40 from 42.—To a solution of bis(17-hydroxy-3,20-bisethylenedioxy-11-oxopregn-5-en-21-yl) carbonate[2] (200 mg) in pyridine (4 ml) at −12° was added 0.8 ml of thionyl chloride. After 3 hr at 5° the product was recovered in the usual manner and crystallized from methanol, affording 147 mg (76%) of needles, mp 165–166°. A mixture melting point with **40** prepared by phosgenation of **38** was 168–174° and their ir spectra were identical.

Bis(3,20-dioxopregna-4,16-dien-21-yl) Carbonate (29) from 25.—Phosgenation of 21-hydroxypregna-4,16-diene-3,20-dione (66 mg, 0.2 mmol) under condition A followed by tlc analysis showed approximately 40% of starting material. The reaction mixture was therefore rephosgenated, and the recovered material was crystallized from methanol as plates (44 mg, mp 238–240°) in a yield of 65%: $[\alpha]_D$ +152°; λ_{max} 240 mμ (ε 44,700); ν_{max} 1760, 1275, and 792 (bisteroidal carbonate), 1670 (C-3 and C-20 ketone), 1619 (Δ^4), 1590 cm^{-1} (Δ^{15}).

Anal. Calcd for $C_{43}H_{54}O_7$: C, 75.63; H, 7.97. Found: C, 75.85; H, 8.10.

29 from 39.—To a solution of bis(3,20-bisethylenedioxypregna-5,16-dien-21-yl) carbonate (50 mg) in methylene chloride (10 ml) and methanol (15 ml) was added 8% aqueous sulfuric acid (2 ml). The mixture was boiled until most of the methylene chloride was gone, then refluxed for an additional 90 min. The product, recovered after concentration *in vacuo* and methylene chloride extraction, crystallized from methanol as needles, mp 238–242°, in quantitative yield. A mixture melting point with **29** prepared by phosgenation of **25** was 240–244° and their ir spectra were identical.

Bis(3,11,20-trioxopregna-4,16-dien-21-yl) Carbonate (30) from 26.—Phosgenation of 21-hydroxypregna-4,16-diene-3,11,20-trione (68 mg, 0.2 mmol) under condition A and crystallization of the product from methanol gave 48 mg (68%) of needles: mp 171–173°; $[\alpha]_D$ +250°; λ_{max} 238 mμ (ε 48,500); ν_{max} 1760, 1272, and 786 (bisteroidal carbonate), 1670 (C-3 and C-20 ketones), 1619 (Δ^4), 1591 cm^{-1} (Δ^{16}).

Anal. Calcd for $C_{43}H_{50}O_9$: C, 72.65; H, 7.09. Found: C, 72.43; H, 6.91.

30 from 40.—Acid hydrolysis of bis(3,20-bisethylenedioxy-11-oxopregna-5,16-dien-21-yl) carbonate (50 mg) as in the preparation of **29** from **39** and crystallization from methanol furnished 35 mg (88%) of needles, mp 176–178°. The ir spectrum was identical with that of **30** prepared by phosgenation of **26** under condition A.

Registry No.—**1**, 64-85-7; **2**, 26987-64-4; **3a**, 39703-91-8; **3b**, 39703-92-9; **4**, 39833-00-6; **5**, 39833-01-7; **6**, 36675-01-1; **7**, 57-83-0; **8a**, 39833-03-9; **8b**, 39833-04-0; **9**, 72-23-1; **10**, 39833-05-1; **11a**, 39704-16-0; **11b**, 39704-17-1; **12**, 516-15-4; **13**, 13382-00-8; **14b**, 26437-02-5; **15b**, 26437-04-7; **16**, 5598-02-7; **17**, 39833-10-8; **18**, 39833-11-9; **19**, 39833-12-0; **20**, 39833-13-1; **21**, 39833-14-2; **22**, 39900-65-7; **23**, 39833-15-3; **24**, 39833-16-4; **25**, 39833-17-5; **26**, 39833-18-6; **27**, 39833-19-7; **28**, 39703-59-8; **29**, 39833-21-1; **30**, 39833-22-2; **31**, 39833-23-3; **32**, 39900-66-8; **33**, 39833-24-4; **34**, 39833-25-5; **35**, 39833-26-6; **36**, 39833-27-7; **37**, 39833-28-8; **38**, 39833-29-9; **39**, 39833-30-2; **40**, 39833-31-3; **41**, 36675-03-3; **42**, 36623-32-2; bis(17β-methyl-3,20-bisethylenedioxy-18-nor-17α-pregna-5,13(14)-dien-21-yl) carbonate, 39833-32-4.

Acknowledgment.—The author is obliged to Dr. John J. Schneider for his generous assistance throughout the course of this work.

Reactions of α-Ketols and Other 21-Hydroxy Steroids with Phosgene. III. Dehydrohalogenation Products from 20-Chloro-20,21-cyclic Carbonates[1]

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Received February 1, 1973

Dehydrohalogenation of the cyclic chlorocarbonate mixture (**1a,b**) from 11-deoxycorticosterone either in hot pyridine or acetone–sodium iodide–triethylamine affords the $\Delta^{20,21}$-20,21-cyclic carbonate **2** and the trans and cis $\Delta^{17,20}$-20,21-cyclic carbonates **3** and **4**, respectively. Sequential treatment of the cis isomer **4** with sodium borohydride and chromic anhydride–pyridine provides the 20β,21-cyclic carbonate **5b**, whereas similar reaction of the trans isomer **3** gives the 20β-hydroxy-21-camylate **6b**. Definitive configurational assignments for **3** and **4** were made by their independent synthesis *via* dehydration with thionyl chloride in pyridine of 17-hydroxy-20,21-cyclic carbonates of known orientation at C-20. Dehydrohalogenation of the cyclic chlorocarbonate mixture (**19a,b**) from 11-dehydrocorticosterone also provides three unsaturated cyclic carbonates (**20**, **21**, and **22**). The geometric isomers from **19a,b** were also synthesized *via* 17-hydroxy-20,21-cyclic carbonates. It was also found that Δ^{16} compounds, which are minor products in the dehydration of hydroxy cyclic carbonates, can be obtained in good yield when 17-hydroxy-20,21-diacetates are substrates. Structural correlations among Δ^{16}-cyclic carbonates, Δ^{16}-diacetates, and Δ^{16}-α-ketols in both the 11-deoxy and 11-keto series were made *via* Δ^{16}-20-hydroxy-21-camylates.

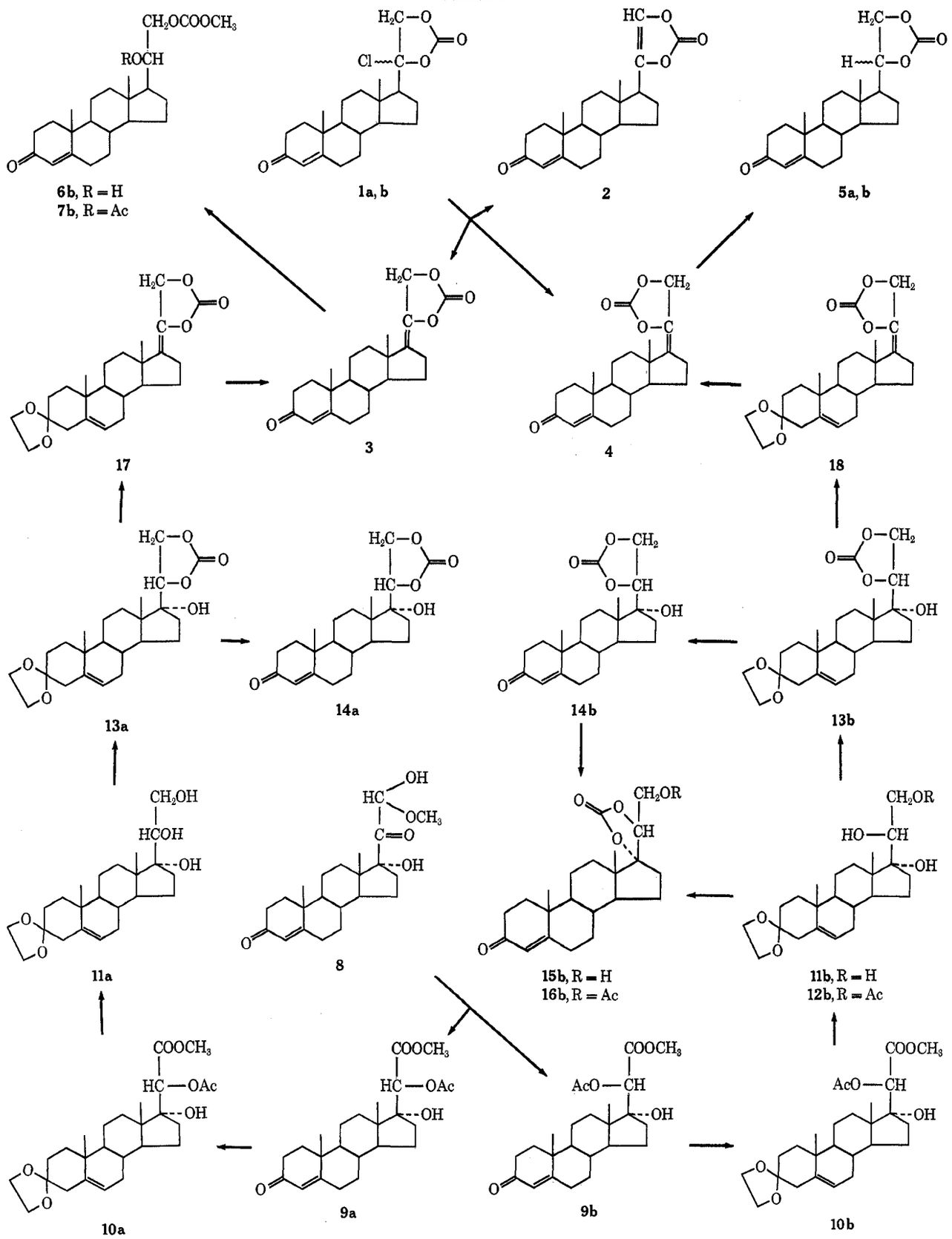
In the preceding paper[2] we reported that novel 20-chloro-20,21-cyclic carbonates are generated in the reaction of 11-deoxy- and 11-dehydrocorticosterone in pyridine with excess phosgene in benzene (condition B). The chlorocarbonates from the former α-ketol could be obtained only as an epimeric mixture (**1a,b**, Scheme I), but the corresponding 11-ketones (**19a** and **19b**, Scheme II) were isolated in pure form. Preliminary experiments directed toward purification of the epimeric mixture **1a,b** showed that loss of hydrogen chloride occurs readily, and the resulting products appeared to be of sufficient interest to warrant a separate, detailed investigation of their formation and reactions. In the present paper we describe the isolation and identification of the dehydrohalogenation products both from cyclic chlorocarbonates **1a,b** and **19a,b** as well as their independent syntheses. In the course of these studies a number of C-20-epimeric Δ^{16}-20,21-diols and their derivatives were encountered. A description of their preparation and properties will also be presented.

As described earlier,[2] addition of either steroidal or nonsteroidal primary alcohols to a solution of **1a,b** in pyridine affords mixed carbonates in good yield. It

(1) This research was supported wholly by a 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 work.

(2) M. L. Lewbart, *J. Org. Chem.*, **38**, 2328 (1973).

