Preparation and Properties of Steroidal 17,20- and 20,21-Cyclic Carbonates Epimeric at C-20[1]

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Several methods for the preparation of 17,20- and 20,21-cyclic carbonates from steroidal 17,20α(and 20β),21-triols are described. Direct preparation of the former can be achieved by reaction of the glycerol 21-acetates **1a** and **1b** with phosgene in pyridine, whereas the latter compounds can be obtained by similar treatment of the free glycerols. In addition, the 17,20-cyclocarbonyldioxy-21-ols **5a** and **5b** or the 17-hydroxy-20,21-cyclic carbonates **4a** and **4b** can be prepared selectively from the 17,20-cyclocarbonyldioxy-21-acetates **2a** and **2b** or 20-cathyl-21-acetates **3a** and **3b** under conditions which promote deacetylation and/or cyclization with or without isomerization of the cyclic carbonate grouping. The influence of configuration at C-20 on the relative amounts of 17,20- and 20,21-cyclic carbonates which are formed is discussed in stereochemical terms. The utility of side-chain cyclic carbonates as intermediates in partial syntheses was demonstrated by the ready conversion of certain 11β-ols to the 11-ones with chromic anhydride in pyridine and by the development of an improved route to 17,20-diols **12a** and **12b** *via* 17,20-cyclocarbonyldioxy-21-tosylates **11a** and **11b**. Cyclic carbonates from the glycols **12a** and **12b** have also been prepared either directly by reaction with phosgene in pyridine or by alkaline cyclization of the 20-cathylates **16a** and **16b**. In contrast to side-chain acetonides which are strongly resistant to alkaline hydrolysis, cyclic carbonates are easily cleaved by aqueous alkali. However, they are unaffected by relatively strong mineral acid. The resistance of these new derivatives to forcing acetylation conditions was shown in the reaction of the 11β,17-dihydroxy-20,21-cyclic carbonates **4a** and **4b**. Acetylation proceeds readily at C-11, but the presence of the bulky substituent on the side chain greatly inhibits acetylation at C-17.

In the preceding communication[2] we describe the ready formation of methyl ester 17,20-cyclic carbonates from 20-cathyl-21,17-lactones in methanolic sodium hydroxide. These findings with the glycolic acid derivatives prompted a systematic study of the formation and reactions of cyclic carbonates derived from the glycerol side chain since compounds of this type have not been described previously. In this paper will be detailed methods for preparation of both 17,20- and 20,21-cyclic carbonates epimeric at C-20, the stereochemical factors which influence their isomerization, and examples of their use in partial syntheses.

Treatment of the 21-monoacetates of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (Reichstein's substance epi-E)[3] and 11β,17,20β,21-tetrahydroxypregn-4-en-3-one (Reichstein's substance E)[4] (**1a** and **1b**, Scheme I) with phosgene in a mixture of benzene and pyridine at 0° gave the respective 17,20-cyclic carbonates **2a** and **2b**, each in a yield of 88%. An attempt was made to prepare **2a** and **2b** by cyclization of the 20-cathyl-21-acetates **3a** and **3b**. However, reaction of both **3a** and **3b** in methanolic sodium hydroxide or methanolic potassium bicarbonate resulted in rapid loss of the acetoxyl group. From either the 20β-cathylate **3b** or the 17,20β-cyclic carbonate **2b** was obtained a single product readily identified as the 17,20β-cyclocarbonyldioxy-21-ol **5b** since treatment with acetic anhydride–pyridine afforded the 21-acetate **2b**. Reaction of the 20α epimers **2a** or **3a** with methanolic alkali resulted in the formation of two products. The minor, more polar product was identified as the 17,20α-cyclic carbonate **5a** because its acetylation product was identical with **2a**. Since the major, more mobile cyclic carbonate contained an unacetylable hydroxyl group, it was assigned the 17-hydroxy-20α,21-cyclic carbonate structure **4a**. Confirmation was obtained through its independent synthesis from Reichstein's substance epi-E[5] by reaction with phosgene in pyridine. Treatment of either **4a** or **5a** with methanolic alkali gave the same equilibration mixture of both cyclic carbonates.

The reaction of the epimeric cyclic carbonates **2a** and **2b** and cathylates **3a** and **3b** with ethanolic sulfuric acid was also studied. From **2a** was obtained the 17,20α-cyclocarbonyldioxy-21-ol **5a** in a yield of 88%; in contrast, **3a** afforded the 17-hydroxy-20α,21-cyclic carbonate **4a** in the same yield. Treatment of **2b** with ethanolic sulfuric acid provided the 17,20β-cyclocarbonyldioxy-21-ol **5b** in a yield of 80%. However, under the same conditions **3b** was converted to a roughly 1:1 mixture of **5b** and the 17-hydroxy-20β,21-cyclic carbonate **4b**. The latter compound was synthesized independently by reaction of Reichstein's substance E with phosgene in pyridine. Treatment of **4b** with alcoholic base resulted in its complete isomerization to the 17,20β-cyclic carbonate **5b**. It is evident from these results that by proper choice of substrate and reaction conditions any of the four possible hydroxy cyclic carbonates can be prepared selectively.

A likely explanation for the differences in reactivity of the epimeric cyclic carbonates **2a** and **2b** and cathylates **3a** and **3b** in alcoholic alkali stems from our previous observations on the relative stabilities of 17,20-acetonides.[6] The additional C-21/C-18 interaction undergone by 17,20α-cyclic carbonates would tend to favor partial isomerization to the 17-hydroxy-20α,21-cyclic derivatives *via* the 20-carbomethoxyl intermediate. The greater stability of 17,20β-cyclocarbonyldioxy-21-ols is to be expected since the terminal hydroxymethyl group faces away from the angular methyl group at C-18. That the direction of reaction is independent of the original location of an actual or potential cyclic carbonate grouping in the side chain was shown with the 21-cathylates **6a** and **6b**. The location of the cathyl group in these derivatives, prepared by selective reaction of the respective glycerols

(1) This work was supported wholly 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 work.

(2) M. L. Lewbart, *J. Org. Chem.*, **37**, 1224 (1972).

