on the water bath for 40 min. This was followed by the addition of 20 cc. of water and repeated extractions with ethyl acetate. The organic phase was washed with three 15-cc. portions of *N* sodium bicarbonate and five 10-cc.

(27) R. T. Milner and M. S. Sherman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 427 (1936).

(28) *Cf.* also ref. 4.

(29) Prepared from ethylnitrosourea according to the Organic Syntheses directions for diazomethane. *Cf.* ref. 30.

portions of water. After drying over sodium sulfate, the solution was evaporated to dryness, yielding a crystalline residue which, by recrystallization from ethanol-water gave 1.888 g. (84%) of V, m.p. 244.5–246.5°. The analytical sample, m.p. 246–249°, was secured by recrystallization from acetone-hexane $[\alpha]_D^{22.5}$ +89.4°; $M_D^{22.5}$ +351° (29.82 mg., α + 2.67°).

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.48): C, 67.32; H, 8.22. Found: C, 67.23; H, 8.09. Weight loss, 1.27.

8,19-Epoxy-21-diazo-3β-acetoxy-5-hydroxy-5β-pregnan-20-one (VI) *from 8,19-epoxy-3β-acetoxy-5-hydroxy-5β-etianic acid.* (V). To a solution of 392.4 mg. (1 mmole) of V, m.p. 250–253° (recrystallized from methanol-water), in 12 cc. of ethanol was added 85 mg. (approx. 1 mmole) of sodium bicarbonate in 4 cc. of water. The mixture was brought to dryness *in vacuo* and the residue was completely freed from moisture by successively treating it with absolute ethanol and dry benzene and evaporating each time to dryness *in vacuo*. Finally, the dry residue was suspended in a mixture of 20 cc. of dry benzene and 16 drops of pyridine. After freezing the suspension in an ice-salt bath and adding 2.5 cc. of oxalyl chloride, the mixture was exposed to room temperature for 3 min. and subsequently evaporated to dryness *in vacuo*. The material was repeatedly treated with dry benzene followed by removal of the solvent *in vacuo*. The resulting residue was taken up in 20 cc. of dry benzene and the suspension was filtered through sintered glass under nitrogen pressure into ethereal diazomethane (ice-salt bath) which had been freshly prepared from 8 g. of nitrosomethylurea[30] and dried successively over potassium hydroxide and sodium. The residue of salts was washed with 10 cc. of dry benzene, and the reaction mixture was left at room temperature for 1 hr. It was then evaporated to dryness (room temperature), yielding 583 mg. of brownish material. This was chromatographed over 15 g. of alumina (12 × 130 mm.). Benzene-ether (range of ether content: 2.5–25%) eluted a total of 272.6 mg. (65.5%) of crude crystalline VI; m.p.'s 240–245°. Recrystallization from carbon tetrachloride gave pale yellow crystals which sintered at 150–155° and melted after resolidification at 250–254°. Since these crystals apparently contained carbon tetrachloride as crystal solvent, this product was rechromatographed and the resulting crude crystalline VI was recrystallized from benzene-hexane, yielding pale yellow crystals; m.p. sintering between 140 and 150°, followed by partial resolidification, final melting at 243–250°. Although the result of the C—H determination deviated considerably from the calculated figures (presence of crystal solvent?), this product proved satisfactory for the preparation of VII.

8,19-Epoxy-3β-acetoxy-5-hydroxy-5β-pregnan-20-one (VII) *from 8,19-epoxy-21-diazo-3β-acetoxy-5-hydroxy-5β-pregnan-20-one* (VI). A solution of 423 mg. of the diazo ketone VI, m.p. 240–253°, in 100 cc. of chloroform was shaken for 45 seconds with 8 cc. of 48% hydriodic acid (Baker's Analyzed Reagent). After adding 300 cc. of chloroform and 15 cc. of an almost saturated solution of aqueous potassium iodide, the organic layer was washed successively with two 5-cc. portions of the aqueous potassium iodide, 10 cc. of water, two 10-cc. portions of *N* sodium thiosulfate, and two 10-cc. portions of water. After drying over sodium sulfate, the chloroform was evaporated *in vacuo*, leaving 396 mg. of an almost colorless, almost completely crystalline residue. This was chromatographed over 14 g. of alumina (diam. of column: 12 mm.). Petroleum ether–benzene, range 1:2 to 1:14, benzene, and benzene-ether, range 49:1 to 23:2, eluted a total of 220.5 mg. (55.8%) of crystalline fractions representing VII. Recrystallization from acetone-hexane gave 203 mg. of crystals, m.p. 190–192°. The m.p. of the analytical sample was 193–194.5° $[\alpha]_D^{22.5}$ +126.3°; $M_D^{22.5}$ +493° (9.02 mg., α + 1.14°).

