Naturvidenskabelige Forskningsraad, Copenhagen, to whom we are also grateful for a travel grant to one of us (H.E.). Partial financial support by NATO (Grant RG 939) and the National Institutes of Health (Grants No. AM-17896 and GM 06840) is also acknowledged. One of us (N.S.B.) acknowledges the assistance of Dr. Felix Werli of Varian A. G., Zug, Switzerland.

**Registry No.**—1, 2287-84-5; 2, 15064-05-8; 3, 15064-07-0; 4, 2287-91-4; 5, 20707-85-1; 6, 1225-47-4; 7, 604-17-1; 8, 7657-50-3; 9, 516-95-0; 10, 1224-92-6; 11, 80-97-7; 12, 20707-77-1; 13, 19586-33-5; 14, 20707-78-2; 15, 566-50-7; 16, 910-19-0; 17, 19043-45-9; 18, 32215-75-1; 19, 19037-32-2; 20, 19037-34-4; 21, 2872-91-5; 22, 25814-80-6; 23, 25814-82-8; 24, 5672-61-7; 25, 1090-01-3; 26, 57031-40-0, 27, 734-66-7; 28, 1032-14-0; 29, 1032-15-1; 30, 19037-37-7; 31, 1225-43-0; androstane, 438-22-2; cholestane, 481-21-0.

## References and Notes

(1) (a) University of Copenhagen, The H. C. Orsted Institute, DK-2100 Copenhagen, Denmark; (b) Stanford University; (c) Louisiana State University.
(2) H. Eggert and C. Djerassi, *J. Org. Chem.*, **38**, 3788 (1973).
(3) H. Eggert and C. Djerassi, to be published.
(4) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959.
(5) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 3289 (1956).
(6) C. W. Shoppee, R. E. Lack, S. C. Sharma, and L. R. Smith, *J. Chem. Soc. C*, 1155 (1967).
(7) T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. Pharm. Bull.*, **11**, 465 (1963).
(8) D. M. S. Wheeler and M. M. Wheeler, "Organic Reactions in Steroid Chemistry", Vol. I, J. Fried and J. A. Edwards, Ed., Van Nostrand-Reinhold, Princeton, N.J., 1972.
(9) D. Varech and J. Jacques, *Bull. Soc. Chim. Fr.*, 67 (1965).
(10) R. Stevenson and L. F. Fieser, *J. Am. Chem. Soc.*, **78**, 1409 (1956).
(11) H. V. Anderson, E. R. Garret, F. H. Lincoln, Jr., A. H. Nathan, and J. A. Hogg, *J. Am. Chem. Soc.*, **76**, 743 (1954).
(12) C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *J. Chem. Soc.*, 630 (1959).
(13) C. Djerassi, R. H. Shapiro, and M. Vandewalle, *J. Am. Chem. Soc.*, **87**, 4892 (1965).
(14) D. H. Williams, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2091 (1963).
(15) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **75**, 1282 (1953).
(16) C. Djerassi and L. Tökés, *J. Am. Chem. Soc.*, **88**, 536 (1966).
(17) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).
(18) I. M. Clark, A. S. Clegg, W. A. Denny, E. R. H. Jones, G. D. Meakins, and A. Pendlebury, *J. Chem. Soc., Perkin Trans. 1*, 499 (1972).
(19) C. Djerassi and G. von Mutzenbecher, *Proc. Chem. Soc., London*, 377 (1963).
(20) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972); C. A. Brown, *ibid.*, **95**, 4100 (1973).
(21) Dr. Paul N. Demarco, Eli Lilly Research Laboratories, Indianapolis, Ind.
(22) P. A. Plattner, T. Petrzilka, and W. Lang, *Helv. Chim. Acta*, **27**, 513 (1944).
(23) J. W. ApSimon, H. Beierbeck, and J. K. Saunders, *Can. J. Chem.*, **51**, 3874 (1973).
(24) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 7445 (1969).
(25) A. Pancrazi and Q. Khuong-Huu, *Tetrahedron*, **30**, 2337 (1974).
(26) D. J. Chadwich and D. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1903 (1974).
(27) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(28) E. Breitmeier and W. Voelter, "$^{13}C$ NMR Spectroscopy", Verlag Chemie, Weinheim/Bergstr., Germany, 1974.
(29) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958).
(30) W. B. Smith, D. L. Deavenport, J. A. Swanzy, and G. A. Pate, *J. Magn. Reson.*, **12**, 15 (1973).
(31) M. Christl, H. J. Reich, and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 3463 (1971).
(32) A. Allerhand, D. Doddrell, and R. Komoroski, *J. Chem. Phys.*, **55**, 189 (1971).
(33) S. H. Grover and J. B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).
(34) G. W. Buchanan, D. A. Ross, and J. B. Stothers, *J. Am. Chem. Soc.*, **88**, 4301 (1966).
(35) G. W. Buchanan and J. B. Stothers, *Can. J. Chem.*, **47**, 3605 (1969).
(36) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(37) D. Leibfritz and J. D. Roberts, *J. Am. Chem. Soc.*, **95**, 4996 (1973).
(38) D. K. Dalling, D. M. Grant, and E. G. Paul, *J. Am. Chem. Soc.*, **95**, 3718 (1973).
(39) S. A. Knight, *Tetrahedron Lett.*, 83 (1973).
(40) G. Lukacs, F. Khuong-Huu, C. R. Bennett, B. L. Buckwalter, and E. Wenkert, *Tetrahedron Lett.*, 3515 (1972).
(41) E. Wenkert and B. L. Buckwalter, *J. Am. Chem. Soc.*, **94**, 4367 (1972).
(42) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).
(43) B. V. Cheney and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 5319 (1967).
(44) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(45) E. Lippmaa, T. Pehk, and J. Paasivirta, *Org. Magn. Reson.*, **5**, 277 (1973).
(46) S. H. Grover, J. P. Guthrie, J. B. Stothers, and C. T. Tan, *J. Magn. Reson.*, **10**, 227 (1973).
(47) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8**, 1 (1974).