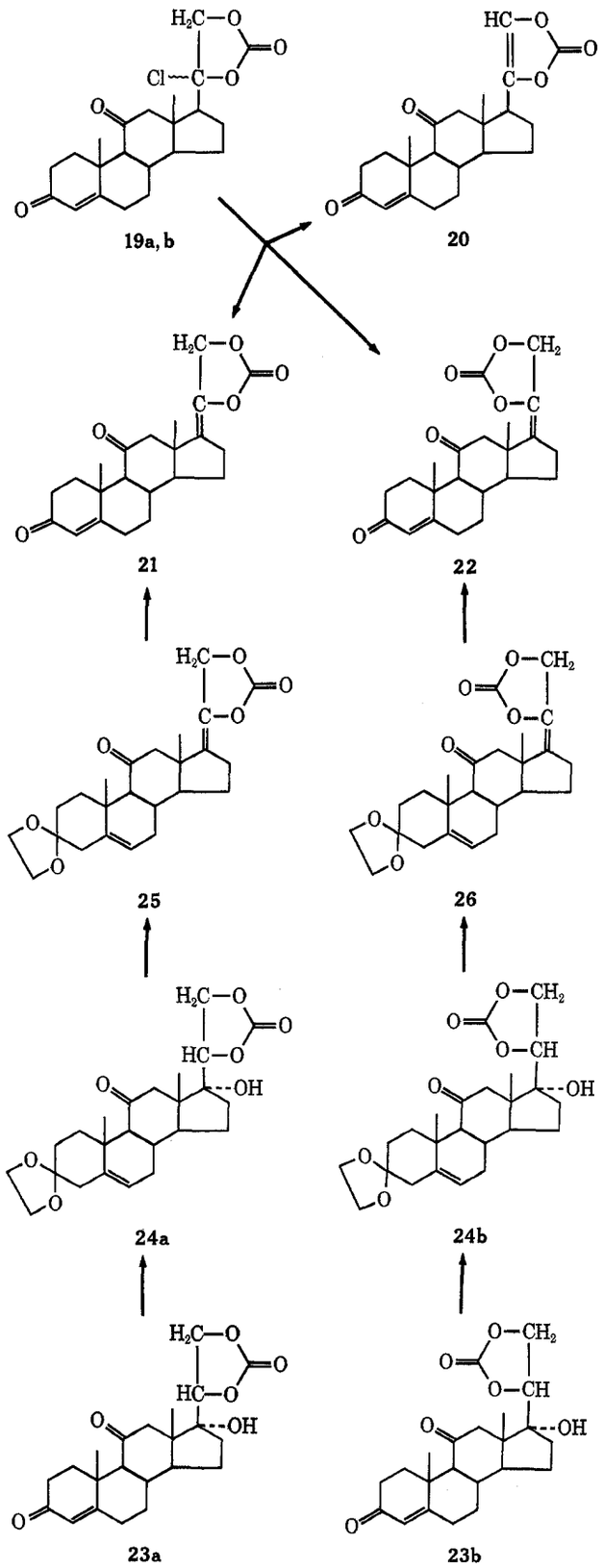
SCHEME I[a]



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

was found in control experiments that, although a solution of **1a,b** in pyridine is relatively stable for prolonged periods at room temperature, heating on the steam bath brings about a heavy deposition of water-soluble crystals (presumably pyridinium chloride) within 15 min. Analysis of the reaction mixture by tlc showed, in addition to roughly 10% each of products with the same mobilities as the 21,21′-bisteroidal

SCHEME II



carbonate[3] and free 11-deoxycorticosterone, the presence of three more mobile products which also reduce alkaline blue tetrazolium (BT). Successive fractionation of the mixture on silica gel and partitioning-type columns[4] afforded the latter substances in yields (according to decreasing mobility) of 4.5, 20.0, and 5.7%. Dehydrohalogenation of **1a,b** with acetone–sodium iodide–triethylamine at room temperature afforded two of the products in considerably better yields (3.5, 50.6, and 9.3%, respectively). Alternatively, the crude product from phosgenation of 11-deoxycorticosterone under condition B was treated directly with the latter reagent, furnishing the three products in overall yields of 1.8, 28.6, and 7.2%, respectively. When this procedure was employed the halogen exchange product, 21-iodoprogesterone,[5] was also recovered in a yield of 12.5%. The close chemical relationship of the isomeric dehydrohalogenation products was shown by conversion of all three to 11-deoxycorticosterone acetate after sequential treatment with methanolic sodium hydroxide and acetic anhydride–pyridine. In addition, prolonged refluxing of each in methanol afforded another common product, namely 21-*O*-carbomethoxypregn-4-ene-3,20-dione.[2] The infrared spectra of all three compounds exhibited intense carbonyl bands above 1800 cm^{-1}, indicating that the five-membered cyclic carbonate ring was retained. The most mobile product possessed no other carbonyl band above 1700 cm^{-1}, but the intermediate and most polar products also showed absorption maxima in the vicinity of 1735 cm^{-1}. Nmr analysis proved especially helpful in establishing the structures of these products.[6] No 21-methylene signals were observed in the most mobile product, but the 21-methylene protons which are present in the two companion substances exhibit considerable fine structure which was attributed to long-range spin coupling. This view was confirmed when irradiation in the τ 7.5 region caused collapse of the multiplets in both compounds. The nmr spectra also strongly suggested the presence of a double bond in all three products somewhere between C-16 and C-21. Based on these spectral properties and the structures of the precursors **1a,b**, the most mobile dehydrohalogenation product was assigned the $\Delta^{20,21}$-20,21-cyclic carbonate structure **2**, and its companions have been formulated as the cis and trans $\Delta^{17,20}$-20,21-cyclic carbonates **3** and **4**. However, individual configurational assignments for **3** and **4** could not be made on the basis of spectral data. The latter formulations were made with some reluctance at the time because **3** and **4** exhibited an unexplained band in the carbonyl region of their infrared spectra. However, our attention was called to recent reports[7] that anhydrohirundigenin, a 15-oxa steroid which contains no carbonyl group, also exhibits a conspicuous band at 1715 cm^{-1} (in KBr) which was attributed to a trisubstituted, heteroannular enol ether (>C=CO–) grouping. It is not surprising, therefore, that in cyclic carbonates **3** and **4**, which possess the same system but with the olefinic bond in an exocyclic position, the infrared spectra should not only contain such a band

(3) M. L. Lewbart, *J. Org. Chem.*, **37**, 3892 (1972).

(4) Control experiments showed that preliminary group separation on silica gel was essential (for reasons which are not apparent), since direct fractionation of the mixture on the Celite column led to both incomplete separations and formation of artifacts, resulting in much lower yields.

(5) T. Reichstein and O. Schindler, *Helv. Chim. Acta*, **25**, 669 (1940).

(6) The author is especially indebted to Dr. Byron H. Arison of the Merck Institute, whose determination and interpretation of the nmr spectra first made us aware of the structures of **2**, **3**, and **4**.

(7) (a) O. Kennard, J. K. Fawcett, D. G. Watson, K. A. Kerf, K. Stockel, W. Stocklin, and T. Reichstein, *Tetrahedron Lett.*, **35**, 3799 (1968); (b) K. Stockel, W. Stocklin, and T. Reichstein, *Helv. Chim. Acta*, **52**, 1175 (1969).

but that it is both intensified and displaced to a higher frequency.

Solution of the only remaining problem, the respective geometric isomerism of **3** and **4**, was attempted by chemical means. Initial experiments centered around relating them to side chain saturated cyclic carbonates of known configuration at C-20. Hydrogenation of **3** and **4** in the presence of platinum or palladium catalysts resulted in reduction of the A ring double band but not that in the side chain. Under more vigorous hydrogenation conditions reductive elimination of the C-3 oxygen also occurred. As a means of preventing this side reaction **3** and **4** were first treated with sodium borohydride in methanol in order to generate the more resistant Δ^4-3-ol system. It was found, however, that the side chain was also affected by this treatment, since the major products did not reduce BT. This finding was pursued by treating **3** and **4** successively with sodium borohydride and chromic anhydride–pyridine in order to regenerate the Δ^4-3-keto system. The identity of the major product (70%) from **4** as the 20β,21-cyclic carbonate **5b** was confirmed through its independent synthesis by phosgenation of 20β,21-dihydroxypregn-4-en-3-one.[8] In the expectation that **3** would afford the 20α,21-cyclic carbonate **5a**, this compound was also prepared by phosgenation of 20α,21-dihydroxypregn-4-en-3-one.[8] However, the major reduction–oxidation product from **3** is the 20β-hydroxy-21-camylate **6b**, which was also prepared by camylation of 20β,21-dihydroxypregn-4-en-3-one. Fixation of the camyl group at C-21 in **6b** followed from the demonstration that its acetylation product **7b** is identical with the camylation product of 20β,21-dihydroxypregn-4-en-3-one 20-acetate.[8] Proof that the cyclic carbonate **5b** is a direct hydrogenation product from **4** was forthcoming in a control experiment where successive sodium borohydride and chromic anhydride–pyridine treatment of the 21-camylate **6b** resulted in nearly complete recovery of starting material. The formation of **6b** from **3** suggests for this isomer initial methanolysis of the carbonate bond (which would be more accessible in the trans configuration) to the 20-oxo-21-camylate followed by reduction at C-20 in the normal manner It is noteworthy that the hydroxyl group in **6b** is not oxidized by chromic anhydride–pyridine, presumably because of steric hindrance imposed by the bulky camyl group at C-21.

The nature of the products obtained by sequential reduction and allylic oxidation of the $\Delta^{17,20}$-20,21-cyclic carbonates **3** and **4** suggests but by no means proves that they possess the trans and cis configurations, respectively. An independent synthesis of **3** and **4** was therefore considered essential for definitive structural assignments. A promising route appeared to be *via* dehydration of 17α-hydroxy 20,21-cyclic carbonates. Since the use of thionyl chloride in pyridine was anticipated, protection of ring A was a necessary preliminary.[9] A convenient starting point was the glyoxal hemiacetal **8**, prepared in 95% yield by oxidation of 11-deoxycortisol with methanolic cupric acetate.[10] Sequential reaction of **8** with sodium hydroxide, diazomethane, and acetic anhydride–pyridine as described in earlier papers,[11] followed by column chromatography, furnished the acetoxy methyl esters **9a** and **9b** in yields of 36 and 21%, respectively. Ketalization of **9a** and **9b** by the direct procedure of Bernstein and coworkers[12] provided the corresponding 3-ethylene ketals **10a** and **10b** in respective yields of 58 and 63%. Lithium aluminum hydride reduction of **10a** and **10b** gave the glycerol 3-ketals **11a** and **11b** in high yields. A superior route to **11b** was *via* sodium borohydride–dimethylformamide reduction of 21-acetoxy-17-hydroxypregn-5-ene-3,20-dione 3-ethylene ketal[12] to the 20β-hydroxy 21-acetate **12b** followed by saponification. Phosgenation of the glycerol 3-ketals **11a** and **11b** supplied the desired 20,21-cyclic carbonates **13a** and **13b**. As a convenient alternative the reaction sequence leading from glyoxal hemiacetal **8** to the cyclic carbonate 3-ketals can be carried out without isolating the intermediates. The overall yields of **13a** and **13b** by this procedure were 24 and 11%, respectively. Further characterization of **13a** and **13b** was accomplished by their deketalization in acetone–*p*-TSA to the corresponding Δ^4-3-ones **14a** and **14b**.[13] Since sodium borohydride reduction of 20-keto pregnanes gives 20β-ols almost exclusively,[15] the interrelationship of **12b** with the minor glycolic acid derivative **9b** speaks strongly for the 20β configuration in this series. Furthermore, it was shown that the deketalization product **14a** is identical with the phosgenation product from 17,20α,21-trihydroxypregn-4-en-3-one,[16] thus establishing unequivocally the 20α orientation of the major glycolic acid derivative **9a**.

