residue taken up in chloroform (15 ml). This solution was extracted with 14% aqueous ammonia (1 ml), dried ($MgSO_4$), and concentrated. The product was homogeneous on tlc[8] ($R_{alstonisidine}$ 1.1): micro-ir ν^{KBr} 1740, 1735 (ester C=O), no -OH; micro-nmr τ ($CDCl_3$) new 3H singlet at τ 7.92 (CH_3COO-): mass spectrum M^+ at m/e 714.

Detection of an Amino-Ketal Group in Alstonisidine.—Lithium aluminum hydride (15 mg) was added to a solution of alstonisidine (2 mg) in tetrahydrofuran (1 ml). The mixture was heated under reflux for 8 hr, cooled, and quenched with wet tetrahydrofuran. Addition of 25% sodium hydroxide (10 ml) dissolved the inorganic precipitate, and the alkaline solution was then extracted with chloroform (10 ml). The chloroform extract was dried (K_2CO_3) and solvent removed. Tlc[8] showed no alstonisidine remaining. The product was treated with acetic anhydride (0.5 ml) and pyridine (0.5 ml) at 65° for 2 hr and at 20° for 60 hr. Solvents were removed under reduced pressure at 45°, and the residue was dissolved in chloroform. The solution was then washed with 5% ammonia and dried (K_2CO_3). Removal of solvent gave an oily residue which solidified on trituration with methanol: micro-ir ν^{KBr} 1740 cm^{-1}; M^+ 772 (calcd for $C_{47}H_{56}N_4O_6$, 772).

Treatment of macralstonidine with lithium aluminum hydride under the same conditions returned pure starting material. Villalstoninetriol was prepared by the published method.[4]

Chromotropic Acid Tests.—These were performed essentially as described for macralstonidine,[12] except that 4 mg of alstonisidine was used, and the colors were developed by adding chromotropic acid (1 mg) and 12 *N* sulfuric acid (2 ml) to 1–2-ml cuts of distillate. Blanks developed no color under these conditions, and the reaction with macralstonidine was used as a standard.

Registry No.—**5**, 27141-90-8; **5** monoacetate, 27248-70-0.

Acknowledgments.—We are greatly indebted to Drs. Norbert Neuss and John Occolowitz, Lilly Research Laboratories, for the indispensable high-resolution mass spectrometry, and to Gloria Cook and Mr. Forrest MacKellar for other spectral data. The MS-902 mass spectrometer at the University of Michigan was purchased with funds provided by the National Science Foundation. We gratefully acknowledge a Faculty Research Fellowship and Grant from the Horace H. Rackham School of Graduate Studies, University of Michigan (to P. W. Le Q.), and the award of a NASA Fellowship (to J. M. C.).

Preparation and Properties of Steroidal 17,20- and 20,21-Acetonides Epimeric at C-20. III. Dioxolone Derivatives of α-Hydroxy Acids[1]

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The common chromic anhydride–pyridine oxidation product of the 17,20α- and 17,20β-acetonido-21-ols **1a** and **1b** has been identified as the etienic acid acetonide (dioxolone) **2**. In a study of the reaction sequence involved in its formation, it was shown that the 20-methylene derivative **7** is not an intermediate, and that the 17,20-acetonido-21-aldehydes are the immediate precursors of **2**. A general method for the synthesis of dioxolones from α-hydroxy acids, using acetone–perchloric acid, was devised, and the preparation of eight examples from 17-hydroxyetianic and 20-hydroxypregnanoic acids in the 11-oxygenated Δ^4-3-keto series is described. All dioxolones are readily cleaved by dilute alkali, but are considerably more resistant to hydrolysis with 60% acetic acid at room temperature than isopropylidene derivatives of the corresponding glycols. Dioxolones from 17-hydroxyetianic and 17-deoxy- and 17-hydroxy-20-hydroxypregnanoic acids can be distinguished by their ir and nmr spectra.

We recently reported[2] that prolonged reaction of the 17,20α- and 17,20β-acetonido-21-ols **1a** and **1b** (Scheme I) with chromic anhydride in pyridine gives rise to not only the respective 21-aldehydes and 21-oic acids, but also a common neutral product with the empirical formula $C_{23}H_{30}O_5$. This substance has been identified as the etienic acid acetonide (dioxolone) **2**. In addition to presenting evidence for this structure, this paper includes a general procedure for the independent preparation of dioxolones not only from 17-hydroxyetianic acids, but also from homologous 20-hydroxypregnan-21-oic acids epimeric at C-20. Finally, some of the properties of the new derivatives will be discussed.

Structural assignment of the etiodioxolone **2** was based on the following considerations: (a) infrared spectroscopy indicated a new carbonyl band at 1782 cm^{-1} and retention of the isopropylidene group as evidenced by a characteristic doublet at 1385 and 1377 cm^{-1}; (b) its mass spectrum displayed a prominent molecular $(M)^+$ ion, m/e 386, as well as the m/e 328 ion, representing M less the elements of acetone [However, ions such as M − 15 (CH_3) and M − 15 − 60 (HOAc), which have been observed in both 17,20- and 20,21-acetonides, were not seen. Their absence is understandable in view of the greater complexity and, accordingly, lessened stability of the dioxolone ring.];[3] and (c) treatment of **2** with methanolic sodium hydroxide or methanolic hydrogen chloride gave the methyl etienate **3**.

