Reactions of α-Ketolic and Other 21-Hydroxy Steroids with Phosgene. I. Preparation and Properties of Bis(pregnan-21-yl) Carbonates and 17,21-Cyclic Carbonates[1]

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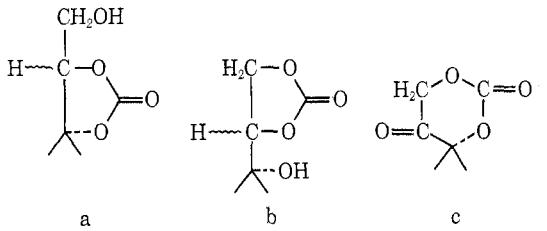
Reaction of phosgene in benzene with excess α-ketolic steroids in pyridine at 0° affords symmetrical bis(pregnan-21-yl) carbonates in good yield; binary mixtures of α-ketols give mixed carbonates in low yield. The new bisteroidal carbonates are stable to chromic anhydride–pyridine and strong mineral acid, but are readily cleaved to the parent α-ketols in weak alkali. Reaction of 11-deoxycortisol with excess phosgene results in excellent conversion to the 21-chlorocarbonate, but this product is quantitatively hydrolyzed to starting material during the work-up. In contrast, reaction of cortisone with excess phosgene provides the 17,21-cyclic carbonate **21** in 36% yield. Refluxing **21** in methanol affords both the 21-camylate **19** and a novel rearrangement product, the 20β-methoxy 17,20α-cyclic carbonate **22**. The formation of the latter compound can readily be understood in terms of a four-center-type mechanism. A number of nonketolic 17,21-diols also react with phosgene; the relative amounts of 21,21′-bisteroidal and 17,21-cyclic carbonates formed are determined both by the reaction conditions and the nature of the substituent at C-20.

We recently described[2] the preparation of five-membered ring 17,20- and 20,21-cyclic carbonates (partial formulas a and b, respectively, Scheme I) from the

SCHEME I



a b c

glycerol side chain. It seemed of interest to extend these studies to the synthesis of six-membered ring 17,21-cyclic carbonates (c) from the dihydroxyacetone side chain. However, it became evident as the work progressed that, although a 17,21-cyclic carbonate of type c could be prepared under suitable conditions, other products of both practical and theoretical interest are formed when α-ketols react with phosgene. The scope of this investigation was therefore enlarged to include the reactions of 17-deoxy-α-ketols and other 21-ols with various substituents at C-20. In this paper will be described the preparation and reactions of 21,-21′-bisteroidal carbonates and 17,21-cyclic carbonates.

When a solution of cortisone in pyridine was treated with phosgene in benzene under conditions suitable for the preparation of a and b, *i.e.*, the slow addition of reagent to excess steroid at 0° (condition A), the major product (83%) was not the expected 17,21-cyclic carbonate. Infrared analysis showed significant hydroxyl absorption and a new carbonyl band of moderate intensity at 1760 cm^{-1}. The product reduced alkaline blue tetrazolium and, although unaffected by methanolic cupric acetate and acetic anhydride–pyridine, it was readily converted to starting material in alkaline methanol. On the basis of these properties and a confirmatory molecular weight determination [calculated, 747; found, 791 (thermoelectric)], the product was identified as bis(cortison-21-yl) carbonate (**1**) (Table I).

As far as we are aware, the only other bisteroidal carbonate described previously is that from cholesterol.[3] For this reason a number of symmetrical carbonates having in common the Δ^4-3-one grouping were prepared under condition A. Constants obtained for bisteroidal carbonates from cortisol, 11-deoxycortisol, 11-dehydrocorticosterone, corticosterone, and 11-deoxycorticosterone (**2**–**6**, respectively) are given in Table I. Yields from 11-deoxy- and 11-keto-α-ketols averaged from 70 to 80%, but those from the two 11β-ols were significantly lower because of the formation in 15–20% yield of mixed carbonates **7** and **8** of the parent α-ketols and their $\Delta^{9,11}$ dehydration products. Structural assignments for mixed carbonates **7** and **8** were made by examination of the cleavage products generated in alkaline methanol.[4]

Mixed carbonates could also be prepared in low yield by treating equivalent amounts of different α-ketols under condition A. For example, reaction of a mixture of cortisol and 11-deoxycorticosterone gave, in addition to the symmetrical carbonates **2** and **6**, a product with intermediate chromatographic mobility. Its identity as cortisol-21-yl-11-deoxycorticosteron-21′-yl carbonate (**9**) was established by alkaline hydrolysis to roughly equal amounts of the parent α-ketols. Similar treatment of mixtures of cortisone and 11-deoxycorticosterone and of corticosterone and 11-deoxycorticosterone provided mixed carbonates **10** and **11**, respectively.

The chemical properties of the new bisteroidal carbonates are similar to those of five-membered ring cyclic carbonates. The stability of the carbonate bond to chromic anhydride–pyridine was demonstrated by oxidizing the 11β-ols **2**, **5**, **9**, and **11** to the corresponding 11-ones **1**, **4**, **10**, and **12**. Bisteroidal carbonates are readily cleaved by weak alkali, but are very resistant to mineral acids. For example, refluxing a solution of **1** in 3 *N* 90% ethanolic sulfuric

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

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

(3) F. Schadendorff and A. Verdino, *Monatsh.*, **65**, 338 (1935).

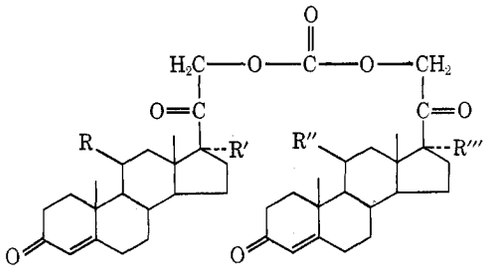
(4) The acetylated hydrolysis products from **7** were identified as cortisol acetate and 17-hydroxy-21-acetoxypregna-4,9(11)-diene-3,20-dione.[5] The corresponding products from **8** were corticosterone acetate and 21-acetoxypregna-4,9(11)-diene-3,20-dione.[6]

(5) J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.*, **79**, 1130 (1957). The author is indebted to Dr. Walter R. Benn of G. D. Searle & Co. for a reference sample of this compound.