# Reactions of $\alpha$-Ketols and Other 21-Hydroxy Steroids with Phosgene. IV. Formation of 20-Chloro-17,20-cyclic Carbonates from 17$\alpha$-Hydroxy-20-ones[1]

Marvin L. Lewbart[2]

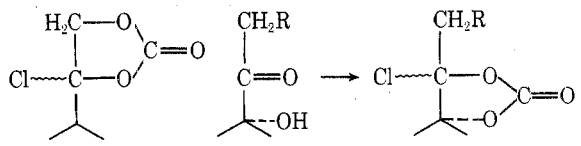
*Department of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania 19107*

*Received May 14, 1975*

Reaction of 17-hydroxy-20-oxopregnenes and the homologous 21-norpregnenes with excess phosgene in methylene chloride–pyridine (condition C) affords chiefly 20$\beta$-chloro-17,20$\alpha$-cyclic carbonates. The epimeric 20$\alpha$-chloro-17,20$\beta$-cyclic carbonates are minor products. Configurational assignments at C-20 were based primarily on optical rotatory properties. Unlike 20$\xi$-chloro-20,21-cyclic carbonates, the new isomeric chlorocarbonates do not undergo dehydrohalogenation in hot pyridine or acetone–sodium iodide–triethylamine. However, treatment of chlorocarbonates **9a**, **2a**, and **4a** with zinc in acetic acid gave the corresponding $\Delta^{20,21}$-17,20-cyclic carbonates **21**, **22**, and **23** in modest yields. Similar reaction of the C-21-unsubstituted derivatives **7a** and **11a** furnished the corresponding 20$\beta$-acetates **26a** and **25a**. Chlorocarbonates of the latter type were converted in refluxing methanol to an epimeric mixture of 20-methoxy-17,20-cyclic carbonates (**27a,b** and **28a,b**). Acid hydrolysis of the 21-acetates **9a** and **10a** gave the respective 21-ols **29a** and **30a** in good yield together with smaller amounts of the 17-*O*-carbomethoxy-21-acetates **31** and **32**. The stability of the 17,20-cyclic carbonate ring to acidic reagents was also illustrated by the oxidation in chromic anhydride–acetic acid of the 21-ol **30a** to the 21-oic acid, obtained as the methyl ester **36a**.

In the second paper of this series[3] we reported that reaction of 17-deoxy-$\alpha$-ketols in pyridine with excess phosgene at 0° (condition B) affords chiefly an epimeric mixture of 20-chloro-20,21-cyclic carbonates (partial formula a, Scheme I). Unpublished experiments at that time showed that hindered tertiary $\alpha$-ketols such as cortisone acetate are not affected by these heterogeneous reaction conditions, and can be recovered in nearly quantitative yields.

Scheme I



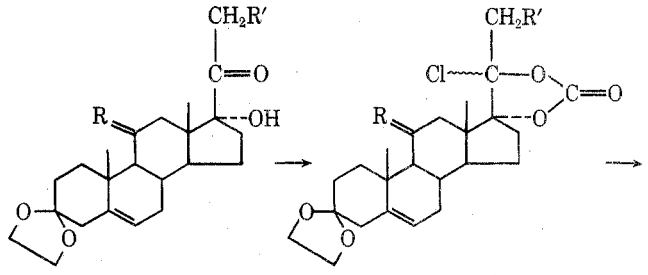
a b c

However, more recent investigations have shown that 17α-hydroxy-20-ones variously substituted at C-21 (partial formula b) react slowly with excess phosgene at room temperature under homogeneous conditions achieved by the addition of excess methylene chloride (condition C), giving 20ξ-chloro-17,20-cyclic carbonates (partial formula c). Because the $\Delta^4$-3-keto grouping possessed by all compounds studied is also attacked under these more strenuous conditions, protection of ring A was a necessary preliminary. In this paper will be presented the preparation and properties of a number of cyclic chlorocarbonates from both pregnene and 21-norpregnene precursors.

Phosgenation of 11-deoxycortisol acetate 3-ethylene ketal (**1**, Scheme II) by condition C followed by fractional crystallization and column chromatography on silica gel in toluene–ethyl acetate furnished epimeric mobile minor and polar major cyclic chlorocarbonates (**2a,b**). Structural assignments were based primarily on positive Beilstein tests and infrared spectroscopy which showed replacement of hydroxyl and 20-ketone absorption by a very strong band in the vicinity of 1825 $cm^{-1}$ and a medium band near 775 $cm^{-1}$ (see Table I for constants). Application of condition C to cortisone acetate 3-ethylene ketal (**3**) provided, after chromatography, the mobile and polar epimeric chlorocarbonates **4a,b.** The corresponding C-21-unsubstituted α-ketols were also subjected to homogeneous phosgenation. The 11-deoxy analogue **5**[4] gave a major cyclic chlorocarbonate (**7a**) in good yield. The minor epimer **7b** could be obtained only as the deketalization product **11b.** Preparation of **7b** by ketalization of **11b** was unsuccessful because of significant concomitant dehydrohalogenation to the $\Delta^{20,21}$-17,20-cyclic carbonate (vide infra). The 11-keto analogue **6**[6] afforded cyclic chlorocarbonate **8a** in good yield. The minor epimer **8b** could not be recovered in pure form either as the 3-ethylene ketal or as the $\Delta^4$-3-ketone **12b.** Deketalization of cyclic chlorocarbonates **2a, 2b, 4a, 4b, 7a,** and **8a** with *p*-TSA in acetone furnished the corresponding $\Delta^4$-3-ketones **9a, 9b, 10a, 10b, 11a,** and **12a** in high yields.