Treatment of cyclic carbonates **13a** and **13b** with thionyl chloride in pyridine for 15 min at 5° afforded in each case a major, mobile BT-positive and a minor, polar BT-negative substance (for elucidation of the structures of the minor products, see below). Following column chromatographic separation on silica

(8) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **29**, 2559 (1964).

(9) C. C. Beard, "Organic Reactions in Steroid Chemistry," Vol. 1, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1972, p 322. The authors state that Δ^4-3-ketones are stable to thionyl chloride–pyridine at −30°, but that 17α-ols are not dehydrated at this temperature. Experience in this laboratory has shown that at the higher temperatures essential for dehydration of 17α-ols (−20 to 5°) almost quantitative loss of material from the neutral fraction occurs in the absence of a protecting group.

(10) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 2001 (1963).

(11) M. L. Lewbart and V. R. Mattox, *ibid.*, **28**, 1773 (1963).

(12) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *ibid.*, **18**, 70 (1953).

(13) The 20β,21-cyclic carbonates **13b** and **14b** appeared to undergo some alteration when methanol was used as a crystallizing solvent. It was later found that refluxing **14b** in methanol for 4 hr resulted in its almost complete conversion to a more polar hydroxy cyclic carbonate. Since treatment of **14b** with methanolic sodium hydroxide (a reagent known to isomerize 17α-hydroxy-20β,21-cyclic carbonates[14]) afforded in 86% yield the same product, the artifact was identified as the 17,20β-cyclocarbonyldioxy-21-ol **15b**. Confirmation of this structural assignment was obtained by showing that its acetylation product **16b** is identical with the phosgenation product from 21-acetoxy-17,20β-dihydroxypregn-4-en-3-one (M. L. Lewbart, unpublished synthesis). Further investigation showed that of three 11-oxygenated 17α-hydroxy-20β,21-cyclic carbonates,[14] only the 11β-ol undergoes isomerization in refluxing methanol to the 17,20β-cyclocarbonyldioxy-21-ol[14] in 92% yield. The other compounds which bear β-acetyl and carbonyl functions at C-11 and all four 17α-hydroxy-20α,21-cyclic carbonates are not affected by refluxing methanol. Isomerization of glycerol 20,21-cyclic carbonates is therefore limited to 20β-oriented compounds which are either unsubstituted or bear a β-hydroxyl group at C-11. The highly selective nature of the rearrangement which depends on long-range effects at C-11 is of some theoretical interest.

(14) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).

(15) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p 139.

(16) P. L. Julian, E. W. Meyre, W. J. Karpel, and W. Cole, *J. Amer. Chem. Soc.*, **73**, 1982 (1951). The 20α glycerol was prepared in this laboratory by an unpublished procedure which involves solvolysis of a 20β-tosyl-17α,21-diacetate.[17]

(17) D. K. Fukushima, N. S. Leeds, H. L. Bradlow, T. H. Kritchevsky, M. B. Stokem, and T. F. Gallagher, *J Biol. Chem.*, **212**, 449 (1955).

gel, the products from **13a** were isolated in yields of 40 and 24%. Similar fractionation of the mixture from **13b** gave the pure components in yields of 48 and 18%. Since deketalization in acetone–*p*-TSA of the major dehydration products from **13a** and **13b** gave Δ^4-3-ones identical with the dehydrohalogenation products **3** and **4**, their geometric isomerism at trans and cis,[18] respectively, can be assigned with certainty. These conclusions are valid because dehydrations involving thionyl chloride are known to occur stereospecifically.[19] The structures of the major dehydration products from **13a** and **13b** are therefore those of **17** and **18**, respectively.

A study of the dehydrohalogenation products from the 11-oxochlorocarbonates **19a** and **19b** (Scheme II) was also undertaken. For preparative purposes, it was found convenient to employ as substrate the crude product from phosgenation of 11-dehydrocorticosterone. After treatment of this material with acetone–sodium iodide–triethylamine and silica gel chromatography, a number of products could be isolated. A mobile, amorphous, Beilstein-positive component (21% yield) was identified as 21-iodopregn-4-ene-3,11,20-trione through its conversion with zinc in acetic acid to 11-ketoprogesterone. Thereafter emerged three Beilstein negative substances in overall yields (according to decreasing mobility) of 3.4, 2.0, and 16.7%. When dehydrohalogenation of the phosgenation mixture was effected in hot pyridine, only the mobile (4.4%) and polar (11.8%) products could be recovered. The companion substance with intermediate mobility was assigned the $\Delta^{20,21}$-20,21-cyclic carbonate structure **20** because its infrared spectrum is very similar to that of the 11-deoxy analog **2**.

Infrared analysis showed the remaining products to be the isomeric $\Delta^{17,20}$-20,21-cyclic carbonates **21** and **22**. Definitive configurational assignments followed from a reaction sequence similar to that used in the 11-deoxy series. Ketalization of the 20,21-cyclic carbonates **23a** and **23b**[14] afforded ketals **24a** and **24b**. Treatment of **24a** with thionyl chloride in pyridine gave a mobile BT-positive product in 55% yield and a polar BT-negative substance in 19% yield. Similar reaction of **24b** furnished in 62% yield a BT-positive compound. A more polar, unknown by-product which also reduced BT was recovered, but no significant amount of BT-negative material could be detected. Deketalization of the major dehydration products (**25** and **26**) from **24a** and **24b** gave Δ^4-3-ones indistinguishable from **21** and **22**, thus establishing their configurations as trans and cis, respectively.

At this point it seemed of interest to establish the configurations of the chlorocarbonates **19a** and **19b** by determining the nature of their dehydrohalogenation products. Treatment of the more mobile epimer with hot pyridine followed by tlc analysis indicated nearly quantitative conversion to a product with the same mobility as the cis $\Delta^{17,20}$-20,21-cyclic carbonate **22**. Under the same conditions the more polar chlorocarbonate gave a roughly 1:1 mixture of cis and trans isomers. Isomerization between cis and trans forms in hot pyridine was ruled out in control experiments. It is on the basis of these findings that the mobile chlorocarbonate, which appears to lose hydrogen chloride in a stereospecific manner, was assigned the 20β,21-cyclocarbonyldioxy-20α-chloro structure, and that the polar chlorocarbonate, which affords a significant quantity of the trans isomer, was assigned the 20α,21-cyclocarbonyldioxy-20β-chloro formulation.[2]

In the course of independent syntheses of the cis and trans $\Delta^{17,20}$-20,21-cyclic carbonates, BT-negative by-products were isolated after three of four dehydrations with thionyl chloride. Because of our general interest in the reactions of pregnan-17α-ols these substances were also investigated. On the assumption that the by-products are Δ^{16}-20,21-cyclic carbonates, efforts were directed toward devising conditions under which Δ^{16}-20,21-diols or their derivatives are major products. Dehydration of 17α-hydroxy-20,21-diacetates offered a logical approach to this series. Reaction of the acetylation products (**27a** and **27b**, Scheme III) from the glycerol 3-ketals **11a** and **11b** with thionyl chloride in pyridine afforded BT-negative products (**28a** and **28b**) in yields of 57 and 73%, respectively. Only small amounts of BT-positive products (presumably $\Delta^{17,20}$-20,21-diacetates) were detected. Saponification of **28a** and **28b** gave the glycols **29a** and **29b** in excellent yields. In order to relate the dehydration products from the glycerol diacetates to the minor dehydration products from 17-hydroxy-20,21-cyclic carbonates, and at the same time establish the location of the olefinic bond, additional transformations were carried out as follows. Treatment of glycols **29a** and **29b** with ethyl chlorocarbonate–pyridine gave the 21-cathylates **30a** and **30b** in yields of 54 and 58%, respectively. Cyclization of **30a** and **30b** in methanolic sodium hydroxide afforded in high yields the Δ^{16}-20,21-cyclic carbonates **31a** and **31b** which proved identical with the respective BT-negative by-products from **13a** and **13b**. Oxidation of 21-cathylates **30a** and **30b** with chromic anhydride–pyridine furnished a common product which was identified as the Δ^{16}-α-ketol 21-cathylate **32**, since successive saponification and acetylation gave the known Δ^{16}-α-ketol 21-acetate **33**.[20]

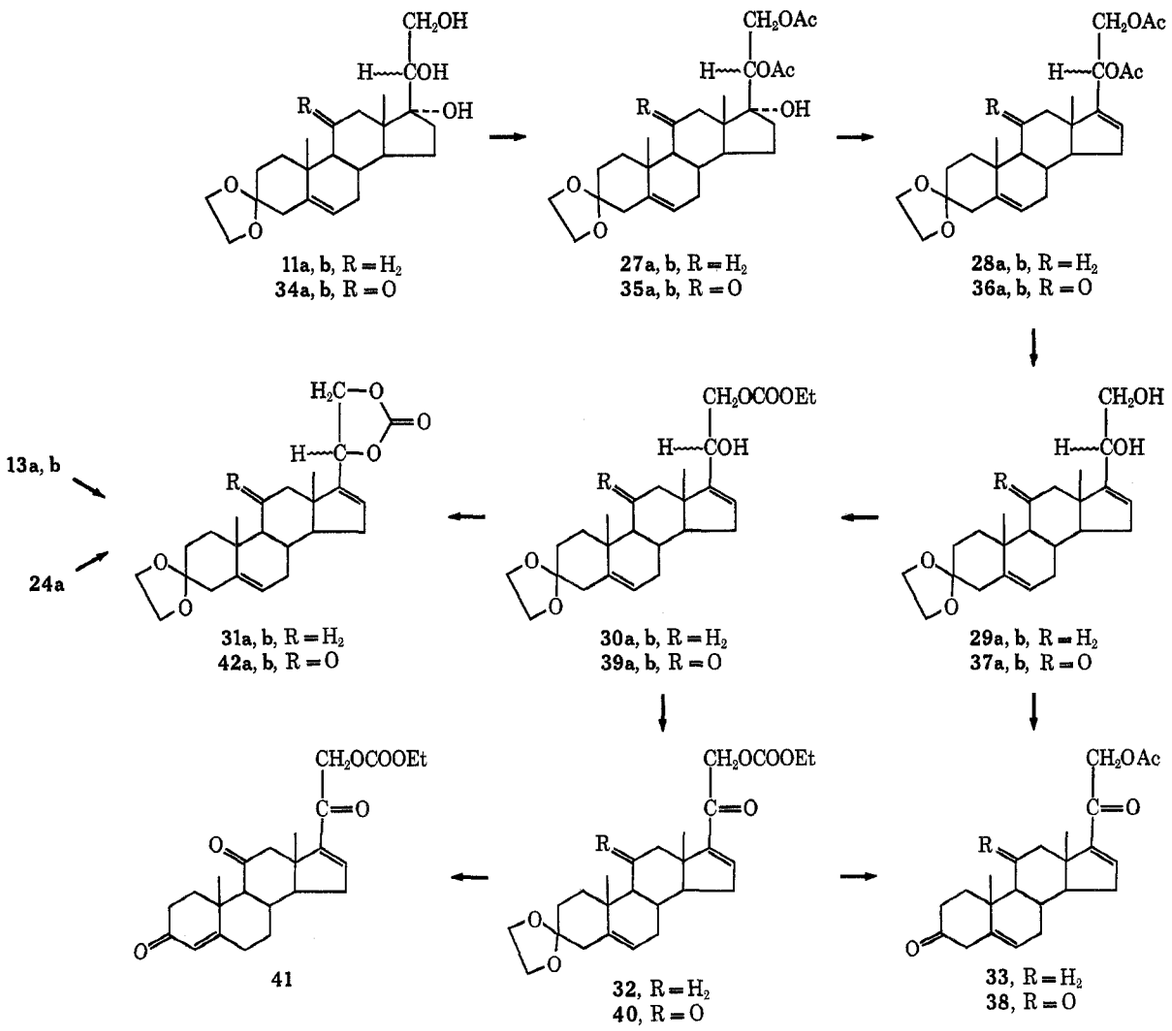
A similar reaction sequence was employed in the 11-keto series. Saponification of the cyclic carbonate 3-ketals **24a** and **24b** gave the glycerol 3-ketals **34a** and **34b**. Treatment of the acetylation product (**35a**) from **34a** with thionyl chloride gave in 78% yield the Δ^{16}-diacetate **36a** which could be saponified to the Δ^{16}-glycol **37a**. Similar dehydration of **35b** gave a major BT-negative and a minor BT-positive product which could not be separated by fractional crystallization or column chromatography. It was found, however, that following saponification of the mixture the Δ^{16}-20β,21-diol **37b** could be isolated directly in 79% yield. Acetylation of **37b** furnished a pure sample of Δ^{16}-diacetate **36b**. Structural correlation of the 11-keto Δ^{16}-glycols was accomplished in two ways. First, treatment of **37a** and **37b** with dichlorodicyanobenzoquinone (DDQ) in *tert*-butyl alcohol followed by acetylation gave in low yield a common product, namely the known Δ^{16}-α-ketol 21-acetate **38**.[20] Second, treatment of Δ^{16}-glycols **37a** and **37b** with ethyl chlorocarbonate–pyridine furnished the 21-cathylates **39a** and **39b** in yields

(18) It is understood that in $\Delta^{17,20}$-20,21-cyclic carbonates a trans configuration exists when the cyclocarbonyldioxy ring faces a direction opposite that of the angular methyl group at C-18, and that in a cis configuration the ring is oriented toward the C-18 methyl group.