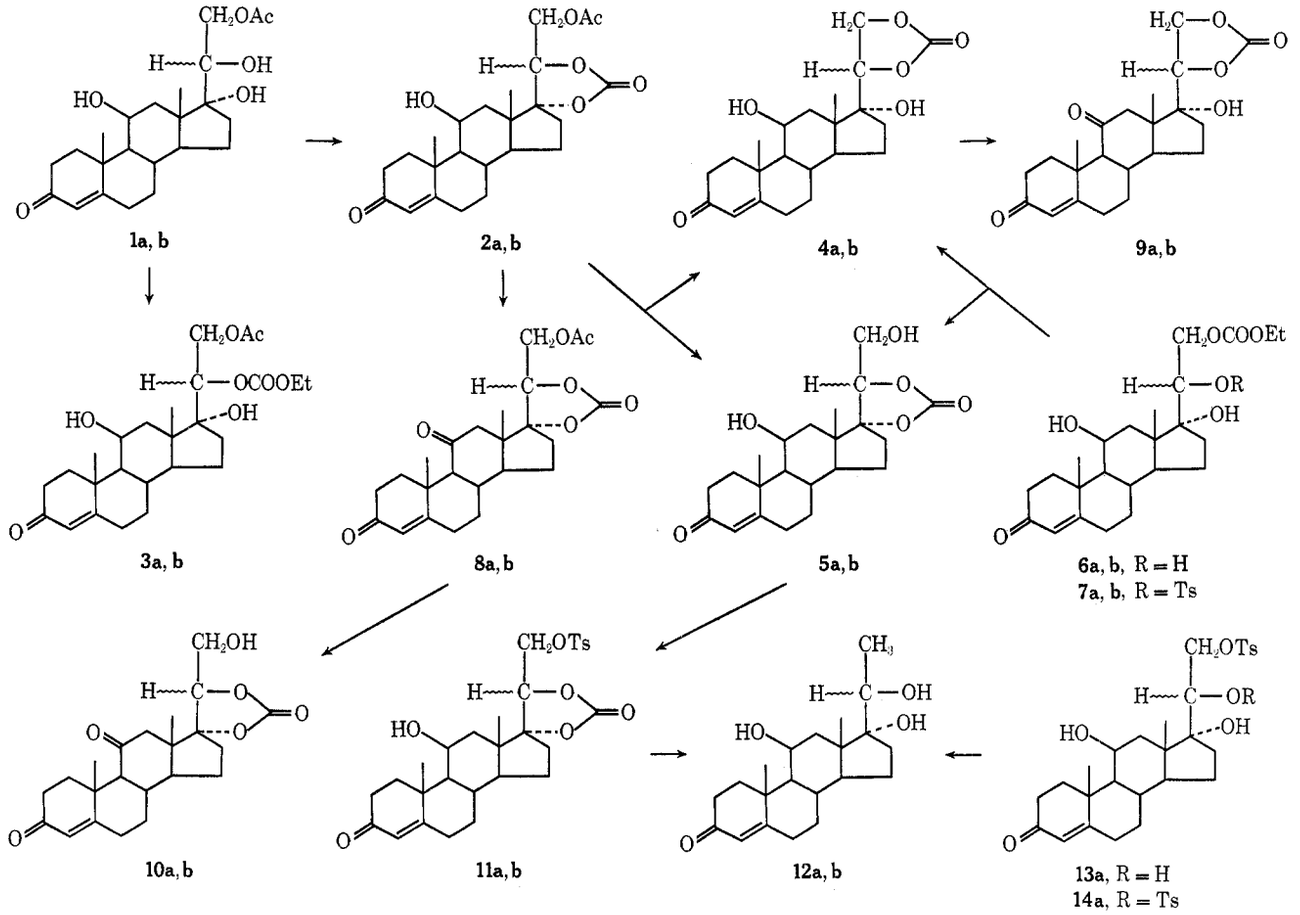
(3) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal, and J. Korman, *J. Amer. Chem. Soc.*, **77**, 4438 (1955).

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

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

(6) M. L. Lewbart and J. J. Schneider, *ibid.*, **34**, 3505 (1969).

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.

with ethyl chlorocarbonate–pyridine, was established by preparing the 20-acetates **7a** and **7b**. These possessed infrared spectra similar to but not identical with those of the isomeric 20-cathyl-21-acetates **3a** and **3b**. Reaction of **6b** with ethanolic alkali gave the 17,20β-cyclocarbonyldioxy-21-ol **5b** as the sole product; similar treatment of **6a** afforded the same equilibrium mixture obtained from **2a** and **3a**.

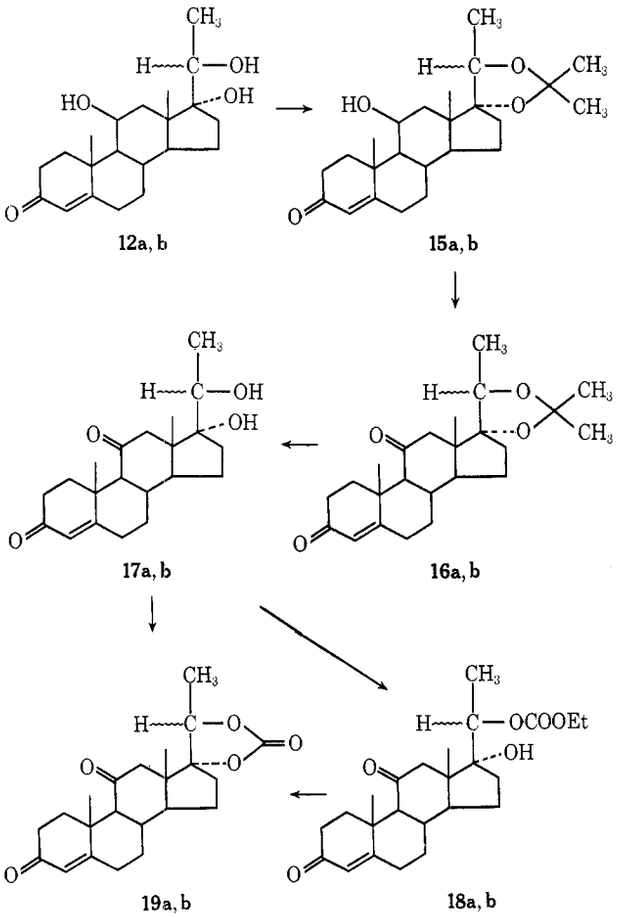
The conversion of both 17,20-cyclocarbonyldioxy-21-acetates (**2a** and **2b**) to the corresponding 21-ols in ethanolic sulfuric acid suggested that isomerization cannot occur in this medium. Confirmation of this lack of interconvertibility was obtained by demonstrating that the 17-hydroxy-20,21-cyclic carbonates **4a** and **4b** were unaffected by treatment with ethanolic sulfuric acid for 1 week at room temperature. In the reaction of the 20-cathyl-21-acetates **3a** and **3b** under acidic conditions the situation differs in that the possibility of cyclization in either direction exists. Presumably the steric factors which are operative in the behavior in alcoholic alkali also obtain in this case since the 20α epimer affords the sterically unstrained 17-hydroxy-20,21-cyclic carbonate **4a** as the only product in a yield of 88%. On the other hand, treatment of the 20β-cathyl-21-acetate **3b** with ethanolic sulfuric acid provided roughly equal amounts of both possible hydroxy cyclic carbonates which suggests that competition between rates of deactylation at C-21 and cyclization involving the tertiary hydroxyl group at C-17 are the controlling factors.

The stability of the cyclocarbonyldioxy system to oxidation with chromic anhydride in pyridine was shown by the following reaction sequence. Oxidation of the 17,20-cyclocarbonyldioxy-21-acetates **2a** and **2b** gave the 11-ketones **8a** and **8b** in excellent yield. Similar treatment of the 17-hydroxy-20,21-cyclic carbonates **4a** and **4b** afforded the corresponding 11-ketones **9a** and **9b**. The controlling effect of configuration at C-20 on the direction of reaction which was established in the 11β-ols was utilized to complete the 11-ketone series. Reaction of **8a** with ethanolic sulfuric acid gave the 17,20α-cyclocarbonyldioxy-21-ol **10a**; treatment of **8b** with ethanolic sodium hydroxide furnished with 20β epimer **10b**.

A practical use of cyclic carbonates as intermediates was made in the synthesis of the 21-deoxy analogs of Reichstein's substances epi-E and E (**12a** and **12b**). Reaction of the 17,20-cyclocarbonyldioxy-21-ols **5a** and **5b** with tosyl chloride in pyridine provided the respective 21-tosylates **11a** and **11b**. Lithium aluminum hydride reduction followed by selective oxidation at C-3 with DDQ[7] gave the desired triols **12a** and **12b** in overall yields from **5a** and **5b** in excess of 50%. The superiority of this route to **12a** and **12b** was easily demonstrated since the yield of **12a** *via* the glycerol 21-tosylate **13a** was only 31%. The reason for the lower yield by the more conventional route is in part

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

SCHEME II



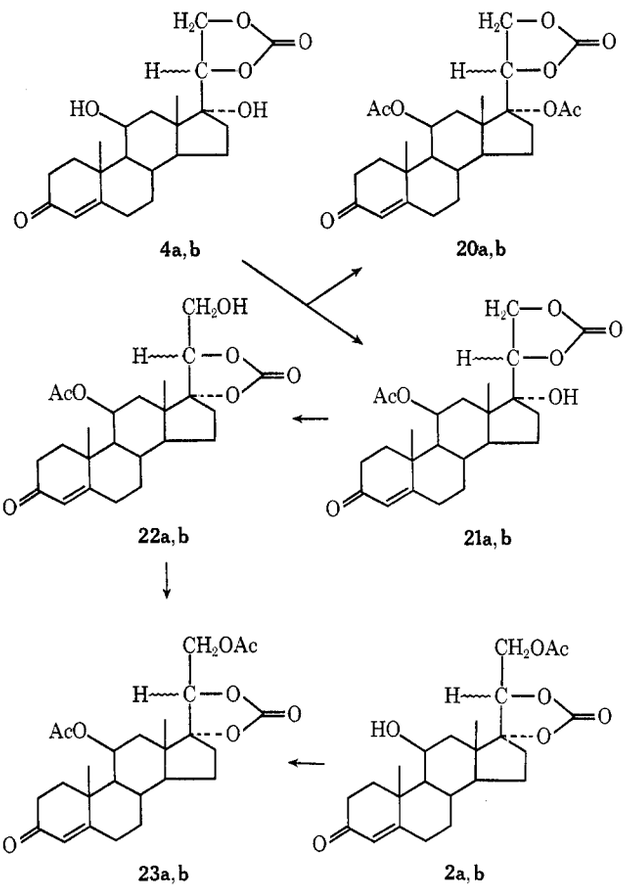
due to the formation in 10% yield of the 20,21-ditosylate **14a** from the tosylation of the free glycerol.

