Reaction of Triphenylphosphine Hydrobromide with Crude Dioxane.—A suspension of 10.0 g. (0.0292 mole) of triphenylphosphine hydrobromide in 250 ml. of crude dioxane was stirred at room temperature for 2 hr. The unchanged triphenylphosphine hydrobromide (6.1 g.) was removed by filtration and the filtrate was evaporated to dryness to give 5.9 g. of viscous liquid. The viscous liquid, upon stirring with water, gave 3.01 g. (96% yield based on the used triphenylphosphine hydrobromide) of triphenylphosphine oxide, m.p. 155–56°.

Reaction of N,N-Diethyl 3-Methylacrylamide Dibromide (XI) with Triphenylphosphine.—A solution containing 30.1 g. (0.10 mole) of XI and 52.4 g. (0.20 mole) of triphenylphosphine in 470 ml. of anhydrous acetone was stirred at room temperature for 12 hr. The solid material, 6.1 g., was collected by filtration. The filtrate was evaporated under reduced pressure to about 250 ml. and additional 11.5 g. of solid was collected. The combined solid after recrystallization from chloroform–ether gave an unidentified colorless solid, m.p. 149–150°, with the following analysis: C, 66.30; H, 5.19; P, 9.65; Br, 11.95. This solid, upon treatment with water, gave triphenylphosphine oxide. The acetone filtrate was evaporated to dryness and the residue recrystallized from acetone–ether. There was obtained 27.6 g. of a colorless solid, m.p. 97–98°. The elemental analysis indicated the compound to be the monohydrate of XII. The yield was 47%.

Anal. Calcd. for $C_{26}H_{32}Br_2NO_2P \cdot H_2O$: C, 53.70; H, 5.50; N, 2.41; Br, 27.50; P, 5.34; mol. wt., 581. Found: C, 53.58; H, 5.45; N, 2.42; Br, 27.05; P, 5.29; mol. wt., 606.

The Preparation of 14β,21-Epoxy Steroids

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The 14β,21-epoxy steroidal moiety has been synthesized by a basic displacement cyclization reaction of a C-20-methoxyimino derivative of a 14β-hydroxy-21-methanesulfonyloxy-20-ketopregnane. Mineral acid hydrolysis removed the C-20 protective grouping to provide the desired 14β,21-epoxy-20-ketopregnane. 14β,21-Epoxy-14β-pregn-4-ene-3,20-dione has been prepared by a multi-stage synthesis from digitoxigenin acetate.

This laboratory[1] has been concerned for some time in the preparation of epoxy steroids, more particularly in the ether formed by attachment of the C-21 hydroxymethyl grouping to the various positions on the steroid D ring. In this connection we became interested in the suggestion of Tschesche and Buschauer[2] that a 14β,21-epoxy moiety constituted a part of the structure of diginigenin.[3] This paper describes a synthetic pathway to the 14β,21-epoxy-20-ketone grouping.

An appropriate starting material for this investigation was selected from the cardiac aglycones which contain a 14β-hydroxyl group. Accordingly, digitoxigenin acetate was ozonized by the procedure of Oliveto and coworkers[4] to give the desired 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I). The latter was evidently less contaminated with 17-iso compound than the preparation described by Meyer and Reichstein.[6]

Since cyclizing reactions that might be utilized to prepare a 14β,21-epoxide from I would involve basic conditions, it was considered desirable to protect the base sensitive ketol grouping in I by preparing a C-20 carbonyl derivative which would withstand these conditions. The first consideration was given to the ethylene ketal grouping because of its well known base stability properties. Since it is also evident that the 14β-hydroxyl group is quite acid sensitive, various methods of ketalization were attempted. While it was possible to produce a 20-ketal by any of several methods, it was not possible to maintain the 14β-hydroxyl function. In every case dehydration occurred to give 3β-acetoxy-20-ethylenedioxypregn-14-en-21-ol (II). That the unsaturation was at position 14:15 and not the alternatively possible 8:14 position was determined by ultraviolet absorption measurements in the 190–225-$m\mu$ region and also by a proton magnetic resonance spectrum of II. As pointed out by Bladon, Henbest, and Wood[7a] and later expanded by Ellington and Meakins[7b] it is possible in the ultraviolet spectrum to distinguish by the shape of the curves[8] between a doubly exocyclic tetrasubstituted ethylenic linkage as in a $\Delta^{8(14)}$-compound and an exocyclic trisubstituted double bond as in a Δ^{14}-compound. The n.m.r. spectrum of II clearly showed the vinyl proton at C-15, thereby eliminating any consideration of a $\Delta^{8(14)}$-compound. The ketal II was hydrolyzed in acid to afford 3β-acetoxy-21-hydroxypregn-14-en-20-one (III), which also revealed a vinyl proton in the n.m.r. spectrum.

The 20-carbonyl group of I was protected successfully by reaction with methoxyamine hydrochloride in the presence of potassium acetate without concomitant destruction of the 14β-hydroxyl function. The resultant methoxyimino[9] derivative IVa was an uncrystallizable glass which, however, could be smoothly converted into the crystalline 3β-acetoxy-21-methanesulfonyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb). The desired displacement cyclization and simultaneous deacetylation was then readily achieved by treatment of the mesylate IVb with potassium hydroxide in methanol. The methoxyimino group of the cyclic product Va was

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[1] W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1955); W. S. Allen and S. Bernstein, *ibid.*, **78**, 3223 (1956).