An investigation was made of the mechanism of formation of **2** from **1a** and **1b**. A plausible sequence of reactions at C-21 would be $CH_2OH \rightarrow CHO \rightarrow COOH$, followed by decarboxylation. Subsequent oxidation of the resulting 20-methylene group to a carbonyl would afford the dioxolone **2**. Accordingly, the hypothetical 20-methylene intermediate **7** was prepared as follows. Treatment of the methyl etienate **4** with pyrrolidine in hot methanol[4] gave the crystalline 3-enamine. Its lithium aluminum hydride reduction, followed by buffered hydrolysis of the product, afforded the glycol **6** which was characterized by periodic acid oxidation to

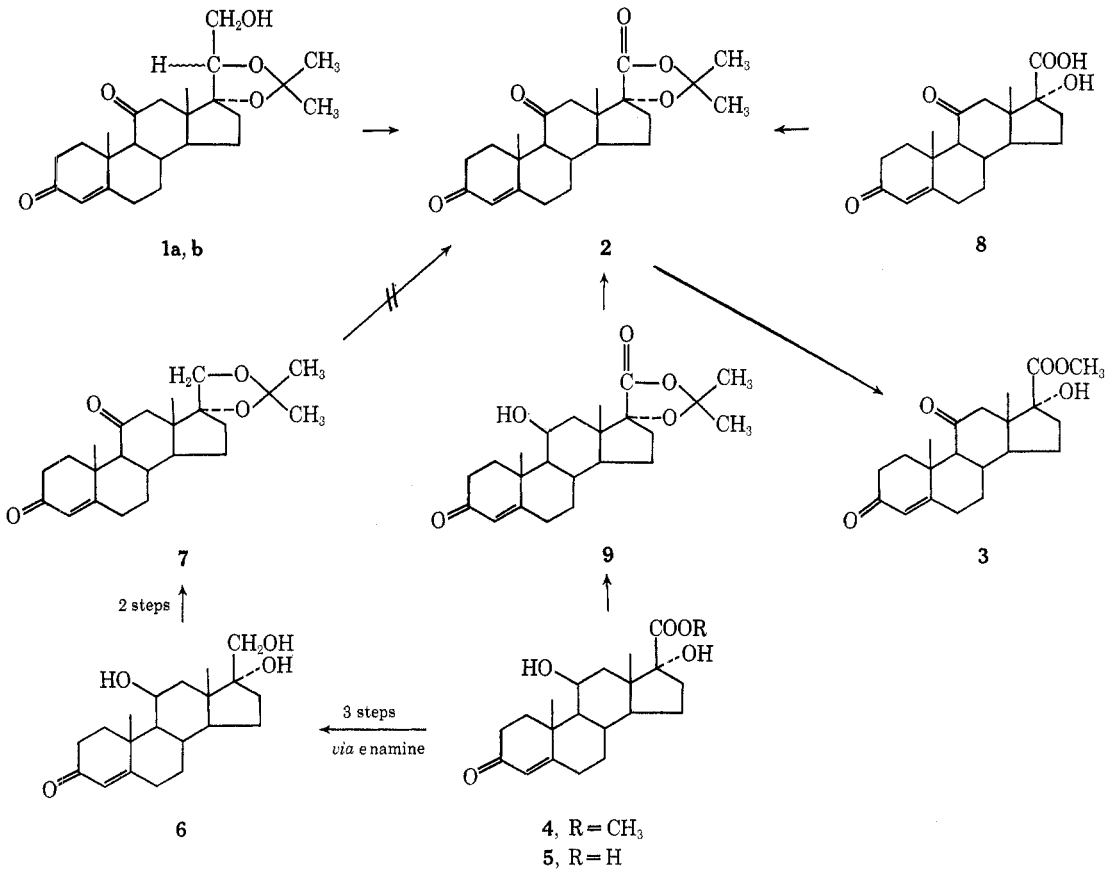
(1) This work was supported by a research grant, AM01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(2) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3513 (1969).

(3) A detailed study of the mass spectral characteristics of a number of cyclic derivatives of the steroid side chain, including acetonides and dioxolones, will be presented at a later date.

(4) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Amer. Chem. Soc.*, **78**, 430 (1956).

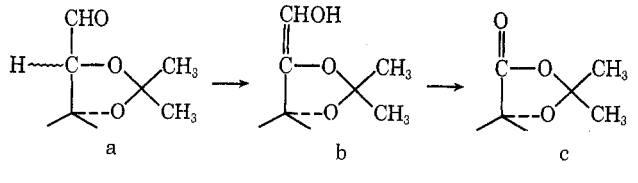
SCHEME I[a]



[a] In this and other schemes, the substituent at C-20 is α oriented in "a" compounds and β oriented in "b" compounds.