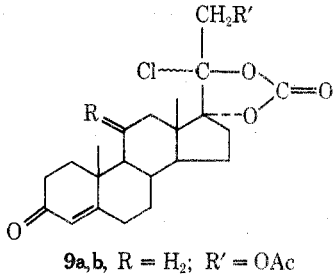
The 3-ethylene ketals of two 17β-formyl-17α-ols (**13** and **14,** Scheme III), prepared by buffered periodate oxidation of the corresponding 20β-glycerols, were also phosgenated under condition C. The 11-deoxy precursor gave mobile and polar epimeric cyclic chlorocarbonates (**15a,b**); from the 11-ketone **14** the corresponding derivatives (**16a,b**) were recovered in roughly equal yields. It is therefore evident from the examples given that the greater the size of the terminal group attached to the C-20 carbonyl the greater the stereospecificity in cyclic chlorocarbonate formation. It was later determined that where the terminal group is a proton, as in the 17β-formyl-17α-ols, phosgenation under the more mild condition B proceeds readily, obviating the need for protection of ring A. Thus such treatment of the 11-ketone **17** gave, in yields of 41 and 31%, the epimeric mobile and polar chlorocarbonates **19a** and **19b.** These compounds were identical with the deketalization products from **16a** and **16b.** Similar phosgenation of the 11-deoxy aldehyde **18** afforded an epimeric mixture (**20a,b**) which, unlike the corresponding 3-ethylene ketals, could not be separated by either fractional crystallization or column chromatography. The pure epimers **20a** and **20b** could be obtained by deketalization of **15a** and **15b.**

Scheme II

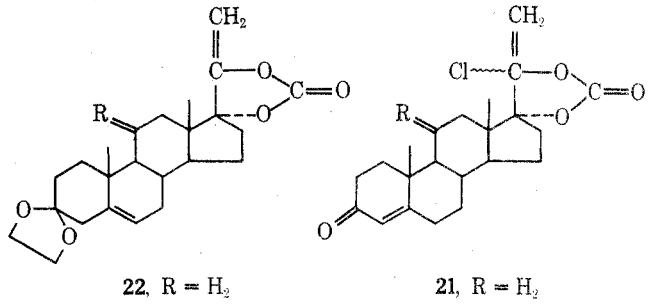


**1**, R = $H_2$; R′ = OAc
**3**, R = O; R′ = OAc
**5**, R = $H_2$; R′ = H
**6**, R = O; R′ = H

**2a,b**, R = $H_2$; R′ = OAc
**4a,b**, R = O; R′ = OAc
**7a,b**, R = $H_2$; R′ = H
**8a,b**, R = O; R′ = H

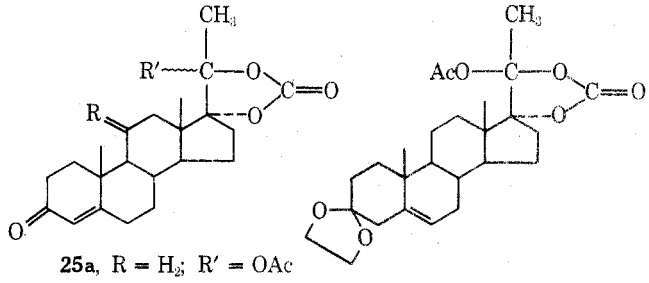


**9a,b**, R = $H_2$; R′ = OAc
**10a,b**, R = O; R′ = OAc
**11a,b**, R = $H_2$; R′ = H
**12a,b**, R = O; R′ = H
**29a**, R = $H_2$; R′ = OH
**30a**, R = O; R′ = OH



**22**, R = $H_2$
**23**, R = O

**21**, R = $H_2$
**24**, R = O

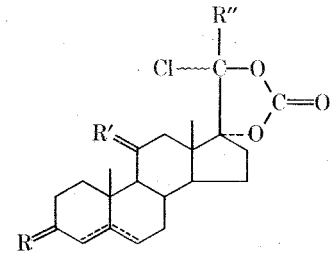


**25a**, R = $H_2$; R′ = OAc
**27a,b**, R = $H_2$; R′ = $OCH_3$
**28a,b**, R = O; R′ = $OCH_3$

**26a**

The chemical properties of the new cyclic chlorocarbonates were investigated. In the pregnene series studies were limited to the major products which on the basis of evidence given below were assigned 20β-chloro-17,20α-cyclic chlorocarbonate structures. Unlike 20ξ-chloro-20,21-cyclic chlorocarbonates, which readily undergo dehydrohalogenation during silica gel chromatography, in hot pyridine, or in acetone–sodium iodide–triethylamine,[7] the new cyclic chlorocarbonates including the 21-norpregnenes are completely unaffected by these reagents. Reaction with zinc in acetic acid was also studied since this reagent had previously been found to bring about both reductive ring opening and direct substitution of acetate for chloride at C-20 in 20ξ-

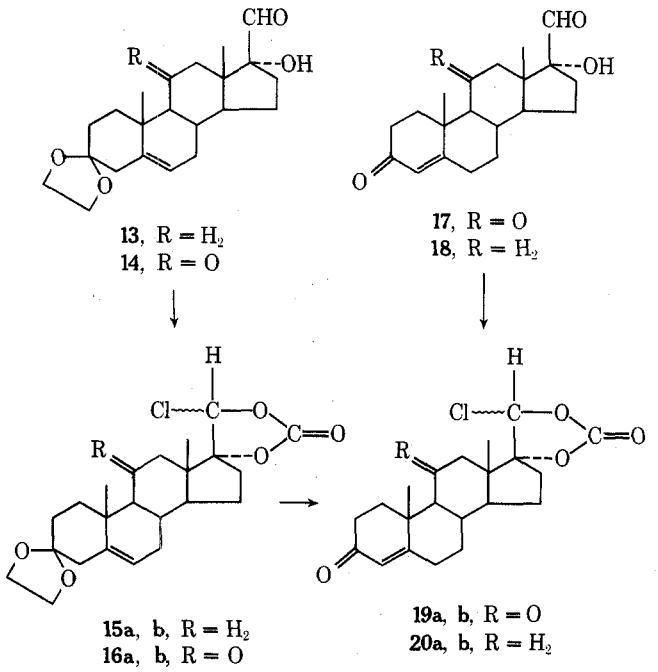
Table I
Structures and Constants of 20ξ-Chloro-17,20-cyclic Carbonates