Anal. Calcd. for $C_{23}H_{34}O_6$ (390.50): C, 70.74; H, 8.78. Found: C, 70.56; H, 8.57. Residue, 0.85.

In a total of three experiments, the average yield of recrystallized VII was 59.2%.

8,19-Epoxy-3β,5-dihydroxy-5β-pregnan-20-one (VIII) *from 8,19-epoxy-3β-acetoxy-5-hydroxy-5β-pregnan-20-one* (VII). A solution of 176 mg. of VII, m.p. 190–192°, in 40 cc. of 1% methanolic potassium hydroxide was kept at room temperature for 16 hr. The reaction mixture, from which some crystals had separated, was then concentrated *in vacuo* with simultaneous addition of water until the methanol was completely removed. The precipitated crystalline material was extracted by treatment with four 50-cc. portions of ethyl acetate. The extract was washed to neutrality with water, dried over sodium sulfate and evaporated to dryness; yield of crude crystalline VIII: 150.4 mg. (96%). Recrystallization from acetone-hexane gave 135.6 mg. (86.4%) of crystals, m.p. 286–288°. The analytical sample, m.p. 287–289°, was derived from a repeat experiment $[\alpha]_D^{20}$ +111.5°; M_D^{20} +389° (13.05 mg. in 2.0 cc. of chloroform containing 2 drops of ethanol, α + 1.46°).

Anal. Calcd. for $C_{21}H_{32}O_4$ (348.47): C, 72.38; H, 9.26. Found: C, 72.23; H, 9.25. Residue, 0.25.

8,19-Epoxy-5-hydroxy-5β-pregnane-3,20-dione (IX) *from 8,19-epoxy-3β,5-dihydroxy-5β-pregnan-20-one* (VIII). To a total of 34.8 mg. of VIII (pooled material: 24.5 mg., m.p. 278–281°; 10.3 mg., m.p. 286–288°) in 2.5 cc. of glacial acetic acid was added in three equal portions over a period of 1 hr. a solution of 7.16 mg. of chromium trioxide in 1.3 cc. of 90% acetic acid. After standing overnight, the mixture was evaporated to dryness and the residue was treated with 5 cc. of water and 10 cc. of chloroform. The aqueous phase was again extracted with 10 cc. of chloroform, and the combined extracts were washed with 3 cc. of water, dried over sodium sulfate, and evaporated to dryness, leaving a somewhat brownish crystalline residue. This was treated with Norit and recrystallized from acetone-hexane, yielding 30.4 mg. (88%) of IX, m.p. 232–235°. Renewed recrystallization gave 22.6 mg. (65%) of the analytical sample, m.p. 242–245° $[\alpha]_D^{21}$ +103°; M_D^{21} +357° (13.27 mg. α ±1.37°).

Anal. Calcd. for $C_{21}H_{30}O_4$ (346.45): C, 72.80; H, 8.73. Found: C, 72.63; H, 8.69.