11β-hydroxyandrostenedione. To our knowledge, side-chain glycols of this type have not previously been prepared. Acetonation of **6** in the presence of *p*-toluenesulfonic acid (*p*-TSA)[5] provided an amorphous acetonide which was oxidized with chromic anhydride in pyridine to the crystalline 11-keto acetonide **7** in an overall yield of 87% from the glycol **6**. The acetonide **7** is not an intermediate in the formation of the dioxolone **2** since prolonged treatment with chromic anhydride in pyridine was without effect. A further investigation of the reaction sequence was made by the small-scale treatment with chromic anhydride–pyridine of 17,20β-acetonides with alcoholic, aldehydic, and carboxylic functions at C-21.[2] Paper chromatographic analysis of the reaction mixtures showed that only the alcohol and aldehyde can give rise to the dioxolone **2**. These results suggest that the 21-aldehyde (a, Scheme II) is the immediate precursor of the dioxolone c. In

SCHEME II



view of the relative ease of epimerization at C-20 of 17,20-acetonides with a carbonyl function at C-21,[2] the oxidative cleavage of the C-20/C-21 bond probably occurs *via* the chromate ester of the enolic form b. Such a mechanism has been proposed by Best, *et al.*, for the oxidative cleavage of cyclic ketones.[6]

The original preparation of acetonides from α-hydroxy acids was by Willstätter and Königsberger[7] who made such derivatives from glycolic, mandelic, and benzilic acids by the dropwise addition of sulfuric acid to an acetone solution at reduced temperature. Dioxolones of this type have received scant attention generally, and to our knowledge have not previously been described in the steroid field. It was therefore of interest to devise a general method for the preparation of such derivatives from steroidal α-hydroxy acids. Preliminary studies showed that *p*-TSA in acetone has no effect on 17-hydroxyetianic acids, and that reaction with 20-hydroxy-21-oic acids is slow and incomplete after 1 week at room temperature. However, conditions suitable for the acetonation of hindered 17,20-glycols, namely the use of perchloric acid as catalyst,[5] proved satisfactory. For example, treatment of the etienic acid **8** with acetone–perchloric acid for 6 hr provided in 68% yield a product identical with **2**. Similar acetonation of the 11β-hydroxyetienic acid **5** afforded the dioxolone **9** in a yield of 69%. The facile oxidation of **9** to **2** with chromic anhydride–pyridine illustrates the utility of the dioxolone ring as a protecting group in this reaction.

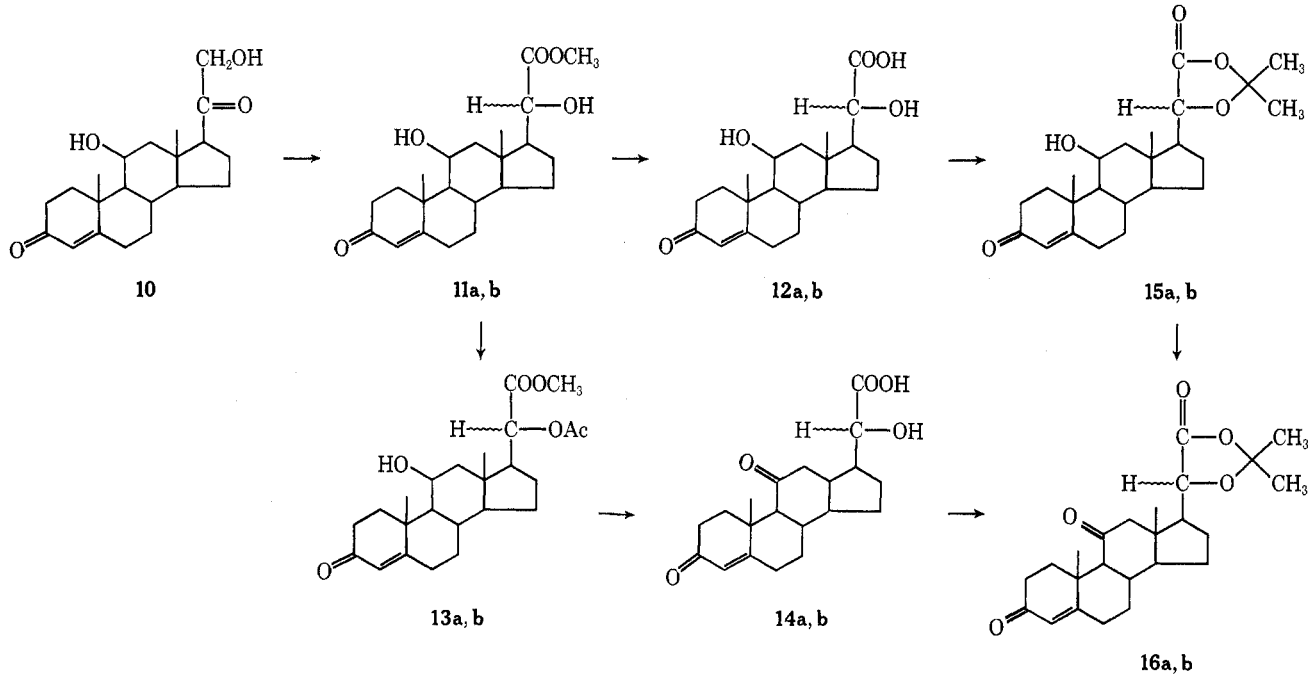
In order to obtain additional dioxolones in the 11-oxygenated Δ^4-3-keto series, the homologous C-20 epimeric acids derived from the 21-aldehydes of corticosterone and 11-dehydrocorticosterone were synthe-

(5) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).

(6) P. A. Best, J. S. Littler, and W. A. Walters, *J. Chem. Soc.*, 822 (1962).

(7) R. Willstätter and F. Königsberger, *Ber.*, **56**, 2108 (1923).

