Preparation and Properties of β-Lactones from Steroidal 17,20-Dihydroxy-21-oic Acids[1]

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The major neutral products from the reaction of the 17,20-dihydroxy-21-oic acids **1a** and **1b** with acetic anhydride–pyridine are the 20-acetyl-21,17α-lactones **4a** and **4b**. A mechanism is presented to explain the controlling effect of configuration at C-20 on the extent of acetylation at C-17 *vs.* C-21,C-17 cyclization. Spontaneous or thermal decarboxylation of **4a** and **4b** leads stereospecifically to **6** and **7**, the respective trans and cis enol acetates of the 17-aldehyde **8**. Reaction of glycolic acids **1a** and **1b** with ethyl chlorocarbonate–pyridine affords the 20-cathyl-21,17α-lactones **13a** and **13b**. Treatment of **13a** with methanolic sodium hydroxide results both in cleavage of the β-lactone ring and formation of an epimeric mixture of the methyl ester 17,20-cyclic carbonates **18a** and **18b**, in which the 20β epimer predominates. Similar treatment of β-lactone **13b** gives the methyl ester cyclic carbonate without epimerization of C-20. Decarboxylation of **13a** and **13b** in refluxing methanol affords the trans and cis enol cathylates **16** and **17**. Configurational assignments for both the latter compounds and the enol acetates **6** and **7** were made on the basis of their nmr spectral properties. Selective peracid oxidation of **16** and **17** furnished their respective 17,20-epoxides **20** and **21**. Successive reaction of the epoxides with methanolic potassium bicarbonate and methanolic hydrogen chloride gave the 17α-hydroxy-20,20-dimethoxy derivative **22** as a common product. In order to assess the contribution of the oxygen function at C-20 in β-lactone formation, the 20-deoxy acid **34** was prepared. The essential role of the 20-acyl group is evident since treatment of **34** with either acylating reagent resulted in no appreciable formation of β-lactone. Instead, reaction with acetic anhydride–pyridine provided the 17-acetate **36**, and reaction with ethyl chlorocarbonate–pyridine gave the ethyl ester **37**, presumably by acylative decarboxylation.

In an earlier communication[2] we noted that reaction of the 17,20-dihydroxy-21-oic acids **1a** and **1b** (Scheme I) with acetic anhydride–pyridine at room temperature affords the 17,20-diacetoxy-21-oic acids **2a** and **2b** as major products. We also recorded that a significant neutral fraction was generated in the reaction, but this material was not studied in detail at that time. Our more recent interest in cyclic derivatives of the pregnane side chain led us to reinvestigate this reaction. We have found, as originally postulated,[3] that the major neutral products are the 20-acetoxy-21,17α-lactones **4a** and **4b**. This paper describes a general procedure for the direct preparation of 21,17α-lactones, some of the typical reactions which these compounds undergo, and a study of the structural features which favor β-lactone formation.

Treatment of the 17,20α-dihydroxy-21-oic acid **1a** with equal volumes of acetic anhydride and pyridine for 18 hr at 5° followed by careful partitioning of the reaction mixture between methylene chloride and cold, dilute sodium bicarbonate solution provided roughly equal amounts of acidic and neutral fractions. In accord with our previous findings the 17,20α-diacetoxy-21-oic acid **2a** was obtained in a yield of 41%. Direct crystallization of the neutral fraction gave the β-lactone **4a** in a yield of 33%. Similar treatment of the 17,20β-dihydroxy-21-oic acid **1b** resulted in the formation of predominantly acidic material from which both the 17,20β-diacetoxy-21-oic acid **2b** and the 17-hydroxy-20β-acetoxy-21-oic acid **3b** (as the methyl ester) were each obtained in a yield of 33%. The minor neutral fraction furnished the β-lactone **4b** in 8% yield.

Assignment of β-lactone structures to **4a** and **4b** was made on the basis of the following evidence: (a) the ir spectrum which showed no hydroxyl absorption and the presence of a new intense carbonyl band at 1820 cm^{-1} which is characteristic of β-lactones;[4] (b) the ready loss of carbon dioxide in the mass spectrograph coupled with a fragmentation pattern consistent with the proposed structures; and (c) the conversion of **4a** and **4b** in methanolic sodium hydroxide to the known methyl esters **5a** and **5b**.

Only a few examples of the direct formation of β-lactones from β-hydroxy acids have been recorded in the literature[5] since an earlier review by Zaugg[6] stated categorically that "...β-lactones cannot be prepared from their corresponding hydroxy acids or esters." It is of interest to speculate on the mechanism of the reaction which must necessarily be highly dependent on the steric factors which promote either acetylation at C-17 or cyclization to β-lactones. A plausible mechanism (Scheme II) involves initial conversion of the dihydroxy acid (a) to the mixed anhydride (b). The point of nucleophilic attack by the hydroxyl oxygen at C-17 determines the nature of the resulting products. Attack on the acetate carbonyl group followed by cleavage of the anhydride bond (pathway 1) affords the 17-acetoxy acid (c); attack on the carboxyl carbonyl group followed by elimination of acetic acid (pathway 2) gives the β-lactone (d). Such a mechanism is similar to that postulated by Diassi and Dylion in the conversion of yohimbine to its β-lactone, β-yohimbine.[7] Examination of Dreiding models of the glycolic acids **1a** and **1b** serves to explain the lower yields of β-lactone from the 20β epimer. Pathway 2 is less favored in the reaction of **1b** because approach of the C-17 oxygen to the anhydride carboxyl carbonyl group would be accompanied by serious impingement of the 20-hydroxyl (or acetoxyl) on the angular methyl group at C-18. This steric hindrance also manifests itself in an inhibition of pathway 1, since only half of the isolated acidic material was acetylated at C-17.

(1) This work was supported largely by a research grant, AM01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service. We are grateful to this institute for its continued and generous support of our research.

(2) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1773 (1963).

(3) M. L. Lewbart, Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., 1961.

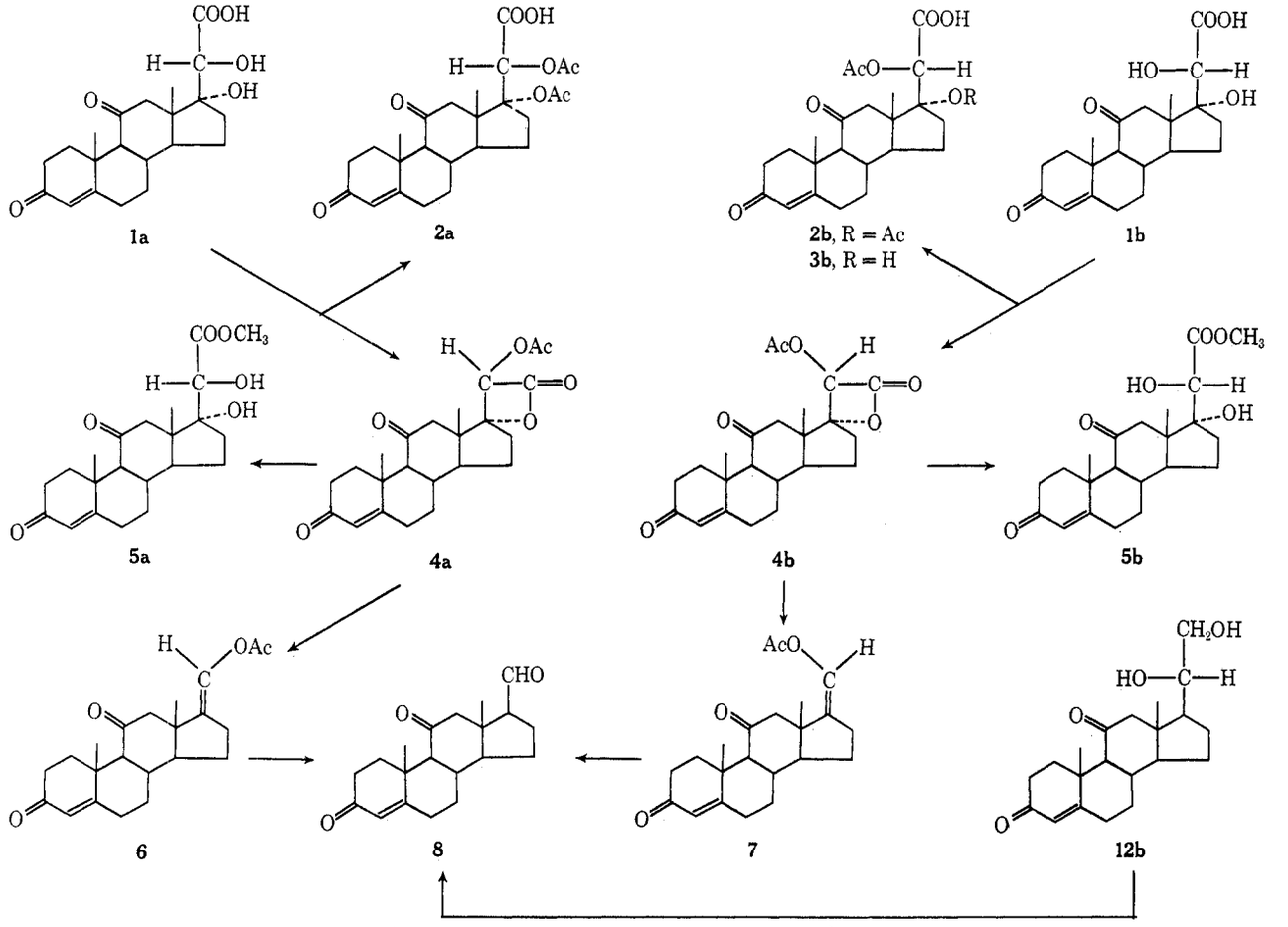
(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 179.