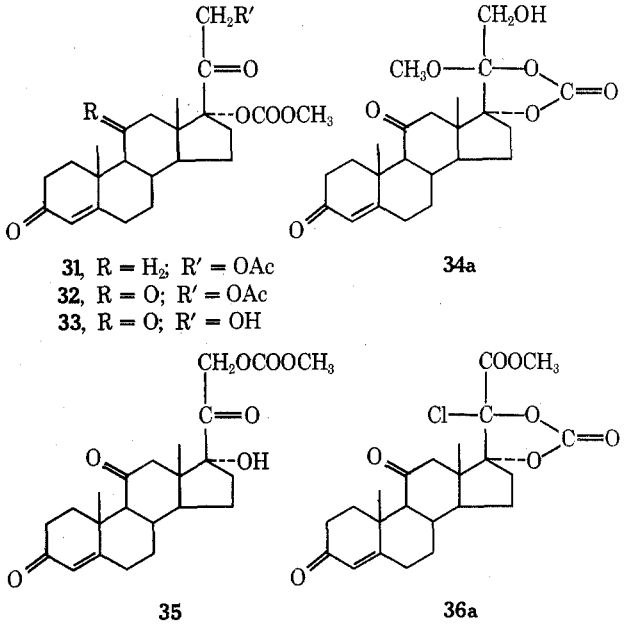

| Compd | R | R′ | R″ | 20-Cl | Mp, °C | $[\alpha]_D$, deg | $\lambda_{max}$, nm | $\epsilon$ | $\nu_{max}$, $cm^{-1}$ | Empirical formula | Calcd, % C | Calcd, % H | Found,[a] % C | Found,[a] % H | Yield,[b] % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | $\Delta^5$-3-ketal | $H_2$ | $CH_2OAc$ | β | 192.5–193.5 | −91.0 | | | 1825, 770 | $C_{26}H_{35}O_7Cl$ | 63.08 | 7.13 | 63.09 | 7.15 | 70 |
| **2b** | $\Delta^5$-3-ketal | $H_2$ | $CH_2OAc$ | α | 187–188 | 1.19 | | | 1828, 771 | $C_{26}H_{35}O_7Cl$ | 63.08 | 7.13 | 62.88 | 6.93 | 1.5 |
| **4a** | $\Delta^5$-3-ketal | O | $CH_2OAc$ | β | 197.5–198.5 | −67.2 | | | 1830, 769 | $C_{26}H_{33}O_8Cl$ | 61.35 | 6.53 | 61.53 | 6.44 | 73 |
| **4b** | $\Delta^5$-3-ketal | O | $CH_2OAc$ | α | 210–211 | 7.03 | | | 1830, 772 | $C_{26}H_{33}O_8Cl$ | 61.35 | 6.53 | 61.54 | 6.53 | 2 |
| **7a** | $\Delta^5$-3-ketal | $H_2$ | $CH_3$ | β | 177–179 | −135 | | | 1820, 775 | $C_{24}H_{33}O_5Cl$ | 65.96 | 7.61 | 65.90 | 7.50 | 64 |
| **8a** | $\Delta^5$-3-ketal | O | $CH_3$ | β | 177–178 | −105 | | | 1834, 774 | $C_{24}H_{31}O_6Cl$ | 63.92 | 6.93 | 63.87 | 6.91 | 78 |
| **9a** | $\Delta^4$-3-one | $H_2$ | $CH_2OAc$ | β | 193–195 | 13.4 | 240 | 16700 | 1824, 770 | $C_{24}H_{31}O_6Cl$ | 63.92 | 6.93 | 64.08 | 7.04 | 95 |
| **9b** | $\Delta^4$-3-one | $H_2$ | $CH_2OAc$ | α | 195–196 | 127 | 240 | 16600 | 1830, 771 | $C_{24}H_{31}O_6Cl$ | 63.92 | 6.93 | 64.09 | 6.86 | 88 |
| **10a** | $\Delta^4$-3-one | O | $CH_2OAc$ | β | 178–180 | 74.5 | 238 | 16100 | 1828, 770 | $C_{24}H_{29}O_7Cl$ | 62.00 | 6.29 | 62.17 | 6.36 | 95 |
| **10b** | $\Delta^4$-3-one | O | $CH_2OAc$ | α | 209–209.5 | 174 | 238 | 15800 | 1830, 772 | $C_{24}H_{29}O_7Cl$ | 62.00 | 6.29 | 62.21 | 6.35 | 89 |
| **11a** | $\Delta^4$-3-one | $H_2$ | $CH_3$ | β | 167–168 | −14.4 | 240 | 15400 | 1820, 774 | $C_{22}H_{29}O_4Cl$ | 67.25 | 7.44 | 67.10 | 7.35 | 97 |
| **11b** | $\Delta^4$-3-one | $H_2$ | $CH_3$ | α | 172–174 | 136 | 240 | 16200 | 1825, 775 | $C_{22}H_{29}O_4Cl$ | 67.25 | 7.44 | 67.34 | 7.43 | 18 |
| **12a** | $\Delta^4$-3-one | O | $CH_3$ | β | 188 | 57.0 | 238 | 16200 | 1835, 772 | $C_{22}H_{27}O_5Cl$ | 64.93 | 6.69 | 64.98 | 6.71 | 94 |
| **15a** | $\Delta^5$-3-ketal | $H_2$ | H | β | 209–212 | −125 | | | 1830, 781 | $C_{23}H_{31}O_5Cl$ | 65.31 | 7.38 | 65.21 | 7.41 | 50 |
| **15b** | $\Delta^5$-3-ketal | $H_2$ | H | α | 244–246 | 0.79 | | | 1830, 776 | $C_{23}H_{31}O_5Cl$ | 65.31 | 7.38 | 65.20 | 7.31 | 20 |
| **16a** | $\Delta^5$-3-ketal | O | H | β | 238–238.5 | −98.5 | | | 1830, 780 | $C_{23}H_{29}O_6Cl$ | 63.22 | 6.69 | 63.00 | 6.60 | 44 |
| **16b** | $\Delta^5$-3-ketal | O | H | α | 267–269 | 21.8 | | | 1822, 779 | $C_{23}H_{29}O_6Cl$ | 63.22 | 6.69 | 63.10 | 6.55 | 29 |
| **19a** | $\Delta^4$-3-one | O | H | β | 267–269 | 73.6 | 238 | 16100 | 1839, 780 | $C_{21}H_{25}O_5Cl$ | 64.20 | 6.41 | 64.33 | 6.43 | 41 |
| **19b** | $\Delta^4$-3-one | O | H | α | 274–277 | 221 | 238 | 15700 | 1822, 780 | $C_{21}H_{25}O_5Cl$ | 64.20 | 6.41 | 64.26 | 6.43 | 33 |
| **20a** | $\Delta^4$-3-one | $H_2$ | H | β | 245–247 | −8.49 | 240 | 16700 | 1820, 780 | $C_{21}H_{27}O_4Cl$ | 66.56 | 7.18 | 66.39 | 7.11 | 93 |
| **20b** | $\Delta^4$-3-one | $H_2$ | H | α | 254–256 | 138 | 240 | 16500 | 1822, 778 | $C_{21}H_{27}O_4Cl$ | 66.56 | 7.18 | 66.46 | 7.22 | 95 |
| **29a** | $\Delta^4$-3-one | $H_2$ | $CH_2OH$ | β | 182–183 dec | 5.06 | 241 | 16200 | 1825, 771 | $C_{22}H_{29}O_5Cl$ | 64.62 | 7.15 | 64.83 | 7.19 | |
| **30a** | $\Delta^4$-3-one | O | $CH_2OH$ | β | 205–207 | 82.8 | 238 | 15500 | 1828, 767 | $C_{22}H_{27}O_6Cl$ | 62.48 | 6.44 | 62.59 | 6.47 | |
| **36a** | $\Delta^4$-3-one | O | $COOCH_3$ | β | 214–215 | 62.1 | 238 | 15500 | 1835, 785 | $C_{23}H_{27}O_7Cl$ | 61.26 | 6.04 | 61.12 | 5.97 | |