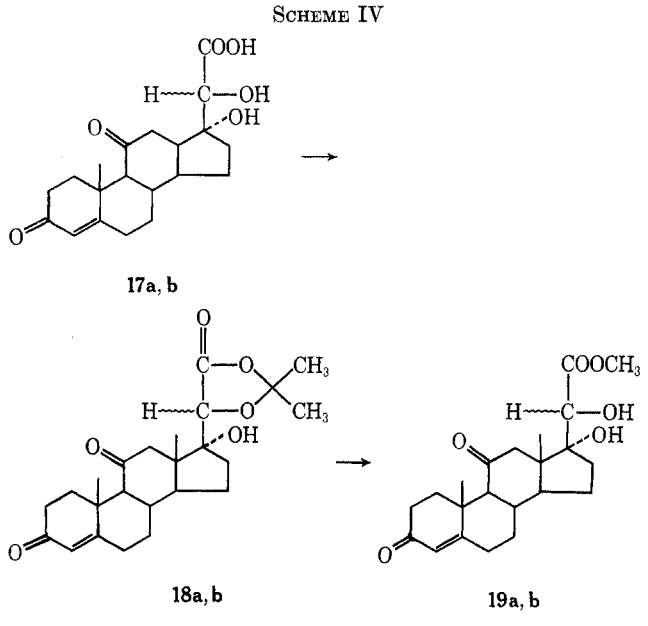
SCHEME III



sized. The glycolic acids from corticosterone (**10**, Scheme III) were prepared by rearrangement of the crude glyoxal in methanolic cupric acetate,[8] column chromatographic separation of the methyl esters **11a** and **11b**, followed by saponification to the free acids **12a** and **12b**. The glycolic acids from 11-dehydrocorticosterone were obtained by oxidation of the 11β-hydroxy methyl ester 20-acetates **13a** and **13b** with chromic anhydride–pyridine followed by saponification to the 11-keto acids **14a** and **14b**.[9] Configurational assignments at C-20 for the new glycolic acids and esters followed from their characteristic optical rotatory properties[8,10] and the identity of the oxidation product from **13b** with the known 11-keto methyl ester 20β-acetate.[10]. Acetonation of the two pairs of glycolic acids afforded the respective dioxolones **15a**, **15b**, **16a**, and **16b** in yields somewhat less than those obtained from the analogous 20,21-glycols.[5] Oxidation of the 11β-ols **15a** and **15b** with chromic anhydride–pyridine gave products identical with the acetonation products from **14a** and **14b**.

It was of interest to subject the glycolic acid pair from cortisone glyoxal[11] to the acetonation conditions since not only the 17-hydroxy-20,21-dioxolones, but also the 17,20-acetonido-21-oic acids and 20-hydroxy-17,21-dioxolones could be formed. However, treatment of **17a** and **17b** (Scheme IV) with acetone–perchloric acid afforded a single, neutral product in each case which was not affected by acetic anhydride–pyridine, and which possessed a carbonyl band close to 1800 cm^{-1}. They were therefore assigned the 17-hydroxy-20,21-dioxolone structures **18a** and **18b**, thus indicating the preferred reaction of acetone with the C-20 and carboxyl hydroxyls. Treatment of **18a** and **18b** with methanolic sodium hydroxide gave the respective

SCHEME IV



methyl 17,20-dihydroxy-21-oates **19a** and **19b**[11] unaccompanied by epimerization at C-20. This is not surprising since the steric factors believed responsible for the epimerization of 17,20α-acetonido-21-oates under these conditions[2] are not operative in 20,21-dioxolones.

In contrast to the isopropylidene derivatives of steroidal glycols, all dioxolones studied, by virtue of their lactonic nature, are readily hydrolyzed by dilute alklai to the parent α-hydroxy acids. However, dioxolones are considerably more resistant to room temperature hydrolysis with 60% aqueous acetic acid than 20,21-acetonides.[5] For example, under conditions where the latter are cleaved completely in 30 min, the 17-deoxydioxolones **16a** and **16b** required 24 hr and the 17-hydroxydioxolones **18a** and **18b** approximately 48 hr for complete hydrolysis. Because of the tertiary linkage at C-17, the etiodioxolones were considerably more

(8) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).
(9) Direct preparation of the epimeric glycolic acids from 11-dehydrocorticosterone 21-aldehyde was not possible because neither the methyl esters nor the methyl ester 20-acetates were separable chromatographically.
(10) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **29**, 2559 (1964).
(11) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, 1773 (1963).

TABLE I

INFRARED AND NMR SPECTRAL CHARACTERISTICS OF STEROIDAL DIOXOLONES

Compd	Type	Infrared bands (cm^{-1})				Chemical shifts (Hz)		
		Lactone carbonyl	*gem*-Dimethyl	1137–1120	938–879	C-18	C-19	Dioxolone methyls
9	11β-OH etiodioxolone	1784	1384, 1376	1136 (vs)	938 (vs)	77	90	94, 94
2	11-Keto etiodioxolone	1782	1385, 1377	1137 (vs)	936 (vs)	60	88	94, 97
15a	11β-OH, 20α,21-dioxolone	1789	1387, 1379	1120 (vs)	889 (vs)	62	90	95, 99
15b	11β-OH, 20β,21-dioxolone	1788	1386, 1378	1125 (vs)	886 (vs)	64	89	95, 97
16a	11-Keto, 20α,21-dioxolone	1786	1389, 1381	1121 (m)	884 (s)	45	88	95, 100
16b	11-Keto, 20β,21-dioxolone	1785	1384, 1376	1125 (vs)	884 (vs)	49	88	94, 96
18a	11-Keto, 17-OH, 20α,21-dioxolone	1795	1386, 1378	1126 (vs)	895 (s), 880 (s)	51	88	96, 102
18b	11-Keto, 17-OH, 20β,21-dioxolone	1790	1387, 1379	1130 (vs)	898 (vs), 879 (s)	52	88	95, 100

resistant, requiring refluxing for 3 hr to effect complete hydrolysis.