(5) F. Merger, *Chem. Ber.*, **101**, 2413 (1968), and other work cited.

(6) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).

(7) P. A. Diassi and C. M. Dylion, *J. Amer. Chem. Soc.*, **80**, 3746 (1958).

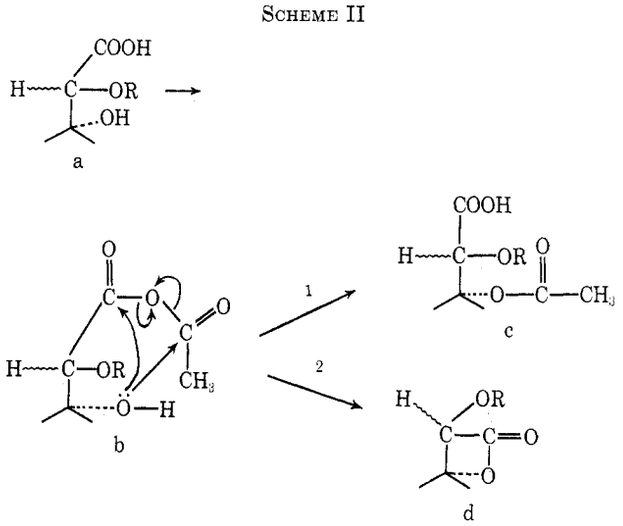
SCHEME I[a]



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

The crystalline β-lactones **4a** and **4b** are stable at −20° but decompose slowly at room temperature as evidenced by a progressive decrease in their melting points and the formation from each of a chromatographically more mobile product. The same products could be obtained by refluxing **4a** and **4b** in benzene for several days and were identified as decarboxylation products, namely the trans and cis enol acetates **6** and **7**. The stereochemical assignments were made on the basis of nmr spectral properties (*vide infra*). Enol acetates of this type have not been described previously, and it is likely that they can be prepared only by decarboxylation of 21,17α-lactones, since forced acetylation of the aldehyde **8** affords the geminate diacetate as sole product.[8] Treatment of the enol acetates **6** and **7** with methanolic sodium hydroxide afforded the aldehyde **8** as a common product. Confirmation of the structure of **8** was obtained by its independent synthesis from the glycol **12** by oxidation with 1 equiv of metaperiodic acid.[9]

SCHEME II



In view of the successful use by Diassi and Dylion of ethyl chlorocarbonate–pyridine in the preparation of β-yohimbine, it seemed of interest to study the reaction of glycolic acids **1a** and **1b** (Scheme III) with this reagent. Treatment of **1a** in cold pyridine with excess ethyl chlorocarbonate for 1 hr at room temperature gave the 20α-cathyl-β-lactone **13a** in nearly quantitative yield. The reaction of **1b** proved to be considerably more complex in that a significant acidic fraction was obtained, and the neutral fraction consisted of several components. From the acidic fraction was re-

(8) M. L. Lewbart, unpublished experiments.

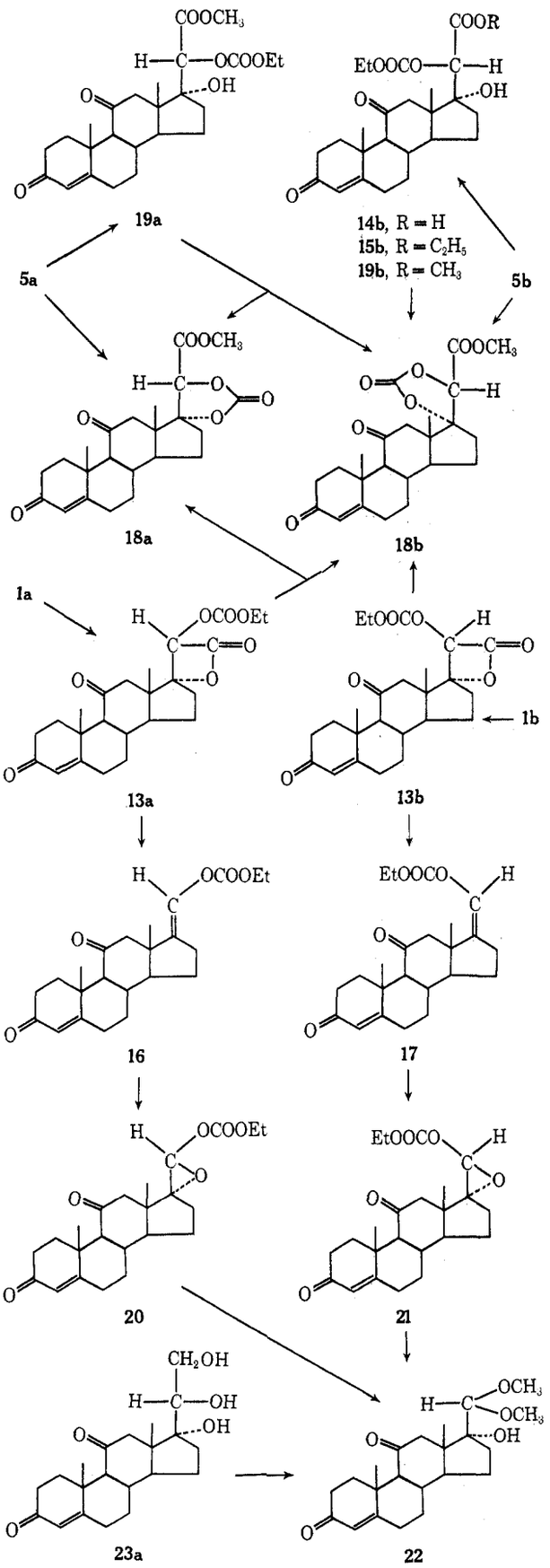
(9) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938). The glycol **12** which had first been described by Sarett,[10] was prepared for the present study by a three-step reaction sequence from 11β,20β,21-trihydroxypregn-4-en-3-one (**9**).[11] Acetonation of **9** in the usual manner[12] furnished 20β,21-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (**10**) which was oxidized with chromic anhydride–pyridine to 20β,21-isopropylidenedioxypregn-4-ene-3,11-dione (**11**). The oxidation product **11** was then hydrolyzed to the desired glycol **12** in 60% acetic acid.[12]

(10) L. H. Sarett, *J. Amer. Chem. Soc.*, **68**, 2478 (1946).

(11) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *ibid.*, **81**, 3291 (1959).

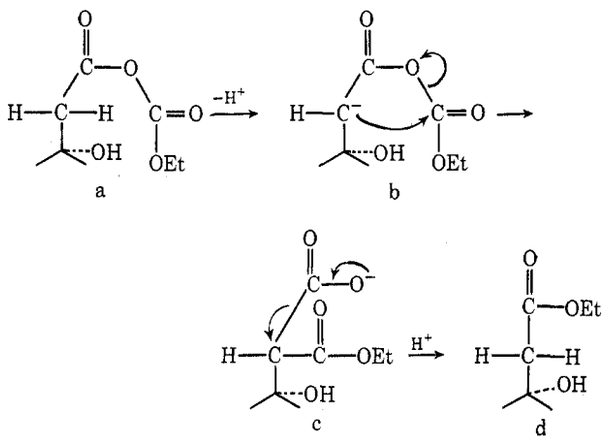
(12) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).

SCHEME III



covered the 17-hydroxy-20β-cathyl-21-oic acid **14b**. Silica gel chromatography of the neutral fraction provided in addition to the desired 20β-cathyl-β-lactone

SCHEME IV



13b (18%) its decarboxylation product **17** (*vide infra*) which was generated during chromatography. Further development of the column gave the 20β-cathyl ethyl and methyl esters **15b** and **19b** whose identity was established by independent synthesis. The formation of the ethyl ester **15b** probably results from acylative decarboxylation of the mixed anhydride (Scheme IV); the methyl ester **19b** probably arises as a transesterification artifact resulting from manipulation of the original neutral fraction in methanol. The much lower yield of β-lactone from **1b** as compared with its 20α epimer, together with the nature of the by-products formed in the reaction with ethyl chlorocarbonate–pyridine, again confirms the reduced ability of mixed anhydrides from 17,20β-dihydroxy-21-oic acids to undergo 17,21 interaction. It is also of interest to note that acylation at C-17 does not occur with this reagent, most probably because the negative ethoxyl group inactivates inductively the cathyl carbonyl group in the mixed anhydride.