(19) Reference 15, p 102.

(20) W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, **77**, 1028 (1955).

SCHEME III



of 54 and 75%, respectively. Oxidation of **39a** and **39b** with chromic anhydride–pyridine afforded the Δ^{16}-α-ketol 21-cathylate **40**. The structure of **40** was confirmed by demonstrating that its deketalization product **41** is identical with the cathylation product of 21-hydroxypregna-4,16-diene-3,11,20-trione.[20] Treatment of the 20α-hydroxy-21-cathylate **39a** with methanolic sodium hydroxide afforded the Δ^{16}-cyclic carbonate **42a** which is identical with the BT-negative by-product from **24a**. Similar reaction of **39b** gave the Δ^{16}-20β,21-cyclic carbonate **42b**, which had not been encountered previously.

When the optical rotatory properties of the four pairs of $\Delta^{17,20}$-20,21-cyclic carbonates were reviewed it was noted that in all cases the trans isomers are more levorotatory than the cis isomers by a margin of from -97 to -210 M_D units. Acetylation increments for the two pairs of Δ^{16}-20,21-diols described in this paper are of the order exhibited by D ring-saturated 20-ols,[21] namely negative shifts in M_D of -81 and -76 units in the 20α epimers and positive shifts of $+174$ and $+141$ units in the 20β epimers. An opposite effect was observed, however, when Δ^{16}-glycols are converted to cyclic carbonates. In the two available examples the 20α epimers undergo positive M_D shifts of $+48$ and $+64$ units, and the 20β epimers exhibit negative shifts of -150 and -326 units. This behavior of the Δ^{16}-20,21-cyclic carbonates is of interest, since no significant differences in M_D had been noted between epimeric 20,21-cyclic carbonates saturated in ring D.[14]

Comparison of the infrared spectral properties of the new side chain-unsaturated cyclic carbonates also proved interesting. In all four cis $\Delta^{17,20}$ isomers the carbonate carbonyl absorption is split into a major band at 1830 cm^{-1} and a minor band at 1815–1810 cm^{-1}, while in the trans $\Delta^{17,20}$ isomers carbonate carbonyl absorption appears as a single band in the range 1830–1810 cm^{-1}. Another point of difference in the infrared spectra of the $\Delta^{17,20}$ isomers lies in the location of the intense, displaced olefin band discussed earlier. The frequency range of this band is consistently higher (1741–1737 cm^{-1}) in the cis isomers than in the trans isomers (1732–1728 cm^{-1}). Other strong to very strong bands in the fingerprint region which are common to both isomers were found in the ranges 1376–1369, 1135–1124, 775–768, and 734–728 cm^{-1}. Both $\Delta^{20,21}$-cyclic carbonates exhibit moderately intense C=C stretch bands above 3100 cm^{-1} and split carbonate carbonyl bands. Other strong to very strong fingerprint bands common to both analogs appear at 1127 and 1067 cm^{-1}.

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

Experimental Section

General experimental procedures are detailed in the previous paper.[2] Unless otherwise indicated, tlc and column systems are designated in the text by a number which corresponds to one of the following compositions [in each case the number is followed (in parentheses) by that volume of ethyl acetate which, diluted to 25 ml with isooctane (or, in the case of system 8, with toluene), comprises the system]: 1 (10), 2 (11.2), 3 (12.5), 4 (8.8), 5 (16.2), 6 (15), 7 (13.8), and 8 (3).

Reaction of 20ξ,21-Cyclocarbonyldioxy-20ξ-chloropregn-4-en-3-one (1a,b) with Hot Pyridine.—A solution of the chlorocarbonates (350 mg) in pyridine (3 ml) was heated in the rings of a steam bath for 1 hr. The reaction mixture was processed in the usual fashion and the crude product was chromatographed on a silica gel column in system 1. The mixture (130 mg) was rechromatographed on a Celite column in the system isooctane–toluene–formamide (260:40:5).

20,21-Cyclocarbonyldioxypregna-4,20(21)-dien-3-one (2).—The most mobile fraction afforded 14 mg (4.5%) of prisms from ethyl acetate: mp 185–186°; $[\alpha]_D$ +140°; λ_{max} 240 mμ (ε 17,400); ν_{max} 3180 (shoulder), 3160, 1837 (1808) cm^{-1} ($\Delta^{20,21}$-cyclic carbonate); nmr δ 9.30 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.21, 5.18 (d, 1, 21-methine).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.05; H, 7.77.

20,21-Cyclocarbonyldioxypregna-4,*cis*-17(20)-dien-3-one (4).—From the intermediate fraction was obtained 63 mg (20.0%) of prisms from ethyl acetate: mp 199–201°; $[\alpha]_D$ +165°; λ_{max} 240 mμ (ε 17,400); ν_{max} 1830 (1815), 1741 cm^{-1} (cis $\Delta^{17,20}$-cyclic carbonate); nmr δ 9.04 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.18, 5.16, 5.14 (m, 2, 21-CH_2).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.09; H, 7.90.

20,21-Cyclocarbonyldioxypregna-4,*trans*-17(20)-dien-3-one (3).—The least mobile band supplied 17.6 mg (5.7%) of prisms from ethyl acetate: mp 253–254°; $[\alpha]_D$ +106°; λ_{max} 241 mμ (ε 17,150); ν_{max} 1810, 1728 cm^{-1} (trans $\Delta^{17,20}$-cyclic carbonate); nmr δ 9.07 (s, 3, 18-CH_3), 8.80 (s, 3, 19-CH_3), 5.0, 4.99, 4.97, 4.96, 4.93 (m, 2, 21-CH_2).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.10; H, 7.95.

Reaction of 1a,b with Sodium Iodide–Acetone–Triethylamine.—To a solution of the chlorocarbonates (350 mg) in acetone (23 ml) was added an equal volume of 10% sodium iodide in acetone and 0.175 ml of triethylamine. After 22 hr in the dark at room temperature most of the solvent was removed in a nitrogen stream and the residue was partitioned between methylene chloride and dilute hydrochloric acid. The crude product was chromatographed on a Celite column of the same composition as that used in fractionating the reaction mixture from hot pyridine, giving 15 mg (3.5%) of **2**, mp 184–185°, 158 mg (50.6%) of **4**, mp 199–201°, and 29 mg (9.3%) of **3**, mp 252–253°.

21-Iodopregn-4-ene-3,20-dione, 2, 3, and 4 from 11-Deoxycorticosterone.—Phosgenation of the α-ketol (1.65 g, 5 mmol) under condition B was followed by treatment of the reaction mixture in acetone (230 ml) with sodium iodide (11.5 g) and triethylamine (0.9 ml) for 20 hr. The crude product was chromatographed on a silica gel column (system 1). The 21-iodide emerged first and crystallized from acetone–*n*-hexane as rosettes [275 mg, mp 111.5° dec (on stage at 110°)] in a yield of 12.5%: $[\alpha]_D$ +217°; λ_{max} 241 mμ (ε 17,400); ν_{max} 1718 cm^{-1} (20-ketone) (lit.[5] no constants given).

Anal. Calcd for $C_{21}H_{29}O_3I$: C, 57.27; H, 6.64; I, 28.82. Found: C, 57.11; H, 6.68; I, 28.77.

Continued development of the column furnished the unsaturated cyclic carbonates (1.15 g). Rechromatography on the Celite column gave 32 mg (1.8%) of **2**, mp 183.5–185°, 509 mg (28.6%) of **4**, mp 198–200°, and 128 mg (7.2%) of **3**, mp 252–253°.

20β,21-Cyclocarbonyldioxypregn-4-en-3-one (5b) from 4.—To a solution of 20,21-cyclocarbonyldioxypregna-4,*cis*-17(20)-dien-3-one (50 mg) in methylene chloride (0.2 ml) and methanol (1.8 ml) was added 20 mg of sodium borohydride. After 30 min at 5° excess acetic acid was added and after dilution with methylene chloride the solution was washed successively with dilute sodium bicarbonate and water. To the crystalline residue in pyridine (3 ml) was added 50 mg of chromic anhydride and after 18 hr at room temperature the product was recovered in the usual manner. Crystallization from methanol gave prismatic needles (17 mg, mp 164–166°; 17 mg, mp 162–164°): $[\alpha]_D$ +93.9°; λ_{max} 239 mμ (ε 17,200); ν_{max} 1805 (1785), 780 cm^{-1} (cyclic carbonate[14]).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.59; H, 8.20.

5b from 20β,21-Dihydroxypregn-4-en-3-one.—Phosgenation of the glycol (332 mg, 1 mmol) under condition A and crystallization of the product from methanol gave prismatic needles (278 mg, mp 167.5–168°; 32 mg, mp 164–166°) in a yield of 87%. The ir spectrum was identical with that of **5b** prepared from **4**.

20α,21-Cyclocarbonyldioxypregn-4-en-3-one (5a).—Phosgenation of 20α,21-dihydroxypregn-4-en-3-one (25 mg) under condition A and crystallization from methanol gave 19 mg of prisms: mp 230–232°; $[\alpha]_D$ +101°; λ_{max} 240 mμ (ε 17,600); ν_{max} 1805, 786 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.56; H, 8.22.

21-*O*-Carbomethoxy-20β-hydroxypregn-4-en-3-one (6b) from 3.—Reduction of 20,21-cyclocarbonyldioxypregna-4,*trans*-17(20)-dien-3-one (25 mg) in 4:1 methanol–methylene chloride (2 ml) with 10 mg of sodium borohydride was followed by oxidation of the crude product with pyridine–chromic anhydride as in the preparation of **5b** from **4**. The reaction mixture was chromatographed on a silica gel column in system 1, affording 11.5 mg of needles from ethyl acetate: mp 190.5–192.5°; $[\alpha]_D$ +84.5°; λ_{max} 241 mμ (ε 16,800); ν_{max} 3480 (hydroxyl), 1756, 1275, and 798 cm^{-1} (camylate[14]).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.72; H, 8.77. Found: C, 70.74; H, 8.88.