(6) C. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

TABLE I

STRUCTURES AND CONSTANTS OF BIS(20-OXOPREGNEN-21-YL) CARBONATES

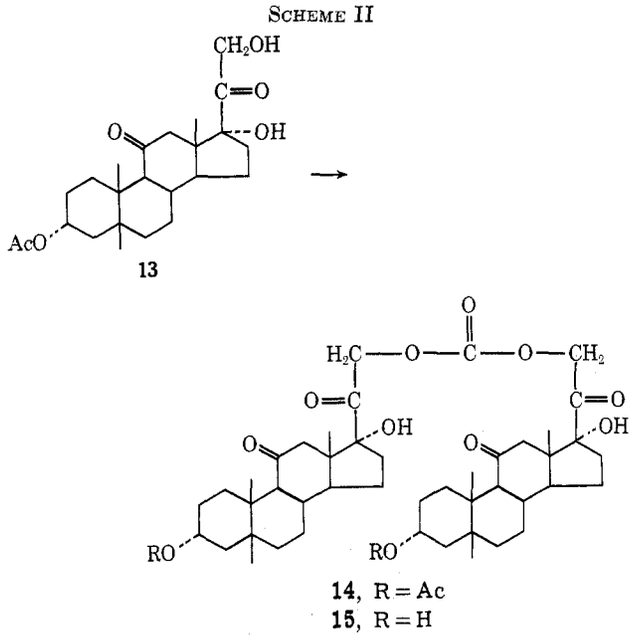


Compd	R	R′	R″	R‴	Mp, °C	[α]D	λmax, mμ	ε	νmax, cm⁻¹	Empirical formula	Calcd,[a] % C	Calcd,[a] % H	Found, % C	Found, % H	Yield, %
1	=O	OH	=O	OH	235–237	+268	238	30,400	1760, 1275, 785	$C_{43}H_{54}O_{11}$	69.15	7.29	68.86	7.34	83
2	β-OH	OH	β-OH	OH	193–194	+215	242	30,800	1755, 1285 789	$C_{43}H_{58}O_{11}$	63.45	8.05	63.42	8.11	56
3	H	OH	H	OH	275–276	+218[b]	241	31,400	1762, 1290, 785	$C_{43}H_{58}O_9$	71.84	8.13	71.66	8.22	82
4[c]	=O	H	=O	H	136–139	+290	238	31,300	1763, 1272 789	$C_{43}H_{54}O_9$	72.24	7.61	72.23	7.71	68
5	β-OH	H	β-OH	H	256–259	+253	241	29,700	1760, 1275, 790	$C_{43}H_{58}O_9$	71.84	8.13	71.71	8.16	50
6	H	H	H	H	115–118	+194	240	29,200	1760, 1270, 786	$C_{43}H_{58}O_7$	72.34	8.61	72.30	8.23	84
7	Δ9,11	OH	β-OH	OH	178–180	+188	241	31,400	1759 1278, 785	$C_{43}H_{56}O_{10}$	68.78	7.79	68.54	7.82	20
8	Δ9,11	H	β-OH	H	134–135	+220	241	29,700	1760, 1275, 790	$C_{43}H_{56}O_8$	73.68	8.05	73.55	8.08	15
9	H	H	β-OH	OH	154–156	+202	242	29,700	1759, 1278, 785	$C_{43}H_{58}O_9$	66.81	8.35	66.95	7.95	29
10	H	H	=O	OH	231–234	+250	240	31,400	1759, 1272 785	$C_{43}H_{56}O_9$	72.04	7.87	71.89	7.89	22
11	H	H	β-OH	H	135–137	+224	241	31,500	1760, 1270, 785	$C_{43}H_{58}O_8$	68.89	8.46	70.27	8.10	27
12[c]	H	H	=O	H	129–131	+250	240	31,400	1760, 1270, 785	$C_{43}H_{56}O_8$	73.68	8.05	73.37	7.97	62[d]

[a] Calculated values for compounds **2**, **6**, **7**, **9**, and **11** include 3.5, 1.5, 1, 3, and 2 molecules of water, respectively. [b] Determined in chloroform–methanol (1:1). [c] Obtained as a filterable solid from aqueous methanol. The remaining compounds were crystallized from methanol. [d] Indicates yields from chromic anhydride–pyridine oxidation of **11**.

acid for 2 hr was without effect. Advantage was taken of this property in the synthesis of bis(tetrahydrocortison-21-yl) carbonate (**15**) (Scheme II). Reaction

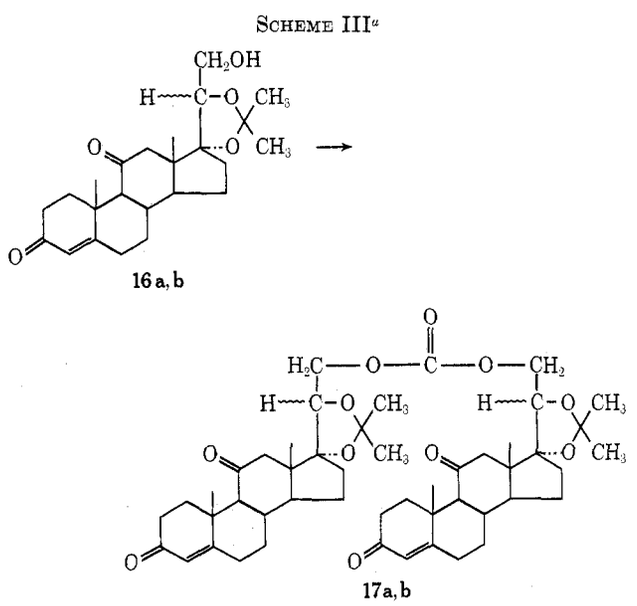
SCHEME II



of tetrahydrocortisone 3-monoacetate (**13**) with phosgene under condition A afforded the 3,3′-diacetate **14** in 80% yield. Treatment of **14** with methanolic sulfuric acid at room temperature resulted in deacetylation only, providing the 3,3′-diol **15** in 85% yield.