The infrared spectral properties of the α-hydroxy acid acetonides have been determined and the bands are presented in Table I. Justification for these assignments is based upon the constant occurrence of certain bands in these derivatives together with their absence in the corresponding α-hydroxy acids. All dioxolones exhibit a carbonyl band at 1795–1782 cm^{-1}, which is characteristic of saturated γ-lactones.[12] The symmetrical methyl deformation bands attributable to the *gem*-dimethyl group[13] appear as a doublet separated by 8 cm^{-1} and ranging from 1389 to 1384 and 1381 to 1376 cm^{-1}. In addition, a very strong band at 1274–1265 cm^{-1} (not listed in Table I) is common to all dioxolones. The presence of bands at 1137–1136 and 938–936 cm^{-1} serve to distinguish the etiodioxolones from 20,21-dioxolones in which these bands occur at somewhat lower frequencies (1130–1120 and 889–879 cm^{-1}). Differentiation between 17-deoxy- and 17-hydroxy-20,21-dioxolones rests on the observation that the 938–879-cm^{-1} band is distinctly split in the latter case.

Examination of the nmr spectra (Table I) shows four methyl resonances for each compound. Although dioxolones are not included in the tables compiled by Zürcher,[14] the following assignments can reasonably be made. The proton resonances of the C-19 methyl group, which is well removed from the dioxolone ring, fall within the expected narrow range of 88–90 Hz. Comparison of the C-18 methyl resonances among the 11β-ols and the 11-ketones show an average downfield shift of 14 Hz for the etiodioxolone *vs.* the homologous derivatives. This is ascribable to the fixed position of the dioxolone ring in the former case and its closer approach to the C-18 methyl group. The dioxolone methyl resonances, with one exception, appear as doublets within the limits of 94–102 Hz, but it is not possible to make individual assignments. The C-20 proton resonances in the pregnenoic acid derivatives fall within the range of 252–273 Hz, but it was not possible to distinguish between 20α and 20β protons.

Experimental Section

Melting points were taken on a Fisher–Johns apparatus and are uncorrected. Optical rotations were determined at 365 and 589 mμ (D line of sodium) in a Zeiss 0.005° photoelectric polarimeter. Measurements were made in methanol solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Ultraviolet spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. Infrared (ir) spectra were obtained as KBr pellets with a Beckman IR-8 instrument. The mass spectrum was obtained at the Morgan–Schaffer Corp., Montreal, Canada, with a Hitachi Perkin-Elmer RMU-6D spectrometer; the sample was introduced directly at an inital voltage of 70 V. Nmr spectra were determined in $CDCl_3$ solution by Spectratec, Washington, D. C. using a JEOL 60-MHz instrument with TMS as the internal standard of reference. Elemental analyses were by August Peisker-Ritter, Brugg, Switzerland.

Descriptions of our column and paper chromatographic techniques appear in papers previously cited.[10] Thin layer chromatography (tlc) was performed on plates coated with silica gel 1B-F. The processing of reaction mixtures from acetylations, lithium aluminum hydride reductions, and chromic anhydride–pyridine oxidations have also been previously described or cited.[2]

17,20-Isopropylidenedioxy-3,11-dioxoetiochol-4-en-20-oate (2) from 8.—To a solution of 17-hydroxy-3,11-dioxoetiochol-4-enic acid[15] (100 mg) in acetone (100 ml) was added 70% perchloric acid (0.25 ml). After 6 hr at room temperature, the solution was concentrated *in vacuo* to a small volume and partitioned between methylene chloride and water. The oily residue was chromatographed on a 13 × 550 mm silica gel column in ethyl acetate–isooctane (1:1), collecting 3 ml of effluent per 10 min. Crystallization of material obtained from fractions 53–90 gave prisms from methanol (67 mg, mp 243–244°; 9 mg, mp 240–241°) in a yield of 68%. The ir spectrum was identical with that of the common chromic anhydride–pyridine oxidation product from **1a** and **1b**: $[\alpha]_{365}$ +591°, $[\alpha]_D$ +120°; λ_{max} 238 mμ, ε 15,800.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.51; H, 7.90.

Methyl 17-Hydroxy-3,11-dioxoetiochol-4-enoate (3) from 2. A. With Methanolic Sodium Hydroxide.—To a solution of the etiodioxolone (20 mg) in methanol (9.5 ml) was added 1 *N* methanolic sodium hydroxide (0.5 ml). After 20 hr at room temperature, the reaction mixture was added to methylene chloride (50 ml). The solution was washed with water and concentrated to dryness. Crystallization from methanol gave 18 mg of prisms, mp 230–231.5°. A mixture melting point with **3**[16] was 230–232° and their ir spectra were identical.

B. With Methanolic Hydrogen Chloride.—Treatment of **2** (7 mg) in methanol (2.2 ml) with 5.2 *N* HCl in methanol (0.3 ml) for 48 hr at room temperature followed by silica gel chromatography of the product in ethyl acetate–isooctane (1:1) afforded 2.7 mg of prisms, mp 229–230°, which were identical in all respects with the methyl ester **3**.