The triols **12a** and **12b** served as convenient starting materials for the preparation of 11-keto-17,20-cyclic carbonates in the 21-deoxy series. Oxidation of their acetonation products **15a** and **15b** (Scheme II) with chromic anhydride in pyridine afforded the 11-ketones **16a** and **16b**. These were hydrolyzed respectively with 60% acetic acid at room temperature and 80% refluxing acetic acid, as described previously,[6] to the dioldiones **17a** and **17b**. Preparation of the 17,20-cyclic carbonates **19a** and **19b** was carried out either directly by reaction with phosgene in pyridine or *via* alkaline cyclization of the 20-cathylates **18a** and **18b**.

In striking contrast to the great resistance of steroidal side-chain acetonides to alkaline hydrolysis, the corresponding cyclic carbonates are readily cleaved even in dilute, aqueous bicarbonate solution. Cyclic carbonates, however, are very stable to acidic reagents. For example, treatment of the 17,20-cyclic carbonates **19a** and **19b** with aqueous ethanolic sulfuric acid for 70 hr at room temperature was without effect; refluxing in the same reagent for 2 hr resulted in only approximately 10% hydrolysis to the 17,20-diols. It would therefore appear that as in the carbohydrate field[8] cyclocarbonyldioxy derivatives of the steroid side chain can be used as protecting groups for transformations elsewhere in the molecule involving acidic reagents. In this connection it seemed of interest to study the reactivity and/or stability of the 11β,-

(8) L. Hough, J. E. Priddle, and R. S. Theobald, *Advan. Carbohyd. Chem.*, **15**, 1 (1960).

SCHEME III



17-dihydroxy-20,21-cyclic carbonates (**4a** and **4b**, Scheme III) to forcing acetylation conditions. Treatment of **4a** with *p*-TSA in a mixture of acetic acid and acetic anhydride at room temperature followed by silica gel column chromatography afforded a major mobile product (71%) and a minor polar product (11%). Similar treatment of **4b** gave a minor mobile product (10%) and a major polar product (64%). The hydroxyl-free minor products from each epimer were assigned the 11,17-diacetate structures **20a** and **20b**. The monohydroxylic major products were identified as the 11β-acetates **21a** and **21b** rather than the 17-acetates since they were not affected by chromic anhydride in pyridine. These results show that the bulky cyclic carbonate ring prevents the complete acetylation at C-17 which normally occurs with this reagent.[9] The facile acetylation of 11β-ols under these conditions was first described by Oliveto, *et al.*[10] The preparation of a complete series of 11β-acetoxy cyclic carbonates was completed as follows: alkaline rearrangement of the 20,21-cyclic carbonates **21a** and **21b** provided the 17,20-cyclocarbonyldioxy-21-ols **22a** and **22b**; treatment of **22a** and **22b** with acetic anhydride–pyridine furnished the 11β,21-diacetates **23a** and **23b**. Alternatively, the latter compounds could be prepared by forced acetylation at C-11 of the 17,20-cyclocarbonyldioxy-21-acetates **2a** and **2b**.

Oliveto, *et al.*, recorded that acetylation of an 11β-hydroxyl group results in a hypsochromic shift of 2 mμ for the λ_{max} of the Δ^4-3-keto system.[10] The ultra-

(9) R. B. Turner, *J. Amer. Chem. Soc.*, **75**, 3489 (1953).

(10) E. P. Oliveto, C. Gerold, L. Weber, H. E. Jorgensen, R. Rausser, and E. B. Hershberg, *ibid.*, **75**, 5486 (1953).

TABLE I

λ_{max} VALUES AND MD INCREMENTS OF 11β-ACETOXY CYCLIC CARBONATES

Pairs	C-11	C-17	C-20	C-21	λ_{max}, mμ 20α	λ_{max}, mμ 20β	MD 20α	MD 20β	ΔMD 20α	ΔMD 20β
1	OH	OH	CCS[a]		242	242	+272	+237	+102	+149
2	OAc	OH			240	240	+374	+386		
3	OH		CCS	OH	240	242	+106	+488	+108	+82
4	OAc		CCS	OH	239	239	+214	+570		
5	OH		CCS	OAc	242	242	+162	+565	−8	−1
6	OAc		CCS	OAc	238	238	+154	+564		
7	OAc	OAc	CCS		239.5	239.5	+366	+195		

[a] CCS denotes cyclic carbonate system.

violet absorption maxima of the 11β-acetates prepared in the present study appear to reflect subtle influences of the side-chain substituents, showing a gradation of hypsochromic shifts from 2 to 4 mμ (Table I). The molecular rotational increments resulting from 11β-acetylation are also presented in Table I. The values, ranging from +82 to +149 units for pairs 1–4, are within the range of from +3 to +165 units given by Fox, *et al.*[11] In contrast, acetylation at C-11 of the 17,20-cyclocarbonyldioxy-21-acetates is associated with a slight negative shift in optical rotation (pairs 5 and 6).

Although no significant trends in optical activity were noted for 20,21-cyclic carbonates generally, consistent differences between C-20 epimeric 17,20-cyclic carbonates were present. In all cases 17,20β-cyclic carbonates were considerably more dextrorotatory than their 20α counterparts, with α − β differences of from −283 to −430 MD units, a range similar to that recorded by us for 20-acetates.[12] It should therefore be possible to assign configurations at C-20 for new pairs of 17,20 cyclic carbonates which may be encountered.

The infrared spectral properties of the new steroidal cathylates and cyclic carbonates were also studied. Eleven side-chain cathylates had a very strong band at 1265–1260 cm^{-1} and a strong to very strong band at 792–784 cm^{-1}. Of the 26 five-membered ring cyclic carbonates examined, all gave rise to a very strong band in the carbonyl region ranging from 1818 to 1778 cm^{-1}. In a number of instances, splitting of the carbonyl band occurs with the two maxima separated by approximately 25 cm^{-1}. Another strong to very strong band characteristic of all 17,20- and 20,21-cyclic carbonates is present in the region from 789 to 769 cm^{-1}. However, in the 21-tosylates **11a** and **11b** this band is apparently displaced to 750 cm^{-1}. Ready differentiation between the two types of side-chain cyclic carbonates by infrared analysis is therefore not possible.

Experimental Section

General experimental procedures are detailed in the previous paper.[2]

20α-Carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (3a) from 1a.—To a solution of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one[3] (5 g) in cold pyridine (50 ml) was added ethyl chlorocarbonate (ECC) (5 ml), and the mixture was stored at 5°. Tlc analysis of an aliquot removed after 18 hr showed approximately 50% conversion to a more mobile product. The reaction mixture was therefore retreated with 5 ml of ECC for an additional 5 hr at 5°. Repeat tlc analysis showed a small amount only of starting material. The product was recovered in the usual manner and crystallized from methanol as long, fine needles (4.0 g, mp 216.5–218.5°; 0.4 g, mp 213.5–215°) in a yield of 81%: $[\alpha]_{365}$ −79.5°, $[\alpha]_D$ 48.7°; λ_{max} 242 mμ (ε 16,000); ν_{max} 1740 1265, and 790 (cathylate), 1740 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00; CH_3CO, 8.99; C_2H_5O, 9.41. Found: C, 64.87; H, 8.12; CH_3CO, 9.60; C_2H_5O, 9.72.