The extraordinary resistance to acid hydrolysis of the carbonate bond suggested a possible route to 21,21′-bisteroidal carbonates derived from the glycerol side chain. Since we had shown previously that some 17,20-acetonides can be cleaved by aqueous acetic acid,[7] it was hoped that phosgenation of the 21-ols followed by selective deacetonation would afford the desired bis(17,20-dihydroxypregnan-21-yl) carbonates. Accordingly, the 17,20-acetonides **16a** and **16b**[8] (Scheme III)

SCHEME III[a]

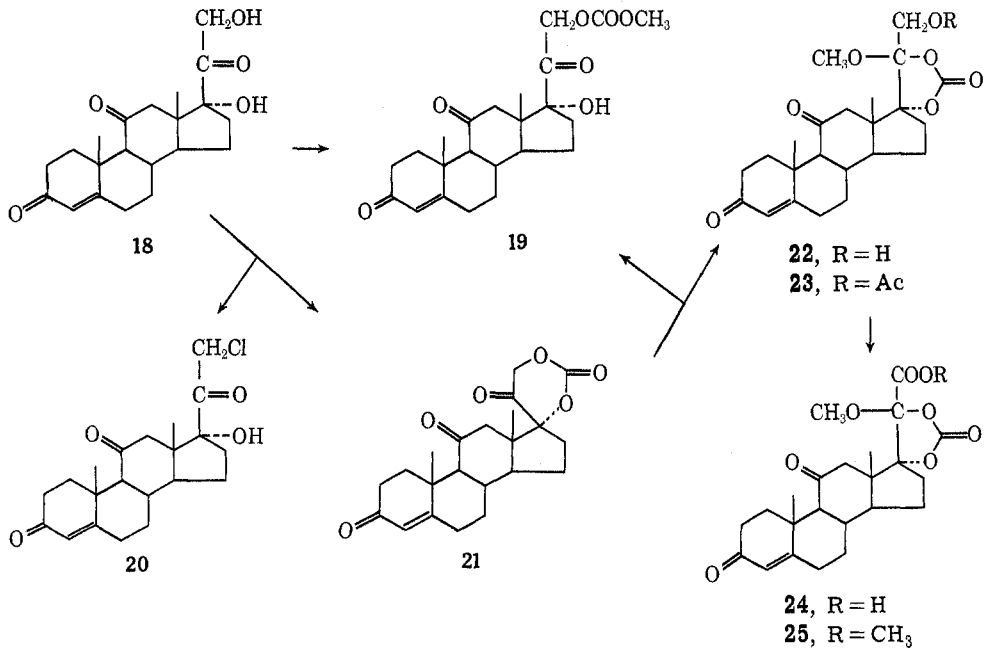


[a] The substituent at C-20 is α oriented in a compounds and β oriented in b compounds.

were converted to the corresponding bisteroidal carbonates **17a** and **17b** in yields of nearly 90%. Treatment of **17a** in 80% acetic acid for 24 hr at 65° resulted in its complete transformation to three identifiable products. These are 20α,21-cyclocarbonyldioxy-17-

(7) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).
(8) M. L. Lewbart and J. J. Schneider, *ibid.*, **34**, 3513 (1969).

SCHEME IV



hydroxypregn-4-ene-3,11-dione[8] (52%), 17,20α,21-trihydroxypregn-4-ene-3, 11-dione (32%), and 21-acetoxy-17,20α-dihydroxypregn-4-ene-3,11-dione (6%). In agreement with our earlier observations on the greater difficulty in hydrolyzing 17,20β-acetonides,[7] treatment of **17b** under the same conditions employed for **17a** had no effect. However, refluxing the 20β epimer in the same solvent for 8 hr resulted in nearly 75% loss of starting material. The two chief products which could be recovered are 17,20β-cyclocarbonyldioxy-21-hydroxypregn-4-ene-3,11-dione[8] (14%) and 17,20β,21-trihydoxypregn-4-ene-3,11-dione (12%). These results indicate that under the conditions employed both carbonate and acetonide bonds are ruptured, and, although the generation of cyclic carbonates as major products is of some interest, it is evident that selective deacetonation can not be achieved by this approach.

In the course of these investigations phosgenation of 11-deoxycortisol was carried out in a reverse manner, *i.e.*, by the slow addition of steroid in pyridine to a large excess of phosgene in benzene at 0° (condition B). It was found that under this condition the bisteroidal carbonate **3** is a minor product, and starting material was recovered in nearly quantitative yield. It was shown in a separate experiment, however, that, if methanol instead of ice is added to decompose excess reagent, the 21-*O*-carbomethoxy derivative (camylate) could be isolated in 88% yield. These findings suggest that, although a 21-chlorocarbonate is formed, it is quickly hydrolyzed in the course of the work-up. On the other hand, reaction of cortisone (**18**, Scheme IV) under condition B provided very little starting material after the usual work-up. The 21-chlorocarbonate is also evidently a minor product, since addition of methanol to a reaction mixture provides cortisone 21-camylate (**19**) in only 20% yield. Another minor product (10%) was identified as the 21-chloride **20**.[9] The major product (36%) from the reaction of cortisone with excess phosgene is the 17,21-cyclic carbonate **21**. This structural assignment is based chiefly on infrared analysis, which shows the absence of hydroxyl and the presence of a new carbonyl band at 1770 cm^{-1}. Treatment of **21** with methanolic potassium bicarbonate regenerated the α-ketol **18**.

In comparing the behavior of 11-deoxycortisol and cortisone under condition B, it is apparent that, although both α-ketols are converted to chlorocarbonates, the subsequent fate of these respective intermediates is strikingly different. Our results suggest that the 11-deoxy chlorocarbonate is unable to undergo elimination of hydrogen chloride followed by 17,21 cyclization, and is therefore completely hydrolyzed to starting material during the work-up. It would therefore appear that spontaneous dehydrochlorination leading to 17,21 cyclization occurs only in the presence of a carbonyl group at C-11.

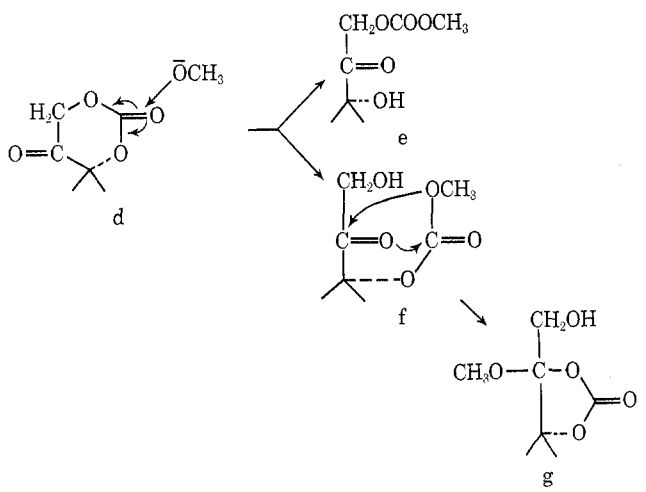
In the course of manipulating the cyclic carbonate **21** in methanol it was noted that prolonged heating brought about generation of two chromatographically less mobile artifacts. Refluxing **21** in methanol for 19 hr resulted in its complete conversion to roughly equal amounts of these two products. The mixture was resolved by silica gel column chromatography into a major mobile component (54%), the 21-camylate **19**, and a minor polar substance (19%). Since the latter product was found to have limited stability on silica gel, the low yield does not reflect the amount originally present in the reaction mixture. Organic microanalysis and mass spectroscopy showed that the unknown product contains one methoxyl group and is isomeric with the 21-camylate **19**. The presumption that it is the 17-camylate was supported by its conversion to a monoacetate under mild conditions. However, the infrared spectrum of the minor product exhibited strong bands at 1810 and 790 cm^{-1} which are characteristic of five-membered ring cyclic carbonates.[2] On the basis of these findings the compound is formulated as the 20-methoxy 17,20-cyclic carbonate **22** and its acetate as **23**. This structural assignment was substantiated by

(9) The author thanks Dr. Norman G. Brink of Merck Research Laboratories for a reference sample of 21-chloro-17-hydroxypregn-4-ene-3,11,20-trione.

the oxidation of 22 with chromic anhydride in acetic acid to the pregnenoic acid 24, which was further characterized as the methyl ester 25.