[2] R. Tschesche and G. Buschauer, *Ann.*, **603**, 59 (1957).

[3] C. W. Schoppee, R. Lack, and A. V. Robertson, *J. Chem. Soc.*, 3610 (1962), have disclosed that the structure of diginigenin is 12α,20α-epoxy-3β-hydroxy-14β,17α-pregn-5-ene-11,15-dione.

[4] E. P. Oliveto, L. Weber, C. G. Finckenor, M. M. Pechet, and E. B. Herschberg, *J. Am. Chem. Soc.*, **81**, 2831 (1959), have described an ozonolysis procedure which eliminates the bicarbonate[5] treatment of the intermediate 21-glyoxylic ester.

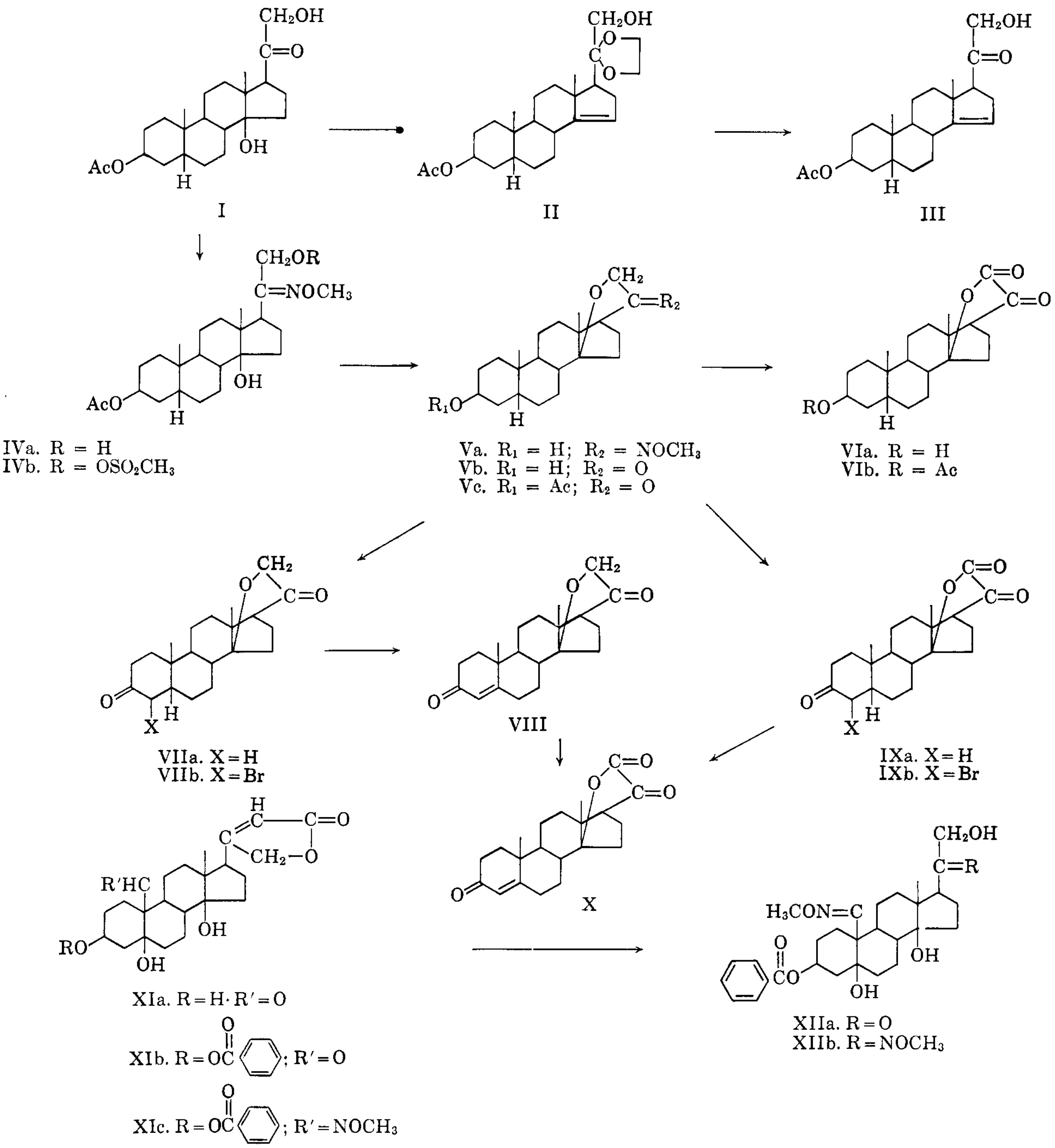
[5] C. P. Balant and M. Ehrenstein, *J. Org. Chem.*, **17**, 1576 (1952), have shown that bicarbonate hydrolysis invites considerable isomerization at C-17 in this type of compound.

[6] K. Meyer and T. Reichstein, *Helv. Chim. Acta*, **30**, 1508 (1947).

[7] (a) P. Bladon, H. B. Henbest, and G. W. Wood, *J. Chem. Soc.*, 2739 (1952); (b) P. S. Ellington and G. D. Meakins, *ibid.*, 697 (1960).