[a] Chlorine analyses for compounds **2a, 2b, 4a, 4b, 7a, 8a, 11b, 15a, 15b, 16a, 16b, 19a,** and **19b** were in close agreement with the calculated values. [b] Yields of **9a, 9b, 10a, 10b, 11a, 12a,** and **20b** represent recovery from the corresponding $\Delta^5$-3-ketals after treatment with acetone–*p*-TSA.

Scheme III




Scheme IV




chloro-20,21-cyclic carbonates.[3] Treatment of the 11-deoxy-21-acetate **9a** for 3.5 hr on a high-speed rotary shaker at room temperature resulted in nearly complete conversion of substrate to a single more mobile uv-positive product as well as a number of very mobile uv-negative substances. The latter products presumably arise from reduction in ring A. Fractional crystallization and column chromatography afforded in 38% yield a Beilstein-negative, five membered ring cyclic carbonate with new olefinic bands in the infrared at 3145 and 1685 $cm^{-1}$. Similar treatment of the 3-ethylene ketal **2a** furnished the corresponding unsaturated cyclic carbonate in 36% yield as well as 11-deoxycorticosterone acetate 3-ethylene ketal (11%). The identity of the dehydrohalogenation products as the $\Delta^{20,21}$-17,20-cyclic carbonates **21** and **22** was confirmed by NMR spectroscopy, which demonstrated an unusually large geminal coupling constant (3.8–3.9 Hz) for the terminal methylene protons. Published examples[8] lie in a range of from 0 to 3 Hz with values of 1.0–2.0 Hz being the most common. Since the coupling constant is related to the magnitude of the H–C–H bond angle, it must be concluded that this angle is considerably displaced in 17,20-cyclic carbonates.[9] Reaction of the 11-ketone **4a** with zinc in acetic acid afforded the $\Delta^{20,21}$-17,20-cyclic carbonate **23** in 39% yield. Deketalization of **23** with acetone–*p*-TSA gave the $\Delta^4$-3-one **24** in 87% yield.

The reaction of C-21-unsubstituted cyclic chlorocarbonates with zinc in acetic acid was found to be slower and more complex. Treatment of the 17-hydroxyprogesterone derivative **11a** for 6 hr provided in low yields progesterone, 17-hydroxyprogesterone, and the $\Delta^{20,21}$-17,20-cyclic carbonate **21**. Infrared analysis of the Beilstein-negative major product (30%) showed retention of the cyclic carbonate ring and generation of new bands at 1760 and 1240 $cm^{-1}$. On the basis of these properties and functional group analysis, which indicated the presence of one acetyl group, the product was formulated as the 20β-acetyl-17,20α-cyclic carbonate **25a**. When the reaction was applied to the chlorocarbonate 3-ketal **7a**, the 20β-acetate **26a** was obtained only as a minor product (11%). The major product (54%) was progesterone 3-ethylene ketal. This quantitative difference between the reaction mixtures obtained from cyclic chlorocarbonates differing only in ring A substituents suggests the operation of long-range effects. Similar effects were also evident when the 11-ketone **8a** was treated with zinc in acetic acid. The major component of the reaction mixture was starting material (74%), and the only isolable product was 11-ketoprogesterone 3-ethylene ketal (13%). It was also found that despite minimal steric hindrance the corresponding 21-norpregnenes **19a** and **19b** were not affected by zinc in acetic acid.