Reaction of the 20β-cathyl-β-lactone **13b** with methanolic sodium hydroxide gave a single product which by ir analysis lacked hydroxyl groups and possessed an intense carbonyl band at 1812 cm^{-1}. Its identity as the methyl ester 17,20β-cyclic carbonate **18b** was established by its independent synthesis from the methyl ester **5b** both by treating its cathylation product **19b** with methanolic sodium hydroxide and by reaction of **5b** with phosgene in pyridine.[13] Reaction of the 20α-cathyl-β-lactone **13a** with methanolic sodium hydroxide resulted in a more complex mixture which gave after chromatography a small amount of the dihydroxy methyl ester **5a** and a mixture ([α]D 151°) of methyl ester 17,20-cyclic carbonates **18a** and **18b**, in which the 20β epimer predominated (for pure **18a**, [α]D 120°; for pure **18b**, [α]D 160°). Of the synthetic pathways explored, the methyl ester 17,20α-cyclic carbonate **18a** could be prepared only by reaction of the methyl ester **5a** with phosgene in pyridine, since treatment of the 20α-cathylate **19a** with methanolic sodium hydroxide also afforded an epimeric mixture of cyclic carbonates. Similar reaction of the cyclic carbonate **18a** also effected epimerization at carbon 20 giving a mixture with [α]D 157°. We believe that this unidirectional epimerization is analogous to that seen in 17,20-acetonido-21-oates[14] and that the steric factors which

(13) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).
(14) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3513 (1969).

favor formation of the 20β epimer are also operative in the case of methyl ester 17,20-cyclic carbonates. A practical application of the epimerization undergone by methyl ester 17,20α-cyclic carbonates was made to improve the yield of the 20β-hydroxyglycolic acid **1b** obtained in the alkaline rearrangement of 17-hydroxy-3,11,20-trioxopregn-4-en-21-al (cortisone glyoxal). Normally the yields of 20α and 20β epimers are approximately 50 and 30%, respectively.[2] However, when the original crude methyl esters were converted to the 17,20-cyclic carbonates *via* the 20-cathylates and epimerized in methanolic alkali, the yield of 20β epimer (as the methyl ester 20-acetate) was nearly doubled (55%) at the expense of the 20α epimer (9%).

Decarboxylation of the 20-cathyl-β-lactones **13a** and **13b** to the respective trans and cis enol cathylates **16** and **17** could be effected in refluxing methanol. Also formed in small amounts were the respective methyl ester 20-cathylates **19a** and **19b**. Preparation of the enol cathylates **16** and **17** was also achieved without isolation of the β-lactones by successive reaction of the glycolic acids **1a** and **1b** with ethyl chlorocarbonate–pyridine and refluxing methanol. Following column chromatography the trans and cis enol cathylates were obtained in overall yields of 75 and 37%, respectively.

Stereochemical assignments of the enol acetates **6** and **7** and the enol cathylates **16** and **17** were made by comparison of their nmr spectra.[15] The most important criteria are as follows: (1) the larger long-range coupling constants of the vinylic protons at C-20 in **6** and **16** (J = 2.7 Hz) are associated with the transoid form;[16] (2) the presence of a selectively deshielded 12β proton near τ 7 in **7** and **17** is indicative of a substituent close to the C ring; and (3) the slight downfield shifts of about 0.05 ppm in **7** and **17** of the C-18 angular methyl groups are as expected because of the greater proximity of the acyl groups in the cis isomers.

Further information as to the properties of the enol cathylates **16** and **17** was obtained by treating them with *m*-chloroperbenzoic acid in methylene chloride. From each reaction mixture was isolated a product in which the cathyl group and the Δ^4-3-keto system were intact. These products which have been designated the epoxy cathylates **20** and **21** gave, after sequential reaction with methanolic potassium bicarbonate and methanolic hydrogen chloride, a common product, namely the 17α-hydroxy-17β-formyl dimethyl acetal **22**. This compound was also prepared in 86% yield by reaction of the glycerol **23a**[14] with 1 equiv of metaperiodic acid in aqueous methanol followed by treatment of the crude aldehyde with methanolic hydrogen chloride.

As an approach to the better definition of steric requirements for β-lactone formation in the reaction of the glycolic acids **1a** and **1b** with acetic anhydride– and ethyl chlorocarbonate–pyridine, it seemed of interest to establish what role if any is played by the hydroxyl group at C-20. This study required the synthesis of the 20-deoxy acid **34** (Scheme V). A key intermediate in the projected reaction sequence is the heretofore undescribed 20-deoxycortisol **29**. We have previously described the preparation of 17,21-diols in the 5β-pregnane series by lithium aluminum hydride reduction of 17,20-oxido-21-ols.[17] Utilizing this same approach, both possible epoxides **26a** and **26b** were prepared, the 20β epimer by reaction with alkali of the 20α-tosylate **25a** [which was obtained from 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one (**24a**)[14] with tosyl chloride in pyridine]; the 20α epimer by perbenzoic acid oxidation of the commercially available *cis* dienediol **28**.[18] Lithium aluminum hydride reduction of either **26a** or **26b** followed by selective oxidation at C-3 with DDQ[19] and column chromatography gave the 17,21-diol **29** in a yield of 40–50%. The compound was recovered either as a nicely crystalline solvate with methylene chloride or as its 21-acetate **30**. Oxidation of **30** with chromic anhydride–pyridine afforded the 11-ketone **32** which on saponification gave 20-deoxycortisone **31**. Oxidation of **31** with chromic anhydride in acetic acid followed by treatment of the acidic fraction with diazomethane gave the methyl ester **33** in a yield of 30%; saponification of **33** furnished the desired β-hydroxy acid **34**.

Reaction of **34** with acetic anhydride–pyridine under the same conditions used in the synthesis of β-lactones **4a** and **4b** from glycolic acids **1a** and **1b** provided only a small neutral fraction which was composed of three products in roughly equal amounts. Since the ir spectrum of this mixture showed no significant absorption in the carbonyl region above 1750 cm^{-1}, it was concluded that β-lactone formation did not occur. After treatment of the acidic fraction with diazomethane, the major product was isolated and identified as the methyl ester 17-acetate **35**. It is therefore evident that in the reaction of the 20-deoxy acid **34** with acetic anhydride–pyridine formation of the 17-acetoxy acid **36** predominates. The structure of **35** was proven by its synthesis in low yield from the 17-hydroxy methyl ester **33** by forced acetylation.

In contrast to the reaction of the 20-deoxy acid **34** with acetic anhydride–pyridine, treatment with ethyl chlorocarbonate–pyridine gave a negligible acidic fraction. Examination of the neutral fraction by ir analysis showed a moderate band at 1822 cm^{-1}, indicating only minimal conversion of **34** to its β-lactone. The major product was the ethyl ester **37**, as confirmed by its synthesis from the methyl ester **33** by transesterification in ethanolic sodium hydroxide. These experiments demonstrate the necessity of the 20-hydroxyl group (as its acylate) in β-lactone formation. This finding is in agreement with the general view[20] that the presence of electronegative substituents in the α position facilitates ring closure. Further comment may be made on the divergent reaction pathways from the 20-deoxy acid **34** brought about by the two acylating reagents. As in the reaction of glycolic acids **1a** and **1b** with acetic anhydride–pyridine, acetylation at C-17 in **34** occurs *via* pathway 1 in Scheme II. In the reaction of **34** with ethyl chlorocarbonate–pyridine, however, neither pathway in Scheme II occurs to a significant extent. Instead, we propose that the mixed anhydride (a, Scheme IV) undergoes acylative decarboxyla-

(15) We wish to thank Dr. Byron H. Arison of the Merck Institute for the determination and interpretation of the nmr spectra.

(16) S. Steinhell and G. P. Newsoroff, *Tetrahedron Lett.*, **No. 58**, 6117 (1968).