[8] Subsequent papers considering techniques to determine the exact maximum of an isolated double bond in the ultraviolet absorption spectrum have led to considerable discussion. *Cf.*, D. W. Turner, *ibid.*, 30 (1959); K. Stich, G. Rotzler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 1480 (1959); Ref. 7b; J. H. Chapman and A. C. Parker, *J. Chem. Soc.*, 2075 (1961); T. H. Applewhite and R. A. Micheli, *J. Org. Chem.*, **27**, 345 (1962); R. Bührer and T. Reichstein, *Helv. Chim. Acta*, **45**, 389 (1962).

[9] The bismethoxyimino derivatives of certain corticoids have been described[10a] and a patent application[10b] describing the use of this protective grouping has been printed.



I

II

III

IVa. R = H
IVb. R = OSO_2CH_3

Va. R_1 = H; R_2 = $NOCH_3$
Vb. R_1 = H; R_2 = O
Vc. R_1 = Ac; R_2 = O

VIa. R = H
VIb. R = Ac

VIIa. X = H
VIIb. X = Br

VIII

IXa. X = H
IXb. X = Br

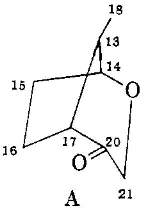
X

XIa. R = H· R' = O
XIb. R = $\overset{O}{\overset{\|}{OC}}$; R' = O
XIc. R = $\overset{O}{\overset{\|}{OC}}$; R' = $NOCH_3$

XIIa. R = O
XIIb. R = $NOCH_3$

cleaved by mineral acid hydrolysis[10] to yield the desired 3β-hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb).

The new ring system locked together with the steroidal D ring forms a 2-oxabicyclo[3.2.1]octane system A



A

(steroid numbering shown) which has been known for many years.[11] In this particular case Dreiding models suggest strongly that the six-membered oxygen containing ring preferably would exist in a chair form since in a boat conformation there would be extreme steric interaction of one hydrogen of the C-21 methylene grouping and the C-18 angular methyl group. It is not apparent why the infrared absorption spectrum of Vb reveals a peak as high as 1730 cm.$^{-1}$ for the C-20 carbonyl function. No examples of a system such as A containing infrared data could be found. However, the infrared absorption peak of bicyclo[3.2.1]octan-2-one at 1717[12a] cm.$^{-1}$ and that of 5,8,8-trimethylbicyclo-[3.2.1]octan-2-one (homoepicamphor)[12b] at 1716 cm.$^{-1}$, the models of which indicate no significant strain differences from an oxygen containing system such as A, show that the bicyclo system as such does not necessarily account for the high absorption band of Vb.

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(10) (a) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958); (b) A. G. Long and S. Eardley, Union of South Africa Patent Application 595,054 (December 3, 1959).

(11) C. Harries and H. Neresheimer, *Ber.*, **39**, 2846 (1906).

(12) (a) R. Zbinden and H. K. Hall. Jr., *J. Am. Chem. Soc.*, **82**, 1215 (1960); (b) H. Fabre, B. Marinier, and J-C. Richer, *Can. J. Chem.*, **34**, 1329 (1956).

The n.m.r. spectrum of Vb and that of its 3-acetate derivative Vc was instructive since the signal due to the C-21-methylene grouping was revealed to be that of an AB system in which the two hydrogen are nonequivalent to about the same degree as in the 21-acetoxy-20-one moiety mentioned by Shoolery and Rogers.[13] For the particular case of Vb the J_{AB} is about 17 c.p.s. and the calculated chemical shifts for the two hydrogens are at 3.96 and 4.15 p.p.m. Also of interest is the fact that the n.m.r. spectra of all the 14β,21-epoxides revealed only one signal for the combined C-18 and C-19 methyl hydrogens. These were at 0.97, 1.00, and 1.01 p.p.m., respectively, for compounds Va, Vb, and Vc.

In order to provide further proof for the 14β,21-epoxy-structure, the acetate derivative Vc was oxidized with chromic acid in acetic acid to give 3β-acetoxy-14β-hydroxy-20-keto-14β-pregnan-21-oic acid 21,14-lactone (VIb). The latter compound has been prepared by other investigators[14] utilizing different pathways. Also within our own laboratory the lactone VIb has been obtained in poor yield by adaptation of a method[15] used previously on another cardenolide. Direct comparison of our preparations with an authentic sample[14a,16] revealed the absolute identity of these preparations.

Finally it was considered advantageous to prepare the Δ^4-3-one analogs of the 14β,21-epoxides. Accordingly, the 3β-ol Vb was treated with chromic acid–sulfuric acid–acetone[17] to afford 14β,21-epoxy-14β-pregnane-3,20-dione (VIIa). The latter compound was brominated at −40°[18] in acetic acid to give presumably the thermodynamically stable 4β-bromo-3,20-dione VIIb which in turn was dehydrohalogenated with lithium chloride in dimethylformamide to 14β,21-epoxy-14β-pregn-4-ene-3,20-dione (VIII). Oxidation of the 14β,-21-epoxy-3β-ol Vb with chromic acid-acetic acid yielded 14β-hydroxy-3,20-diketo-14β-pregnan-21-oic acid 21,14-lactone (IXa). Treatment of IXa with bromine then gave the 4β-bromo lactone IXb which was dehydrohalogenated to 14β-hydroxy-3,20-diketo-14β-pregn-4-en-21-oic acid 21,14-lactone (X). The latter compound was also prepared by chromic acid–acetic acid oxidation of the Δ^4-3-one 14β,21-epoxide VIII. An interesting observation was made with respect to the ultraviolet absorption spectrum of the diketo lactone X. No obvious reason can be seen from a study of models for the hypsochromic effect which occurs when the normal behaving 14β,21-epoxy compound VIII (λ_{max} 240 mμ, ϵ 15,600) was oxidized to X with an ultraviolet absorption maximum of 232–234 mμ and a molecular extinction coefficient of 13,000–14,000.