20β-Carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (3b) from 1b.—To a solution of 21-acetoxy-11β,17,20β-trihydroxypregn-4-en-3-one (500 mg) in cold pyridine (5 ml) was added ECC (0.3 ml). Tlc analysis after 3 hr at room temperature showed only a roughly 20% conversion to the desired product. The crude product was recovered and retreated in pyridine (5 ml) with ECC (0.6 ml) for three additional times. Repeated crystallization from ethanol of the final reaction mixture afforded plates (250 mg): mp 225–227°; $[\alpha]_{365}$ 310°, $[\alpha]_D$ 175°; λ_{max} 242 mμ (ε 15,750); ν_{max} 1740, 1260, and 784 (cathylate), 1740 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.24; H, 8.01.

17,20α-Cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2a) from 1a.—To a solution of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one (4.06 g, 10 mmol) in pyridine (50 ml) at 0° was added dropwise with magnetic stirring a mixture of 12.5% phosgene in benzene (15 ml) and benzene (35 ml) over a 1.5-hr period. After an additional 15 min at 0°, the product was recovered and crystallized from methanol as needles (3.7 g, mp 239–241°; 0.1 g, mp 237.5–239°) in a yield of 88%: $[\alpha]_{365}$ −123°, $[\alpha]_D$ 37.5°; λ_{max} 242 mμ (ε 16,100); ν_{max} 1790 and 776 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.63; H, 7.49.

17,20β-Cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2b) from 1b.—A solution of 21-acetoxy-11β,17,20β-trihydroxypregn-4-en-3-one (1624 mg, 4 mmol) in pyridine (20 ml) was treated with a mixture of 12.5% phosgene in benzene (7 ml) and benzene (18 ml) for 2 hr as in the preparation of **2a** from **1a**. The product crystallized from methanol as needles (1360 mg, mp 250–253°; 160 mg, mp 244–246°) in a yield of 88%: $[\alpha]_{365}$ 142°, $[\alpha]_D$ 131°; λ_{max} 242 mμ (ε 15,900); ν_{max} 1792 and 769 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.62; H, 7.44.

20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4a). From Phosgene–Pyridine on Reichstein's Substance Epi-E.—To a stirred solution of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (182 mg) in pyridine (2.5 ml) at 0° was added a mixture of phosgene solution (0.75 ml) and benzene (1.75 ml). After 10 min at 0° the product was recovered and crystallized from methanol as prisms (148 mg, mp 235–236.5°; 16 mg, mp 236.5–238.5°) in a yield of 84%: $[\alpha]_{365}$ −24.6°, $[\alpha]_D$ 69.7°; λ_{max} 242 mμ (ε 16,050); ν_{max} 1788 and 777 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.29; H, 7.66.

From Ethanolic Sulfuric Acid on 3a.—To a solution of 20α-carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (200 mg) in ethanol (40 ml) was added concentrated sulfuric acid (0.1 ml). After 48 hr at room temperature methylene chloride (250 ml) was added; the solution was washed with water and concentrated to dryness. Crystallization from methanol afforded leaflets (115 mg, mp 232.5–235°; 40 mg, mp 234–236°) in a yield of 88%. The ir spectrum was identical with that of the phosgenation product from Reichstein's Substance epi-E.

17,20α-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one

(11) S. M. Fox, V. E. Origoni, and L. L. Smith, *J. Amer. Chem. Soc.*, **82**, 2580 (1960).

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

(**5a**) **from 2a.**—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (1 g) in a mixture of methylene chloride (100 ml) and ethanol (500 ml) was added concentrated sulfuric acid (1.2 ml). After 10 days at room temperature anhydrous sodium acetate (1.8 g) was added and the reaction mixture was concentrated *in vacuo* nearly to dryness. The product was recovered by extraction with methylene chloride and successive washing with dilute sodium hydroxide and water. Crystallization of the residue from methanol afforded prisms (735 mg, mp 246–248°; 60 mg, mp 244–246°) in a yield of 88%: $[\alpha]_{365}$ −130°, $[\alpha]_D$ 27.1° (methanol); λ_{max} 240 mμ (ε 15,800); ν_{max} 1788 and 778 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.32; H, 7.58.

Treatment of **5a** with acetic anhydride–pyridine afforded a product identical in all respects with the starting material.

20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4a) and 17,20α-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (5a) from 3a.—To a solution of 20α-carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (4 g) in ethanol (250 ml) was added 0.1 *N* ethanolic sodium hydroxide (12.5 ml). After 10 min at room temperature, 1 *N* hydrochloric acid (1.25 ml) was added, and the solution was concentrated *in vacuo* to a small volume, and the residue was partitioned between methylene chloride and water. The reaction mixture was applied in pyridine (10 ml) to a 70 × 540 mm silica gel column prepared with the system ethyl acetate–isooctane (3:1). Fractions (15 ml) were collected at intervals of 10 min. At fraction number 750 the system was changed to ethyl acetate.

20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one. Fractions 300–800.—Crystallization from methanol gave prisms (1510 mg, mp 235–237°; 190 mg, mp 230–232°) in a yield of 48%. The ir spectrum was identical with that of the phosgenation product from Reichstein's substance epi-E.

17,20α-Cyclocarbonyldioxy-11β,21-hydroxypregn-4-en-3-one. Fractions 850 to End of Band.—Crystallization from methanol furnished small prisms (750 mg, mp 244–247°; 50 mg, mp 240–243°) in a yield of 23%. The ir spectrum was identical with that of **5a** prepared from **2a**.

4a and 5a from 2a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (3.82 g) in ethanol (500 ml) was added 0.1 *N* ethanolic sodium hydroxide (25 ml). After 10 min the reaction mixture was processed and chromatographed as in the preparation of **4a** and **5a** from **3a**.

Fractions 331–800.—The 20,21-cyclic carbonate **4a** crystallized from methanol (1940 mg, mp 235–237°) in a yield of 56%.

Fractions 831 to End of Band.—The 17,20-cyclic carbonate **5a** crystallized from methanol (877 mg, mp 245–247°) in a yield of 25%.

20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4b) from Reichstein's Substance E.—Phosgenation of 11β,17,20β,21-tetrahydroxypregn-4-en-3-one monohydrate (182 mg) as in the preparation of **4a** from Reichstein's substance epi-E and crystallization of the product from ethanol provided 151 mg of long needles, mp 155–160° and 229–230° in a yield of 82%: $[\alpha]_{365}$ −11.6°, $[\alpha]_D$ 60.7° (methanol); λ_{max} 242 mμ (ε 15,050); ν_{max} 1803 (1781) and 777 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6 \cdot H_2O$: C, 64.68; H, 7.90. Found: C, 65.03; H, 8.10.

17,20β-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (5b) from 2b. With Ethanolic Sodium Hydroxide.—To a solution of 17,20β-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (1200 mg) in ethanol (230 ml) was added 0.1 *N* ethanolic sodium hydroxide (12 ml). After 10 min the solution was neutralized with hydrochloric acid and the recovered product crystallized from methanol as needles (934 mg, mp 242–243°) in a yield of 86%: $[\alpha]_{365}$ 173°, $[\alpha]_D$ 125° (methanol); λ_{max} 242 mμ (ε 15,750); ν_{max} 1778 and 774 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.73; H, 7.79.