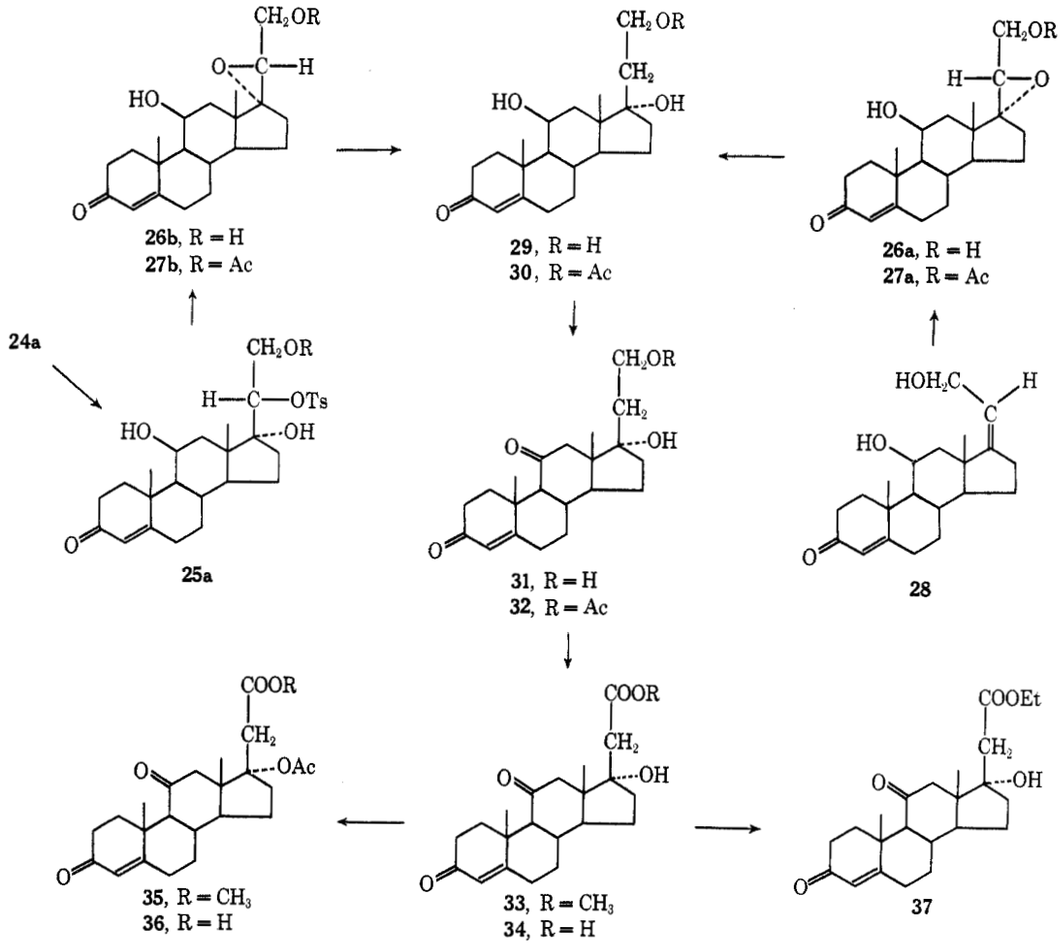
(17) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **33**, 1707 (1968).

(18) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Amer. Chem. Soc.*, **77**, 4436 (1955).

(19) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Lett.*, **No. 9**, 14 (1960).

(20) Y. Etienne and N. Fischer, *Chem. Heterocycl. Compounds*, **19** (2), 796 (1964).

SCHEME V



tion[21] through initial loss of a proton at C-20, giving the anion (b). Attack by the carbanion on the cathylate carbonyl group accompanied by an electron shift gives the carboxylate (c) which readily loses carbon dioxide, and affords after protonation the ethyl ester (d).

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. Unless noted otherwise measurements were made in chloroform solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Infrared (ir) spectra were determined as KBr pellets with a Beckman IR-8 instrument. Nmr spectra were determined with a Varian HA-100D instrument in $CDCl_3$, using TMS as an internal standard. Ultraviolet (uv) spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. General procedures for column and thin layer (tlc) chromatographic techniques and the processing of reaction mixtures have been cited earlier.[12] Elemental analyses were by August Peisker-Ritter, Brugg, Switzerland, E. Thommen, Basel, Switzerland, and the Merck Institute, Rahway, N. J.

Reaction of 17,20α-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (1a) with Acetic Anhydride–Pyridine.—The glycolic acid[2] (500 mg) was treated with 1 ml each of acetic anhydride and pyridine for 20 hr at 5°. The solution was added to an ice–water mixture and the milky suspension was extracted with methylene chloride. An initial wash with cold, dilute hydrochloric acid was discarded. The organic layer was washed with two 25-ml portions of cold, 2% sodium bicarbonate solution. The combined aqueous washings were carefully acidified with 1 *N* hydrochloric acid and the liberated acid was extracted with methylene chloride. Concentration of the water-washed organic solvent to dryness gave the acidic fraction (333 mg). Crystallization from acetone–ether afforded 252 mg (41%) of prisms, mp 204.5–206°, which possessed an ir spectrum identical with that of **17,20α-diacetoxy-3,11-dioxopregn-4-en-21-oic acid (2a)**.[2]

The neutral fraction (270 mg) was obtained from the original methylene chloride extract. Crystallization from methanol provided **20α-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (4a)** as fine needles (174 mg, mp 109–110°) in a yield of 33%: $[\alpha]_{365}$ 719°, $[\alpha]_D$ 187° (methanol); λ_{max} 238.5 mμ (ε 15,600); ν_{max} 1838 (β-lactone), 1758, 1215 cm^{-1} (acetoxyl).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; CH_3CO, 10.75. Found: C, 69.41; H, 7.25; CH_3CO, 11.04.

Treatment of **4a** (10 mg) in methanol (1.9 ml) with 1 *N* methanolic sodium hydroxide (0.1 ml) for 1.5 hr and partitioning of the reaction mixture between methylene chloride and water afforded 8 mg of prisms from acetone–*n*-hexane, mp 198–200°. A mixture melting point with **methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (5a)**[2] was 197–199.5° and their ir spectra were identical.

Reaction of 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (1b) with Acetic Anhydride–Pyridine.—Treatment of the glycolic acid (500 mg) with acetic anhydride–pyridine and separation of the crude product into acidic and neutral fractions was carried out as in the reaction of **1a**. From the acidic fraction (534 mg) was obtained 204 mg (33%) of prisms, mp 156–158°, which possessed an ir spectrum indistinguishable from that of **17,20β-diacetoxy-3,11-dioxopregn-4-en-21-oic acid (2b)**.[2] The mother liquor was treated with excess diazomethane and the crude methyl ester was chromatographed on a 20 × 750 mm silica gel column in ethyl acetate–isooctane (65:35). Fractions (6 ml) were collected at 10-min intervals. Crystallization of the contents of **fractions 121–300** from acetone–ether furnished **methyl 20β-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate** (methyl ester of **3b**)[2] as rosettes (137 mg, mp 190–190.5°; 53 mg, mp 181–183°) in a yield of 33%.

Crystallization of the neutral fraction (74 mg) from methanol

(21) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).

furnished 42 mg (8%) of **20β-acetoxy-3,11-dioxopregn-4-ene-21-17α-lactone (4b)** as needles: mp 117–118.5°, 146–147°; $[\alpha]_{365}$ 697°, $[\alpha]_D$ 180° (methanol); λ_{max} 238.5 mμ (ε 15,200); ν_{max} 1838 (β-lactone), 1759, 1212 cm^{-1} (acetoxyl).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; CH_3CO, 10.75. Found: C, 69.36; H, 7.40; CH_3CO, 10.61.

Treatment of **4b** (10 mg) with methanolic sodium hydroxide afforded 8.6 mg of prisms from acetone–ether, mp 211–213°. This product was identical in all respects with a reference sample of **methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (5b)**.[2]

20-Acetoxy-21-norpregna-4,*trans*-17(20)-diene-3,11-dione (6). From Spontaneous Decarboxylation of 4a.—A crystalline sample of 20α-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (88 mg) which had been stored at room temperature for 2 months had mp <95°. Tlc analysis in isooctane–ethyl acetate (3:2) showed considerable conversion of the β-lactone (R_f 0.12) to a more mobile artifact (R_f 0.23). Silica gel chromatography of the mixture on a 20 × 750 mm column in ethyl acetate–isooctane (1:1) was carried out, collecting 3-ml fractions every 10 min. **Fractions 126–221** furnished 49 mg of prismatic needles from ether: mp 177–178°; $[\alpha]_{365}$ 718°, $[\alpha]_D$ 186°; λ_{max} 233 mμ (ε 17,200); ν_{max} 1750, 1225 cm^{-1} (enolic acetoxyl);[4] nmr δ 9.13 (s, 3, 18-CH_3), 8.57 (s, 3, 19-CH_3), 7.88 (s, 3, CH_3CO), 3.15 (t, 1, J = 2.7 Hz, 20 H).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; CH_3CO, 12.07. Found: C, 74.60; H, 8.13; CH_3CO, 11.18.

From Refluxing Benzene on 4a.—A solution of 20α-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (95 mg) in benzene (20 ml) was refluxed for 49 hr. The residue was chromatographed on a 13 × 550 mm silica gel column under the same conditions used in the recovery of **6** from the spontaneous decarboxylation of **4a**. **Fractions 27–55** (52 mg) afforded 38 mg of prisms from methanol, mp 177–178°. The ir spectrum was identical with that of the spontaneous decarboxylation product **6**.

20-Acetoxy-21-norpregna-4,*cis*-17(20)-diene-3,11-dione (7). From Spontaneous Decarboxylation of 4b.—A crystalline sample of 20β-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (46 mg) which had been stored at room temperature for several months had mp <100° and contained a more mobile artifact with the same R_f as the trans enol acetate **6**. Silica gel chromatography furnished 5.6 mg of prisms from ether: mp 159.5–160.5°; $[\alpha]_{365}$ 680°, $[\alpha]_D$ 178°; λ_{max} 233 mμ (ε 17,650); ν_{max} 1750, 1220 cm^{-1} (enolic acetoxyl);[4] nmr δ 9.08 (s, 3, 18-CH_3), 8.57 (s, 3, 19-CH_3), 7.88 (s, 3, CH_3CO), 7.05, 6.92 (d, 1, 12β H), 3.11 (t, 1, J = 2.0 Hz, 20 H).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; CH_3CO, 12.07. Found: C, 73.99; H, 8.31; CH_3CO, 11.45.