Finally, in an investigation designed to study the usefulness of strophanthidin (XIa) as a starting material for a 14β,21-epoxide structure while maintaining a C-19 aldehyde function in the molecule, strophanthidin benzoate (XIb)[19] was treated with methoxyamine hydrochloride and potassium acetate to form the methoxime XIc. This compound was ozonized in the usual fashion to afford 3β-benzoyloxy-5β,14β,21-trihydroxy-19-methoxyimino-14β-pregnan-20-one (XIIa). The latter compound was further treated with methoxyhydrochloride and potassium acetate to give the bismethoxyimino derivative XIIb. Unfortunately, XIIb dib not react suitably with either methanesulfonyl chloride or *p*-toluenesulfonyl chloride in pyridine so that further reactions to form a 14β,21-epoxide as indicated above could not be attempted. Furthermore, the usual acid hydrolysis conditions would not remove the methoxyimino grouping in XIIa, casting additional doubt upon the practicability of this pathway for the desired product.

Experimental[20]

3β-Acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I).—A solution of digitoxigenin acetate (5.0 g.) in pyridine (480 ml.) and ethyl acetate (480 ml.) was cooled to −60°. The solution was treated with a stream of ozone at a rate of 0.3 mmole per minute for 70 min. Excess ozone was removed from the reaction mixture with a stream of oxygen until the blue solution turned colorless. To the stirred solution was added acetic acid (48 ml.) and zinc dust (9.7 g.) and the reaction temperature was allowed to come to room temperature. The mixture was then heated to 60° and filtered through diatomaceous earth. The filtrate was evaporated under reduced pressure, the residue was dissolved in toluene, and the evaporation was repeated. The residual dark brown sirup was dissolved in a mixture of ethyl acetate (250 ml.) and water (100 ml.). The organic layer was separated, dried with magnesium sulfate, and evaporated under reduced pressure leaving a dark brown gum. The crude gum was dissolved in a minimum amount of methylene chloride and placed on a Florisil[21] (200 g.) column. The column was washed with methylene chloride (750 ml.) and then with 2% acetone–methylene chloride (750 ml.). The polarity of the solvent mixture was increased to 10% acetone–methylene chloride and 500-ml. cuts of eluate were taken and evaporated under reduced pressure. Only those cuts which on evaporation produced a solid were combined affording 2.3 g. of solid. Crystallization of this material from acetone–petroleum ether yielded 1.85 g. of I as white crystals, m.p. 159–163°[22]; ν_{max} 3400, 1715, 1720, 1250, 1230, cm.$^{-1}$; $[\alpha]^{25}\text{D}$ +52.5° (chloroform).

Anal. Calcd. for $C_{23}H_{36}O_5$ (392.52): C, 70.37; H, 9.24. Found: C, 70.40; H, 9.33.

3β-Acetoxy-20-ethylenedioxypregn-14-en-21-ol (II).—A mixture of 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I, 200 mg.), benzene (30 ml.), and ethylene glycol (2 ml.) was refluxed with *p*-toluenesulfonic acid monohydrate (30 mg.) (Dean–Stark water separator) for 4.5 hr. The reaction was cooled and water and sodium bicarbonate solution was added. The benzene solution was separated, washed with water, and dried with magnesium sulfate. Evaporation of the benzene produced a white solid which was crystallized from acetone–water to yield 130 mg. of II as white crystals, m.p. 122–127°. Several recrystallizations from the same solvent pair afforded 55 mg. of white needles, m.p. 124–125°, but satisfactory combustion values were not obtained; ν_{max} 3480, 1730, 1715, 1258, 1247 cm.$^{-1}$.

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(13) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(14) (a) F. Hunziker and T. Reichstein, *Helv. Chim. Acta*, **28**, 1472 (1945); (d) K. Meyer, *ibid.*, **30**, 1976 (1947).

(15) G. W. Barber and M. Ehrenstein, *J. Org. Chem.*, **26**, 1230 (1961); Our experiments involved permanganate oxidation of digitoxigenin to the free 3β-ol VIa followed by acetylation to VIb.

(16) We thank Professor T. Reichstein for the authentic sample of VIb.

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

(18) J. T. Day, U. S. Patent 2,907,776 (October 6, 1959).

(19) A. Windaus and L. Hermanns, *Ber.*, **48**, 979 (1915).

(20) All melting points are uncorrected. The infrared spectra were determined in a potassium bromide disk. The n.m.r. spectrum of compound II was done on a Varian Associates HR60 spectrometer. All other n.m.r. spectra were done on a Varian Associates A60 spectrometer. The petroleum ether used had a b.p. 60–70°. The thin layer chromatogram was carried out at room temperature on a glass plate coated with approximately 0.25 mm. of Silica Gel G prepared according to E. Stahl, *Chem. Ztg.*, **82**, 323 (1958), and dried for 2 hr. at 70°. The developing system was the upper phase of a benzene:acetone:water partition (2:1:2).