A plausible mechanism which explains the formation of the 21-camylate 19 and the methoxy cyclic carbonate 22 from 21 involves initial attack by methoxide ion on the carbonate carbonyl (d, Scheme V) with re-

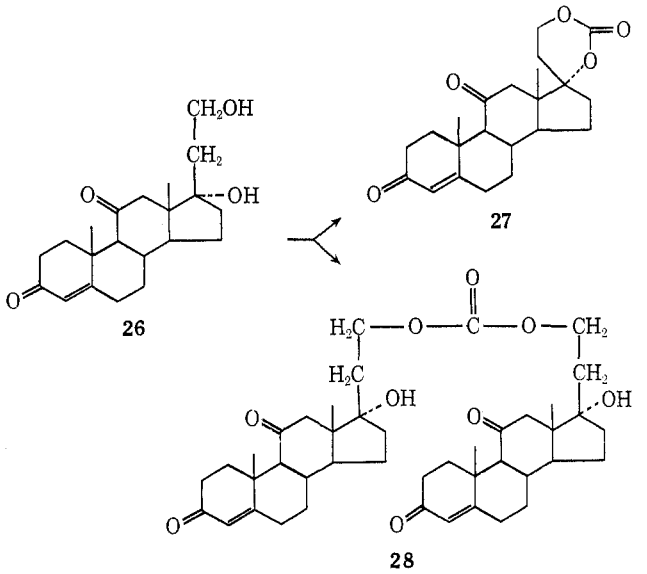
SCHEME V



sultant ring opening and generation in equal amounts of the 21- and 17-camylates e and f. Further reaction of the 17-camylate occurs by a four-center-type mechanism[10] in which attack by the C-20 carbonyl oxygen on the carbonate carbonyl is accompanied by migration of the methoxyl group to C-20, affording g. A point of special interest in the step from f to g is the stereospecific nature of the rearrangement. Nmr analysis indicated the presence of only one C-20 epimer, but attempts to establish the configurations of the substituents at C-20 by this technique were unsuccessful.[11] However, examination of a Dreiding model of the 17-camylate f reveals that under the postulated mechanism close approach of the reacting carbonyl groups can occur only when the hydroxymethylene group at C-21 is facing toward the angular methyl at C-18, *i.e.*, in the configuration assumed by 17,20α-cyclic carbonates.[2] This would restrict migration of the methoxyl group to the 20β position, giving the configuration for 22 and its derivatives as indicated in Scheme IV. Additional support for this configurational assignment was obtained when it was noted that the average of the molecular rotations of the four methoxy cyclic carbonates 22–25 (+431 units) is in much closer agreement with that of the corresponding C-20-unsubstituted 17,20α-cyclic carbonates (+382 units) than that of their 20β epimers (+687 units).

The synthesis of cortisone 17,21-cyclic carbonate 21 in modest yield prompted a study to determine the influence of a given substituent at C-20 on the relative amounts of bisteroidal and cyclic carbonates afforded by 17,21-diols under conditions A and B. A major aim of the investigation was to ascertain to what extent the C-20 carbonyl group facilitates or interferes with 17,21 cyclization. The simplest representative in this series, 20-deoxycortisone[12] (26, Scheme VI), afforded

SCHEME VI



the 17,21-cyclic carbonate 27 in 85% yield after being phosgenated under condition B. Structural assignment was based on the same considerations applied to the corresponding 20-one 21. Unlike the cortisone derivative, 27 was stable to refluxing methanol but, like 21, was readily hydrolyzed in alkaline methanol. When the 17,21-diol 26 was treated under condition A, the yield of cyclic carbonate 27 fell to 61%, and a less mobile substance (12.5%) could also be recovered. This minor procuct was identified as bis(20-deoxycortison-21-yl) carbonate (28) because it exhibits the same characteristic infrared bands seen in its α-ketolic counterparts. One must conclude from these findings that the presence of a C-20 carbonyl group serves to inhibit 17,21 cyclization, since the 20-deoxy analog cyclic carbonate 27 is obtained as the major product even under conditions which bring about conversion of α-ketols to their bisteroidal carbonates in yields exceeding 80%.

The reaction with phosgene of 11-deoxycortisol 3,20-bisketal[13] (29, Scheme VII) and cortisone 3,20-bisketal[14] (30) was also studied. Treatment of 29 and 30 under condition B gave their respective 17,21-cyclic carbonates 31 and 32 in virtually quantitative yields. Treatment of 31 and 32 with *p*-TSA in acetone at room temperature resulted in selective deketalization at C-3, providing the corresponding Δ^4-3-ones 33 and 34. Attempts to remove the remaining ketal group at C-20 without altering the cyclic carbonate ring were not successful. When the bisketals 29 and 30 were phosgenated under condition A, roughly equal amounts of the 17,21-cyclic carbonates 31 and 32 and the bisteroidal carbonates 35 and 36 were obtained. These findings are of interest for two reasons. First, they demonstrate that, in comparison with the reactions of 20-keto- and 20-deoxy-17,21-diols, 20-ethylene ketals show inter-

(10) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956, p 457.