With Ethanolic Sulfuric Acid.—Treatment of **2b** (100 mg) in ethanol (40 ml) with sulfuric acid (0.1 ml) for 90 hr at room temerature was followed by chromatography of the crude product on a 16 × 600 mm silica gel column in ethyl acetate–isooctane (3:1). Fractions of 3 ml were collected at 10-min intervals. After the emergence of fraction 160 the system was changed to ethyl acetate. From **fractions 61–150** was obtained 6.6 mg of needles, mp 252–253.5°, which possessed an ir spectrum identical with that of the starting material. The residue from **fractions 171–320** (72.3 mg, 80%) afforded **5b** as prismatic needles from methanol, mp 242–243.5°.

20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4b) and 17,20β-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (5b) from 3b.—Treatment of 20β-carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (100 mg) with ethanolic sulfuric acid for 90 hr followed by silica gel column chromatography was carried out as in the reaction of **2b**.

20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one. Fractions 66–145.—The pooled material (47.5 mg, 52.5%) gave long needles from aqueous methanol, mp 193.5–195.5°. Recrystallization from ethanol afforded needles, mp 155–160° and 223–225°, which possessed an ir spectrum identical with that of the phosgenation product obtained from Reichstein's substance E.

17,20β-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one. Fractions 188–290.—Crystallization of the crude residue (37.7 mg, 41.7%) from ethyl acetate gave needles, mp 242–243.5°, which were identical in all respects with **5b** prepared from **2b**.

21-Carbethoxy-11β,17,20α-trihydroxypregn-4-en-3-one (6a) from Reichstein's Substance Epi-E.—To a solution of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (500 mg) in pyridine (5 ml) was added ECC (0.15 ml). After 17.5 hr at 5° the product was recovered as platelets by several crystallizations from methanol (329 mg, mp 138–140° and 208–211°) in a yield of 55%: $[\alpha]_{365}$ 54.2°, $[\alpha]_D$ 96.3°; λ_{max} 242 mμ (ε 15,550); ν_{max} 1738, 1260, and 789 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31; C_2H_5O, 10.32. Found: C, 65.88; H, 8.29; C_2H_5O, 10.42.

7a from 6a.—Treatment of the 21-cathylate with pyridine and acetic anhydride for 18 hr at room temperature and crystallization of the product from ethyl acetate gave **21-carbethoxy-20α-acetoxy-11β,17-dihydroxypregn-4-en-3-one** as hairy needles: mp 204–205°; $[\alpha]_{365}$ −60.5°, $[\alpha]_D$ 55.6°; λ_{max} 242 mμ (ε 15,700); ν_{max} 1738, 1265, and 789 (cathylate), 1738 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8 \cdot 0.5H_2O$: C, 64.04; H, 8.06. Found: C, 64.18; H, 7.72.

A mixture melting point of **7a** with **3a** showed no depression, and they possessed the same mobility (R_f 0.10) by tlc in ethyl acetate–isooctane (1:1). However, the ir fingerprint regions were distinctly different.

21-Carbethoxy-11β,17,20β-trihydroxypregn-4-en-3-one (6b) from Reichstein's Substance E.—Cathylation of 11β,17,20β,21-tetrahydroxypregn-4-en-3-one (500 mg) was carried out as in the preparation of **6a**. Several crystallizations from ethyl acetate provided 309 mg (52%) of prisms: mp 167–168.5°; $[\alpha]_{365}$ 89.5°, $[\alpha]_D$ 109°; λ_{max} 242 mμ (ε 15,300); ν_{max} 1738, 1263, and 790 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31; C_2H_5O, 10.32. Found: C, 65.69; H, 8.39; C_2H_5O, 10.30.

7b from 6b.—Acetylation of the 21-cathylate in the usual manner and crystallization of the product from ethanol gave **21-carbethoxy-20β-acetoxy-11β,17-dihydroxypregn-4-en-3-one** as platelets: mp 212–214°; $[\alpha]_{365}$ 289°, $[\alpha]_D$ 168°; λ_{max} 242 mμ (ε 15,700); ν_{max} 1740, 1262, and 790 (cathylate), 1740 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.20; H, 8.07.

17,20α-Cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (8a) from 2a.—Oxidation of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2 g) in pyridine (80 ml) with chromic anhydride (2 g) was carried out for 19 hr in the usual manner. Crystallization of the product from methanol afforded prisms (1730 mg, mp 237–238°; 83 mg, mp 233–234°) in a yield of 91%: $[\alpha]_{365}$ 356°, $[\alpha]_D$ 72°; λ_{max} 238 mμ (ε 16,300); ν_{max} 1805 and 776 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.98; H, 7.05.

17,20β-Cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (8b) from 2b.—Oxidation of 17,20β-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (300 mg) in pyridine (12 ml) with an equal weight of chromic anhydride for 19 hr afforded the 11-ketone as plates from methanol (254 mg, mp 222–225°; 18 mg, mp 213–216°) in a yield of 91%: $[\alpha]_{365}$ 647°, $[\alpha]_D$ 172°; λ_{max} 238 mμ (ε 15,650); ν_{max} 1802 and 770 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.81; H, 7.05.

17,20α-Cyclocarbonyldioxy-21-hydroxypregn-4-ene-3,11-dione

(10a) from 8a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (1 g) in a mixture of methylene chloride (100 ml) and ethanol (500 ml) was added 1.2 ml of sulfuric acid. After 10 days at room temperature the product was recovered as in the preparation of 5a from 2a. Crystallization from methanol gave 869 mg (96%) of leaflets: mp 226–226.5°; $[\alpha]_{365}$ 362°, $[\alpha]_D$ 70.3° (methanol); λ_{max} 238 mμ (ε 15,400); ν_{max} 1801 and 773 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.80; H, 7.50.

17,20β-Cyclocarbonyldioxy-21-hydroxypregn-4-ene-3,11-dione (10b) from 8b.—To a solution of 17,20β-cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (240 mg) in ethanol (46 ml) was added 0.1 *N* ethanolic sodium hydroxide (2.4 ml). After 10 min the solution was neutralized and the product was recovered in the usual manner. Crystallization from methanol gave 174 mg (80%) of needles: mp 266–268°; $[\alpha]_{365}$ 618°, $[\alpha]_D$ 143° (methanol); λ_{max} 238 mμ (ε 15,450); ν_{max} 1790 and 784 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.01; H, 7.29.

20α,21-Cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione (9a) from 4a.—Oxidation of 20α,21-cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (2 g) with chromic anhydride in pyridine as in the previous examples gave, from methanol, 1940 mg (97%) of platelets: mp 204–206°; $[\alpha]_{365}$ 531°, $[\alpha]_D$ 122° (methanol); λ_{max} 238 mμ (ε 15,500); ν_{max} 1795 and 771 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.00; H, 7.30.

20β,21-Cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione (9b) from 4b.—Oxidation of 20β,21-cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (100 mg), as in the preparation of 9a from 4a, gave 83 mg of prisms from methanol: mp 170–175, 225–230, and 259–261°; $[\alpha]_{365}$ 433°, $[\alpha]_D$ 85.7° (methanol); λ_{max} 238 mμ (ε 14,900); ν_{max} 1810 (1784) and 780 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.68; H, 7.89.

17,20α-Cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (11a) from 5a.—Treatment of 17,20α-cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (1 g) in pyridine (10 ml) with an equal weight of tosyl chloride for 64 hr at 5°, and crystallization of the product from methanol gave 1380 mg of platelets: mp 252–252.5°; $[\alpha]_{365}$ −326°, $[\alpha]_D$ −29.5°; λ_{max} 242 mμ (ε 16,850) (sh) and 228 (ε 23,600); ν_{max} 1800 and 749 (cyclic carbonate), 1595, 1490, 1350, 1189, 1175, 1093, 810, and 662 cm^{-1} (tosylate).[13]

Anal. Calcd for $C_{29}H_{36}O_8S$: C, 63.95; H, 6.66. Found: C, 63.74; H, 6.48.