8,19-Epoxyprogesterone[8.19-epoxy-Δ⁴-pregnene-3,20-dione] (X) *from 8,19-epoxy-3β,5-dihydroxy-5β-pregnan-20-one* (VIII) *by way of 8,19-epoxy-5-hydroxy-5β-pregnane-3,20-dione* (IX). To 104.6 mg. of VIII, m.p. 278–281°, in 7.5 cc. of glacial acetic acid was added in four portions over a period of 1.5 hr. a solution of 22.02 mg. of chromium trioxide in 4 cc. of 90% acetic acid. After standing at room temperature for 3 hr., the mixture was worked up as described in the preceding experiment yielding a slightly brownish crystalline product. One recrystallization from acetone-hexane gave 93 mg. (89.5%) of crude IX, m.p. 225–227°. This was dissolved in 8 cc. of ethanol and, after the addition of 200 mg. of Girard's reagent T and 0.28 cc. of glacial acetic acid, the solution was refluxed for 1 hr. and was subsequently concentrated *in vacuo* at room temperature to approximately one half of its original volume. Following the addition of 200 mg. of sodium carbonate, ice, and some water, the mixture was extracted with ethyl acetate, yielding 5.8 mg. of "non-ketonic" material. The aqueous phase was then acidified to Congo Red with 50% sulfuric acid. Subsequent standing at room temperature for 2 hr. resulted in the separation of crystals. The ketonic material was isolated by repeatedly extracting with ethyl acetate, followed by washing the combined extracts with aqueous sodium bicarbonate and with water, drying over sodium sulfate and evaporating to dryness; yield: 78 mg. (88.7% from IX) of crystalline brownish material. This was chromatographed over 6 g. of alumina (diam. of column: 10 mm.). Petroleum ether–benzene, range 1:4 to 1:24, benzene, and benzene-ether, range 24:1 to 22:3, eluted a total of 69.4 mg. (78.8% from IX) of crystalline X. Recrystallization from acetone-hexane gave 62 mg. (70.5% from IX) of X, m.p. 163–165°. By re-

(30) A. H. Blatt, *Org. Syntheses*, Coll. Vol. II, 165, 461 (1943).

peated recrystallization the m.p. was raised to 164–167° $[\alpha]_D^{20}$ −15.4°; M_D^{20} −51° (22.20 mg., α −0.34°); λ_{max}^{alc} 243.5 mμ, ε 16,130.

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.43): C, 76.79; H, 8.59. Found: C, 77.02; H, 8.60. Weight loss, 0.73.

Benzene-ether (range 2:3 to 1:4), ether, and ether-methanol (24:1), eluted a total of 7.5 mg. of crystalline material, m.p. 285°, showing no ultraviolet absorption, probably representing unchanged VIII.

8,19-Epoxy-5-hydroxy-3-oxo-5β-etianic acid (XIII) *and 8,19-epoxy-3-oxo-Δ⁴-etienic acid* (XIV) *from 8,19-epoxy-3β,5-dihydroxy-5β-etianic acid* (IV). To 526 mg. of IV, m.p. 300–305°, in 40 cc. of redistilled glacial acetic acid was added in four portions over a period of 1.5 hr. a solution of 111 mg. of chromium trioxide in 20 cc. of 90% acetic acid. The mixture was kept at room temperature for 16 hr. and was then evaporated to dryness *in vacuo* (room temperature). The residue was taken up in 10 cc. of water and 100 cc. of ethyl acetate, and the aqueous phase was extracted twice (50 cc., 25 cc.) with ethyl acetate. The combined organic phases were washed with three 5-cc. portions of water, dried over sodium sulfate and evaporated to dryness, leaving 448 mg. of a slightly greenish crystalline residue. Recrystallization from acetone-hexane gave 409 mg. (78.2%) of 8,19-epoxy-5-hydroxy-3-oxo-5β-etianic acid (XIII), m.p. 227–229°. The analytical sample, m.p. 226–230° (brown discoloration beginning at 220°), was obtained by renewed recrystallization from acetone-hexane and from acetone-water $[\alpha]_D^{22.5}$ +63.8°; $M_D^{22.5}$ +222° (19.79 mg. in 2 cc. of ethanol, α +1.27°).

Anal. Calcd. for $C_{20}H_{28}O_5$ (348.42): C, 68.94; H, 8.10. Found: C, 69.05; H, 8.03. Residue, 0.15. Weight loss, 0.15.