From Refluxing Benzene on 4b.—A solution of 20β-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (98 mg) in benzene (20 ml) was refluxed for 49 hr. Silica gel chromatography of the residue provided fine needles from ethyl acetate–*n*-hexane (20 mg, mp 159–160°; 27 mg, mp 143–144°). Both crops were homogeneous by tlc analysis. The ir spectrum was identical with that of the spontaneous decarboxylation product **7**.

20β,21-Isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (10b) from 9b.—Acetonation of 11β,20β,21-trihydroxypregn-4-en-3-one[11] [1.5 g; mp 213–215°; $[\alpha]_D$ 136°; λ_{max} 242 mμ (ε 15,600)] by the usual method[12] furnished **10b** as prisms from methanol (1150 mg, mp 213–214.5°; 200 mg, mp 205–209°): $[\alpha]_{365}$ 182°, $[\alpha]_D$ 142°; λ_{max} 242 mμ (ε 15,550); ν_{max} 1209, 1160 and 849 cm^{-1} (20,21-acetonide).[12]

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.31.

20β,21-Isopropylidenedioxypregn-4-ene-3,11-dione (11b) from 10b.—Oxidation of 20β,21-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (200 mg) in pyridine (28 ml) with an equal weight of chromic anhydride for 17 hr and crystallization of the product from acetone gave 197 mg of prisms: mp 186.5–187°; $[\alpha]_{365}$ 770°, $[\alpha]_D$ 189°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1702 (11-ketone), 1212, 1159, and 851 cm^{-1} (20,21-acetonide).[12]

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.60; H, 8.85.

20β-21-Dihydroxypregn-4-ene-3,11-dione (12b) from 11b.—Treatment of 20β,21-isopropylidenedioxypregn-4-ene-3,11-dione (500 mg) with 60% acetic acid (50 ml) for 18 hr at room temperature[12] and crystallization of the product from ethyl acetate provided 410 mg (92%) of needles: mp 223–224°; $[\alpha]_{365}$ 837°, $[\alpha]_D$ 207°; λ_{max} 238 mμ (ε 15,300) [lit.[10] mp 223.5–224.5°; $[\alpha]_D$ 176° (acetone)].

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.92; H, 8.75.

17β-Formylandrost-4-ene-3,11-dione (8) from 12b.—To a solution of 20β,21-dihydroxypregn-4-ene-3,11-dione (160 mg, 0.46 mmol) in methanol (20 ml) was added sodium metaperiodate (114 mg, 0.50 mmol) in water (10 ml). After 18 hr at room temperature several drops of ethylene glycol were added, and, after 1 hr, the solution was concentrated *in vacuo* and the aqueous residue was extracted with methylene chloride. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (1:1) showed roughly equal amounts of two products (R_f 0.12 and 0.23). On the assumption that the more mobile component was the dimethyl acetal of **8**, the mixture was treated in a small volume of methanol with hot water (50 ml) and several drops of 1 *N* hydrochloric acid for 1 hr on the steam bath. Extraction of the cooled reaction mixture with methylene chloride and reexamination by tlc showed a trace only of the more mobile component. Crystallization of the retreated material from ether furnished 106 mg (66%) of prisms: mp 138–140°; $[\alpha]_{365}$ 1630°, $[\alpha]_D$ 402°; λ_{max} 238 mμ (ε 15,100); ν_{max} 2740 cm^{-1} (aldehyde).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.24; H, 8.34.

8 from 6 and 7.—Treatment of 14 mg each of the *trans*- and *cis*-20-acetoxy-21-norpregna-4,17(20)-dienes in methanol (0.9 ml) with 0.2 *N* methanolic sodium hydroxide (0.1 ml) for 15 min at room temperature furnished in each case 6 mg of prisms from acetone–*n*-hexane, mp 138–140°. The products possessed an infrared spectrum identical with that of **8** prepared by periodic acid oxidation of the glycol **12b**.

20α-Carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (13a) from 1a.—To a solution of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (275 mg) in cold pyridine (3.75 ml) was added ethyl chlorocarbonate (0.21 ml). After 1 hr at room temperature the crude product was recovered and separated into acidic and neutral fractions as in the preparation of **4a**. The acidic fraction (14 mg) was discarded. The neutral fraction (326 mg) crystallized readily from methanol as prisms (295 mg, mp 124°) in a yield of 97%: $[\alpha]_{365}$ 720°, $[\alpha]_D$ 198°; λ_{max} 238 mμ (ε 16,050); ν_{max} 1839 (β-lactone), 1760, 1255, and 785 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; C_2H_5O, 10.48. Found: C, 66.73; H, 7.10; C_2H_5O, 10.57.

Reaction of 1b with Ethyl Chlorocarbonate–Pyridine.—Treatment of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (275 mg) was carried out as in the preparation of **13a** from **1a**.

20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oic Acid (14b).—Successive crystallization of the acidic fraction (48 mg) from methanol–ether and methanol furnished 24 mg of prisms: mp 145–149°; $[\alpha]_{365}$ 624°, $[\alpha]_D$ 148°; λ_{max} 238 mμ (ε 14,800); ν_{max} 1745, 1260, and 790 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{24}H_{32}O_8 \cdot 2H_2O$: C, 59.49; H, 7.49. Found: C, 59.63; H, 7.50.

20β-Carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (13b).—Two crystallizations of the neutral fraction from methanol gave 10 mg of fine needles: mp 108–109°; $[\alpha]_{365}$ 703°, $[\alpha]_D$ 183°; λ_{max} 238 mμ (ε 16,200); ν_{max} 1840 (β-lactone), 1758, 1250, and 785 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; C_2H_5O, 10.48. Found: C, 66.94; H, 7.03; C_2H_5O, 10.60.

The mother liquor residue (237 mg) was chromatographed on a 20 × 700 mm silica gel column in isooctane–ethyl acetate (55:45), collecting 5-ml fractions every 10 min. From **fractions 65–115** was obtained **20-carbethoxy-21-norpregna-4,*cis*-17(20)-diene (17**, *vide infra*) as needles from methanol (16 mg, mp 201–202°). From **fractions 125–165** (68 mg) was recovered an additional 46 mg of β-lactone **13b**, mp 112–114°.

Ethyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (15b).—The residue from **fractions 186–246** (32 mg) crystallized as platelets from aqueous methanol: mp 93–95°; $[\alpha]_{365}$ 561°, $[\alpha]_D$ 133°; λ_{max} 238 mμ (ε 15,400); ν_{max} 1745, 1255, and 788 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{26}H_{36}O_8 \cdot H_2O$: C, 63.84; H, 8.06; $2C_2H_5O$, 18.83. Found: C, 63.72; H, 7.68; $2C_2H_5O$, 17.15.

Sequential reaction of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (**5b**, 60 mg) with ethanolic sodium hydroxide and ethyl chlorocarbonate–pyridine as described previously afforded 64 mg of platelets from aqueous ethanol: mp 94–96°; $[\alpha]_{365}$ 568°, $[\alpha]_D$ 132°. The ir spectrum was identical with that of **15b** obtained from **fractions 186–246**.

Methyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19b).—The contents of **fractions 281–380** (23 mg) crystal-

lized from aqueous methanol as prisms, mp 153–154°. The infrared spectrum was indistinguishable from that of the cathylation product from methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (**5b**, *vide infra*).

Methyl 20α-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19a) from 5a.—To a solution of methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (100 mg) in cold pyridine (1 ml) was added ethyl chlorocarbonate (0.075 ml). After 2 hr at room temperature the product was recovered and crystallized from methanol as needles (98 mg, mp 172–173.5°; 13 mg, mp 171–172.5°) in a yield of 94%: $[\alpha]_{365}$ 548°, $[\alpha]_D$ 138°; λ_{max} 238 mμ (ε 15,200); ν_{max} 1745, 1255, and 791 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41; CH_3O and C_2H_5O, 16.45. Found: C, 64.30; H, 7.13; C_2H_5O, 17.78.

Methyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19b) from 5b.—Cathylation of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (100 mg) for 1.5 hr as in the preparation of **19a** afforded 119 mg (98%) of platelets from aqueous methanol: mp 153.5–155°; $[\alpha]_{365}$ 600°, $[\alpha]_D$ 142°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1745, 1255, and 790 cm^{-1} (cathylate).

Anal. Calcd for $C_{25}H_{34}O_8 \cdot 0.5H_2O$: C, 63.68; H, 7.48; CH_3O and C_2H_5O, 16.14. Found: C, 63.90; H, 7 21; C_2H_5O, 18.08.