11β,17,20α-Trihydroxypregn-4-en-3-one (12a) from 11a.—A solution of 17,20α-cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (1380 mg) and lithium aluminum hydride (1380 mg) in tetrahydrofuran (75 ml) was refluxed for 2.5 hr. The product, recovered in the usual manner, was treated in *tert*-butyl alcohol (100 ml) with DDQ (1 g) for 3 hr as described earlier.[2] The reaction mixture was chromatographed on a 30 × 730 mm silica gel column in ethyl acetate, collecting 12-ml fractions every 12 min. From **fractions 116–275** was obtained 490 mg of prisms (ethyl acetate), mp 202–204°, in an overall yield of 55% from **5a**: $[\alpha]_{365}$ 16.4°, $[\alpha]_D$ 105°; λ_{max} 242 mμ (ε 15,050) [lit.[14] mp 193–194° (210–214°), $[\alpha]_D$ 107 ± 2° (chloroform)].

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.28; H, 9.25.

21-Tosyloxy-11β,17,20α-trihydroxypregn-4-en-3-one (13a) from Reichstein's Substance Epi-E.—To a solution of 11β,17,-20α,21-tetrahydroxypregn-4-en-3-one (2 g) in pyridine (10 ml) was added 1450 mg of tosyl chloride. After 24 hr at room temperature the product was recovered and crystallized from acetone as platelets (2.1 g, mp 144.5° dec): $[\alpha]_{365}$ −72.2°, $[\alpha]_D$ 49.9°; λ_{max} 242 mμ (ε 17,600) (sh) and 228 (22,800); λ_{max} 1600, 1495, 1358, 1191, 1176, 1098, 817, and 665 cm^{-1} (tosylate).[13]

Anal. Calcd for $C_{28}H_{38}O_7S$: C, 64.84; H, 7.38. Found: C, 64.91; H, 7.49.

The mother liquor residue was chromatographed on a 35 × 800 mm silica gel column in ethyl acetate–isooctane (1:1), collecting 7.5-ml fractions every 10 min. **Fractions 211–385** afforded a more mobile by-product which crystallized from acetone as needles (358 mg, mp 135–138°). Since ir analysis showed an intensification of the characteristic tosylate bands, the compound was tentatively identified as **20α,21-ditosyloxy-11β,17-dihydroxypregn-4-en-3-one (14a)**: $[\alpha]_{365}$ −117°, $[\alpha]_D$ 20.4°; λ_{max} 242 mμ (ε 17,600) (sh) and 228 (33,800). From **fractions 461–690** was obtained an additional 300 mg of the 21-tosylate, mp 145° dec, raising the yield to 2.4 g (84%).

12a from 13a.—Lithium aluminum hydride reduction of 21-tosyloxy-11β,17,20α-trihydroxypregn-4-en-3-one (2 g) followed by selective reoxidation with DDQ were carried out as in the preparation of **12a** from **11a**. The crude product (1.27 g) was chromatographed on a 42 × 700 mm silica gel column in ethyl acetate–isooctane (85:15), collecting 8 ml per 10 min. Crystallization of the residue from **fractions 451–840** afforded 488 mg (36%) of the triolone, mp 199–202°.

17,20β-Cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (11b) from 5b.—Tosylation of 17,20β-cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (750 mg) was carried out as in the preparation of **11a**. The product crystallized from methanol as platelets (825 mg, mp 232.5–233°; 100 mg, mp 230–231°): $[\alpha]_{365}$ 168°, $[\alpha]_D$ 123°; λ_{max} 242 mμ (ε 16,250) (sh) and 228 (22,900); ν_{max} 1798 and 750 (cyclic carbonate), 1595, 1490, 1358, 1189, 1175, 1091, 811, and 662 cm^{-1} (tosylate).[13]

Anal. Calcd for $C_{29}H_{36}O_8S$: C, 63.95; H, 6.66. Found: C, 63.91; H, 6.65.

11β,17,20β-Trihydroxypregn-4-en-3-one (12b) from 11b.—Subjection of 17,20β-cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (900 mg) to sequential reaction with lithium aluminum hydride and DDQ as in the reaction of **11a** followed by silica gel column chromatography afforded 359 mg of needles from acetone, mp 162–163°, in an overall yield from **5a** of 54%: $[\alpha]_{365}$ 68.8°, $[\alpha]_D$ 125°; λ_{max} 242 mμ (ε 15,250) [lit.[14] mp 149–151°, $[\alpha]_D$ 122 ± 2° (chloroform)].

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.00; H, 9.18.

17,20α-Isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (15a) from 12a.—Acetonation of 11β,17,20α-trihydroxypregn-4-en-3-one (400 mg) with *p*-TSA as catalyst was carried out for 17 hr.[6] Crystallization of the product from acetone–*n*-hexane afforded prismatic needles (220 mg, mp 204.5–206.5°; 126 mg, mp 200–202°; 70 mg, mp 190–192°) in a yield of 93%: $[\alpha]_{365}$ −45.2°, $[\alpha]_D$ 69.8°; λ_{max} 242 mμ (ε 15,050); ν_{max} 1236, 1210, 1154, and 1003 cm^{-1} (17,20α-acetonide).[6]

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.02; H, 9.30.

17,20α-Isopropylidenedioxypregn-4-ene-3,11-dione (16a) from 15a.—Oxidation of 17,20α-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (360 mg) with chromic anhydride in pyridine as in the previous examples provided needles from acetone–*n*-hexane (327 mg, mp 175–177°; 14 mg, mp 164–168°) in a yield of 95%: $[\alpha]_{365}$ 599°, $[\alpha]_D$ 135°; λ_{max} 238 mμ (ε 14,900); ν_{max} 1237, 1214, 1148, and 1003 cm^{-1} (17,20α-acetonide).[6]

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.21; H, 8.70.

17,20α-Dihydroxypregn-4-ene-3,11-dione (17a) from 16a.—A solution of 17,20α-isopropylidenedioxypregn-4-ene-3,11-dione (300 mg) in 60% acetic acid (100 ml) stood for 72 hr at room temperature. The solution was concentrated *in vacuo* to dryness and the product crystallized from acetone as needles (234 mg, mp 216–218°) in a yield of 87%: $[\alpha]_{365}$ 770°, $[\alpha]_D$ 180°; λ_{max} 238 mμ (ε 14,700).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.63; H, 8.71.

17,20β-Isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (15b) from 12b.—To a solution of 11β,17-dihydroxypregn-4-ene-3,20-dione (2 g) in dimethylformamide (50 ml) were added sodium borohydride (150 mg) and sodium bicarbonate (300 mg), each in 2.5 ml of water.[4] After 2 hr at room temperature the crude triolone was recovered and treated in acetone (1 l.) with *p*-TSA (500 mg) for 6 hr. The reaction mixture was chromatographed on a 50 × 890 mm silica gel column in isooctane–ethyl acetate (3:2), collecting 12 ml per 10 min. Several crystallizations of the residue from **fractions 367–656** (acetone and ether) afforded 759 mg (34%) of plates: mp 205–206°; $[\alpha]_{365}$ −33.1°, $[\alpha]_D$ 87.3°; λ_{max} 242 mμ (ε 15,300); ν_{max} 1248, 1216, 1154, and 1008 cm^{-1} (17,20β-acetonide).[6]

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.39; H, 9.18.

17,20β-Isopropylidenedioxypregn-4-ene-3,11-dione (16b) from

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

(14) G. I. Poos, *J. Amer. Chem. Soc.*, **77**, 4438 (1955).

15b.—Oxidation of 17,20β-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (500 mg) with chromic anhydride in pyridine in the usual manner and crystallization of the product gave prisms (408 mg, mp 195–197°; 85 mg, mp 185–187°) in a yield of 99%: $[\alpha]_{365}$ 643°, $[\alpha]_D$ 150°; λ_{max} 238 mμ (ε 15,150); ν_{max} 1248, 1220, 1156, and 1002 cm^{-1} (17,20β-acetonide).[6]

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.56; H, 8.90.