(21) Florisil is the Floridin Co.'s registered trademark for a synthetic magnesium silicate.

(22) Meyer and Reichstein[6] record a melting point of 148–149° and $[\alpha]\text{D}$ +5° (chloroform) for this compound. They also give the specific rotation of 3β,21-diacetoxy-14β-hydroxy-14β-pregnan-20-one as $[\alpha]\text{D}$ +50.5° (chloroform). The magnitude of such a shift in rotation on acetylation of the 21-hydroxyl function appears to be too large, and the inference must be that their monoacetate was contaminated with levorotatory 17-iso compound.

Anal. Calcd. for $C_{25}H_{38}O_5$ (418.55): C, 71.74; H, 9.15. Found: C, 71.13; H, 9.65.

3β-Acetoxy-21-hydroxypregn-14-en-20-one (III).—A solution of 3β-acetoxy-20-ethylenedioxypregn-14-en-21-ol (II, 460 mg.) in methanol (40 ml.) and 8% sulfuric acid (3 drops) was refluxed for 10 min. The solution was diluted with water, concentrated under reduced pressure, and filtered affording 290 mg. of white solid, m.p. 168–172°. Several crystallizations from acetone–water raised the melting point to 171–172°; ν_{max} 3450, 1725, 1256, 1238 cm.$^{-1}$; $[\alpha]^{25}_{D}$ +39° (chloroform).

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 73.94; H, 9.37.

3β-Acetoxy-20-methoxyimino-14β-pregnane-14β,21-diol (IVa).—To a solution of 3β-acetoxy-14β,21-dihydroxy-14β-pregnan-20-one (I, 300 mg.) and methoxyamine hydrochloride (300 mg.) in methanol (45 ml.) was added a solution of potassium acetate (600 mg.) in water (6 ml.). The solution was refluxed for 18 hr. and then diluted with water (30 ml.). Most of the methanol was removed from the solution by concentration under reduced pressure. The aqueous residual mixture was extracted several times with ethyl acetate, and the extract was washed with dilute hydrochloric acid and water. The dried extract was evaporated *in vacuo* to yield 290 mg. of IVa as a white glass which could not be crystallized; ν_{max} 3380, 1734, 1710 (sh), 1252, 1230 cm.$^{-1}$.

3β-Acetoxy-21-methanesulfonyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb).—A solution of crude 3β-acetoxy-20-methoxyimino-14β-pregnane-14β,21-diol (IVa, 290 mg.) in pyridine (5 ml.) was cooled to −32° and methanesulfonyl chloride (0.27 ml.) was added. The reaction mixture was maintained at −5° for 22 hr. The product IVb was precipitated by the dropwise addition of water and collected as 200 mg. of white solid, m.p. 148–149°. Two recrystallizations from acetone–petroleum ether raised the melting point to 149–150° dec.; ν_{max} 3520, 1735, 1720 (sh), 1342, 1270, 1240, 1170 cm.$^{-1}$; $[\alpha]^{25}_{D}$ +14° (chloroform).

Anal. Calcd. for $C_{25}H_{41}O_7NS$ (449.59): C, 60.10; H, 8.27; N, 2.80; S, 6.41. Found: C, 60.45; H, 8.39; N, 2.83; S, 6.60.

20-Methoxyimino-14β,21-epoxy-14β-pregnan-3β-ol (Va).—To a suspension of 3β-acetoxy-21-mesyloxy-20-methoxyimino-14β-pregnan-14β-ol (IVb, 710 mg.) in methanol (71 ml.) was added 3% methanolic potassium hydroxide (10.4 ml.). The solid rapidly dissolved and the resultant solution was refluxed for 3 hr. Water (50 ml.) was added and the solution was concentrated under reduced pressure to remove most of the methanol. The remaining essentially aqueous solution was decanted and the residual gummy solid was triturated several times with water to yield 480 mg. of a tan solid. No satisfactory means of recrystallization of this material could be found. An analytical sample was prepared by dissolving 400 mg. of material in 20 ml. of hot cyclohexane and filtering from a small amount of insoluble material. The filtrate produced a gel which was collected by filtration and dried under reduced pressure affording 200 mg. of Va as an amorphous white powder; ν_{max} 3450, 1052, 1032, 1092, 1082 cm.$^{-1}$; $[\alpha]^{25}_{D}$ −4° (chloroform).

Anal. Calcd. for $C_{22}H_{35}O_3N \cdot 0.5C_6H_{12}$[23] (393.51): C, 74.13; H, 10.49; N, 3.19. Found: C, 74.40; H, 10.24; N, 3.47.

3β-Hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb).—To a solution of 20-methoxyimino-14β,21-epoxy-14β-pregnan-3β-ol (Va, 2.5 g.) in methanol (250 ml.) and acetone (10 ml.) was added 2 *N* hydrochloric acid (250 ml.). The solution was heated at reflux temperatue for 4 hr. and then concentrated under reduced pressure to afford an off-white solid (1.62 g.), m.p. 177–187°. One recrystallization from acetone–water gave Vb (1.2 g.) as white crystals, m.p. 193–197°. Two additional recrystallizations gave constant melting material, m.p. 194–197°, as a hydrate; ν_{max} 3400, 1730, 1090, 1080 (sh) cm.$^{-1}$; $[\alpha]^{25}_{D}$ −23° (chloroform).