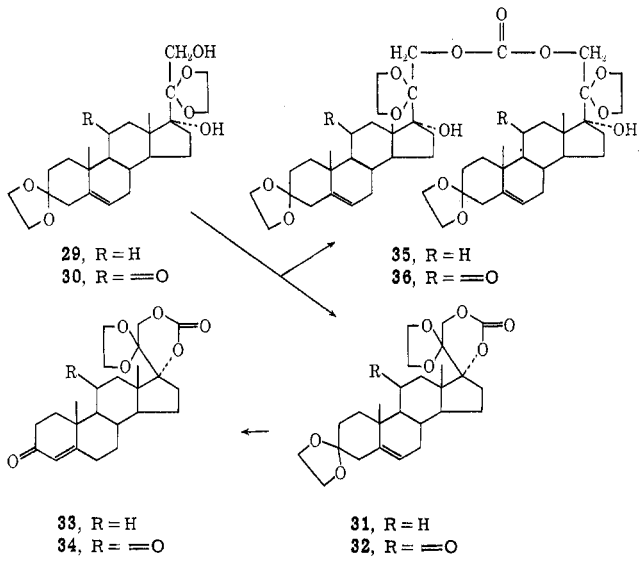
(11) We wish to thank Dr. Byron H. Arison of Merck Research Laboratories for the determination and interpretation of the nmr spectra.

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

(13) R. Antonucci, S. Bernstein, and R. H. Lenhard, *J. Amer. Chem. Soc.*, **76**, 2956 (1954).

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

SCHEME VII



29, R = H
30, R = =O

35, R = H
36, R = =O

33, R = H
34, R = =O

31, R = H
32, R = =O

mediate tendencies when phosgenated under condition A. Second, the presence of an ethylene ketal group at C-20 serves to eliminate the marked difference in behavior observed in the reactions of 11-deoxycortisol and cortisone under condition B.

The infrared spectral properties of the new bisteroidal and 17,21-cyclic carbonates were examined with the aim of establishing characteristic group frequencies. All symmetrical and mixed linear carbonates exhibited an expectedly diminished carbonyl band ranging from 1766 to 1754 cm^{-1}. The only exception was observed for the 20-deoxycortisone derivative **28** (1749 cm^{-1}). Like side-chain cathylates and five-membered ring cyclic carbonates,[2] all bisteroidal carbonates possess a medium to strong band in the region from 790 to 785 cm^{-1}. However, the very strong band which cathylates exhibit at 1265–1260 cm^{-1} is shifted to a significantly higher frequency (1290–1266 cm^{-1}) in bisteroidal carbonates. Within the restrictions imposed by the limited number of samples available, it appears that the absorption frequency of the carbonate carbonyl in six-membered ring cyclic carbonates depends upon the degree of ring strain imposed by the substituent at C-20. As would be predicted, the highest frequency (1775 cm^{-1}) was observed in the 20-ketone **21** and the lowest in the 20-deoxy cyclic carbonate **27** (1745 cm^{-1}). Intermediate carbonyl frequencies centering at 1755 cm^{-1} are exhibited by the four ethylene ketals **31–34**. The only band in the fingerprint region which all six 17,21-cyclic carbonates have in common is a very strong one at 1115–1110 cm^{-1}, but, since ethylene ketals also absorb strongly in this region, this assignment is only tentative.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined at 365 and 589 mμ (D line of sodium) in a Ziess 0.005° photoelectric polarimeter. Unless noted otherwise measurements were made in chloroform solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ±1°. Infrared (ir) spectra were determined as KBr pellets with a Beckman IR-8 instrument. Nmr spectra were determined with a Varian HA-100D instrument in $CDCl_3$, using TMS as an internal standard. Ultraviolet (uv) spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. General procedures for column and thin layer (tlc) chromatographic techniques and the processing of reaction mixtures have been cited earlier.[7] In those cases where column chromatography was required for bisteroidal carbonates from α-ketols, such as in the preparation of mixed carbonates **7–11**, Zaffaroni-type systems[15] were employed, since compounds of this type appear to have limited stability on silica gel. Microanalyses were by August Peisker-Ritter, Brugg, Switzerland, and Alfred Bernhard, Elbach über Engelskirchen, West Germany.

General Procedures for the Phosgenation of 21-Hydroxy Steroids. Condition A.—To a stirred solution of steroid (1 mmol) in pyridine (5 ml) at 0° was added dropwise a 3.75% solution of phosgene in benzene (5 ml) over a 20-min period. After the solution was stirred for another 5 min at 0°, methylene chloride (50 ml) and ice were added, and the product was recovered by successive washing with cold hydrochloric acid and water.

Condition B.—To a stirred 6.25% solution of phosgene in benzene (10 ml) at 0° is added dropwise 1 mmol of steroid in pyridine (10 ml) over a 20-min period. Decomposition of excess reagent and recovery of the product were carried out as in condition A.

17,21-Dihydroxy-3α-acetoxy-5β-pregnane-11,20-dione (13) from Tetrahydrocortisone 3,21-Diacetate.—To a solution of 17-hydroxy-3α,21-diacetoxy-5β-pregnane-11,20-dione (1792 mg, 4 mmol) in a mixture of methanol (180 ml) and methylene chloride (40 ml) was added 1 *N* aqueous sodium hydroxide (0.3 ml). After 2 hr at room temperature 9 drops of acetic acid was added, and the solution was concentrated *in vacuo*. The crude product was chromatographed on a 41 × 800 mm Celite column in chloroform (100 ml), toluene (100 ml), and formamide (5 ml). Fractions (12 ml) were collected every 10 min. The contents of fractions 57–80 crystallized from methanol as long needles (800 mg, mp 195–198°; 90 mg, mp 189–193°) in a yield of 67%: $[\alpha]_{365}$ 412°; $[\alpha]_D$ 92.9°; ν_{max} 1730 (sh), 1245, and 1032 cm^{-1} (3α-acetate).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.82; H, 8.21.

Bis(17-hydroxy-3α-acetoxy-11,20-dioxo-5β-pregnan-21-yl) Carbonate (14) from 13.—Phosgenation of 17,21-dihydroxy-3α-acetoxy-5β-pregnane-11,20-dione (406 mg, 1 mmol) was carried out under condition A. The reaction mixture was chromatographed on a 20 × 750 mm Celite column in toluene (100 ml), isooctane (100 ml), and formamide (5 ml), collecting 5-ml fractions. After the emergence of fraction 295, the system was changed to toluene (200 ml), isooctane (100 ml), and formamide (5 ml). Crystallization from acetone of the residue from fractions 416–425 gave hairy needles (335 mg, 80%): mp 175–177°; $[\alpha]_{365}$ 544°; $[\alpha]_D$ 120°; ν_{max} 3490 (hydroxyl), 1740 (sh), 1245, 1035 (3α-acetate), 1765, 1273, and 796 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{47}H_{66}O_{13}$: C, 67.28; H, 7.93; CH_3CO, 10.26. Found: C, 67.43; H, 8.01; CH_3CO, 9.83.