17,20β-Dihydroxypregn-4-ene-3,11-dione (17b) from 16b.—A solution of 17,20β-isopropylidenedioxypregn-4-ene-3,11-dione (300 mg) in 80% acetic acid (100 ml) was refluxed for 1 hr. The reaction mixture was chromatographed on a 25 × 700 mm silica gel column in ethyl acetate–isooctane (85:15), collecting 6 ml per 10 min. From **fractions 31–55** was obtained 26 mg of starting material, mp 197–201°. The major product emerged in **fractions 140–225** and crystallized from acetone as rosettes (94 mg, mp 197–198°; 79 mg, mp 195–198°): $[\alpha]_{365}$ 840°, $[\alpha]_D$ 198°; λ_{max} 238 mμ (ε 15,000) [lit.[15] mp 108–110° (hydrate)].

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.91; H, 8.65.

20α-Carbethoxy-17-hydroxypregn-4-ene-3,11-dione (18a) from 17a.—Cathylation of 17,20α-dihydroxypregn-4-ene-3,11-dione (100 mg) in pyridine (1 ml) with ECC (0.075 ml) was carried out for 3 hr at room temperature. Several crystallizations from methanol gave 98 mg (88%) of product: mp 205–207°; $[\alpha]_{365}$ 583°, $[\alpha]_D$ 132°; λ_{max} 238 mμ (ε 13,900); ν_{max} 1736, 1260, and 791 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; C_2H_5O, 10.77. Found: C, 68.79; H, 8.24; C_2H_5O, 11.10.

17,20α-Cyclocarbonyldioxypregn-4-ene-3,11-dione (19a) from 18a.—To a solution of 20α-carbethoxy-17-hydroxypregn-4-ene-3,11-dione (20 mg) in ethanol (3.8 ml) was added 0.1 *N* ethanolic sodium hydroxide (0.2 ml). After 5 min the reaction mixture was added to methylene chloride (300 ml), and after being washed with water the solution was concentrated to dryness. Crystallization from ethyl acetate provided 17 mg (86%) of prisms: mp 264–265°; $[\alpha]_{365}$ 520°, $[\alpha]_D$ 120°; λ_{max} 238 mμ (ε 15,350); ν_{max} 1792 and 779 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.91; H, 7.52.

19a from 17a.—To a solution of 17,20α-dihydroxypregn-4-ene-3,11-dione (35 mg) in pyridine (0.5 ml) was added 12.5% phosgene in benzene (0.15 ml). After 1 hr at room temperature the product was recovered and crystallized from ethyl acetate (29 mg, mp 264–265°; 5 mg, mp 260–262°) in a yield of 91%. The ir spectrum was identical with that of the cyclization product from **18a**.

20β-Carbethoxy-17-hydroxypregn-4-ene-3,11-dione (18b) from 17b.—Cathylation of 17,20β-dihydroxypregn-4-ene-3,11-dione (100 mg) was carried out as in the preparation of **18a**. However, examination of the reaction mixture by tlc showed only roughly 50% conversion to the cathylate. The material was therefore retreated with ECC–pyridine overnight at room temperature. The crude product was chromatographed on a 16 × 580 mm silica gel column in ethyl acetate–isooctane (3:1), collecting 3 ml per 10 min. At fraction 172 the system was changed to ethyl acetate. **Fractions 31–100** afforded the 20-cathylate as prismatic needles from methanol (76 mg, mp 92–93°) in a yield of 69%: $[\alpha]_{365}$ 742°, $[\alpha]_D$ 189°; λ_{max} 238 mμ (ε 14,450); ν_{max} 1738, 1261, and 792 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{34}O_6 \cdot CH_3OH$: C, 66.64; H, 8.50; CH_3O- and C_2H_5O, 16.89. Found: C, 66.69; H, 8.69; C_2H_5O, 19.63.

From **fractions 171–270** was obtained 27 mg (27%) of starting material, mp 197–199°.

17,20β-Cyclocarbonyldioxypregn-4-ene-3,11-dione (19b) from 18b.—Treatment of 20β-carbethoxy-17-hydroxypregn-4-ene-3,11-dione (20 mg) with ethanolic sodium hydroxide as in the preparation of **19a** from **18a** and crystallization from methanol provided needles (15 mg, mp 241–242°) in a yield of 79%: $[\alpha]_{365}$ 700°, $[\alpha]_D$ 179°; λ_{max} 238 mμ (ε 16,150); ν_{max} 1792 and 777 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.93; H, 7.52.

19b from 17b.—Phosgenation of 17,20β-dihydroxypregn-4-ene-3,11-dione (35 mg) as in the preparation of **19a** from **17a** and crystallization of the product from methanol furnished needles (29 mg, mp 243–245°; 5 mg, mp 239–240°) in a yield of 92%. The ir spectrum was identical with that of the cyclization product from **18b**.

Forced Acetylation of 20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4a).—To a solution of the cyclic carbonate (1 g) in a mixture of acetic acid (40 ml) and acetic anhydride (8 ml) was added *p*-TSA (800 mg). After 90 min at room temperature the product was recovered and chromatographed on a 38 × 900 mm silica gel column in ethyl acetate–isooctane (55:45). Fractions (8 ml) were collected at 10-min intervals.

20α,21-Cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (21a). Fractions 396–570.—Crystallization from methanol gave needles (789 mg, mp 236–238°) in a yield of 71%. The compound was not affected by treatment with chromic anhydride in pyridine: $[\alpha]_{365}$ 0°, $[\alpha]_D$ 86.7°; λ_{max} 240 mμ (ε 15,150); ν_{max} 1800 and 788 (cyclic carbonate), 1734 and 1255 (acetate), 3450 cm^{-1} (hydroxyl).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.64; H, 7.46. Found: C, 66.38; H, 7.42.

20α,21-Cyclocarbonyldioxy-11β,17-diacetoxypregn-4-en-3-one (20a). Fractions 591–780.—Crystallization from ethyl acetate gave platelets (130 mg, mp 129–132°) in a yield of 11%: $[\alpha]_{365}$ −23.5°, $[\alpha]_D$ 77.5°; λ_{max} 239.5 mμ (ε 15,200); ν_{max} 1815 and 775 (cyclic carbonate), 1740 and 1245 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 66.33; H, 6.86.

Forced Acetylation of 20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4b).—Treatment of the 20β,21-cyclic carbonate (1 g) with acetic acid–acetic anhydride–*p*-TSA as in the reaction of **4a** and crystallization of the crude product from ethanol furnished 490 mg of **20β,21-cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (21b)** as needles: mp 154–156°; $[\alpha]_{365}$ 10.7°, $[\alpha]_D$ 89.4°; λ_{max} 240 mμ (ε 15,300); λ_{max} 1810 (1788) and 775 (cyclic carbonate), 1735 and 1255 (acetate), 3500 cm^{-1} (hydroxyl).

Anal. Calcd for $C_{24}H_{32}O_7 \cdot 0.5H_2O$: C, 65.28; H, 7.53. Found: C, 65.00; H, 7.18.

The compound was unchanged after treatment with chromic anhydride in pyridine. Chromatography of the mother liquor on a 30 × 800 mm silica gel column was carried out under the same conditions used for the 20α epimer.

20β,21-Cyclocarbonyldioxy-11β,17-diacetoxypregn-4-en-3-one (20b). Fractions 401–480.—The pooled residue weighed 125 mg (10%) and could be obtained only as a filterable solid from aqueous methanol: mp 130–132°; $[\alpha]_{365}$ −144°, $[\alpha]_D$ 41.2°; λ_{max} 239.5° mμ (ε 16,050); ν_{max} 1818 (1792) and 775 (cyclic carbonate), 1738 and 1240 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.95; H, 7.03.

Further development of the column gave from **fractions 501–700** an additional 221 mg of the 11β-monoacetate, mp 153.5–155°, raising the yield to 64%.