6b from 20β,21-Dihydroxypregn-4-en-3-one.—Treatment of the glycol (100 mg) in pyridine (2 ml) at 0° with a mixture of methyl chlorocarbonate (0.2 ml) and benzene (1.8 ml) as in a condition A phosgenation and crystallization of the product from methanol gave 100 mg (85%) of needles, mp 201–203°. The ir spectrum was identical with that of **6b** prepared from **3**.

21-*O*-Carbomethoxy-20β-acetoxypregn-4-en-3-one (7b) from 6b.—Treatment of 21-*O*-carbomethoxy-20β-hydroxypregn-4-en-3-one (30 mg) with 0.1 ml each of pyridine and acetic anhydride for 3 hr at room temperature (with initial warming to effect solution) and crystallization of the product from methanol gave 21 mg of needles: mp 136–137°; $[\alpha]_D$ +115°; λ_{max} 241 mμ (ε 17,000); ν_{max} 1755, 1275, and 798 (camylate), 1740 (shoulder), 1237 cm^{-1} (acetate).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.52; H, 8.19.

7b from 20β,21-Dihydroxypregn-4-en-3-one 20-Acetate.—Camylation of the 20β-acetoxy-21-ol[8] (7.5 mg) as in the preparation of **6b** followed by purification on a silica gel column (system 1) gave 4.1 mg of platelets from acetone–*n*-hexane, mp 136–137°. The ir spectrum was identical with that of **7b** prepared from **6b**.

17,21-Dihydroxy-21-methoxypregn-4-ene-3,20-dione (8) from 11-Deoxycortisol.—Oxidation of the α-ketol (5.19 g, 15 mmol) in methanol (750 ml) with cupric acetate (750 mg) was carried out in the manner described previously.[10] The hemiacetal crystallized from methanol as rosettes (5.11 g, mp 113–116°; 0.23 g, mp 114–117°) in a yield of 95%: $[\alpha]_D$ +110°; λ_{max} 240 mμ (ε 16,900); ν_{max} 3545, 3440 (hydroxyl), 1732 cm^{-1} (20-ketone).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; CH_3O, 8.24. Found: C, 70.12; H, 8.35; CH_3O, 8.12.

Methyl 20α- (and 20β-) Acetoxy-17-hydroxy-3-oxopregn-4-en-21-oates (9a and 9b) from 8.—To a solution of 17,21-dihydroxy-21-methoxypregn-4-ene-3,20-dione (3.76 g, 10 mmol) in methanol (100 ml) at 0° was added 15 mmol of sodium hydroxide in 400 ml of water. After the clear solution stood for 1 hr at 0°, 1 *N* hydrochloric acid (17.5 ml) was added and the precipitate was extracted with ethyl acetate. The organic layer was washed with brine and concentrated to dryness. The crude acidic mixture was treated sequentially with excess ethereal diazomethane and acetic anhydride–pyridine as described earlier.[11] Several crystallizations from methanol gave **9a** as needles (820 mg, mp 185–186°): $[\alpha]_D$ +91.6°; λ_{max} 240 mμ (ε 16,900); ν_{max} 3570, 3530 (hydroxyl), 1750 (carbomethoxyl), 1750, 1240 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: 68.76; H, 7.97.

The mother liquor was chromatographed on a silica gel column in system 2. The initial fraction afforded an additional 692 mg of **9a**, mp 184–185°, raising the yield to 36%. Later eluates furnished **9b** as prisms from ethyl acetate (688 mg, mp 164–165°; 174 mg, mp 157–159°) in a yield of 21%: $[\alpha]_D$ +87.5°; λ_{max}

241 mμ (ε 17,100); ν_{max} 3500 (hydroxyl), 1750 (carbomethoxyl), 1750, 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.86; H, 8.29.

Methyl 20α-Acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (10a) from 9a.—Direct ketalization of methyl 20α-acetoxy-17-hydroxy-3-oxopregn-4-en-21-oate (1110 mg) for 11 hr was carried out as described in earlier publications.[8] The reaction mixture was treated with acetic anhydride–pyridine, since tlc analysis showed that some deacetylation had occurred. Two crystallizations from methanol gave 610 mg of platelets: mp 208–210°; $[\alpha]_D$ −30.9°; ν_{max} 3605 (hydroxyl), 1745 (carbomethoxyl), 1745, 1245 (acetate), 1092 cm^{-1} (ketal[20]).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.38; H, 8.38.

Silica gel chromatography of the moter liquor in system 3 afforded an additional 100 mg of product, mp 206.5–20.8.5°, raising the yield to 58%. Starting material (200 mg) was also recovered in later fractions.

Methyl 20β-Acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (10b) from 9b.—Ketalization of methyl 20β-acetoxy-17-hydroxy-3-oxopregn-4-en-21-oate (500 mg) as in the preparation of **10a** followed by silica gel column chromatography furnished the ketal as a filterable solid from aqueous methanol (360 mg, mp 128–130°) in a yield of 63%. Recrystallization from ethyl acetate–*n*-hexane gave small prisms: mp 185–187°; $[\alpha]_D$ −40.6°; ν_{max} 3530 (hydroxyl), 1750 (carbomethoxyl), 1750, 1230 (acetate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.68; H, 8.30.

3-Ethylenedioxypregn-5-ene-17,20α,21-triol (11a) from 10a.—An equal weight of methyl 20α-acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (850 mg) and lithium aluminum hydride was refluxed in tetrahydrofuran (100 ml) for 3 hr. The product was recovered in the usual manner except for omission of the acid wash. Crystallization from methanol gave plates (699 mg, mp 230–232°; 28 mg, mp 223–224°) in quantitative yield: $[\alpha]_D$ −51.2°; ν_{max} 3450 (hydroxyl), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.29; H, 9.32.

3-Ethylenedioxypregn-5-ene-17,20β,21-triol 21-Acetate (12b) from 11-Deoxycortisol 21-Acetate 3-Ethylene Ketal.—Reduction of the ketal acetate[12] (3.0 g) in a mixture of methylene chloride (75 ml) and dimethylformamide (150 ml) with sodium borohydride (225 mg) in the presence of sodium bicarbonate (450 mg) and water (15 ml) was carried out for 3 hr in the manner described previously.[8] Several crystallizations of the product from ethyl acetate gave 1.79 g (60%) of prisms: mp 193–194°; $[\alpha]_D$ −39.9°; ν_{max} 3480 (hydroxyl), 1729, 1240 (acetate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.24; H, 8.83.

Acetylation of the mother liquor followed by silica gel column chromatography (system 1) furnished 640 mg (19%) of the 20β,21-diacetate **27a** (*vide infra*) and 95 mg (3%) of the 20α,21-diacetate **27b** (*vide infra*).

3-Ethylenedioxypregn-5-ene-17,20β,21-triol (11b) from 12b.—To a solution of 3-ethylenedioxypregn-5-ene-17,20β,21-triol 21-acetate (868 mg, 2 mmol) in methanol (100 ml) was added 2.4 ml of 1 *N* sodium hydroxide. After 1 hr at room temperature the solution was concentrated *in vacuo* and the product was recovered by extraction with methylene chloride. Crystallization from methanol gave prisms (720 mg, mp 191–192°; 70 mg, 189.5–190°) in a yield of 97%: $[\alpha]_D$ −54.5°; ν_{max} 3450 (hydroxyl), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.51; H, 9.32.

11b from 10b.—Reduction of methyl 20β-acetoxy-17-hydroxy-3-ethylenedioxypregn-5-en-21-oate (250 mg) with lithium aluminum hydride in tetrahydrofuran as in the preparation of **11a** and three crystallizations from methanol provided 100 mg of prisms, mp 198–200°. The ir spectrum was identical with that of **11b** prepared by saponification of **12b**.

20α,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13a) from 11a.—Phosgenation of 3-ethylenedioxypregn-5-ene-17,20α,21-triol (650 mg) under condition A and silica gel column chromatography (system 3) gave 417 mg (60%) of small platelets: mp 265–266°; $[\alpha]_D$ −62.8°; ν_{max} 3480 (hydroxyl), 1805, 778 (cyclic carbonate[14]), 1105 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.08; H, 8.31.

20β,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13b) from 11b.—Phosgenation of 3-ethylenedioxypregn-5-ene-17,20β,21-triol (784 mg) under condition A followed by silica gel column chromatography (system 1) gave a minor, mobile product (247 mg, mp 240–241°) which was not investigated further. The major, less mobile component crystallized from ethyl acetate as needles (418 mg, mp 224–227°) in a yield of 50%: $[\alpha]_D$ −80.3°; ν_{max} 3520 (hydroxyl), 1805 (1785), 779 (cyclic carbonate), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.78; H, 8.29.

20α,21-Cyclocarbonyldioxy-17-hydroxypregn-4-en-3-one (14a) from 13a.—To a solution of 20α,21-cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (25 mg) in acetone (10 ml) was added 5 mg of *p*-TSA. After 18 hr at room temperature the product was recovered and crystallized from methanol as needles (14.7 mg, mp 233–235°; 2.6 mg, mp 228–230°) in a yield of 77%: $[\alpha]_D$ +52.5°; λ_{max} 240 mμ (ε 17,400); ν_{max} 3450 (hydroxyl), 1800, 778 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.45; H, 8.15.

20β,21-Cyclocarbonyldioxy-17-hydroxypregn-4-en-3-one (14b) from 13b.—Deketalization of 20β,21-cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (25 mg) in acetone–*p*-TSA as in the preparation of **14a** gave 18 mg of rosettes from ethyl acetate: mp 191–194 and 240–243°; $[\alpha]_D$ +67.3°; λ_{max} 240 mμ (ε 16,400); ν_{max} 3450 (hydroxyl), 1805 (1785), 779 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.42; H, 7.91.

17,20β-Cyclocarbonyldioxy-21-hydroxypregn-4-en-3-one (15b) from 14b.—A solution of 20β,21-cyclocarbonyldioxy-17-hydroxypregn-4-en-3-one (100 mg) in methanol (50 ml) was refluxed for 4 hr. Crystallization of the residue from acetone afforded prismatic needles (71 mg, mp 254.5–256.5°; 16 mg, mp 253–255°) in a yield of 87%: $[\alpha]_D$ +103°; λ_{max} 240 mμ (ε 17,500); ν_{max} 3400 (hydroxyl), 1790, 778 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.68; H, 8.13.

Treatment of the 20β,21-cyclic carbonate **14b** (50 mg) in methanol (9.5 ml) with 0.1 *N* methanolic sodium hydroxide (0.5 ml) for 10 min at room temperature and crystallization of the product from acetone gave 43 mg (86%) of needles, mp 255–257°, which did not depress the melting point of **15b** prepared by refluxing **14b** in methanol, and their ir spectra were identical.

17,20β-Cyclocarbonyldioxy-21-acetoxypregn-4-en-3-one (16b) from 15b.—Treatment of 17,20β-cyclocarbonyldioxy-21-hydroxypregn-4-en-3-one (25 mg) with acetic anhydride–pyridine followed by crystallization of the product from methanol gave 26 mg of needles: mp 198.5–200°; $[\alpha]_D$ +83.5°; λ_{max} 239 mμ (ε 17,700); ν_{max} 1800, 772 (cyclic carbonate), 1749, 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.06; H, 7.71.

16b from 17,20β,21-Trihydroxypregn-4-en-3-one 21-Acetate.—Phosgenation of the 21-monoacetate[13] (78 mg) under condition A furnished 72 mg (87%) of product, mp 197.5–199°, whose ir spectrum was identical with that of **16b** prepared by acetylation of **15b**.