Bis(3α,17-dihydroxy-11,20-dioxo-5β-pregnan-21-yl) Carbonate (15) from 14.—To a solution of bis(17-hydroxy-3α-acetoxy-11,20-dioxo-5β-pregnan-21-yl) carbonate (100 mg) in 90% aqueous methanol (100 ml) was added 8 ml of concentrated sulfuric acid. After 66 hr at room temperature anhydrous sodium acetate (28 g) was added, the reaction mixture was diluted with methylene chloride (500 ml), and the solution was washed twice with water. Crystallization of the dried residue from methanol–ether gave 76 mg (85%) of rosettes: mp 196–197°; $[\alpha]_{365}$ 594°; $[\alpha]_D$ 112°; ν_{max} 3450 and 1242 (3α-hydroxyl), 1765, 1285, and 790 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{43}H_{62}O_{11}$: C, 68.41; H, 8.28. Found: C, 68.58; H, 8.41.

Bis(17,20α-isopropylidenedioxy-3,11-dioxopregn-4-en-21-yl) Carbonate (17a) from 16a.—Reaction of 17,20α-isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione[8] (1010 mg, 2.5 mmol) was carried out under condition A. The reaction mixture was chromatographed on a 50 × 880 mm Celite column in isooctane (240 ml), toluene (60 ml), and formamide (20 ml). Fractions (10 ml) were collected at intervals of 10 min. At fractions 510 and 795, the mobile phases were changed to isooctane (100 ml), toluene 50 ml), and isooctane (75 ml), toluene (150 ml), respectively. The bisteroidal carbonate **17a** emerged in a broad band from fractions 591–900. Crystallization from benzene afforded prismatic needles which slowly lost weight on drying *in vacuo* at

(15) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

room temperature. The product was dried to constant weight (922 mg, 88%) *in vacuo* at 65° over phosphoric anhydride: mp 170–174° and 272–275°; $[\alpha]_{365}$ 582°; $[\alpha]_D$ 127°; λ_{max} 238 mμ (ε 32,100); ν_{max} 1235, 1160, and 1002 (17,20α-acetonide), 1754, 1275, and 790 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{49}H_{66}O_{11}$: C, 70.82; H, 8.00. Found: C, 70.57; H, 7.95.

Bis(17,20β-isopropylidenedioxy-3,11-dioxopregn-4-en-21-yl) Carbonate (17b) from 16b.—Phosgenation of 17,20β-isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione[8] (1010 mg, 2.5 mmol) and chromatography of the reaction mixture in isooctane (200 ml), toluene (100 ml), and formamide (20 ml) on the same column used in the preparation of **17a** furnished 930 mg (89%) of **17b** as long needles from benzene–isooctane: mp 179–183° and 263–266°; $[\alpha]_{365}$ 690°; $[\alpha]_D$ 174°; λ_{max} 238 mμ (ε 30,500); ν_{max} 1250, 1160, and 1002 (17,20β-acetonide), 1755, 1275, and 795 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{49}H_{66}O_{11}\cdot H_2O$: C, 69.31; H, 8.07. Found: C, 69.41; H, 8.06.

Phosgenation of Cortisone (18) under Condition B.—The reaction mixture from 360 mg (1 mmol) of cortisone afforded a fine reddish precipitate from methylene chloride. After charcoaling in ethyl acetate–methylene chloride and recrystallization, 36 mg of colorless needles were obtained, mp 281–283°. The ir spectrum was identical with that of a reference sample of 21-chloro-17-hydroxypregn-4-ene-3,11,20-trione[9] (**20**). Repeated crystallizations from the mother liquor in ethyl acetate and ethyl acetate–methylene chloride with selective charcoaling afforded 17,21-cyclocarbonyldioxypregn-4-ene-3,11,20-trione (**21**) as prisms (137 mg, 36%), mp 224–225°. Although the cyclic carbonate **21** was homogeneous by tlc, it was also obtained in a higher melting form (mp 270–272°) in those experiments which required column chromatography: $[\alpha]_{365}$ 725°; $[\alpha]_D$ 153°; λ_{max} 238 mμ (ε 16,050); ν_{max} 1775 and 1110 (17,21-cyclic carbonate), 1740 cm^{-1} (20-ketone).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.41; H, 6.81.

21-*O*-Carbomethoxy-17-hydroxypregn-4-ene-3,11,20-trione (19) from 18.—To 100 mg of cortisone in cold pyridine (1 ml) was added 0.075 ml of methyl chlorocarbonate. After 1 hr at room temperature the product was recovered and crystallized from methanol as needles (94 mg, mp 224–225°; 9 mg, mp 221–223°) in a yield of 89%: $[\alpha]_{365}$ 1115°; $[\alpha]_D$ 238°; λ_{max} 238 mμ (ε 15,700); ν_{max} 1765, 1285, and 797 cm^{-1} (camylate).

Anal. Calcd for $C_{25}H_{30}O_7$: C, 66.01; H, 7.23; CH_3O, 7.42. Found: C, 65.92; H, 7.25; CH_3O, 7.60.

17,20α-Cyclocarbonyldioxy-20β-methoxy-21-hydroxypregn-4-ene-3,11-dione (22) and 19 from 21.—A solution of 17,21-cyclocarbonyldioxypregn-4-ene-3,11,20-trione (600 mg) in methanol (50 ml) was refluxed for 19 hr. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (3:2) showed the complete conversion of starting material (R_f 0.29) to roughly equal amounts of two products (R_f 0.20 and 0.14). The mixture was chromatographed on a 30 × 830 mm silica gel column in ethyl acetate–isooctane (3:1), collecting 10-ml fractions every 10 min. Fractions 71–115 afforded 350 mg (54%) of needles from methanol, mp 225–226°. The ir spectrum was identical with that of the 21-camylate **19**, prepared by reaction of cortisone with methyl chlorocarbonate. Crystallization of fractions 131–210 from methanol furnished the methoxy cyclic carbonate **22** as prisms (111 mg, mp 258–261°; 15 mg, mp 251–253°) in a yield of 19%: $[\alpha]_{365}$ 451°; $[\alpha]_D$ 90°; λ_{max} 238 mμ (ε 16,650); ν_{max} 1810 and 788 cm^{-1} (cyclic carbonate); nmr δ 9.05 (s, 3, 18-CH_3), 8.58 (s, 3, 19-CH_3), 7.31 (s, 2, 12-CH_2), 6.52 (s, 3, CH_3O), 6.15, 5.92 (d, d, J = 9.0 and 5.0 Hz, 21-CH_2).

Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23; CH_3O, 7.41. Found: C, 66.11; H, 7.34; CH_3O, 7.72.