17,20-Isopropylidenedioxy-11β-hydroxy-3-oxoetiochol-4-en-20-oate (9) from 5.—Acetonation of 11β,17-dihydroxy-3-oxoetiochol-4-enic acid (200 mg) was carried out for 6 hr as in the preparation of **2** from **8**. The oily residue was chromatographed on a 20 × 700 mm silica gel column in ethyl acetate–isooctane (1:1), collecting 4-ml fractions every 10 min. Crystallization of the residue from fractions 106–174 gave prisms from methanol (127 mg, mp 222.5–223°; 27 mg, mp 218–219°) in a yield of 69%. The analytical sample melted and resolidified at

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

(13) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," New York, N. Y., 1958, p 24.

(14) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(15) H. L. Mason, W. Hoehn, and E. C. Kendall, *J. Biol. Chem.*, **124** 459 (1938).

(16) J. von Euw, C. Meystre, R. Neher, T. Reichstein, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1516 (1958).

approximately 200°, then melted again at 221–221.5°: $[\alpha]_{365}$ +36.9°, $[\alpha]_D$ +78.8°; λ_{max} 241 mμ, ε 16,050.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.11; H, 8.35.

2 from 9.—Oxidation of 17,20-isopropylidenedioxy-11β-hydroxy-3-oxoetiochol-4-en-20-oate (50 mg) with chromic anhydride (50 mg) in pyridine (6 ml) for 19 hr afforded 46 mg of prisms from methanol, mp 244.5–246°. The product did not depress the melting point of the acetonation product from **8** and their ir spectra were identical.

17β-Hydroxymethyl-11β,17-dihydroxyandrost-4-en-3-one (6) from 4.—To a solution of methyl 11β,17-dihydroxy-3-oxoetiochol-4-enoate[17] (1 g) in hot methanol (5 ml) was added 0.4 ml of pyrrolidine.[4] The enamine crystallized directly as yellow, prismatic needles (1080 mg, mp 167–178° dec) in a yield of 92%: ν_{max} 1640 and 1610 cm^{-1} ($\Delta^{3,5}$-pyrrolidinyl).[4]

A solution of methyl 3-(1-pyrrolidinyl)-11β,17-dihydroxyetiochola-3,5-dienoate (1 g) and an equal weight of lithium aluminum hydride were refluxed in tetrahydrofuran (135 ml) for 2 hr. After the cautious addition of ethyl acetate and water, most of the solvent was removed in a nitrogen stream. The residue was suspended in 50 ml of 50% aqueous methanol and the pH was adjusted to 4 by the dropwise addition of 1 *N* hydrochloric acid. Acetate buffer[18] (90 ml) was added, and the mixture was refluxed for 4 hr. The solvent was removed *in vacuo* and the product was recovered in the usual manner. Crystallization from ethyl acetate provided leaflets (385 mg, mp 157–158°; 195 mg, mp 155–156°) in a yield of 74%: $[\alpha]_{365}$ +56.2°, $[\alpha]_D$ +97.5°; λ_{max} 242 mμ, ε 14,900.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.80; H, 9.09.

Treatment of the glycol **6** (50 mg) with periodic acid in aqueous ethanol for 19 hr gave 34 mg (75%) of needles from ethanol, mp 198–200°; reported[19] for **11β-hydroxyandrostenedione**, mp 199–200°. The ir spectrum was identical with that of the reference compound.

17β-Hydroxymethyl-17-hydroxyandrost-4-ene-3,11-dione Acetonide (7) from 6.—Acetonation of 17β-hydroxymethyl-11β,17-dihydroxyandrost-4-en-3-one (100 mg) in the presence of *p*-TSA was carried out as described previously.[5] The product was homogeneous (R_f 0.16) by tlc in isooctane–ethyl acetate (3:2) but could not be obtained in crystalline form. Oxidation of the amorphous 17β-hydroxymethyl-11β,17-dihydroxyandrost-4-en-3-one acetonide was therefore performed with chromic anhydride (100 mg) in pyridine (11 ml) for 20 hr. The product crystallized as prisms from acetone–*n*-hexane (86.5 mg, mp 174.5–176°; 10 mg, mp 172–174°) in an overall yield from the glycol **6** of 87%: $[\alpha]_{365}$ +510°, $[\alpha]_D$ +110°; λ_{max} 238 mμ, ε 15,600; ν_{max} 1159 and 996 cm^{-1} (17,20-acetonide).[5]

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.20; H, 8.62.

Methyl 11β,20α- and -20β-Dihydroxy-3-oxopregn-4-en-21-oates (11a and 11b) from 10.—Corticosterone (1384 mg, 4 mmol) was treated with methanolic cupric acetate for 120 hr as described previously.[8] The epimeric methyl ester mixture was chromatographed on 50 × 900 mm Celite column in toluene (120), isooctane (80), methanol (160), and water (40 ml). Fractions (12 ml) were collected every 10 min. Several mobile by-products which emerged between fractions 101 and 300 were discarded.

Methyl 11β,20β-Dihydroxy-3-oxopregn-4-en-21-oate (11b). Fractions 326–460.—Crystallization from aqueous methanol provided 516 mg (34%) of needles: mp 104–106°; $[\alpha]_{365}$ +27.6°, $[\alpha]_D$ +78.3°; λ_{max} 242 mμ, ε 15,700.

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; OCH_3, 8.24. Found: C, 69.49; H, 8,60; OCH_3, 8.02.