17,20α-Cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (22a) from 21a.—To a solution of 20α,21-cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (100 mg) in a mixture of ethanol (8 ml) and water (4 ml) was added 5% aqueous sodium bicarbonate solution (4 ml). After 15 min at room temperature the solution was added to methylene chloride (100 ml) and washed with water. The residue was chromatographed on a 16 × 680 mm silica gel column in ethyl acetate–isooctane (3:1). At fraction 128 the system was changed to ethyl acetate. **Fractions 64–111** afforded 56 mg of starting material, mp 239–239.5°. **Fractions 162–220** provided **22a** (41 mg) as prisms from acetone: mp 202.5–205°; $[\alpha]_{365}$ −126°, $[\alpha]_D$ 49.5°; λ_{max} 239 mμ (ε 16,400); ν_{max} 1805 and 783 (cyclic carbonate), 1734 and 1255 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{32}O_7 \cdot H_2O$: C, 63.98; H, 7.60. Found: C, 64.23; H, 7.04.

17,20β-Cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (22b) from 21b.—To a solution of 20β,21-cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (100 mg) in methanol (25 ml) was added an equal volume of 0.5% methanolic potassium bicarbonate. After 30 min at room temperature the solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water. Crystallization from methanol gave prisms (66 mg, mp 267–268° dec; 6 mg, mp 255–256°) in a yield of 72%: $[\alpha]_{365}$ 130°, $[\alpha]_D$ 132°; λ_{max} 239 mμ (ε 16,500); ν_{max} 1798 and 780 (cyclic carbonate), 1736 and 1255 cm^{-1} (acetate).

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

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.64; H, 7.46. Found: C, 66.83; H, 7.61.

17,20α-Cyclocarbonyldioxy-11β,21-diacetoxypregn-4-en-3-one (23a) from 22a.—Treatment of 17,20α-cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (20 mg) with acetic anhydride–pyridine for 2 hr and crystallization of the product from ethyl acetate gave 14 mg of prisms: mp 207.5–209.5°; $[\alpha]_{365}$ −141°, $[\alpha]_D$ 32.5°; λ_{max} 238 mμ (ε 16,600); ν_{max} 1805 and 782 (cyclic carbonate), 1738 and 1245 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.80; H, 7.37.

23a from 2a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (500 mg) in acetic acid (20 ml) and acetic anhydride (4 ml) was added *p*-TSA (400 mg). After 2 hr the product was recovered and chromatographed on a 25 × 760 mm silica gel column in ethyl acetate–isooctane (65:35), collecting 6 ml of effluent every 10 min. **Fractions 161–400** afforded prisms from ethyl acetate (335 mg, mp 206.5–209.5°; 37 mg, mp 199–202°) in a yield of 68%. The ir spectrum was identical with the acetylation product from **22a**.

17,20β-Cyclocarbonyldioxy-11β,21-diacetoxypregn-4-en-3-one (23b) from 22b.—Acetylation of 17,20β-cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (20 mg) as in the preparation of **23a** from **22a** furnished 17 mg of prisms from ethyl acetate: mp 232–234°; $[\alpha]_{365}$ 120°, $[\alpha]_D$ 119°; λ_{max} 238 mμ (ε 16,200); ν_{max} 1805 and 778 (cyclic carbonate), 1740 and 1240 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.83; H, 7.18.

23b from 2b.—A suspension of 17,20β-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (500 mg) in acetic acid (20 ml) and acetic anhydride (4 ml) containing *p*-TSA (400 mg) was stirred and warmed slightly to effect solution. After an additional hour at room temperature the product was recovered and crystallized from ethyl acetate (272 mg, mp 231.5–233.5°). The mother liquor was chromatographed on a 20 × 700 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 4-ml fractions at 10-min intervals. From **fractions 166–350** was obtained an additional 96 mg of product, mp 230–232°, raising the yield to 67%. The ir spectrum was identical with that of the acetylation product from **22b**.

Registry No.—**2a**, 33537-28-9; **2b**, 33487-57-9; **3a**, 33487-58-0; **3b**, 33487-59-1; **4a**, 33487-60-4; **4b**, 33487-61-5; **5a**, 33537-24-5; **5b**, 33487-62-6; **6a**, 33608-34-3; **6b**, 33487-63-7; **7a**, 33487-64-8; **7b** 33487-65-9; **8a**, 33487-66-0; **8b**, 33487-67-1; **9a**, 33487-68-2; **9b**, 33487-69-3; **10a**, 33487-70-6; **10b**, 33487-71-7; **11a**, 33487-72-8; **11b**, 33487-73-9; **12a**, 33537-25-6; **12b**, 33487-74-0; **13a**, 33537-26-7; **14a**, 33487-75-1; **15a**, 33487-76-2; **15b**, 33487-77-3; **16a**, 33487-78-4; **16b**, 33487-79-5; **17a**, 33487-81-9; **17b**, 33487-80-8; **18a**, 33487-82-0; **18b**, 33487-83-1; **19a**, 33537-27-8; **19b**, 33487-84-2; **20a**, 33487-85-3; **20b**, 33487-86-4; **21a**, 33487-87-5; **21b**, 33487-88-6; **22a**, 33487-89-7; **22b**, 33487-90-0; **23a**, 33487-91-1; **23b**, 33487-92-2.

The Olefin Selectivity for the Dehydration of 2-Octanol by Alumina and Thoria

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The primary olefin distribution was determined for the dehydration of 2-octanol over several alumina and thoria catalysts. Rather than attempt the elimination of secondary reactions, the isomerization of a very similar olefin, 1-heptene, was used to determine the extent of isomerization of the primary olefin products. For acidic alumina the initial olefin products were 45% 1-octene, 5% *trans*-2-octene, and 50% *cis*-2-octene. The presence of alkali metals in the alumina to decrease acidity caused an increase in the amount of the trans isomer and a corresponding decrease in the 1 isomer.

The mechanism for alcohol dehydration has been widely studied. The results of an early kinetic study with ethanol were interpreted by Brey and Krieger[1] to favor a carbonium ion intermediate. More recent investigators have altered or abandoned a carbonium ion intermediate for secondary alcohols. For instance, Pines and coworkers[2] have expanded the idea of Schwab and coworkers[3] that dehydration occurred in the catalyst pores. Pines attributed a pseudosolvent character to alumina and thus explained dehydration as a typical concerted trans elimination reaction.[4]

A large portion of the data used for mechanism proof has been olefin product distributions. For this distribution to be meaningful one must use the primary olefin product distribution unaltered by later isomerization. Various means have been used to reduce isomerization: adding alkali metal ions to the catalyst, addition of nitrogen bases during the reaction, low conversion, etc. The use of these additives requires us to assume that the isomerization may be poisoned more easily than dehydration if both reactions occur on the same catalyst site or that dehydration and isomerization occur on different sites.

In the present study we have determined the olefin product distribution from 2-octanol dehydration using several alumina and thoria catalyst preparations. Rather than try to eliminate secondary isomerization reactions we have used the isomerization of a very similar olefin, 1-heptene added to the reactant, to determine the extent of isomerization of the olefin product during the dehydration of 2-octanol.

Results

In Table I the selectivity for olefin formation (1-, *trans*-2-, and *cis*-2-octene) from 2-octanol over several catalysts are presented with some results from the literature for other 2-ols. Our selectivity data are taken for the sample collected after about 150–200 min on stream. It is noted that there are two sets of selectivity: over acidic alumina where the amount of *trans*-2-octene is less than 10% of the total octenes and non-acidic alumina, chromia, and molybdena catalysts where the trans isomer comprised 10–25% of the olefin products. Over all catalysts, including those from the

(1) W. S. Brey, Jr., and K. A. Krieger, *J. Amer. Chem. Soc.*, **71**, 3637 (1949).

(2) E. J. Blanc and H. Pines, *J. Org. Chem.*, **33**, 2035 (1968), and references cited therein.

(3) G. M. Schwab and E. Schwab-Agallidis, *J. Amer. Chem. Soc.*, **71**, 1806 (1949).

(4) R. T. Morrison and R. N. Boyd, "Organic Chemistry," Allyn and Bacon, Boston, Mass., 1966.