Anal. Calcd. for $C_{21}H_{32}O_3 \cdot 1.5H_2O$ (359.49): C, 70.17; H, 9.81; H_2O, 7.50. Found: C, 70.49; H, 9.98; H_2O, 7.40.

3β-Acetoxy-14β,21-epoxy-14β-pregnan-20-one (Vc).—To a solution of 3β-hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb, 800 mg.) in pyridine (75 ml.) was added acetic anhydride (0.61 ml.). The solution was allowed to remain at room temperature for 18 hr. and then diluted with water. The yield of Vb was 750 mg. of white solid, m.p. 120–125°. One recrystallization from acetone–water afforded white crystals (660 mg.), m.p. 130–134°. Further recrystallizations did not alter the melting point; ν_{max} 1732, 1710 (sh), 1257, 1238, 1090, 1083 (sh) cm.$^{-1}$; $[\alpha]^{25}_{D}$ −19° (chloroform).

Anal. Calcd. for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15. Found: C, 73.12; H, 9.63; H_2O, 1.66.

3β,14β-Dihydroxy-20-keto-14β-pregnan-21-oic Acid 21,14-Lactone (VIa).—To a stirred suspension of digitoxigenin (3 g.) in 0.1 *N* sodium hydroxide (270 ml.) was added dropwise 5% potassium permanganate solution (68.5 ml.). The addition required 1 hr., and then 5.5 ml. of 6 *N* hydrochloric acid was added. The precipitated manganese dioxide sludge was extracted with hot ethyl acetate and crude digitoxigenin (0.85 g.) was recovered.

The aqueous filtrate was concentrated to about 10 ml. The addition of 6 *N* hydrochloric acid (2 ml.) and aging at 5° for 18 hr. produced white solid (1.9 g.). A poor crystallization from acetone–water afforded VIa (130 mg.) as white crystals, m.p. 220–224°; ν_{max} 3550, 1742, 1710 (sh), 1285, 1274, 1262 (triplet), 1153, 1130 cm.$^{-1}$.

The material was difficult to purify and was converted directly into the acetate VIb.

3β-Acetoxy-14β-hydroxy-20-keto-14β-pregnan-21-oic Acid 21,14-Lactone (VIb). **A.**—To a solution of 3β-acetoxy-14β,21-epoxy-14β-pregnan-20-one (Vc, 500 mg.) in acetic acid (12 ml.) was added a solution of chromic acid (500 mg.) in 90% acetic acid (5 ml.). The reaction mixture was allowed to remain at room temperature for 18 hr. and then diluted with methanol (10 ml.). The solution was poured into water and the aqueous solution was extracted several times with ethyl acetate. The extract was washed with sodium bicarbonate solution and with water, dried with magnesium sulfate, and evaporated under reduced pressure with minimal heating. The resultant solid (300 mg.) was crystallized from acetone–water to yield VIb (160 mg.) as white crystals, m.p. 211–214°. Several recrystallizations from the same solvent pair raised the melting point to 230–232°[24]; ν_{max} 1740, 1718 (sh), 1274 (sh), 1260, 1237, 1220, 1153, 1132 cm.$^{-1}$; $[\alpha]^{25}_{D}$ −64° (chloroform).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 70.66; H, 8.18.

B.—A solution of 3β,14β-dihydroxy-20-keto-14β-pregnan-21-oic acid 21,14-lactone (VIa, 130 mg.) in pyridine (2 ml.) was acetylated with acetic anhydride (0.1 ml.) for 50 min. at 100°. The addition of water produced VIb (90 mg.) as white crystals, m.p. 226–229°. The infrared spectrum was identical to that of the sample prepared in A and also an authentic sample.[12a,14] A mixture melting point with sample A and the authentic sample was not depressed.

14β,21-Epoxy-14β-pregnane-3,20-dione (VIIa).—To a solution of 3β-hydroxy-14β,21-epoxy-14β-pregnane-20-one (Vb, 370 mg.) in acetone (43 ml.) at 5° was added a solution of chromic acid (109 mg.) and concentrated sulfuric acid (0.093 ml.) brought to a volume of 0.41 ml. with water. The mixture was stirred at 5° for 5 min. and then diluted with water (190 ml.). The resultant white solid (320 mg.), m.p. 226–231°, was recrystallized five times from acetone–water, m.p. 232–236°; ν_{max} 1738, 1700 (sh), 1086, 1075 cm.$^{-1}$; $[\alpha]^{25}_{D}$ −5° (chloroform).

Anal. Calcd. for $C_{21}H_{30}O_3$ (330.45): C, 76.32; H, 9.15. Found: C, 75.76; H, 9.23.

4β-Bromo-14β,21-epoxy-14β-pregnane-3,20-dione (VIIb).—A solution of 14β,21-epoxy-14β-pregnane-3,20-dione (VIIa, 330 mg.) in chloroform (4.5 ml.), methylene chloride (4.5 ml.), and glacial acetic acid (1.13 ml.) was stirred and cooled to −40°. To the stirred solution was added a solution of bromine (0.052 ml.) in 30% hydrogen bromide in acetic acid (0.245 ml.) and glacial acetic acid (0.75 ml.) dropwise over a period of 1 hr. The reaction solution was stirred at −40° for an additional hour and then allowed to come to room temperature.