Treatment of **11b** (500 mg) with 1 ml each of acetic anhydride and pyridine for 18 hr afforded **methyl 20β-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (13b)** as prisms (469 mg) from methanol: mp 229–231°; $[\alpha]_{365}$ +91.3°, $[\alpha]_D$ +88.5°; λ_{max} 242 mμ, ε 15,900.

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.80; H, 8.24.

Saponification of **11b** (188 mg) in methanol (2 ml) with 1 *N* aqueous sodium hydroxide (1 ml) for 30 min at room temperature gave **11β,20β-dihydroxy-3-oxopregn-4-en-21-oic acid (12b)** as prismatic needles (160 mg) from ethyl acetate: mp 200–200.5°; $[\alpha]_{365}$ +22.8°, $[\alpha]_D$ +75.4°; λ_{max} 242 mμ, ε 15,100.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.30; H, 8.44.

Methyl 11β,20α-Dihydroxy-3-oxopregn-4-en-21-oate (11a). Fractions 551–850.—Crystallization from ethyl acetate provided prisms (253 mg, mp 182–183°; 54 mg, mp 173–175°) in a yield of 20%: $[\alpha]_{365}$ +145°, $[\alpha]_D$ +116°; λ_{max} 242 mμ, ε 15,500.

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; OCH_3, 8.24. Found: C, 70.02; H, 8.53; OCH_3, 7.95.

Conversion of **11a** (500 mg) to **methyl 20α-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (13a)** was carried out as in the preparation of **13b** from **11b**. The product crystallized as prisms (461 mg) from methanol: mp 201–202.5°; $[\alpha]_{365}$ +211°, $[\alpha]_D$ +137°; λ_{max} 242 mμ, ε 16,000.

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.70; H, 8.16.

Saponification of **11a** (188 mg) with methanolic sodium hydroxide as in the preparation of **12b** from **11b** gave **11β,20α-dihydroxy-3-oxopregn-4-en-21-oic acid (12a)** as needles (146 mg) from ethyl acetate: mp 201.5–202°; $[\alpha]_{365}$ +148°, $[\alpha]_D$ +122°; λ_{max} 242 mμ, ε 15,900.

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.51; H, 8.39.

20α-Hydroxy-3,11-dioxopregn-4-en-21-oic Acid (14a) from 13a.—Oxidation of methyl 20α-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (400 mg) with an equal weight of chromic anhydride in pyridine (6 ml) for 16 hr afforded the 11-ketone which could be obtained only as a filterable solid from aqueous methanol: mp 70–72°; $[\alpha]_{365}$ +657°, $[\alpha]_D$ +166°.

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.89; H, 7.86.

The product was saponified and the free acid **14a** crystallized from methanol as leaflets (320 mg, mp 229–231°) in an overall yield of 93% from **13a**: $[\alpha]_{365}$ +623°, $[\alpha]_D$ +160°; λ_{max} 238 mμ, ε 14,600.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.60; H, 7.90.

20β-Hydroxy-3,11-dioxopregn-4-en-21-oic Acid (14b) from 13b.—Oxidation of methyl 20β-acetoxy-11β-hydroxy-3-oxopregn-4-en-21-oate (400 mg) as in the preparation of **14a** from **13a** gave 334 mg (84%) of the 11-ketone, mp 209–210°, which has been previously described.[10] Saponification gave the free acid **14b** as prisms from methanol: mp 199–201°; $[\alpha]_{365}$ +563, $[\alpha]_D$ +129°; λ_{max} 238 mμ, ε 15,000.

Anal. Calcd for $C_{21}H_{28}O_5 \cdot H_2O$: C, 66.64; H, 7.99. Found: C, 67.07; H, 7.80.

20α,21-Isopropylidenedioxy-11β-hydroxy-3-oxopregn-4-en-21-oate (15a) from 12a.—To a solution of 11β,20α-dihydroxy-3-oxopregn-4-en-21-oic acid (100 mg) in acetone (100 ml) was added 70% perchloric acid (0.25 ml). After 20 min solid sodium bicarbonate (300 mg) was added and the product was recovered in the usual manner. Crystallization from ether gave 98 mg (88%) of needles: mp 195–196°; $[\alpha]_{365}$ +122°, $[\alpha]_D$ +113°; λ_{max} 242 mμ, ε 15,900.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.72; H, 8.57.

20β,21-Isopropylidenedioxy-11β-hydroxy-3-oxopregn-4-en-21-oate (15b) from 12b.—Acetonation of 11β,20β-dihydroxy-3-oxopregn-4-en-21-oic acid (100 mg) was performed as in the preparation of **15a** from **12a**. The product crystallized from methanol as prismatic needles (79.5 mg, mp 239–240°; 9.5 mg, mp 236.5–237.5°) in a yield of 80%. The analytical sample had mp 241–242°; $[\alpha]_{365}$ +138°, $[\alpha]_D$ +106°; λ_{max} 242 mμ, ε 15,850.

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.62; H, 8.52.

20α,21-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (16a) from 15a.—Oxidation of 20α,21-isopropylidenedioxy-11β-hydroxy-3-oxopregn-4-en-21-oate (50 mg) in pyridine (7 ml) with an equal weight of chromic anhydride for 17 hr afforded 37 mg (74%) of prisms from methanol: mp 193–194°; $[\alpha]_{365}$ +631°, $[\alpha]_D$ +166°; λ_{max} 238 mμ, ε 15,700.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.83; H, 8.07.