Treatment of **22** (25 mg) with 0.05 ml each of acetic anhydride and pyridine for 3 hr at room temperature and crystallization from methanol gave 20 mg of 17,20α-cyclocarbonyldioxy-20β-methoxy-21-acetoxypregn-4-ene-3,11-dione (**23**) as rosettes: mp 213–213.5°; $[\alpha]_{365}$ 406°; $[\alpha]_D$ 84.7°; λ_{max} 238 mμ (ε 16,150); ν_{max} 1818 and 782 (cyclic carbonate), 1759 and 1233 cm^{-1} (acetoxyl); nmr δ 9.07 (s, 3, 18-CH_3), 8.59 (s, 3, 19-CH_3), 7.90 (s, 3, CH_3CO), 7.37, 7.25 (d, 2, J = 16 Hz, 12-CH_2), 6.55 (s, 3, CH_3O), 5.76, 5.34 (d, 2, J = 13.0 Hz, 21-CH_2).

Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01; CH_3CO, 9.35; CH_3O, 6.74. Found: C, 65.44; H, 7.51; CH_3CO, 8.92; CH_3O, 5.81.

17,20α-Cyclocarbonyldioxy-20β-methoxy-3,11-dioxopregn-4-en-21-oic Acid (24) from 22.—To a solution of 17,20α-cyclocarbonyldioxy-20β-methoxy-21-hydroxypregn-4-ene-3,11-dione (21 mg, 50 μmol) in acetic acid (0.95 ml) was added 15 mg (150 μmol) of chromic anhydride in water (0.05 ml). After 65 hr at 5° the solvent was evaporated and the residue was partitioned between methylene chloride and 2% sodium bicarbonate solution. The neutral fraction (2.6 mg) was not examined. From the acidic fraction (14.2 mg) were obtained prisms from methanol: mp 277–279°; $[\alpha]_{365}$ 464°; $[\alpha]_D$ 104°; λ_{max} 238 mμ (ε 15,700); ν_{max} 1820 and 773 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.88; H, 6.53. Found: C, 64.05; H, 6.62.

Treatment of **24** with excess ethereal diazomethane and crystallization of the product from methanol furnished methyl 17,20α-cyclocarbonyldioxy-20β-methoxy-3,11-dioxopregn-4-en-21-oate (**25**) as leaflets: mp 218–219°; $[\alpha]_{365}$ 474°; $[\alpha]_D$ 114°; λ_{max} 238 mμ (ε 15,500); ν_{max} 1825 and 786 (cyclic carbonate), 1755 cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{24}H_{30}O_8$: C, 64.56; H, 6.77; CH_3O, 13.90. Found: C, 64.47; H, 6.86; CH_3O, 13.53.

17,21-Cyclocarbonyldioxypregn-4-ene-3,11-dione (27) from 26.—Phosgenation of 17,21-dihydroxypregn-4-ene-3,11-dione[12] (104 mg) under condition B was followed by chromatography of the reaction mixture on a 15 × 500 mm silica gel column in ethyl acetate–isooctane (4:1), collecting 2-ml fractions per 10 min. The pooled contents of fractions 191–420 crystallized from methanol as prismatic needles (89 mg, mp 254.5–255°; 6 mg, mp 256–257.5°) in a yield of 85%: $[\alpha]_{365}$ 600°; $[\alpha]_D$ 140°; λ_{max} 238 mμ (ε 16,200); ν_{max} 1745 and 1115 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 70.94; H, 7.58. Found: C, 70.80; H, 7.62.

Treatment of **27** (20 mg) in methanol (2 ml) with 0.5% methanolic potassium bicarbonate (2 ml) for 21 hr at room temperature afforded 10.6 mg of prisms from acetone, mp 186.5–188.5°. A mixture melting point with 20-deoxycortisone **26** was 187–189° and their ir spectra were identical.

Bis(17-hydroxy-3,11-dioxopregn-4-en-21-yl) Carbonate (28) and 27 from 26.—Phosgenation of **26** (104 mg) under condition A was followed by chromatography on a 15 × 500 mm Celite column in toluene–formamide, collecting fractions of 2 ml each 10 min. From fractions 81–125 was obtained 68 mg (61%) of cyclic carbonate **27**, mp 254.5–256.5°. The residue (17.5 mg) from fractions 151–220 afforded the bisteroidal carbonate **28** as prismatic needles from methanol (13.4 mg, mp 240–241°): $[\alpha]_{365}$ 740°; $[\alpha]_D$ 165°; λ_{max} 238 mμ (ε 31,000); ν_{max} 3510 (hydroxyl), 1749, 1275, and 785 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{43}H_{58}O_9$: C, 71.84; H, 8.13. Found: C, 71.83; H, 8.24.

17,21-Cyclocarbonyldioxypregn-5-ene-3,20-dione 3,20-Bis(ethylene Ketal) (31) from 29.—The product from reaction of 17,21-dihydroxypregn-5-ene-3,20-dione 3,20-bis(ethylene ketal)[13] (434 mg, 1 mmol) under condition B crystallized as platelets from methanol (405 mg, mp 232–235°; 35 mg, mp 228–231°) in a yield of 96%: $[\alpha]_{365}$ −152°; $[\alpha]_D$ −48°; ν_{max} 1755 and 1110 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.82; H, 7.79.

17,21-Cyclocarbonyldioxypregn-4-ene-3,20-dione 20-Ethylene Ketal (33) from 31.—To a solution of 17,21-cyclocarbonyldioxypregn-5-ene-3,20-dione 3,20-bis(ethylene ketal) (50 mg) in a mixture of methylene chloride (2 ml) and acetone (38 ml) was added *p*-TSA (10 mg). After 20 hr at room temperature the product was recovered and crystallized from methanol as leaflets (40 mg, mp 231–232°) in a yield of 88%: $[\alpha]_{365}$ −8.2°; $[\alpha]_D$ 65.5°; λ_{max} 240 mμ (ε 16,600); ν_{max} 1753 and 1112 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75. Found: C, 69.40; H, 7.86.

Bis(17-hydroxy-3,20-bisethylenedioxypregn-5-en-21-yl) Carbonate (35) and 33 from 29.—Phosgenation of 17,21-dihydroxypregn-5-ene-3,20-dione 3,20-bis(ethylene ketal) (87 mg) was carried out under condition A. The reaction mixture was chromatographed on a 20 × 730 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 5 ml per 10 min. The contents of fractions 41–160 crystallized from methanol, giving the bisteroidal carbonate **35** as platelets (32 mg, mp 283–285°) in a yield of 35%: $[\alpha]_{365}$ −109°; $[\alpha]_D$ −36.4°; ν_{max} 3520 (hydroxyl), 1755, 1265, and 790 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{51}H_{74}O_{13}$: C, 68.43; H, 8.33. Found: C, 68.58; H, 8.16.