Methyl 17,20α-Cyclocarbonyldioxy-3,11-dioxopregn-4-en-21-oate (18a) from 5a.—To a solution of methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (190 mg) in cold pyridine (5 ml) was added a 12.5% solution of phosgene in benzene (1.25 ml). After 1 hr at room temperature the product was recovered and crystallized from methanol as prismatic needles (157 mg, mp 263–265°; 22 mg, mp 248–250°) in a yield of 88%: $[\alpha]_{365}$ 491°, $[\alpha]_D$ 120°; λ_{max} 238 mμ (ε 15,800); ν_{max} 1815 and 781 cm^{-1} (cyclic carbonate).[13]

Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; CH_3O, 7.45. Found: C, 66.21; H, 6.80; CH_3O, 7.56.

Methyl 17,20β-Cyclocarbonyldioxy-3,11-dioxopregn-4-en-21-oate (18b) from 5b.—Treatment of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (78 mg) in pyridine (1 ml) with the phosgene solution (0.25 ml) for 1 hr and crystallization from methanol gave needles (70 mg, mp 264–266°; 4 mg, mp 253–255°) in a yield of 88%: $[\alpha]_{365}$ 633°, $[\alpha]_D$ 160°; λ_{max} 238 mμ (ε 15,800); ν_{max} 1810 and 778 cm^{-1} (cyclic carbonate).[13]

Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; CH_3O, 7.45. Found: C, 66.26; H, 6.84; CH_3O, 7.65.

18b from 19b.—Treatment of methyl 20β-carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (50 mg) in methanol (9.5 ml) with 0.1 *N* methanolic sodium hydroxide (0.5 ml) for 15 min at room temperature and crystallization of the product from methanol supplied 40 mg (86%) of needles, mp 264–266°, which were identical in all respects with the phosgenation product of **5b**.

18b from 13b.—Reaction of 20β-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (17 mg) in methanol (3.9 ml) with 0.2 *N* methanolic sodium hydroxide (0.1 ml) for 15 min gave 12 mg of needles from methanol, mp 263–265°. A mixture melting point with **18b** prepared from **5b** showed no depression and their ir spectra were identical.

18b from 18a.—Treatment of methyl 17,20α-cyclocarbonyldioxy-3,11-dioxopregn-4-en-21-oate (100 mg) in methanol (38 ml) with 0.1 *N* methanolic sodium hydroxide (2 ml) for 15 min at room temperature and processing in the usual manner gave 71 mg of needles: mp 260–261°; $[\alpha]_{365}$ 617°, $[\alpha]_D$ 157°. A mixture melting point with starting material was 252–257°; the ir spectrum was identical with that of **18b** prepared from **5b**. Chromatography of the mother liquor residue on a 15 × 600 mm silica gel column in ethyl acetate–isooctane (2:1) was carried out, collecting fractions (2.5 ml) every 10 min. Acetylation of the residue from **fractions 211–400** furnished 12 mg of platelets from methanol, mp 205.5–207°. The ir spectrum was identical with that of **methyl 20α-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate.**[2]

18a and 18b from 13a.—To a solution of 20α-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (50 mg) in methanol (9.5 ml) was added 0.1 *N* methanolic sodium hydroxide (0.5 ml). After 15 min the material was recovered and crystallized from methanol as leaflets: mp 245–247°; $[\alpha]_{365}$ 600°, $[\alpha]_D$ 151°. The mother liquor residue was chromatographed on a 10 × 480 mm silica gel column in ethyl acetate–isooctane (2:1), collecting 2-ml fractions every 10 min. **Fractions 29–42** afforded an additional 10 mg of the cyclic carbonate mixture, mp 241–243°. The contents of **fractions 61–160** crystallized from ethyl acetate as prisms (6 mg, mp 197–199°) which possessed an ir spectrum identical with that of **methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (5a)**.

Enhanced Yield of Methyl 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oate (5b) from Cortisone Glyoxal *via* Epimerization of 18a.—Rearrangement of cortisone glyoxal hemiacetal (3.12 g) with alkali and esterification of the acidic products with diazomethane afforded an epimeric mixture of **5a** and **5b** as described previously.[2] To the crude product in cold pyridine (25 ml) was added ethyl chlorocarbonate (3 ml). After 17 hr at room temperature ice was added to decompose the excess reagent. Repeated addition of a benzene-ethanol mixture and concentration *in vacuo* removed most of the pyridine. The residue was partitioned between methylene chloride and water, and the organic layer was taken to dryness. To the methyl ester 20-cathylate mixture in methanol (200 ml) was added 1 *N* methanolic sodium hydroxide (50 ml). After 1 min 1 *N* aqueous sodium hydroxide (250 ml) was added to the epimerized material and the solution stood for 10 min at room temperature. After concentration *in vacuo* removed most of the methanol, excess hydrochloric acid was added and the liberated glycolic acids were extracted with ethyl acetate. Successive reaction with diazomethane and acetic anhydride–pyridine afforded an epimeric mixture of methyl ester 20-acetates which were chromatographed on a 54 × 840 mm Celite column in toluene–isooctane–formamide (1500:750:250 ml), collecting 12-ml fractions every 10 min. The contents of **fractions 620–830** gave 322 mg (9.3%) of **methyl 20α-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate,**[2] mp 205–206.5°. From **fractions 871–1200** was obtained1911 mg (55.3%) of methyl 20β-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate,[2] mp 199–200°.

20-Carbethoxy-21-norpregna-4,*trans*-17(20)-diene-3,11-dione (16) and Methyl 20α-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19a) from 13a.—A solution of 20α-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (100 mg) in methanol (20 ml) was refluxed for 4 hr. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (1:1) showed that starting material (R_f 0.22) had been completely converted to two products (R_f 0.33 and 0.13). The mixture was chromatographed on a 15 × 630 mm silica gel column in the same system, collecting 2-ml fractions every 10 min.

Fractions 46–76.—Crystallization from ether gave the enol cathylate **16** as prismatic needles (56 mg, mp 137.5–138°) in a yield of 76%: $[\alpha]_{365}$ 644°, $[\alpha]_D$ 169°; λ_{max} 238 mμ (ε 15,500); ν_{max} 1755, 1250, and 785 cm^{-1} (enolic cathylate); nmr δ 9.15 (s, 3, 18-CH_3), 8.68 (s, 3, cathyl methyl), 8.58 (s, 3, 19-CH_3), 5.75 (q, 2, J = 7 Hz, cathyl methylene), 3.37 (t, 1, J = 2.7 Hz, 20 H).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; C_2H_5O, 11.66. Found: C, 71.42; H, 7.82; C_2H_5O, 11.73.

Fractions 131–230.—The residue (21 mg, 20%) crystallized from acetone as platelets, mp 166.5–168.5°. A mixture melting point with the cathylation product from **5a** was 170–173° and their ir spectra were identical.

16 from 1a.—Treatment of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (275 mg) with ethyl chlorocarbonate–pyridine was carried out in the usual manner. The combined acidic and neutral fractions were refluxed in methanol (50 ml) for 4 hr. The crude product gave, following silica gel chromatography, 210 mg (74%) of the enol cathylate **16**, mp 138–138.5°.

20-Carbethoxy-21-norpregna-4,*cis*-17(20)-diene-3,11-dione (17) and Methyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19b) from 13b.—A solution of 20β-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (49 mg) in methanol (4 ml) was refluxed for 4 hr. Tlc analysis in ethyl acetate–isooctane (1:1) revealed a major mobile product (R_f 0.30) and two minor components (R_f 0.08 and 0.17). The residue was chromatographed on a 13 × 620 mm silica gel column in the same system, collecting 2-ml fractions every 10 min.

Fractions 32–60.—Crystallization from methanol furnished the enol cathylate **17** as prisms (31 mg, mp 205–207°) in a yield of 71%: $[\alpha]_{365}$ 691°, $[\alpha]_D$ 179°; λ_{max} 238 mμ (ε 16,000); ν_{max} 1754, 1250, and 788 cm^{-1} (enolic cathylate); nmr δ 9.09 (s, 3, 18-CH_3), 8.68 (s, 3, cathyl methyl), 8.58 (s, 3, 19-CH_3), 6.98, 6.84 (d, 1, 12β H), 5.78 (q, 2, J = 7 Hz, cathyl methylene), 3.31 (t, 1, J = 2.0 Hz, 20 H).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; C_2H_5O, 11.66. Found: C, 71.19; H, 7.80; C_2H_5O, 11.71.

Fractions 70–105.—The crude residue possessed an ir spectrum identical with that of starting material (**13b**).

Fractions 120–220.—The pooled material (8 mg) crystallized from methanol as platelets, mp 154–155.5°. The ir spectrum was identical with that of **19b**, the cathylation product of **5b**.

17 from 1b.—Sequential reaction of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid with ethyl chlorocarbonate–pyridine and refluxing methanol as described in the preparation of **16** from **1a** afforded 104 mg (37%) of enol cathylate **17** as prisms from methanol, mp 208–210°.