To the stirred reaction mixture was added a solution of anhydrous sodium acetate (164 mg.) in water (1.4 ml.) and stirring was continued for 30 min.

The organic solvents were evaporated at a bath temperature of 45–50° and water (19 ml.) was added. The resultant precipitate was collected as a white solid (367.5 mg.), m.p. 178–179° dec. Three recrystallizations from acetone–petroleum ether, and one recrystallization from acetone–water afforded VIIb (110 mg.), m.p. 191–192°; ν_{max} 1724, 1080 cm.$^{-1}$; $[\alpha]^{25}_{D}$ +2.5° (chloroform).

Anal. Calcd. for $C_{21}H_{29}O_3Br$ (409.36): C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.22; H, 7.20; Br, 19.68.

14β,21-Epoxy-14β-pregn-4-ene-3,20-dione (VIII).—To a solution of 4β-bromo-14β,21-epoxy-14β-pregnane-3,20-dione (VIIb,

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[23] The presence of 0.5 mole of cyclohexane in the analytical sample was confirmed by a signal at 1.43 p.p.m. for 6 hydrogens in its n.m.r. spectrum.

[24] Hunziker and Reichstein[14a] record a melting point of 235–237° and a rotation $[\alpha]^{22}_{D}$ −68.7° ± 2° (chloroform) for this compound.

460 mg.) in dimethylformamide (15 ml.) purified over a molecular sieve was added lithium chloride (920 mg.). The mixture was purged with nitrogen and heated at 100–110° in a slow stream of nitrogen for 5.5 hr. The solution was cooled and methylene chloride (50 ml.) was added. The solution was washed with water and sodium bicarbonate solution. The organic extract was dried with magnesium sulfate and evaporated under reduced pressure at a bath temperature of 45–50°. The resultant white solid gave a positive Beilstein test for halogen and was chromatographed on Florisil.[21] The material was placed on the column with methylene chloride and eluted with 2% acetone–methylene chloride. The first four 100-ml. eluates on evaporation afforded white solids which by Beilstein test contained some halogen. The solids from cuts 5 through 14 were combined and the total 250 mg. was crystallized from acetone–water to yield white plates (212 mg.), m.p. 184–188°. Four recrystallizations from the same solvent pair gave VIII (76.5 mg.), m.p. 193–195°; $\lambda_{\max}^{\mathrm{MeOH}}$ 240 mμ (ε 15,600); $\nu_{\max}$ 1730, 1670, 1650 (sh), 1620, 1085, 1072 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ +61° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.68; H, 8.68.

14β-Hydroxy-3,20-diketo-14β-pregnan-21-oic Acid 21,14-Lactone (IXa).—To a solution of 3β-hydroxy-14β,21-epoxy-14β-pregnan-20-one (Vb, 250 mg.) in acetic acid (10 ml.) was added a solution of chromic acid (250 mg.) in 90% acetic acid (2.5 ml.). The mixture was allowed to stand at room temperature for 18 hr., then diluted with methanol and water. The aqueous solution was extracted several times with ethyl acetate. The extract was washed with saturated sodium bicarbonate solution and water, dried with magnesium sulfate, and evaporated under reduced pressure. The residual gum, crystallized from acetone–water, afforded a white solid (130 mg.), m.p. 245–250°. Several recrystallizations from the same solvent pair raised the melting point to 255-256°; $\nu_{\max}$ 1758, 1732, 1720, 1265, 1150 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ −58° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 72.99; H, 8.57.

4β-Bromo-14β-hydroxy-3,20-diketo-14β-pregnan-21-oic Acid 21,14-Lactone (IXb).—To a solution of 14β-hydroxy-3,20-diketopregnan-21-oic acid 21,14-lactone (IXa, 490 mg.) in acetic acid (32 ml.) was added a solution of bromine (0.073 ml.) in acetic acid (8 ml.) over a period of 20 min. Water (80 ml.) was added dropwise and the resultant solid (446 mg.), m.p. 184–190° dec., was collected.

From the mother liquor, additional IXb (51 mg.), m.p. 195–196° dec., was collected. Two recrystallizations from acetone-water raised the melting point to 197° dec. Thin layer chromatographic analysis revealed homogeneity, only a single spot was revealed with phosphomolybdic acid.

Anal. Calcd. for $C_{21}H_{27}O_4Br$ (423.35): C, 59.57; H, 6.43; Br, 18.88. Found: C, 59.52; H, 6.77; Br, 19.84.

14β-Hydroxy-3,20-diketo-14β-pregn-4-en-21-oic Acid 21,14-Lactone (X). A.—To a solution of crude 4β-bromo-14β-hydroxy-3,20-diketo-14β-pregnan-21-oic acid 21,14-lactone (IXb, 230 mg.) in dimethylformamide (10 ml.) was added lithium chloride (430 mg.). The mixture was heated at 100–110° in a nitrogen atmosphere for 16 hr. The solution was cooled, diluted with methylene chloride, and the organic layer was separated and washed with saturated aqueous sodium bicarbonate solution and water, dried with magnesium sulfate, and evaporated *in vacuo*. The resultant gummy solid was chromatographed on Florisil.[21] The material was placed on the column with methylene chloride and eluted with 3% acetone–methylene chloride. The first eight 50-ml. eluates on evaporation afforded white solids which contained some halogen as shown by the Beilstein test. The solids from cuts 9 through 24 were triturated with 2 ml. of ethanol and yielded a white solid (48.2 mg.), m.p. 249–260°. Two crystallizations from acetone–water raised the melting point to 261–262°; $\lambda_{\max}^{\mathrm{MeOH}}$ 234 mμ (ε 13,170); $\nu_{\max}$ 1752, 1676, 1622, 1270, 1150 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ −20° (chloroform).