To 350 mg. of the above XIII, m.p. 227–229°, in 16 cc. of absolute ethanol was added 700 mg. of Girard's reagent T and 1.0 cc. of glacial acetic acid. The solution was refluxed for 1 hr. and, after cooling to 0°, 800 mg. of sodium carbonate in 10 cc. of water was added. Extraction with ethyl acetate gave 13 mg. (4%) of amorphous "nonketonic" material. The aqueous phase was then made acid to Congo Red by the addition of 10% sulfuric acid, followed by repeated extraction with large quantities of ethyl acetate. The combined extracts were washed with water, dried over sodium sulfate, and evaporated to dryness, yielding 270 mg. of a crystalline, almost colorless residue. Recrystallization from acetone-hexane gave 258.7 mg. (78%) of 8,19-epoxy-3-oxo-Δ⁴-etienic acid (XIV), m.p. 235–238°. By repeated recrystallization the m.p. was raised to 243–245° dec. $[\alpha]_D^{20}$ −61.1°; M_D^{20} −202° (20.28 mg. in 2 cc. of ethanol, α −1.24°); λ_{max}^{alc} 243.5 mμ, ε 16,100.

Anal. Calcd. for $C_{20}H_{26}O_4$ (330.41): C, 72.70; H, 7.93. Found: C, 72.75; H, 7.91. Residue, 0.14.

Ethyl 8,19-epoxy-3-oxo-Δ⁴-etienate (XII): A sample (4.5 mg.) of XIV, m.p. 240–245° dec. was treated with diazoethane in the usual fashion (*cf.* the conversion of IV into III). Recrystallization of the crude ester from acetone-hexane gave 3.5 mg. of XII, m.p. 125.5–127.5°, lit.[31] m.p. 122–123°.

8,19-Epoxy-21-diazo-Δ⁴-pregnene-3,20-dione (XV) *from 8,19-epoxy-3-oxo-Δ⁴-etienic acid* (XIV). To 110.1 mg. of XIV (pooled material: 84.6 mg., m.p. 235–238°; 25.5 mg., m.p. 236–240°) in 6 cc. of ethanol was added a solution of 28 mg. of sodium bicarbonate in 3 cc. of water. The mixture was brought to dryness *in vacuo* (room temperature) and the residue was completely freed from moisture by treating it repeatedly with dry benzene and evaporating each time to dryness *in vacuo*. The residue was kept in a vacuum desiccator over phosphorus pentoxide overnight and was then suspended in 7.5 cc. of dry benzene. After the addition of 4 drops of pyridine and freezing the suspension in an ice-salt bath, 1 cc. of oxalyl chloride was added, and the mixture was then slightly agitated and exposed to room temperature for 5 min. After evaporating to dryness *in vacuo*, the material was repeatedly treated with dry benzene (3 × 5 cc.) followed by removal of the solvent *in vacuo*. The residue was taken up in 7 cc. of dry benzene and the suspension was filtered through sintered glass under nitrogen pressure into ethereal diazomethane (prepared from 2 g. of freshly recrystallized nitrosomethylurea[30]; dried over sodium hydroxide and sodium) at 0°. The residue of salts was washed with 3 cc. of dry benzene and, after leaving the reaction mixture at 0° for 1 hr., it was evaporated to dryness (room temperature), yielding 138 mg. of yellowish material. This was dissolved in 40 cc. of benzene and chromatographed over 5 g. of alumina (diam. of column; 10 mm.). Benzene-ether, range 39:1 to 9:1 eluted a total of 49.8 mg. (42.2%) of crude crystalline XV, m.p.'s between 156 and 160°. By repeated recrystallization from acetone-hexane the m.p. was raised to 160–161°; λ_{max}^{alc} 246.5 mμ, ε 23,660.

Anal. Calcd. for $C_{21}H_{26}N_2O_3$ (354.43): N, 7.90. Found: N, 7.42.