Reaction of 20α,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13a) with Thionyl Chloride in Pyridine.—Treatment of the cyclic carbonate 3-ketal (100 mg) in cold pyridine (1.5 ml) with thionyl chloride (0.1 ml) was carried out for 15 min at 5°. The reaction mixture was processed in the usual fashion and the crude product was chromatographed on a silica gel column (system 4). The initial band afforded **20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-dien-3-one ethylene ketal (17)** as needles from ethyl acetate (29 mg, mp 207–209°; 9 mg, mp 205–207°) in a yield of 40%; $[\alpha]_D$ −51.8°; ν_{max} 1825, 1731 (trans $\Delta^{17,20}$-cyclic carbonate), 1115 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.78; H, 7.93.

Later fractions contained a BT-negative by-product which crystallized from ethyl acetate (22 mg, mp 231–233°; 3 mg, 227–229°) in a yield of 24% (*vide infra*).

Reaction of 20β,21-Cyclocarbonyldioxy-3-ethylenedioxypregn-5-en-17-ol (13b) with Thionyl Chloride in Pyridine.—Dehydration of the cyclic carbonate 3-ketal (100 mg) and silica gel chromatography of the product was performed as in the reaction of **13a**.

The mobile component, **20,21-cyclocarbonyldioxypregna-5,*cis*-17(20)-dien-3-one ethylene ketal (18)**, was obtained as needles from ethyl acetate (46 mg, mp 225–225.5°) in a yield of 48%: $[\alpha]_D$ −21.1°; ν_{max} 1830 (1810), 1739 (cis $\Delta^{17,20}$-cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.75; H, 7.89.

A BT-negative, less mobile by-product was recovered as needles from ethyl acetate (17.5 mg, mp 263–263.5°) in a yield of 18% (*vide infra*).

3 from 17.—Deketalization of 20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-dien-3-one ethylene ketal (20 mg) in acetone–*p*-TSA for 19 hr and crystallization of the product from ethyl acetate gave 14.2 mg of prisms, mp 242–253°. A mixture melting point with the least mobile dehydrohalogenation product from **1a,b** was 251.5–252.5° and their ir spectra were identical.

4 from 18.—Treatment of 20,21-cyclocarbonyldioxypregna-5,*cis*-17(20)-dien-3-one ethylene ketal (20 mg) with acetone–*p*-TSA for 17.5 hr and crystallization from ethyl acetate afforded 14.0 mg of prisms, mp 197.5–199.5°. A mixture melting point with the intermediate dehydrohalogenation product from **1a,b** was 197–198.5° and their ir spectra were identical.

Sequential Reaction of 11-Dehydrocorticosterone with Phosgene and Sodium Iodide–Acetone–Triethylamine.—The crude product from phosgenation of the α-ketol (1.72 g, 5 mmol) under condition B was dehydrohalogenated as in the sequential reactions of 11-deoxycorticosterone described previously. The final reaction mixture was chromatographed on a silica gel column (system 3). The contents of the first band (0.5 g, 21%) could not be crystallized, but the Beilstein-positive compound was identified as **21-iodopregn-4-ene-3,11,20-trione** through its conversion with zinc (700 mg) in acetic acid (12 ml) to 300 mg of prisms (methanol), mp 176–178°, whose ir spectrum was identical with that of **11-ketoprogesterone.**

20,21-Cyclocarbonyldioxypregna-4,*trans*-17(20)-diene-3,11-dione (21).—The next band afforded prisms from ethyl acetate (59 mg, mp 255–257°; 4 mg, 250–254°) in a yield of 3.4%: $[\alpha]_D$ +157°; λ_{max} 238 mμ (ε 15,600); ν_{max} 1820, 1728 cm^{-1} (trans $\Delta^{17,20}$-cyclic carbonate).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.20; H, 7.15.

20,21-Cyclocarbonyldioxypregna-4,20(21)-diene-3,11-dione (20).—Succeeding fractions furnished 35 mg (2.0%) of prisms from ethyl acetate: mp 227–228°; $[\alpha]$ +204°; λ_{max} 238 mμ (ε 16,150); ν_{max} 3180, 1839 (1810) cm^{-1} ($\Delta^{20,21}$-cyclic carbonate).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.43; H, 7.09.

20,21-Cyclocarbonyldioxypregna-4,*cis*-17(20)-diene-3,11-dione (22).—The least mobile component crystallized as needles from ethyl acetate (367 mg, mp 193–195°; 26 mg, mp 189–192°) in a yield of 16.7%: $[\alpha]_D$ +189°; λ_{max} 238 mμ (ε 16,000); ν_{max} 1830 (1810), 1738 cm^{-1} (cis $\Delta^{17,20}$-cyclic carbonate).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.27; H, 7.12.

20α,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24a) from 23a.—Direct ketalization of 20α,21-cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione[14] (2.4 g) for 8 hr by the usual procedure and crystallization from methanol gave needles (1.95 g, mp 248.5–250°; 0.20 g, mp 238–240°) in a yield of 81%: $[\alpha]_D$ −40.0°; ν_{max} 3530 (hydroxyl), 1810 (1785), 776 (cyclic carbonate), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.68; H, 7.29.

20β,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24b) from 23b.—Ketalization of 20β,21-cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione[14] (2.4 g) for 8 hr followed by silica gel column chromatography in system 5 gave a total of 2.16 g (82%) as needles from methylene chloride–methanol: mp 291–293°; $[\alpha]_D$ −48.8°; ν_{max} 3460 (hydroxyl), 1790, 774 (cyclic carbonate), 1092 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.23; H, 7.65.

Reaction of 20α,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24a) with Thionyl Chloride in Pyridine.—Treatment of the cyclic carbonate 3-ketal (300 mg) in pyridine (4.5 ml) with thionyl chloride (0.3 ml) for 15 min at 5° and silica gel column chromatography in system 6 afforded **20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-diene-3,11-dione 3-ethylene ketal (25)** as prisms from ethyl acetate (132 mg, mp 220–224°; 26 mg, mp 218–221°) in a yield of 55%: $[\alpha]_D$ −57.5°; ν_{max} 1830, 1732 (trans $\Delta^{17,20}$-cyclic carbonate), 1110 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.54; H, 7.14.

A less mobile, BT-negative by-product was also recovered as needles from ethyl acetate (49 mg, mp 249–251°; 6 mg, mp 242–244°) in a yield of 19% (*vide infra*).

Reaction of 20β,21-Cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (24b) with Thionyl Chloride in Pyridine.—Dehydration of the cyclic carbonate 3-ketal (300 mg) followed by silica gel column chromatography as in the preparation of **25** furnished **20,21-cyclocarbonyldioxypregna-5,*cis*-17(20)-diene-3,11-dione 3-ethylene ketal (26)** as leaflets from ethyl acetate–*n*-hexane (166 mg, mp 161.5–163°; 11 mg, mp 159–160°) in a yield of 62%: $[\alpha]_D$ −34.0°; ν_{max} 1829 (1810), 1739 (cis $\Delta^{17,20}$-cyclic carbonate), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.80; H, 7.43.

A less mobile, BT-positive by-product was also obtained as needles from ethyl acetate (31 mg, mp 277–278°; 17 mg, mp 267–270°). This material was not further characterized.

21 from 25.—Deketalization of 20,21-cyclocarbonyldioxypregna-5,*trans*-17(20)-diene-3,11-dione 3-ethylene ketal (25 mg) in acetone–*p*-TSA and crystallization of the product from acetone gave 18 mg (80%) of prisms, mp 256–260°. A mixture melting point with the most mobile dehydrohalogenation product from **19a,b** was 250–254° and their ir spectra were identical.

22 from 26.—Treatment of 20,21-cyclocarbonyldioxypregna-5,*cis*-17(20)diene-3,11-dione 3-ethylene ketal (25 mg) with acetone–*p*-TSA afforded 18 mg (80%) of needles, mp 188.5–190.5°. A mixture melting point with the most polar dehydrohalogenation product from **19a,b** was 189.5–191.5° and their ir spectra were identical.

3-Ethylenedioxypregn-5-ene-17,20α,21-triol 20,21-Diacetate (27a) from 11a.—Acetylation of 3-ethylenedioxypregn-5-ene-17,20α,21-triol (790 mg) in the usual fashion and crystallization from methanol supplied platelets (680 mg, mp 219–222°; 180 mg, mp 220–222°) in a yield of 90%: $[\alpha]_D$ −72.7°; ν_{max} 3450 (hydroxyl), 1740, 1240 (acetate), 1110 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.02; H, 8.40.

3-Ethylenedioxypregn-5-ene-17,20β,21-triol 20,21-Diacetate (27b) from 11b.—Acetylation of 3-ethylenedioxypregn-5-ene-17,20β,21-triol (500 mg) and crystallization of the product from ethyl acetate gave prisms (450 mg, mp 200–202°; 70 mg, mp, 198–200°) in a yield of 95%: $[\alpha]_D$ +11.8°; ν_{max} 3580 (hydroxyl), 1740, 1240 (acetate), 1112 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.91; H, 8.51.

3-Ethylenedioxypregna-5,16-diene-20α,21-diol Diacetate (28a) from 27a.—Reaction of 3-ethylenedioxypregn-5-ene-17,20α,21-triol 20,21-diacetate (800 mg) in pyridine (12 ml) with thionyl chloride (0.8 ml) was carried out for 15 min at 5°. Crystallization of the product from methanol gave 380 mg of platelets: mp 149–151°; $[\alpha]_D$ −76.2°; ν_{max} 1738, 1240 (acetate), 1670 (Δ^5), 1632 (Δ^{16}), 1099 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.92; H, 8.44.

The mother liquor was chromatographed on a silica gel column in system 8, affording an additional 60 mg of **28a**, mp 146–148°, and raising the yield of 57%. From later fractions was recovered an amorphous, BT-negative by-product (280 mg) which after deketalization in acetone–*p*-TSA and crystallization from aqueous methanol gave 144 mg of needles, mp 97–100°. Since microanalysis showed a close fit for a diacetate with the empirical formula $C_{25}H_{34}O_5$ (*Anal.* Calcd: C, 72.43; H, 8.27; CH_3CO, 20.77. Found: C, 73.08; H, 8.13; CH_3CO, 19.98.), the less mobile companion is tentatively formulated as an isomeric Wagner–Meerwein rearrangement product.

3-Ethylenedioxypregna-5,16-diene-20β,21-diol Diacetate (28b) from 27b.—Dehydration of 3-ethylenedioxypregn-5-ene-17,20β,21-triol 20,21-diacetate (1.0 g) as in the preparation of **28a** and crystallization of the product from *n*-hexane furnished 570 mg of prisms: mp 126–127°; $[\alpha]_D$ +3.54°; ν_{max} 1740, 1240 (acetate), 1670 (Δ^5), 1622 (Δ^{16}), 1090 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.52; H, 8.24.

Silica gel column chromatography of the mother liquor afforded an additional 130 mg of **28b**, mp 125–126°, raising the yield to

73%. A more polar, amorphous, BT-negative by-product (220 mg) was also recovered but was not examined further.

3-Ethylenedioxypregna-5,16-diene-20α,21-diol (29a) from 28a.—To a solution of 3-ethylenedioxypregna-5,16-diene-20α,21-diol diacetate (300 mg) in methanol (40 ml) was added 5 ml of 0.1 *N* methanolic sodium hydroxide. After 30 min at room temperature the reaction mixture was added to methylene chloride (300 ml) and the solution was washed with water. The crude product crystallized from ethyl acetate as platelets (176 mg, mp 215–217°; 41 mg, mp 212–213°) in a yield of 89%: $[\alpha]_D$ −71.7°; ν_{max} 3340 (hydroxyl), 1672 (Δ^5), 1625 (Δ^{16}), 1096 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.65; H, 9.14.