Anal. Calcd. for $C_{21}H_{26}O_4$ (342.42): C, 73.66; H, 7.66. Found: C, 73.56; H, 7.79.

B.—To a solution of 14β,21-epoxy-14β-pregn-4-ene-3,20-dione (VIII, 84 mg.) in acetic acid (3 ml.) was added a solution of chromic acid (84 mg.) in 90% acetic acid (0.8 ml.). The mixture was allowed to stand at room temperature for 20 hr. and was then diluted with methanol and water. The aqueous solution was extracted several times with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate solution and water, dried with magnesium sulfate, and evaporated *in vacuo*. The residual white solid was crystallized from acetone–water and afforded crystals of X (42.8 mg.), m.p. 248–253°. One recrystallization from acetone–water gave white crystals (23 mg.), m.p. 259–262°; $\lambda_{\max}^{\mathrm{MeOH}}$ 232 mμ (ε 14,200). The infrared spectrum was identical to that of the sample prepared in A preceding.

3β-Benzoyloxy-5,14-dihydroxy-19-methoxyimino-5β-card-20-(22)-enolide (XIc).—To a mixture of strophanthidin benzoate (XIb, 500 mg.) methoxyamine hydrochloride (500 mg.) and ethanol (50 ml.) was added a solution of anhydrous potassium acetate (1 g.) in water (10 ml.). The mixture was refluxed for 20 hr., diluted with water, and concentrated under reduced pressure. The resultant precipitate was collected as 440 mg. of white solid, m.p. 255–257°. Two recrystallizations from methanol–water afforded IXc (220 mg.), m.p. 258–260°; $\nu_{\max}$ 3510, 1780, 1750, 715 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ +49° (chloroform).

Anal. Calcd. for $C_{31}H_{39}O_7N$ (537.63): C, 69.25; H, 7.31; N, 2.60; CH_3, 2.61.[25] Found: C, 69.25; H, 7.51; N, 2.66; CH_3, 2.66.

3β-Benzoyloxy-5β,14β,21-trihydroxy-19-methoxyimino-14β-pregnan-20-one (XIIa).—A solution of methoxyimino strophanthidin benzoate (XIc, 2.88 g.) in pyridine (275 ml.) and ethyl acetate (275 ml.) was cooled to −60°. The solution was treated with a stream of ozone at a rate of 0.3 mmole per minute for 75 min. Excess ozone was removed from the reaction with a stream of oxygen until the blue solution turned colorless. To the stirred solution was added acetic acid (27.5 ml.) and zinc dust (5.5 g.) and the reaction temperature was allowed to come to room temperature. The mixture was heated at 60° and filtered through diatomaceous earth. The filtrate was evaporated *in vacuo*, the residue was dissolved in toluene and the evaporation was repeated. The residual dark brown sirup was dissolved in a mixture of ethyl acetate (250 ml.) and water (100 ml.). The organic layer was separated, dried with magnesium sulfate, and evaporated *in vacuo* leaving a dark brown gum (2.7 g.). The crude reaction product was chromatographed on Florisil[21] and the 10% acetone–methylene chloride eluates were evaporated to a clear gum (1.2 g.). Crystallization of the gum from acetone–petroleum ether afforded XIIa (620 mg.), m.p. 187–193°. Four additional crystallizations from the same solvent pair yielded white plates (265 mg.), m.p. 193–196°; $\nu_{\max}$ 3510, 3320, 1718 (sh), 1698, 1282, 722 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{39}O_7N$ (513.61): C, 67.81; H, 7.65; N, 2.73. Found: C, 67.21; H, 7.85; N, 2.77.

3β-Benzoyloxy-19,20-bismethoxyimino-14β-pregnane-5β,14β,-21-triol (XIIb).—To a mixture of ketol XIIa (440 mg.), methoxyamine hydrochloride (440 mg.), and ethanol (44 ml.) was added a solution of anhydrous potassium acetate (880 mg.) in water (8.8 ml.). The mixture was refluxed for 18 hr., diluted with water, and concentrated *in vacuo*. The resultant precipitate was collected, washed with water, and air-dried to yield 420 mg. of XIIb, m.p. 100–135°; $\nu_{\max}$ 3575, 3450, 1718, 1692, 1280, 717 cm.$^{-1}$; $[\alpha]^{25}\mathrm{D}$ +45° (chloroform); negative blue tetrazolium test.

Anal. Calcd. for $C_{30}H_{41}O_7N_2 \cdot H_2O$ (559.65): C, 64.38; H, 7.74; N, 5.00; CH_3, 5.36[25]; H_2O, 3.22. Found: C, 64.43; H, 7.95; N, 5.06; CH_3, 5.21; H_2O, 3.55.

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(25) The Zeisel OCH_3 determination was calculated as CH_3.