Benzene-ether, range 7:3 to 1:3, and ether eluted a total of 14.5 mg. of additional crystalline material which was not investigated. Possibly this represents the amide of the starting material XIV.[32]

8,19-Epoxycortexone acetate [*8,19-epoxy-21-acetoxy-Δ⁴-pregnene-3,20-dione*] (XVI) *from 8,19-epoxy-21-diazo-Δ⁴-pregnene-3,20-dione* (XV). A solution of 93 mg. of XV, m.p. 154–156°, in 8 cc. of glacial acetic acid was heated on the steam bath for 30 min. and was then evaporated to dryness *in vacuo* (room temperature). The residue was taken up in ethanol and the solution was again evaporated to dryness, leaving 104 mg. of yellowish, partly crystalline material. This was chromatographed over 10 g. of alumina (diam. of column, 13 mm.). Elution with petroleum ether-benzene, 1:19, benzene, and benzene-ether, range 39:1 to 17:3, gave a total of 75.1 mg. (74%) of crystalline XVI. Recrystallization from acetone-hexane yielded 73.1 mg. (72%) of pure XVI; m.p. 188–192°. The m.p. of the analytical sample was 191.5–192.5°. $[\alpha]_D^{20}$ +4.0°; M_D^{20} +15° (15.26 mg., α +0.06°); λ_{max}^{alc} 243 mμ, ε 16,480.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.83. Found: C, 71.14; H, 7.60.

8,19-Epoxycortexone [*8,19-epoxy-21-hydroxy-Δ⁴-pregnene-3,20-dione*] (XVII) *from 8,19-epoxycortexone acetate* [*8,19-epoxy-21-acetoxy-Δ⁴-pregnene-3,20-dione*] (XVI). To 73.1 mg. of XVI, m.p 188–192°, in 2 cc. of methylene chloride was added 5 cc. of 0.05*M* potassium carbonate in 75% methanol.[33] After 5 min., 1 cc. of water and a piece of Dry Ice were added, and the mixture was concentrated *in vacuo* until crystals began to separate. After again adding 1 cc. of water and a piece of Dry Ice, the concentration *in vacuo* was continued and, finally, 10 cc. of water was added to the practically methanol-free suspension. The crystals were filtered, washed and dried, yielding 16 mg. (24.6%) of XVII, m.p. 163–173° (slightly pink shiny platelets). The color was removed by treatment with Norit in a solution of methylene chloride. Repeated recrystallization from acetone-hexane gave the analytical sample (C, H determination), m.p. 177–180°. The aqueous filtrate was extracted with five 10-cc. portions of ethyl acetate. From the combined extracts 43 mg. of additional crystalline, though brownish, material was obtained. The latter was chromatographed over 4 g. of silica gel. Elution with benzene-ether, range 3:2 to 1:3, and ether gave 34.6 mg. (53.1%) of slightly orange-colored crystalline XVII.[34] This was treated with Norit in a solution of methyl-

(31) *Cf.* ref. 6, p. 347. On recently repeating the preparation of ethyl 8,19-epoxy-3-oxo-Δ⁴-etienate (XII) according to this previous procedure, the following data were obtained: m.p. 125–129° $[\alpha]_D^{21.5}$ −40.8°; $M_D^{21.5}$ −146°. (Reported previously: m.p. 122–123° $[\alpha]_D^{22.5}$ −46.8°; $M_D^{22.5}$ −168°.)

(32) For a similar observation *cf.* ref. 15.

(33) For method, *cf.* J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, 40, 2291, v.p. 2319 (1957).

(34) Consequently, the total yield of XVII was 77.7%.

ene chloride and was then recrystallized from acetone-hexane, yielding 25.0 mg. of colorless platelets, m.p. 176–179°. This sample was used for the determination of the optical rotation and of the ultraviolet absorption spectrum $[\alpha]_D^{20}$ −20.5°; M_D^{20} −71° (12.82 mg., α −0.26°); λ_{max}^{alc} 243 mμ, ε 15,970.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.43): C, 73.23; H, 8.19. Found: C, 72.80; H, 8.44.

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Steroids and Related Natural Products. VI. The Structure of α-Apoallobetulin[1,2]

GEORGE R. PETTIT, BRIAN GREEN, AND WILLIAM J. BOWYER

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The allobetulin dehydration product, α-apoallobetulin, has been shown to be represented by structure IV. Initial support for this assignment was obtained by oxidizing α-apoallobetulin to a diketone (VII). Direct oxidation of α-apoallobetulin to diketone VII was unexpectedly achieved employing a modified osmium tetroxide-pyridine procedure. The same oxidation product was prepared by ozonization of α-apoallobetulin and by lead tetraacetate oxidation of its glycol derivative (VI). Substantial evidence favoring the proposed endocyclic olefin (IV) formulation was provided by the facile isomerization of δ-apoallobetulin (III) to α-apoallobetulin. The ketone (VIII) obtained following ozonization of δ-apoallobetulin was assigned an A/B *cis*-configuration on the basis of optical rotatory dispersion measurements.