3-Ethylenedioxypregna-5,16-diene-20β,21-diol (29b) from 28b.—Saponification of 3-ethylenedioxypregna-5,16-diene-20β,21-diol diacetate (500 mg) in a mixture of methylene chloride (5 ml) and methanol (50 ml) with 0.1 *N* methanolic sodium hydroxide (5 ml) was carried out for 1 hr as in the preparation of **29a**. The product crystallized from ethyl acetate as platelets (327 mg, mp 198–200°; 41 mg, mp 194.5–197°) in a yield of 90%: $[\alpha]_D$ −42.3°; ν_{max} 3520 (hydroxyl), 1672 (Δ^5), 1621 (Δ^{16}), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.98; H, 9.24.

3-Ethylenedioxypregna-5,16-diene-20α,21-diol 21-Cathylate (30a) from 29a.—To a solution of 3-ethylenedioxypregna-5,16-diene-20α,21-diol (150 mg) in pyridine (1.5 ml) was added 50 μl of ethyl chlorocarbonate. After 19 hr at 5° the reaction mixture was chromatographed on a silica gel column (system 1). The major product was recovered as long needles from ethyl acetate–*n*-hexane (83 mg, mp 131–133°; 13 mg, mp 126–128°) in a yield of 54%: $[\alpha]_D$ −65.9°; ν_{max} 3520 (hydroxyl), 1741, 1270, and 792 (cathylate), 1096 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.87; H, 8.58.

3-Ethylenedioxypregna-5,16-diene-20β,21-diol 21-Cathylate (30b) from 29b.—Cathylation of 3-ethylenedioxypregna-5,16-diene-20β,21-diol (300 mg) in pyridine (3 ml) with ethyl chlorocarbonate (110 μl) proceeded for 19 hr at 5°. The major product, recovered as in the preparation of **30a**, crystallized as needles from ethyl acetate–*n*-hexane (205 mg, mp 163.5–165°; 3 mg, mp 159–162°) in a yield of 58%: $[\alpha]_D$ −29.6°; ν_{max} 3500 (hydroxyl), 1749 (1725), 1270 and 792 (cathylate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.13; H, 8.67.

20α,21-Cyclocarbonyldioxypregna-5,16-dien-3-one Ethylene Ketal (31a) from 30a.—Cyclization of 3-ethylenedioxypregna-5,16-diene-20α,21-diol 21-cathylate (25 mg) in methanol (3.8 ml) with 0.1 *N* methanolic sodium hydroxide (0.2 ml) for 5 min at room temperature and crystallization of the product from ethyl acetate gave 19.5 mg (87%) of needles: mp 230–233°; $[\alpha]_D$ −54.9°; ν_{max} 1800, 775 (cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.87; H, 8.18.

A mixture melting point with the minor dehydration product from **13a** showed no depression and their ir spectra were identical.

20β,21-Cyclocarbonyldioxypregna-5,16-dien-3-one Ethylene Ketal (31b) from 30b.—Cyclization of 3-ethylenedioxypregna-5,16-diene-20β,21-diol 21-cathylate (25 mg) as in the reaction of **30a** furnished 19.2 mg (86%) of needles from ethyl acetate: mp 262–264°; $[\alpha]_D$ −76.9°; ν_{max} 1794, 775 (cyclic carbonate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.86; H, 7.92.

A mixture melting point with the minor dehydration product from **13b** was 263–264° and their ir spectra were identical.

***21-O*-Carboethoxypregna-5,16-diene-3,20-dione 3-Ethylene Ketal (32) from 30a.**—Oxidation of 3-ethylenedioxypregna-5,16-diene-20α,21-diol 21-cathylate (25 mg) with chromic anhydride–pyridine by the usual procedure and crystallization of the product from ethyl acetate–*n*-hexane gave plates (13.1 mg, mp 173–175°; 7 mg, mp 170.5–172.5°) in a yield of 82%: $[\alpha]_D$ −19.8°; λ_{max} 240 mμ (ε 9000); ν_{max} 1751, 1265, and 794 (cathylate), 1679, 1588 (Δ^{16}-20-ketone), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.22.

32 from 30b.—Oxidation of 3-ethylenedioxypregna-5,16-diene-20β,21-diol 21-cathylate (100 mg) as in the reaction of **30a** furnished plates from ethyl acetate–*n*-hexane (65 mg, mp 173–175°; 21 mg, mp 166–168°) in a yield of 87%. The ir spectrum was indistinguishable from that of the chromic anhydride–pyridine product from **30a**.

21-Acetoxypregna-5,16-diene-3,20-dione 3-Ethylene Ketal (33) from 32.—To a solution of 21-*O*-carboethoxypregna-5,16-diene-3,20-dione 3-ethylene ketal (20 mg) in methanol (3 ml) was added 0.2 ml of 5% aqueous sodium bicarbonate. After 2 hr at room temperature the product was recovered by extraction with methylene chloride and treated with acetic anhydride–pyridine. The final product crystallized from acetone–*n*-hexane as rosettes (10.3 mg, mp 164–167°): $[\alpha]_D$ −19.9°; λ_{max} 240 mμ (ε 9200); λ_{max} 1750, 1240 (acetate), 1681, 1588 (Δ^{16}-20-ketone), 1097 cm^{-1} (ketal) [lit.[20] mp 190–192°; $[\alpha]_D$ −23°; λ_{max} 239.5 mμ (ε 8800)]. The ir spectrum was identical with that of a sample of **33** prepared by ketalization of **21-acetoxypregna-4,16-diene-3,20-dione**.[20]

17,20α,21-Trihydroxypregna-5-ene-3,11-dione 3-Ethylene Ketal (34a) from 24a.—Saponification of 20α,21-cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (2 g) in methanol (500 ml) with 0.2 *N* sodium hydroxide (50 ml) for 21 hr at room temperature and crystallization of the product from methanol gave needles (1.53 g, mp 200–201.5°; 0.19 g, mp 199–201°) in a yield of 92%: $[\alpha]_D$ −27.0°; ν_{max} 3430 (hydroxyl), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 68.03; H, 8.38.

20α,21-Diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (35a) from 34a.—Treatment of 17,20α,21-trihydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.72 g) with 2 ml each of pyridine and acetic anhydride for several hours at room temperature and crystallization of the product from methylene chloride–ethyl acetate gave platelets (1.6 g, mp 250–253°; 0.13 g, mp 248–251°) in a yield of 92%: $[\alpha]_D$ −30.6°; λ_{max} 3460 (hydroxyl), 1742, 1240 (acetate), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.94; H, 7.75.

17,20β,21-Trihydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (34b) from 24b.—Saponification of 20β,21-cyclocarbonyldioxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (2.0 g) as in the preparation of **34a** and crystallization of the product from benzene gave prisms (1.20 g, mp 184–186°; 0.43 g, mp 182.5–184°) in a yield of 87%: $[\alpha]_D$ −20.8°; ν_{max} 3450 (hydroxyl), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{34}O_6 \cdot 0.5H_2O$: C, 66.48; H, 8.49. Found: C, 66.03; H, 7.95.

20β,21-Diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-Ethylene Ketal (35b) from 34b.—Acetylation of 17,20β,21-trihydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.0 g) in the usual fashion gave prisms from methanol (1.2 g, mp 261–263°) in a yield of 100%: $[\alpha]_D$ +22.8°; ν_{max} 3570 (hydroxyl), 1744, 1240 (acetate), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.96; H, 7.60.

20α,21-Diacetoxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (36a) from 35a.—Dehydration of 20α,21-diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.0 g) in pyridine (15 ml) with thionyl chloride (1 ml) for 15 min at 5° and crystallization of the product from *n*-hexane afforded needles (720 mg, mp 123.5–124.5°; 30 mg, mp 121.5–123°) in a yield of 78%: $[\alpha]_D$ −43.5°; ν_{max} 1745, 1230 (acetate), 1670 (Δ^5), 1635 (Δ^{16}), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.77; H, 7.72.

20α,21-Dihydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (37a) from 36.—Saponification of 20α,21-diacetoxypregna-5,16-diene-3,11-dione 3-ethylene ketal (500 mg) with methanolic sodium hydroxide as in the preparation of **29a** and crystallization of the product from ethyl acetate furnished platelets (310 mg, mp 176–178°; 59 mg, mp 173–176°) in a yield of 90%: $[\alpha]_D$ −33.5°; ν_{max} 3400 (hydroxyl), 1670 (Δ^5), 1626 (Δ^{16}), 1094 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.26; H, 8.23.

20β,21-Dihydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (37b) from 35b.—Dehydration of 20β,21-diacetoxy-17-hydroxypregn-5-ene-3,11-dione 3-ethylene ketal (1.0 g) as in the preparation of **36a** followed by tlc analysis of the reaction mixture in system 3 showed a major BT-negative product (R_f 0.20) and a minor BT-positive product (R_f 0.17). Saponification of the

mixture in methanolic sodium hydroxide and crystallization from ethyl acetate gave the glycol **37b** as needles (550 mg, mp 185.5–188°; 75 mg, mp 184–186°) in a yield of 79%: $[\alpha]_D$ −5.42; ν_{max} 3440 (hydroxyl), 1670 (Δ^5), 1625 (Δ^{16}), 1098 cm^{-1} (ketal).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.04; H, 8.32.

The mother liquor was treated with acetic anhydride–pyridine and the reaction mixture was chromatographed on a silica gel column in system 3. The most mobile component, **20β,21-diacetoxypregna-5,16-diene-3,11-dione 3-ethylene ketal (36b)**, was recovered as prisms from *n*-hexane (48 mg, mp 116–117°): $[\alpha]_D$ +25.4°; ν_{max} 1740, 1230 (acetate), 1670 (Δ^5), 1622 (Δ^{16}), 1100 cm^{-1} (ketal).

Anal. Calcd for $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. Found: C, 68.53; H, 7.54.

The least mobile component, **21-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal,**[22] was obtained as needles from acetone (70 mg, mp 185–186.5°) in a yield of 8%: $[\alpha]_D$ +58.6°; ν_{max} 1751, 1230 (acetate), 1731 (20-ketone), 1672 (Δ^5), 1099 cm^{-1} (ketal) [lit.[22] mp 193.5–194°; $[\alpha]^{25}D$ +52°; λ_{max} 5.71, 5.77, 5.86 μ]. The generation of this by-product *via* saponification and acetylation reflects the extent to which $\Delta^{17,20}$ dehydration occurs in the diacetate **35b**.

21-Acetoxypregna-5,16-diene-3,11,20-trione 3-Ethylene Ketal (38) from 37a.—To a solution of 20α,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (100 mg) in *tert*-butyl alcohol (7 ml) was added an equal weight of DDQ. After 95 hr at room temperature the reaction mixture was added to methylene chloride (50 ml) and the solution was washed successively with cold, dilute sodium hydroxide and water. The crude product was treated with acetic anhydride–pyridine and the resulting mixture was chromatographed on a silica gel column (system 6). The initial band gave 14.3 mg of starting material as the diacetate **36a**; from later fractions was obtained the Δ^{16}-α-ketol acetate **38** as prisms from ether (26 mg, mp 159–160°). The ir spectrum was indistinguishable from that of a reference sample[20] of **38**.

38 from 37b.—Sequential allylic oxidation and acetylation of 20β,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (110 mg) followed by silica gel chromatography as in the preparation of **38** from **37a** gave 46 mg of the diacetate **36b** and 6.8 mg of the Δ^{16}-α-ketol acetate **38**, mp 155–157°, as confirmed by ir spectroscopy.

21-*O*-Carboethoxy-20α-hydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (39a) from 37a.—Cathylation of 20α,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (300 mg) in pyridine (3 ml) with ethyl chlorocarbonate (120 μl) for 19 hr at 5° was followed by silica gel column chromatography in system 7. The first fraction crystallized from ethanol as platelets (72 mg, mp 144.5–145°; 2 mg, mp 139–142°) in a yield of 18%. Because ir analysis of this mobile by-product showed no hydroxyl and intensification of the cathylate bands, it is designated as **20α,21-di-*O*-carboethoxypregna-5,16-diene-3,11-dione 3-ethylene ketal:** $[\alpha]_D$ −38.1°; ν_{max} 1750, 1275, and 792 (cathylate), 1668 (Δ^5), 1631 (Δ^{16}), 1092 cm^{-1} (ketal).