In the course of these studies it was noted that some cyclic chlorocarbonates were adversely affected in hot methanol. In confirmation, prolonged refluxing of the C-21-unsubstituted derivatives in this solvent resulted in their complete conversion to Beilstein-negative products. A minor product (22%) in the reaction of the 11-deoxy compound **11a** is the $\Delta^{20,21}$-17,20-cyclic carbonate **21**. The major components (78%) were shown by NMR analysis to be an epimeric mixture of 20-methoxy-17,20-cyclic carbonates (**27a,b**). Repeated crystallization permitted recovery of pure **27b** in a yield of 58%. Similar reaction of the 11-keto chlorocarbonate **12a** furnished a more complex mixture from which the pure 20-methoxy-17,20-cyclic carbonates **28a** and **28b** could be isolated in modest yields. Unlike their C-21-unsubstituted counterparts, the 21-acetates **9a** and **10a** were unaffected by refluxing methanol as were the aldehyde derivatives **19a,b** and **20a,b**.

The unusual stability to acidic reagents of linear and cyclic carbonate bonds illustrated in earlier papers was exemplified in the present study by acid hydrolysis of the 21-acetates **9a** and **10a** to the corresponding 21-ols **29a** and **30a** in yields of 62 and 63%, respectively. Following acetylation of the mother liquors a significant by-product could be isolated in each case. Because both camylate (*O*-carbomethoxy) and acetate bands were present in their infrared spectra, the substances were formulated as the 17-camylates **31** and **32** (Scheme IV). Acid hydrolysis of the 11-ketone **32** afforded the 17-camylate-21-ol **33**, the structure of which was established by reacetylation to **32**. The availability of **32** and **33** made possible the testing of an hypothesis presented in an earlier publication[10] relating to the mechanism responsible for conversion in refluxing methanol of cortisone 17,21-cyclic carbonate to the 20β-methoxy-17,20α-cyclic carbonate **34a**. Cyclization to **34a** was believed to proceed via the 17-camylate **33** by a four center type mechanism. However, this assumption was not con-

Table II
MD Contributions of 20-Substituted 17,20-Cyclic Carbonates

| Compd | Ring A (B) | C-11 | C-20 | Terminal group | MD 20α | MD 20β | $MD^{\alpha-\beta}$ |
|---|---|---|---|---|---|---|---|
| 15a,b | $\Delta^5$-3-ketal | $H_2$ | Cl | H | −529 | +3 | −532 |
| 20a,b | $\Delta^4$-3-one | $H_2$ | Cl | H | −32 | +523 | −555 |
| 16a,b | $\Delta^5$-3-ketal | O | Cl | H | −430 | +95 | −525 |
| 19a,b | $\Delta^4$-3-one | O | Cl | H | +290 | +870 | −580 |
| 7a | $\Delta^5$-3-ketal | $H_2$ | Cl (β) | $CH_3$ | −590 | | |
| 11a,b | $\Delta^4$-3-one | $H_2$ | Cl | $CH_3$ | −57 | +535 | −592 |
| 8a | $\Delta^5$-3-ketal | O | Cl (β) | $CH_3$ | −474 | | |
| 12a | $\Delta^4$-3-one | O | Cl (β) | $CH_3$ | −232 | | |
| 2a,b | $\Delta^5$-3-ketal | $H_2$ | Cl | $CH_2OAc$ | −450 | +6 | −456 |
| 9a,b | $\Delta^4$-3-one | $H_2$ | Cl | $CH_2OAc$ | +61 | +574 | −513 |
| 29a | $\Delta^4$-3-one | $H_2$ | Cl (β) | $CH_2OH$ | +21 | | |
| 4a,b | $\Delta^5$-3-ketal | O | Cl | $CH_2OAc$ | −342 | +36 | −378 |
| 10a,b | $\Delta^4$-3-one | O | Cl | $CH_2OAc$ | +346 | +810 | −464 |
| 30a | $\Delta^4$-3-one | O | Cl (β) | $CH_2OH$ | +350 | | |
| 26a | $\Delta^5$-3-ketal | $H_2$ | AcO (β) | $CH_3$ | −81 | | |
| 25a | $\Delta^4$-3-one | $H_2$ | AcO (β) | $CH_3$ | +421 | | |
| 27b | $\Delta^4$-3-one | $H_2$ | $CH_3O$ (α) | $CH_3$ | | +450 | |
| 28a,b | $\Delta^4$-3-one | O | $CH_3O$ | $CH_3$ | +281 | +728 | −447 |
| 36a | $\Delta^4$-3-one | O | Cl (β) | $COOCH_3$ | +280 | | |
| Ref 9 | $\Delta^4$-3-one | O | $CH_3O$ (β) | $CH_2OH$ | +376 | | |
| | $\Delta^4$-3-one | O | $CH_3O$ (β) | $CH_2OAc$ | +389 | | |
| | $\Delta^4$-3-one | O | $CH_3O$ (β) | COOH | +441 | | |
| | $\Delta^4$-3-one | O | $CH_3O$ (β) | $COOCH_3$ | +509 | | |

firmed experimentally since the 21-acetate **32** was not affected by refluxing methanol and the 21-ol **33** underwent transcamylation to the known 21-*O*-carbomethoxy derivative **35**. It therefore follows that methoxy cyclic carbonate formation must proceed by a more concerted mechanism.