Conversion of betulin (Ia) to the formate of an isomeric substance designated allobetulin (IIa), in the presence of hot 90–95% formic acid, was reported by Schulze and Pieroh in 1922.[3] Allobetulin was subsequently found to readily lose one molecular equivalent of water, upon treatment with phosphorus pentachloride or pentoxide in chloroform solution, giving rise to a new compound termed apo-allobetulin.[3] Several years later Dischendorfer and Juvan noted that apo-allobetulin could also be prepared by heating betulin with palladium-charcoal or with fuller's earth suspended in refluxing xylene.[4]

A concise structural and mechanistic interpretation of the interesting transformation of betulin to allobetulin was unavailable until 1951.[5] More recently, Simonsen and Ross[6] suggested that apo-allobetulin, now known as α-apoallobetulin,[7] might be represented by formulations III or IV. As α-apoallobetulin, if indeed represented by structure III, was needed as starting material for another investigation, it became necessary to determine exactly the position of unsaturation.

The exocyclic olefin III appeared to most accurately represent α-apoallobetulin, as it is well known that reagents such as phosphorus pentachloride favor this type of Wagner-Meerwein rearrangement product.[8] However, Ruzicka and colleagues were able to prove, for example, that fuller's earth dehydration of 18-isooleanolic acid lactone (V) in refluxing xylene solution yields the endocyclic olefin analogous to IV, while dehydration in petroleum ether solution with phosphorus pentachloride afforded the exocyclic isomer.[9]

The most direct procedure for establishing or eliminating structure III for α-apoallobetulin appeared to simply involve studying the reaction of ozone with this substance. Consequently, α-apoallobetulin, prepared by fuller's earth dehydration of betulin essentially as described by Dischendorfer,[4] was treated in chloroform solution at −30° with excess ozone. Following zinc dust-acetic acid reduction of the ozonides, two discrete products were isolated. The first substance, obtained by fractional recrystallization of the crude reduction product, was an oxidation product melting at 240–242°.[10] Further recrystallization of the residual

(1) Consult G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, 26, 1685 (1961) for the preceding contribution.

(2) This investigation was supported by PHS Research Grants CY-4074(C1) and CY-4074(C1S1) from the National Cancer Institute, Public Health Service.

(3) H. Schulze and K. Pieroh, *Ber.*, 55, 2332 (1922).

(4) O. Dischendorfer and H. Juvan, *Monatsh.*, 56, 272 (1930).

(5) G. S. Davy, T. G. Halsall, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2702 (1951).

(6) J. Simonsen and W. C. J. Ross, *The Terpenes*, Vol. IV, Cambridge University Press, New York, 1957, p. 305.

(7) L. Ruzicka, H. Brungger, and E. L. Gustus, *Helv. Chim. Acta*, 15, 634 (1932).

(8) For example, consult: (a) L. Ruzicka, M. Montavon, and O. Jeger, *Helv. Chim. Acta*, 31, 819 (1948); (b) D. H. R. Barton, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 3147 (1951); (c) W. Voser, D. E. White, H. Heusser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 35, 830 (1952); (d) D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 2639 (1955); and (e) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, 10, 44 (1956).

(9) L. Ruzicka, A. Rudowski, J. Norymberski, and O. Jeger, *Helv. Chim. Acta*, 29, 210 (1946). An interesting application of the fuller's earth dehydration reaction has recently been described by K. Schaffner, L. Caglioti, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 41, 152 (1958).

(10) A stable ozonide structure was excluded when this product (m.p. 240–242°) proved to be unaffected by hydrogenation (in ethyl acetate solution during 12 hr.) over 5% palladium-barium carbonate. *Cf.* L. Ruzicka, E. Volli, and O. Jeger, *Helv. Chim. Acta*, 28, 1628 (1945). The structure of this substance was not pursued further.