17,20α-Oxido-20-carbethoxy-21-norpregn-4-ene-3,11-dione (20) from 16.—To a solution of 20-carbethoxy-21-norpregna-4,*trans*-17(20)-diene-3,11-dione (90 mg, 0.24 mmol) in methylene chloride (5 ml) was added 80 mg (0.46 mmol) of *m*-chloroperbenzoic acid. After 3.5 hr at room temperature the solution was washed with dilute alkali and water and concentrated to dryness. Direct crystallization of the product did not free it from an uv-negative contaminant. The mixture was therefore chromatographed on a 13 × 600 mm silica gel column in isooctane–ethyl acetate (7:3), collecting 3-ml fractions at 10-min intervals. **Fractions 118–170** afforded 39 mg of prisms from methanol: mp 201.5–202°; $[\alpha]_{365}$ 716°, $[\alpha]_D$ 187°; λ_{max} 238 mμ (ε 15,000); ν_{max} 1760, 1255, and 786 (cathylate), 882 cm^{-1} (epoxide).[22]

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; C_2H_5O, 11.20. Found: C, 68.97; H, 7.71; C_2H_5O, 10.61.

17,20β-Oxido-20-carbethoxy-21-norpregn-4-ene-3,11-dione (21) from 17.—Peracid oxidation of 20-carbethoxy-21-norpregna-4,*cis*-17(20)-diene-3,11-dione (90 mg) was effected as in the preparation of **20** from **16** and the crude product was similarly chromatographed on silica gel. From **fractions 151–215** were obtained 36 mg of prisms from methanol: mp 191–192°; $[\alpha]_{365}$ 620°, $[\alpha]_D$ 141°; λ_{max} 238 mμ (ε 15,050); ν_{max} 1760, 1250, and 792 (cathylate), 878 cm^{-1} (epoxide).[22]

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; C_2H_5O, 11.20. Found: C, 68.82; H, 7.70; C_2H_5O, 10.99.

20,20-Dimethoxy-17-hydroxy-21-norpregn-4-ene-3,11-dione (22) from 23a.—To a solution of 17,20α,21-trihydroxypregn-4-ene-3,11-dione[14] (181 mg, 0.5 mmol) in methanol (20 ml) was added 114 mg (0.5 mmol) of metaperiodic acid in water (10 ml). After 2 hr at room temperature several drops of ethylene glycol were added, and after 1 hr the product was recovered by extraction with methylene chloride. The crude aldehyde was treated with methanol, 0.75 *N*, in hydrogen chloride (80 ml) for 1 hr at room temperature. The reaction mixture was added to methylene chloride (250 ml) and after being washed twice with water the solution was concentrated to dryness. The residue was chromatographed on a 20 × 700 mm Celite column in the system *n*-hexane–toluene–formamide (85:65:10 ml), collecting fractions of 4 ml every 10 min. Crystallization of the residue from **fractions 146–195** gave prisms (147 mg, mp 228–229°; 15 mg, mp 226–229°) in a yield of 86%: $[\alpha]_{365}$ 777°, $[\alpha]_D$ 181°; λ_{max} 238 mμ (ε 15,500).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; CH_3O, 16.48. Found: C, 70.74; H, 8.85; CH_3O, 16.28.

22 from 20 and 21.—Solutions of the 17,20α- (and 20β-)oxido-20-carbethoxy-21-norpregn-4-ene-3,11-diones (25 mg) in methanol (5 ml) were treated with an equal volume of 0.5% methanolic potassium bicarbonate. Tlc analysis in ethyl acetate–isooctane (2:1) of the reaction mixtures after 2.5 hr at room temperature showed complete conversion of both epoxy cathylates to a more polar product (R_f 0.24). However, the recovered material consisted in each case of a binary mixture (R_f 0.24 and 0.10). To each mixture in methanol (1.5 ml) was added 3 *N* hydrogen chloride in methanol. After 1 hr at room temperature a new binary mixture (R_f 0.14 and 0.10) was recovered and chromatographed on a 12 × 580 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 2.5-ml fractions every 15 min. From the 17,20α-oxide **20** was obtained a mobile component (**fractions 106–155**, 7 mg) which crystallized from methanol as prisms, mp 216–219°, and a polar component (**fractions 196–300**, 8 mg) which could not be crystallized. The 17,20β-oxide **21** also furnished a mobile product (**fractions 111–180**, 11 mg) which crystallized from methanol as prisms, mp 218–221°, and a polar product (**fractions 221–350**, 4 mg) which had the same ir spectrum as the polar product from **20**. The mobile products were identical by ir spectroscopy with the dimethyl acetal **22** obtained by periodic acid oxidation of the glycerol **23a**.

20α-Tosyloxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (25a) from 24a.—A solution of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one 21-acetate[14] (5 g) and tosyl chloride (5 g) in pyridine (25 ml) stood for 115 hr at 5°. Addition of ice and water gave a crystalline precipitate which was washed with water and dried *in vacuo* over anhydrous calcium chloride (7.02 g, mp 175° dec). The analytical sample was obtained by recrystallization from methanol: mp 176–177° dec; $[\alpha]_{365}$ −143°, $[\alpha]_D$ 20.8°; λ_{max} 228 mμ (ε 23,100) and 242 (16,850); ν_{max} 1600, 1495, 1189, 1175, 1099, 815, and 670 (tosylate),[22] 1742 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{30}H_{40}O_8S$: C, 64.26; H, 7.19. Found: C, 64.18; H, 7.20.

17,20β-Oxido-11β,21-dihydroxypregn-4-en-3-one (26b) from 25a.—To a solution of 20α-tosyloxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (7.02 g) in methanol (300 ml) was added 1 *N* aqueous sodium hydroxide (30 ml). After 18 hr at room temperature excess ethyl acetate was added and the solution was concentrated *in vacuo* to a small volume. The product was extracted with methylene chloride and crystallized from methanol as plates (3.60 g, 85% overall from **24a**): mp 155–157° (softening at 148°); $[\alpha]_{365}$ 113°; $[\alpha]_D$ 133°; λ_{max} 242 mμ (ε 15,500); ν_{max} 1168 and 870 cm^{-1} (17,20-epoxide).[22]

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.67; H, 8.70.

Treatment of **26b** with acetic anhydride–pyridine and crystallization of the product from ether gave **17,20β-oxido-21-acetoxy-11β-hydroxypregn-4-en-3-one (27b)** as needles: mp 145–147°; $[\alpha]_{365}$ 166°, $[\alpha]_D$ 143°; λ_{max} 242 mμ (ε 16,050); ν_{max} 1742 and 1230 (acetate), 1169 and 870 cm^{-1} (17,20-epoxide).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.09; H, 8.35.

17,20α-Oxido-11β,21-dihydroxypregn-4-en-3-one (26a) from 28.—To a solution of 11β,21-dihydroxypregna-4,*cis*-17(20)-dien-3-one[18] (3.5 g) in chloroform (50 ml) was added solid perbenzoic acid (1.75 g). A crystalline precipitate began to separate after several minutes. After 2 hr at room temperature the product was filtered off and recrystallized from methanol as needles (1.95 g, mp 225–227°). The original supernatant liquid was washed with dilute alkali and water, and the residue afforded an additional 0.89 g of product, mp 222–224°, raising the yield to 77%: $[\alpha]_{365}$ 106°, $[\alpha]_D$ 137°; λ_{max} 242 mμ (ε 15,950): ν_{max} 1159 and 880 cm^{-1} (17,20-epoxide).

Treatment of **26a** with acetic anhydride–pyridine and crystallization from methanol provided **17,20α-oxido-21-acetoxy-11β-hydropregn-4-en-3-one** as needles: mp 220–222°; $[\alpha]_{365}$ 135°, $[\alpha]_D$ 133°; λ_{max} 242 mμ (ε 15,600); ν_{max} 1740 and 1230 (acetate), 1162 and 881 cm^{-1} (17,20-epoxide).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3CO, 11.08. Found: C, 71.30; H, 8.26; CH_3CO, 13.10.

11β,17,21-Trihydroxypregn-4-en-3-one (29) from 26a.—A solution of 3 g each of 17,20α-oxido-11β,21-dihydroxypregn-4-en-3-one and lithium aluminum hydride in tetrahydrofuran (250 ml) was refluxed for 2 hr. The crude product, recovered by the cautious addition of ethyl acetate and water followed by extraction with ethyl acetate, was treated in *tert*-butyl alcohol (250 ml) with DDQ (3 g) for 2.5 hr with stirring. The orange-red solution was concentrated *in vacuo* and diluted well with methylene chloride. The solution was washed successively with cold 2 *N* sodium hydroxide and water, filtered through anhydrous sodium sulfate, and concentrated to dryness. The residue was chromatographed on a 46 × 940 mm Celite column in the system chloroform–formamide (40% impregnation),[23] collecting 12-ml fractions every 10 min. The residue from **fractions 90–125** crystallized from methylene chloride as well-formed prisms (1874 mg, mp 87–90° and 145–145.5°) in a yield of 50%. For analysis a sample was crystallized from benzene (rosettes): mp 106–108°; $[\alpha]_{365}$ 35.2°, $[\alpha]_D$ 111°; λ_{max} 242 mμ (ε 15,500).

Anal. Calcd for $C_{21}H_{32}O_4 \cdot 0.5C_6H_6$: C, 74.38; H, 9.10. Found: C, 74.24; H, 9.12.