16α from 14a.—Acetonation of 20α-hydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg) in the usual manner provided 68 mg of prisms, mp 190–191°, which did not depress the melting point of **16a** prepared from **15a**, and their ir spectra were identical.

20β,21-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (16b) from 15b.—Oxidation of 20β,21-isopropylidenedioxy-11β-hy-

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droxy-3-oxopregn-4-en-21-oate (50 mg) as in the preparation of **16a** from **15a** gave needles from methanol (35 mg, mp 208–210°; 9.1 mg, mp 204–206°) in a yield of 89%: $[\alpha]_{365}$ +579°, $[\alpha]_D$ +141°; λ_{max} 238 mμ, ε 15,200.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.65; H, 8.20.

16b from 14b.—Acetonation of 20β-hydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg) provided 68 mg of needles from methanol, mp 208–210°, which possessed an ir spectrum identical with that of **16b** prepared from **15b**.

20α,21-Isopropylidenedioxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (18a) from 17a.—Acetonation of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg)[11] for 3.5 hr and crystallization of the product from methanol gave 76 mg (69%) of leaflets, mp 269–271°. The analytical sample had mp 271–272°; $[\alpha]_{365}$ +395°, $[\alpha]_D$ +85.7°; λ_{max} 238 mμ, ε 15,500.

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.19; H, 7.74. Found: C, 69.32; H, 7.65.

Treatment of **18a** (10 mg) in methanol (2.5 ml) with an equal volume of 0.1 *N* methanolic sodium hydroxide for 2 hr followed by dilution with methylene chloride and washing with water afforded 7.7 mg of prisms from acetone–ether, mp 197–198°. A mixture melting point with **methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (19a)**[11] was 196–197.5°, and their ir spectra were identical.

20β,21-Isopropylidenedioxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (18b) from 17b.—Acetonation of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (100 mg)[11] for 3.5 hr and crystallization from methanol provided 45 mg of needles, mp 293.5–294°. Fractionation of the mother liquor on a small silica gel column in ethyl acetate–isooctane (3:2) afforded an additional 35 mg of product, mp 293.5–294°, raising the yield to 72%: $[\alpha]_{365}$ +499°, $[\alpha]_D$ +107°; λ_{max} 238 mμ, ε 15,500.

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.19; H, 7.74. Found: C, 69.30; H, 7.68.

Treatment of **18b** (10 mg) with methanolic sodium hydroxide gave 8.4 mg of prisms from acetone–ether, mp 211.5–213°. The identity of this product with **methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (19b)**[11] was shown by mixture melting point and ir comparisons.

Registry No.—**2**, 27149-60-6; **3**, 3941-62-6; **6**, 3941-65-9; **7**, 27149-63-9; **9**, 27149-64-0; **11a**, 27149-65-1; **11b**, 27149-66-2; **12a**, 27149-67-3; **12b**, 27149-68-4; **13a**, 27149-69-5; **13b**, 27149-70-8; **14a**, 27149-71-9; **14b**, 27149-72-0; **15a**, 27150-71-6; **15b**, 27150-72-7; **16a**, 27150-73-8; **16b**, 27150-74-9; **18a**, 27189-20-4; **18b**, 27189-21-5; methyl 20α-acetoxy-3,11-dioxopregn-4-en-21-oate, 27150-75-0.

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Notes

Disulfides of 2-Mercaptocyclohexanol

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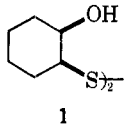
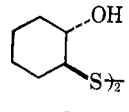
During the course of studies in our laboratory, we had need to prepare the disulfides **1** and **2** derived from *cis*- and *trans*-2-mercaptocyclohexanol, respectively. The trans,trans disulfide **2** has been reported by Mousseron[2] to be obtained by the reaction of sodium disulfide with *trans*-2-chlorocyclohexanol, while the cis,cis disulfide **1** has not been described in the literature.

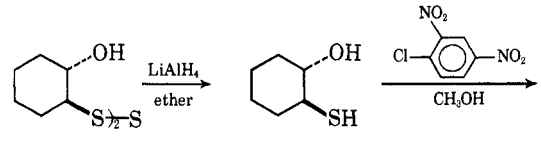


1

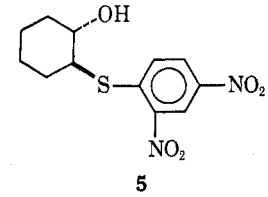


2

Repetition of Mousseron's procedure gave, as reported, a compound having a melting point of 156°. However, the molecular weight of this material, as determined by mass spectrometry, was found to be 294 rather than 262 as expected for the disulfide **2**. This difference of 32 mass units is indicative that Mousseron's product is the trisulfide **3** rather than the disulfide **2**. That this is the case was established by elemental analysis and by preparation, following a known procedure,[3] of the trisulfide **3**, which was shown to be identical with Mousseron's product. The trisulfide **3** has been reported[4] to possess a melting point of 157–158°. The all-trans stereochemistry of the trisulfide **3** was confirmed by reduction[5] with lithium aluminum hydride to give *trans*-2-mercaptocyclohexanol (**4**)[6] characterized as the known 2,4-dinitrophenyl thio ether derivative **5**.[4,6,7]



3 **4**



5

The trans,trans disulfide **2** was obtained by oxidation of *trans*-2-mercaptocyclohexanol (**4**)[6] with iodine. The disulfide **2** has a melting point of 82–83°, gives a molecular ion peak at *m/e* 262, and upon reduction with lithium aluminum hydride regenerates **4**.

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