Resistance of the 17,20-cyclic chlorocarbonate ring to strong oxidizing agents was demonstrated by conversion of the 21-ol **30a** with chromic anhydride in acetic acid to the 21-oic acid. Treatment of the crude acidic fraction with diazomethane followed by column chromatography gave the methyl ester **36a** in low yield.

Configurational assignments at C-20 for the new pairs of cyclic chlorocarbonates were based chiefly on their optical rotatory properties. As shown in Table II, the major, polar epimers are considerably more levorotatory than their minor, mobile counterparts. The MD differences ($\alpha-\beta$ −378 to −592 units) are of the same order of magnitude previously noted[11] for cyclic carbonates derived from 17,20-diols ($\alpha-\beta$ −283 to −430 units). The absolute values of the appropriate major, polar products are also in general agreement with those of the 20β-methoxy-17,20α-cyclic carbonates derived from cortisone 17,21-cyclic carbonate.[10] For these reasons the major, polar products and their halogen-free derivatives have been assigned a 17,20α-cyclocarbonyldioxy configuration, and the minor, mobile epimers accordingly are formulated as 17,20β-cyclic carbonates.

Additional, although limited, support for these configurational assignments was also obtained from the NMR data. Marked deshielding of 18-$CH_3$ signals (approximately δ 1.0) was evident for both epimeric cyclic chlorocarbonates, indicating the presence of a strongly perturbing side-chain substituent. However, a significant downfield shift of the C-12 protons from the C–H envelope was noted only in the case of 20β-chloro-17,20α-cyclic carbonates. This effect is most likely due to the greater proximity to ring C of the substituent at C-21 in 17,20α-cyclic carbonates as is readily apparent from inspection of Dreiding models.

## Experimental Section

General experimental procedures are detailed in a previous paper.[10] Unless otherwise indicated column chromatography was carried out on silica gel with appropriate mixtures of isooctane and ethyl acetate. Phosgenation under condition C: to a solution of steroid (400 mg) in pyridine (5 ml) and methylene chloride (20 ml) was added a 12.5% solution of phosgene in benzene (2 ml). After 4 hr at room temperature ice and additional methylene chloride (20 ml) were added. The solution was washed successively with cold, dilute hydrochloric acid and water, filtered through anhydrous sodium sulfate, and concentrated to dryness in vacuo.

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-5-en-3-one 3-Ethylene Ketal (2a) with Zinc in Acetic Acid.** To a solution of the chlorocarbonate (600 mg) in 3:1 acetic acid–methylene chloride (24 ml) was added 1200 mg of powdered zinc. The mixture was agitated on a high-speed rotary shaker for 6 hr. The insoluble material was filtered off and washed with methylene chloride. The filtrates were combined and washed successively with cold, dilute sodium hydroxide and water. The reaction mixture was chromatographed on a silica gel column. Crystallization of the mobile product from ethyl acetate furnished 173 mg of **17,20-cyclocarbonyldioxypregna-5,20(21)-dien-3-one 3-ethylene ketal (22)** as prisms: mp 232–233°; $[\alpha]D$ 21.4°; $\nu_{max}$ 3149, 1835 (1815), 1682, and 772 ($\Delta^{20,21}$-17,20-cyclic carbonate), 1100 $cm^{-1}$ (ketal).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.84; H, 8.06.

The polar product crystallized from ethyl acetate as prisms (57 mg, 11%): mp 205–208°. The infrared spectrum was identical with that of **11-deoxycorticosterone acetate 3-ethylene ketal.**

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-4-en-3-one (9a) with Zinc in Acetic Acid.** Treatment of the chlorocarbonate (300 mg) in 12 ml of 3:1 acetic acid–methylene chloride with 600 mg of powded zinc was carried out for 3.5 hr as in the reaction of **2a.** Direct crystallization and silica gel column chromatography provided **17,20-cyclocarbonyldioxypregna-4,20(21)-dien-3-one (21)** in a total yield of 88 mg: mp 177–178°; $\lambda_{max}$ 240 nm (ε 17200); $\nu_{max}$ 3145, 1820, 1685 (sh), and 771 $cm^{-1}$ ($\Delta^{20,21}$-cyclic carbonate); NMR δ 9.11 (s, 3, 18-$CH_3$), 8.80 (s, 3, 19-$CH_3$), 5.59, 5.04 (d, 2, $J$ = 3.8 Hz, 21-$CH_2$=).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.12; H, 7.91. Found: C, 74.33; H, 7.98.

**17,20-Cyclocarbonyldioxypregna-5,20(21)-diene-3,11-dione 3-Ethylene Ketal (23) from 4a.** Treatment of 17,20α-cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-5-ene-3,11-dione 3-ethylene ketal (600 mg) with zinc in acetic acid was carried out as in the preparation of **22.** Silica gel chromatography and crystallization from ethyl acetate–isooctane gave 215 mg of prisms: mp 178–179°; $[\alpha]D$ 49.0°; $\nu_{max}$ 3150, 1830, 1682, and 770 ($\Delta^{20,21}$-cyclic carbonate), 1100 $cm^{-1}$ (ketal).

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.43; H, 7.39.

Treatment of **23** (50 mg) with acetone–*p*-TSA in the usual manner furnished **17,20-cyclocarbonyldioxypregna-4,20(21)-diene-3,11-dione (24)** as prisms (39 mg) from ethyl acetate: mp 232–

234°; [α]D 256°; $\lambda_{max}$ 237 nm (ε 15900); $\nu_{max}$ 3149, 1820, and 760 ($\Delta^{20,21}$-cyclic carbonate), 1705 $cm^{-1}$ (11-ketone); NMR δ 9.14 (s, 3, 18-$CH_3$), 8.58 (s, 3, 19-$CH_3$), 7.66, 7.43 (d, 2, $J$ = 15 Hz, 12-$CH_2$), 5.57, 4.97 (d, 2, $J$ = 3.9 Hz, 21-$CH_2$=).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.19; H, 7.19.