Further processing of the mother liquor from **35** gave the cyclic carbonate **31** in a total yield of 30 mg (33%), mp 235–238°. Continued development of the column with ethyl acetate–isooctane (4:1) provided 11 mg of starting material (**29**) mp 212–214°.

17,21-Cyclocarbonyldioxypregn-5-ene-3,11,20-trione 3,20-Bis(ethylene Ketal) (32) from 30.—Phosgenation of 17,21-dihydroxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal)[14] (448 mg, 1 mmol) was effected using condition B. Crystallization of the product from methanol gave platelets (385 mg, mp 286–288°; 70 mg, mp 278–281°) in a yield of 96%: $[\alpha]_{365}$ −23.2°; $[\alpha]_D$ −31.3°; ν_{max} 1755 and 1110 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.99; H, 7.27.

17,21-Cyclocarbonyldioxypregn-4-ene-3,11,20-trione 20-Ethylene Ketal (34) from 32.—Treatment of 17,21-cyclocarbonyldioxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal) (50 mg) with *p*-TSA in methylene chloride–acetone was carried out as in the preparation of **33** from **31**. The product crystallized from methanol as needles (37 mg, mp 259–261°) in a yield of 82%: $[\alpha]_{365}$ 553°; $[\alpha]_D$ 131°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1755 and 1115 cm^{-1} (17,21-cyclic carbonate).

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 67.05; H, 7.11.

Bis(17-hydroxy-3,20-bisethylenedioxy-11-oxopregn-5-en-21-yl) Carbonate (36) and 32 from 30.—The reaction mixture from phosgenation under condition A of 17,21-dihydroxypregn-5-ene-3,11,20-trione 3,20-bis(ethylene ketal) (90 mg) was chromatographed on a 20 × 730 mm silica gel column in ethyl acetate–isooctane (3:2). After emergence of fraction 300 the system was changed to ethyl acetate–isooctane (4:1). Fractions (5 ml) were collected every 10 min. Fractions 171–280 contained the 17,21-cyclic carbonate **32**. Crystallization from methanol gave 38 mg (40%) of platelets, mp 285–286°. Crystallization of the residue from fractions 311–400 gave the bisteroidal carbonate **26** as needles (34 mg, 37%): mp 254–257°; $[\alpha]_{365}$ 91.8°, $[\alpha]_D$ −0.94°; ν_{max} 1760, 1265, and 787 cm^{-1} (bisteroidal carbonate).

Anal. Calcd for $C_{51}H_{70}O_{15}$: C, 66.36; H, 7.64. Found: C, 66.47; H, 7.48.

Registry No.—**1**, 36674-99-4; **2**, 36623-73-1; **3**, 36623-74-2; **4**, 36623-75-3; **5**, 36623-76-4; **6**, 36675-00-0; **7**, 36623-11-7; **8**, 36623-12-8; **9**, 36675-01-1; **10**, 36623-13-9; **11**, 36623-14-0; **12**, 36623-15-1; **13**, 36623-16-2; **14**, 36623-17-3; **15**, 36623-18-4; **17a**, 36623-19-5; **17b**, 36623-20-8; **19**, 36623-21-9; **21**, 36623-22-0; **22**, 36623-23-1; **23**, 36623-24-2; **24**, 36623-25-3; **25**, 36623-26-4; **27**, 36623-27-5; **28**, 36623-28-6; **31**, 36675-02-2; **32**, 36623-29-7; **33**, 36623-30-0; **34**, 36623-31-1; **35**, 36675-03-3; **36**, 36623-32-2; phosgene, 75-44-5.

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Nucleosides. LXXVI. A Synthesis of a Carbon–Carbon Bridged Pyrimidine Cyclonucleoside[1]

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The synthesis of a pyrimidine cyclonucleoside containing a carbon to carbon linkage between C-6 and C-5′ has been achieved. Oxidation of 5-acetoxy-2′,3′-*O*-isopropylideneuridine (**2**) with DMSO–DCC gave the corresponding 5′ aldehyde isolated as its 1,3-diphenylimidazolidine derivative **3**. Hydrolysis of the ester **3** gave the 5-hydroxy derivative **4**, which upon treatment with Dowex-50 (H^+) in aqueous THF afforded the 5′ aldehyde of 2′,3′-*O*-isopropylidene-5-hydroxyuridine (**5**). Base-catalyzed intramolecular hydroxyalkylation of **5** proceeded stereoselectively to give cyclonucleoside **6**, which on treatment with acid yielded the free cyclonucleoside **6a**. Formation of **6** from **5**, facilitated by the presence of the isopropylidene group, is thought to proceed by addition of the C-6 anion to the 5′ aldehyde group. Experimental evidence supporting this mechanism is discussed.

Cyclonucleosides containing a bond from a ribose carbon to a purine or pyrimidine carbon were first reported by Hogenkamp[2] and by Johnson and coworkers.[3] Thus aerobic photolytic cleavage of coenzyme B_{12} gave, among other products, the so-called Nucleoside A. The latter nucleoside was identical with the product obtained by anaerobic photolysis of coenzyme B_{12} and it was tentatively identified as 8,5′-cycloadenosine.[2] Likewise, photolysis of 5′-deoxyinosylcobalamin gave the cyclic nucleoside of hypoxanthine.[3a] In contrast to these results, the anaerobic photolysis of 5′-deoxy-2′,3′-*O*-isopropylideneuridinylcobalamin gave hydroxycobalamin and a crystalline nucleoside which was tentatively identified as 2′,3′-*O*-isopropylidene-6,5′-cyclo-5,6-dihydrouridine.[3b] On the other hand, Keck and Hagen[4] reported the formation of 8,5′-cycloadenylic acid by irradiation of adenylic acid. Presumably all of these reactions involve free-radical mechanisms. Of related interest is the reported synthesis[5] of 2,2′-methylene cyclonucleosides by the photolysis of pyrimidine nucleoside oxosulfonium ylides. More recently Harper and Hampton[6] reported that treatment of 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid with methyllithium in tetrahydrofuran gave a complex mixture of products from which 2′,3′-*O*-isopropylidene-5′-keto-8,5′-cycloadenosine was isolated in ~5% yield. This latter nucleoside was reduced with sodium borohydride to 2′,3′-*O*-isopropylidene-8,5′-cycloadenosine.[6]

Since hydroxymethylation of 5-hydroxy-1-methyluracil had been shown to proceed readily to yield 5-

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