Anal. Calcd for $C_{29}H_{40}O_9$: C, 65.39; H, 7.57. Found: C, 65.24; H, 7.71.

The 21-cathylate **39a** emerged in later fractions and crystallized from ethanol–ether as needles (193 mg, mp 123–125°) in a yield of 54%: $[\alpha]_D$ −34.4°; ν_{max} 3530 (hydroxyl), 1742, 1265, and 790 (cathylate), 1675 (Δ^5), 1628 (Δ^{16}), 1092 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.90; H, 8.01.

The residue from the least mobile fraction furnished a second by-product as needles from aqueous ethanol (26 mg, mp 119–122°) in a yield of 7%. The presence of both hydroxyl and cathylate bands in its ir spectrum served to identify it as **20α-*O*-carboethoxy-21-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal.** However, since a moderate carbonyl band at 1810 cm^{-1} was also present (indicating that partial cyclization had occurred during manipulation), this product was not further characterized.

21-*O*-Carboethoxy-20β-hydroxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (39b) from 37b.—Cathylation of 20β,21-dihydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (200 mg) in pyridine (2 ml) with ethyl chlorocarbonate (80 μl) as in the preparation of **39a** and two crystallizations of the product from ether gave needles (134 mg, mp 154–156°): $[\alpha]_D$ −10.6°; ν_{max} 3440 (hydroxyl), 1739, 1265, and 792 (cathylate), 1671 (Δ^5), 1629 (Δ^{16}), 1090 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.84; H, 7.86.

The mother liquor was chromatographed on a silica gel column (system 6). A mobile, minor dicathylate fraction was discarded; subsequent fractions afforded an additional 43 mg of the 21-cathylate **39b**, mp 157–160°, raising the yield to 75%.

20α,21-Cyclocarbonyldioxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (42a) from 39a.—Treatment of 21-*O*-carboethoxy-20α-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) with methanolic sodium hydroxide as in the synthesis of **31a** and crystallization of the product from ethyl acetate gave needles (11.7 mg, mp 248–250°; 6.7 mg, mp 243–248°) in a yield of 82%: $[\alpha]_D$ −15.8°; ν_{max} 1795, 772 (cyclic carbonate), 1670 (Δ^5), 1625 (Δ^{16}), 1096 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.54; H, 7.11.

A mixture melting point with the minor dehydration product from **24a** and 248–250° and their ir spectra were identical.

20β,21-Cyclocarbonyldioxypregna-5,16-diene-3,11-dione 3-Ethylene Ketal (42b) from 39b.—Cyclization of 21-*O*-carboethoxy-20β-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) as in the reaction of **39a** and crystallization of the product from ethyl acetate furnished 19.3 mg (86%) of platelets: mp 234–237°; $[\alpha]_D$ −79.0°; ν_{max} 1790, 770 (cyclic carbonate), 1675 (Δ^5), 1627 (Δ^{16}), 1090 cm^{-1} (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.39; H, 7.10.

21-*O*-Carboethoxypregna-5,16-diene-3,11,20-trione 3-Ethylene Ketal (40) from 39a.—Oxidation of 21-*O*-carboethoxy-20α-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) in pyridine (3 ml) with an equal weight of chromic anhydride for 17 hr and crystallization of the product from ether gave 22 mg (88%) of needles: mp 137–139°; $[\alpha]_D$ −6.20°; λ_{max} 236 mμ (ε 9450); ν_{max} 1752, 1265, and 792 (cathylate), 1695, 1591 (Δ^{16}-20-ketone), 1095 cm^{-1} (ketal).

Anal. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 67.93; H, 7.58.

40 from 39b.—Oxidation of 21-*O*-carboethoxy-20β-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal (25 mg) with pyridine–chromic anhydride as in the reaction of **39a** and crystallization from ether afforded 20 mg of needles, mp 135–137°, in a yield of 80%. The ir spectrum was identical with that of **40** prepared from **39a**.

21-*O*-Carboethoxypregna-4,16-diene-3,11,20-trione (41) from 40.—To a solution of 21-*O*-carboethoxypregna-5,16-diene-3,11,20-trione 3-ethylene ketal (15 mg) in acetone (10 ml) was added 5 mg of *p*-TSA. After 18 hr the product was recovered and crystallized from ethanol as prisms (11.8 mg, mp 167–169°). A mixture melting point with the cathylation product from 21-hydroxypregna-4,16-diene-3,11,20-trione[2] showed no depression and their ir spectra were identical.

Registry No.—**1a**, 39703-91-8; **1b**, 39703-92-9; **2**, 39703-93-0; **3**, 39703-94-1; **4**, 39703-95-2; **5a**, 39703-96-3; **5b**, 39703-97-4; **6b**, 39703-98-5; **7b**, 39703-99-6; **8**, 39704-00-2; **9a**, 39704-01-3; **9b**, 39704-02-4; **10a**, 39704-03-5; **10b**, 39704-04-6; **11a**, 39704-05-7; **11b**, 39704-06-8; **12b**, 39704-07-9; **13a**, 39704-08-0; **13b**, 39704-09-1; **14a**, 39704-10-4; **14b**, 39704-11-5; **15b**, 39704-12-6; **16b**, 39704-13-7; **17**, 39704-14-8; **18**, 39704-15-9; **19a**, 39704-17-1; **20**, 39704-18-2; **21**, 39704-19-3; **22**, 39704-20-6; **23a**, 33487-68-2; **23b**, 33487-69-3; **24a**, 39704-22-8; **24b**, 39704-23-9; **25**, 39704-24-0; **26**, 39704-25-1; **27a**, 39704-26-2; **27b**, 39704-27-3; **28a**, 39704-28-4; **28b**, 39703-39-4; **29a**, 39703-40-7; **29b**, 39703-41-8; **30a**, 39703-42-9; **30b**, 39703-43-0; **31a**, 39703-44-1; **31b**, 39703-45-2; **32**, 39703-46-3; **34a**, 39703-47-4; **34b**, 39703-48-5; **35a**, 39703-49-6; **35b**, 39703-50-9; **36a**, 39703-51-0; **36b**, 39703-52-1; **37a**, 39703-53-2; **37b**, 39703-54-3; **38**, 39703-55-4; **39a**, 39703-56-5; **39b**, 39703-57-6; **40**,

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39703-58-7; **41**, 39703-59-8; **42a**, 39703-60-1; **42b**, 39703-61-2; phosgene, 75-44-5; sodium iodide, 7681-82-5; acetone, 67-64-1; triethylamine, 121-44-8; 21-iodopregn-4-ene-3,20-dione, 20576-46-9; 11-deoxycorticosterone, 64-85-7; 20β-21-dihydroxypregn-4-en-3-one, 298-35-1; 20α,21-dihydroxypregn-4-en-3-one, 26437-06-9; 20β,21-dihydroxypregn-4-en-3-one 20-acetate, 7676-48-4; 11-deoxycortisol, 152-58-9; 11-deoxycortisol 21-acetate 3-ethyleneketal, 39703-66-7; thionyl chloride, 7719-09-7; 21-iodopregn-4-ene-3,11,20-trione, 39703-67-8; 21-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal, 39703-68-9; 20α,21-di-*O*-carboethoxypregna-5,16-diene-3,11-dione 3-ethylene ketal, 39703-69-0; 20α-*O*-carboethoxy-21-hydroxypregna-5,16-diene-3,11-dione 3-ethylene ketal, 39703-70-3; 17,20β,21-trihydroxypregn-4-en-3-one 21-acetate, 39703-74-7.

Acknowledgment.—The author is obliged to Dr. John J. Schneider for his generous assistance throughout the course of this work.

The Reformatsky Reaction of Ethyl α-Bromo Esters with Bis(chloromethyl) Ether

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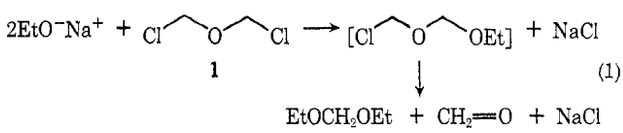
Received January 19, 1973

The Reformatsky reaction of ethyl α-bromoisobutyrate and several other α-bromo esters with bis(chloromethyl) ether has been studied to develop a synthetic procedure for the synthesis of α,α'-substituted dimethyl ethers. Using the techniques developed, the dineopentyl-substituted ether **7a** was synthesized in 66% yield. Less substituted ethers **7b** and **7c** were isolated in smaller yields. The side products of these reactions were isolated and characterized by spectra and alternate syntheses. A dual radical–ionic mechanism is postulated to account for the products observed. An interesting synthesis of **4a** *via* a β-lactone intermediate from β-chloropivalic acid is given.

Recently we reported[1] a new approach to the synthesis of dineopentyl ethers involving the reaction of 2 equiv of anion,[2] in our case Reformatsky reagents, with bis(chloromethyl) ether[3] (**1**). We would now like to report our complete results, including the reactions of ethyl α-bromoisobutyrate, ethyl α-bromopropionate, ethyl α-bromoacetate, and α,α'-dibromoisopropyl ketone with chloromethyl ether **1** and zinc.

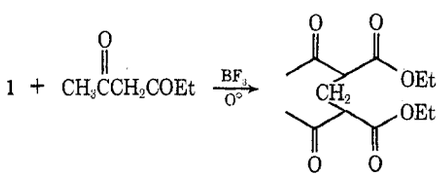
The first attempted dialkylation using chloromethyl ether **1** was reported in 1922 and involved the reaction of sodium ethoxide with the chloromethyl ether.[4] The desired diethoxy diadduct was not obtained but rather formaldehyde diethyl acetal and formaldehyde were isolated (eq 1).



(1)

In 1945 a second unsuccessful attempt at using chloromethyl ether **1** as a dialkylating agent was reported. In this case the enol of ethyl acetylacetate was to displace the bischlorides with the help of a Lewis acid catalyst.[5] This reaction, however, gave a methylene dimer of starting material (eq 2).

While bis(chloromethyl) ether and many monochloromethyl ethers have been employed as monoalkylating agents successfully,[6] it was not until our studies[1] and that reported by Gash[2] that successful didisplacements on bis(chloromethyl) ether were realized. The product studies reported here and recent mechanistic studies on the thermal[7] and metal-catalyzed[8] decomposition of chloromethyl ethers help to explain the earlier failures and the synthetic limits of this potentially useful type of dialkylation reaction, particularly in the synthesis of hindered ethers.



(2)

Results

Our initial studies were concerned with the reactions of ethyl α-bromoisobutyrate and various metals such as zinc and magnesium with chloro ether **1**. Several solvents were employed, including dry ether, glyme, and tetrahydrofuran (THF). Optimum conditions for maximum yield of the desired diadduct, ether diester **7a**, were found to include prior formation of the Reformatsky reagent at a low temperature (10°) in rigorously dried and N_2-degassed glyme (ether worked almost as well as glyme; however, THF gave a multi-

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(2) Since that time a second successful dialkylation using bis(chloromethyl) ether and diethyl methylmalonate anion has been reported. See V. W. Gash, *J. Org. Chem.*, **37**, 2197 (1972).

(3) Chloromethyl ether **1** is a proven carcinogenic material and should be handled with care. See S. Laskin, *et al.*, *Arch. Environ. Health*, **23**, 135 (1971), for a report of its toxic properties. We wish to thank J. A. Vida for bringing this article to our attention.

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