21-Acetoxy-11β,17-dihydroxypregn-4-en-3-one (30) from 29.—Treatment of 11β,17,21-trihydroxypregn-4-en-3-one (1500 mg) with 2 ml each of pyridine and acetic anhydride for 20 hr at room temperature and crystallization of the product from ethyl acetate afforded 1330 mg of prisms: mp 173.5–175.5°; $[\alpha]_{365}$ 17.3°, $[\alpha]_D$ 98.9°; λ_{max} 242 mμ (ε 15,700); ν_{max} 1730 and 1240 cm^{-1} (acetate).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; CH_3CO, 11.02. Found: C, 70.66; H, 8.79; CH_3CO, 11.30.

30 from 26b.—A solution of 2.95 g each of 17,20β-oxido-11β,21-dihydroxypregn-4-en-3-one and lithium aluminum hydride in

(22) M. L. Lewbart, *J. Org. Chem.*, **33**, 1695 (1968).

(23) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, 1779 (1963).

tetrahydrofuran (240 ml) was refluxed for 2 hr. The product was recovered, treated with DDQ, and chromatographed as in the preparation of **29** from **26a**. The residue from **fractions 108–140** was treated with 2 ml each of pyridine and acetic anhydride for 18 hr at room temperature, affording the 21-acetate **30** as prisms from ethyl acetate (1086 mg, mp 174–175°; 84 mg, mp 172–174°) in a yield of 39%.

21-Acetoxy-17-hydroxypregn-4-ene-3,11-dione (32) from 30.—Oxidation of 21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (500 mg) with an equal weight of chromic anhydride in pyridine (70 ml) was carried out for 17.5 hr. The product crystallized from methanol as prisms (485 mg, mp 180.5–181.5°) in a yield of 98%: $[\alpha]_{365}$ 665°, $[\alpha]_D$ 153°; λ_{max} 238 mμ (ϵ 15,500); ν_{max} 1735 (sh) and 1240 (acetate), 1703 cm^{-1} (11-ketone).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3CO, 11.08. Found: C, 71.20; H, 8.32; CH_3CO, 11.23.

17,21-Dihydroxypregn-4-ene-3,11-dione (31) from 32.—Saponification of 21-acetoxy-17-hydroxypregn-4-ene-3,11-dione (485 mg) in methanol (10 ml) with 1 *N* aqueous sodium hydroxide (1.5 ml) for 30 min at room temperature and crystallization of the product from acetone provided prisms (394 mg, mp 188–189°; 15 mg, mp 183–184°) in a yield of 95%: $[\alpha]_{365}$ 825°, $[\alpha]_D$ 191°; λ_{max} 238 mμ (ϵ 15,350).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.60; H, 8.75.

Methyl 17-Hydroxy-3,11-dioxopregn-4-en-21-oate (33) from 31.—To a solution of 17,21-dihydroxypregn-4-ene-3,11-dione (1485 mg) in acetic acid (57 ml) was added chromic anhydride (1290 mg) in water (3 ml). After 20 hr at 5° excess methanol was added and the reaction mixture was concentrated *in vacuo* to a small volume. The residue was divided into acidic and neutral fractions by partitioning between ethyl acetate and dilute sodium hydroxide solution. The neutral fraction (150 mg) was discarded; the acidic fraction (1200 mg) was treated with excess diazomethane and the crude methyl ester was chromatographed on a 35 × 700 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 8-ml fractions at 10-min intervals. The contents of **fractions 224–340** crystallized from ether as prisms (474 mg, mp 183–185°) in a yield of 30%: $[\alpha]_{365}$ 709°, $[\alpha]_D$ 167°; λ_{max} 238 mμ (ϵ 16,100); ν_{max} 1735 (sh) and 1720 (sh) cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08; CH_3O, 8.29. Found: C, 70.50; H, 8.04; CH_3O, 8.48.

17-Hydroxy-3,11-dioxopregn-4-en-21-oic Acid (34) from 33.—Saponification of methyl 17-hydroxy-3,11-dioxopregn-4-en-21-oate (374 mg) in methanol (3 ml) with 1 *N* sodium hydroxide (1.5 ml) was carried out for 20 min at room temperature. After most of the methanol was removed with a nitrogen stream, the aqueous residue was acidified and extracted with ethyl acetate. Crystallization from acetone gave leaflets (225 mg, mp 204–206°; 62 mg, mp 202–205°) in a yield of 80%: $[\alpha]_{365}$ 758°, $[\alpha]_D$ 173°; λ_{max} 238 mμ (ϵ 15,400).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.84; H, 7.78.

Methyl 17-Acetoxy-3,11-dioxopregn-4-en-21-oate (35) from 34.—A solution of 17-hydroxy-3,11-dioxopregn-4-en-21-oic acid (50 mg) in 0.2 ml each of pyridine and acetic anhydride stood for 3 hr at 5°. After addition of ice and water the product was extracted with methylene chloride. The residue, which possessed no significant absorption in the carbonyl region above 1750 cm^{-1}, was treated with excess diazomethane and chromatographed on a 12.5 × 560 mm silica gel column in benzene–ethyl acetate (7:3), collecting 3 ml every 10 min. The residue from **fractions 76–146** crystallized from ether as prisms (33 mg, mp 200–201°) in a yield of 57%: $[\alpha]_{365}$ 477°, $[\alpha]_D$ 110°; λ_{max} 238 mμ (ϵ 15,600); ν_{max} 1735 and 1235 (acetate), 1755 (sh) and 1740 (sh) cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; CH_3CO, 10.34; OCH_3, 7.45. Found: C, 69.31; H, 7.78; CH_3CO, 9.71; OCH_3, 7.17.

35 from 33.—To a solution of methyl 17-hydroxy-3,11-dioxopregn-4-en-21-oate (50 mg) in a mixture of acetic acid (2 ml) and acetic anhydride (0.4 ml) was added *p*-TSA (40 mg). After 2.7 hr at room temperature several drops of water were added and the reaction mixture was partitioned between methylene chloride and dilute sodium hydroxide solution. Examination of the reaction mixture by tlc in isooctane–ethyl acetate (3:2) showed a complex mixture having a minor component with the same mobility (R_f 0.11) as the methyl ester **35**. The residue was chromatographed on a 12 × 550 mm silica gel column in the same system, collecting 2-ml fractions every 10 min. The contents of **fractions 22–40** (11 mg) was shown by ir analysis to consist chiefly of the 17-hydroxy-$\Delta^{3,5}$-enol acetate. **Fractions 71–150** (37 mg) consisted of a mixture which was judged by ir analysis to be largely $\Delta^{4,17(20)}$-dienes. From **fractions 191–280** (5 mg) was obtained 2.4 mg of prisms (ether–*n*-hexane), mp 198–199.5°. A mixture melting point with **35** prepared from **34** was 199–200.5° and their ir spectra were identical.

Ethyl 17-Hydroxy-3,11-dioxopregn-4-en-21-oate (37) from 34.—To a solution of 17-hydroxy-3,11-dioxopregn-4-en-21-oic acid (108 mg) in a cold pyridine (1.5 ml) was added ethyl chlorocarbonate (0.09 ml). After 1 hr at room temperature the product was recovered and chromatographed on a 13 × 620 mm silica gel column in isooctane–ethyl acetate (65:35), collecting 2-ml fractions at 10-min intervals. Beginning at **fraction 69** the broad band which emerged was collected and the pooled material (70 mg) afforded prisms from methanol: mp 203–205° (softening at 197°); $[\alpha]_{365}$ 706°, $[\alpha]_D$ 165°; λ_{max} 238 mμ (ϵ 15,850).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; C_2H_5O, 11.60. Found: C, 70.99; H, 8.26; C_2H_5O, 12.73.

37 from 33.—Treatment of methyl 17-hydroxy-3,11-dioxopregn-4-en-21-oate (20 mg) in ethanol (1.9 ml) with 0.1 *N* ethanolic sodium hydroxide (0.1 ml) for 30 min at room temperature and crystallization of the product from ethanol gave prisms (15 mg), mp 203–205°, which were identical in all respects with **37** prepared from the reaction of **34** with ethyl chlorocarbonate–pyridine.

Registry No.—**4a**, 34647-08-0; **4b**, 34621-18-6; **5a**, 34621-19-7; **5b**, 34621-20-0; **6**, 34621-21-1; **7**, 34621-22-1; **8**, 34621-23-3; **10b**, 19448-40-9; **11b**, 18089-36-6; **12b**, 600-70-4; **13a**, 34647-09-1; **13b**, 34621-27-7; **14b**, 34621-28-8; **15b**, 34621-29-9; **16**, 34621-30-2; **17**, 34621-31-3; **18a**, 34621-32-4; **18b**, 34621-33-5; **19a**, 34621-34-6; **19b**, 34621-35-7; **20**, 34621-36-8; **21**, 34621-37-9; **22**, 34621-38-0; **25a**, 34621-39-1; **26a**, 34647-10-4; **26b**, 34621-40-4; **27a**, 34621-41-5; **29**, 34621-42-6; **30**, 34621-43-7; **31**, 34621-44-8; **32**, 34621-45-9; **33**, 34621-46-0; **34**, 34621-47-1; **35**, 34621-48-2; **37**, 34621-49-3.