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-4-en-3-one (11a) with Zinc in Acetic Acid.** Treatment of the chlorocarbonate (300 mg) for 6 hr as in the reaction of **2a** followed by chromatography of the reaction mixture gave a number of identifiable products. The most mobile component (8.2 mg) crystallized from ethanol as prisms, mp 127–129°. It was identical in all respects with a reference sample of **progesterone.** The next more mobile component was obtained as needles (3.3 mg) from acetone–*n*-hexane, mp 185–187°. The infrared spectrum was identical with that of the $\Delta^{20,21}$-cyclic carbonate **21.** From the succeeding fraction was obtained 33 mg of material which was shown by infrared analysis to be a mixture of 17-hydroxyprogesterone and starting material. The last and major fraction furnished **17,20α-cyclocarbonyldioxy-20β-acetoxypregn-4-en-3-one (25a)** as prisms (94 mg) from ethyl acetate: mp 185–187°; [α]D 101°; $\lambda_{max}$ 239 nm (ε 16900); $\nu_{max}$ 1820 and 780 (cyclic carbonate), 1760 and 1230 $cm^{-1}$ (acetate); NMR δ 8.97 (s, 3, 18-$CH_3$), 8.82 (s, 3, 19-$CH_3$), 8.01 (s, 3, $CH_3CO$), 7.92 (s, 3, 21-$CH_3$).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.75; $CH_3CO$, 10.33. Found: C, 69.16; H, 7.68; $CH_3CO$, 10.01.

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-5-en-3-one 3-Ethylene Ketal (7a) with Zinc in Acetic Acid.** Treatment of the chlorocarbonate ketal (500 mg) for 5 hr as in the reaction of **2a** was followed by chromatography. The mobile product, **pregn-5-ene-3,20-dione 3-ethylene ketal,** crystallized from ethyl acetate–*n*-hexane as long needles (160 mg, mp 171.5–173.5°; 60 mg, mp 170.5–172°) in a yield of 54%. Deketalization of a sample in acetone–*p*-TSA afforded prisms (acetone–*n*-hexane), mp 128–130°, which were identical in all respects with a reference sample of **progesterone.**

Crystallization of the polar fraction from ethyl acetate gave **17,20α-cyclocarbonyldioxy-20β-acetoxypregn-5-en-3-one 3-ethylene ketal (26a)** as rosettes (60 mg, mp 166–169°): [α]D −17.6°; $\nu_{max}$ 1822 and 779 (cyclic carbonate), 1765 and 1230 (acetate), 1103 $cm^{-1}$ (ketal).

Anal. Calcd for $C_{26}H_{36}O_7$: C, 67.80; H, 7.88. Found: C, 67.58; H, 8.00.

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-4-en-3-one (11a) with Refluxing Methanol.** A solution of the chlorocarbonate (300 mg) in methanol (30 ml) containing 0.8 ml of pyridine was refluxed for 4 hr. The residue was chromatographed on a silica gel column. From the mobile fraction was obtained 59 mg (22%) of the $\Delta^{20,21}$-cyclic carbonate **21,** mp 191–193°. The crude polar fraction (230 mg, 78%) was shown by NMR to be an epimeric mixture of 20-methoxy-17,20-cyclic carbonates **(27a,b).** Several crystallizations from methanol furnished pure **27b** (173 mg) as plates: mp 232–235°; [α]D 116°; $\lambda_{max}$ 240 nm (ε 16900); $\nu_{max}$ 1805 and 780 (cyclic carbonate), 1290 $cm^{-1}$ (methoxyl); NMR δ 9.08 (s, 3, 18-$CH_3$), 8.82 (s, 3, 19-$CH_3$), 8.34 (s, 3, 21-$CH_3$), 6.56 (s, 3, 20α-$CH_3O$).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; $CH_3O$, 7.99. Found: C, 71.23; H, 8.38; $CH_3O$, 8.08.

NMR for **27a** component: δ 9.10 (s, 3, 18-$CH_3$), 8.82 (s, 3, 19-$CH_3$), 8.38 (s, 3, 21-$CH_3$), 6.61 (s, 3, 20β-$CH_3O$).

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloropregn-4-ene-3,11-dione (12a) with Refluxing Methanol.** The chlorocarbonate (300 mg) was treated for 22 hr as in the reaction of **11a.** The residue was chromatographed on a silica gel column. Crystallization of the mobile fraction (250 mg) from ethyl acetate–isooctane gave 105 mg of **17,20β-cyclocarbonyldioxy-20α-methoxypregn-4-ene-3,11-dione (28b)** as needles: mp 188–191°; [α]D 181°; $\lambda_{max}$ 238 nm (ε 15800); $\nu_{max}$ 1800 and 780 (cyclic carbonate), 1290 (methoxyl), 1702 $cm^{-1}$ (11-ketone); NMR δ 9.12 (s, 3, 18-$CH_3$), 8.59 (s, 3, 19-$CH_3$), 8.36 (s, 3, 21-$CH_3$), 6.54 (s, 3, 20α-$CH_3O$).

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; $CH_3O$, 7.71. Found: C, 68.80; H, 7.65; $CH_3O$, 7.51.

From the polar fraction (50 mg) was obtained 21 mg of **17,20α-cyclocarbonyldioxy-20β-methoxypregn-4-ene-3,11-dione (28a)** as platelets from methanol: mp 250–253°; [α]D 70.0°; $\lambda_{max}$ 238 nm (ε 15900); $\nu_{max}$ 1802 and 780 (cyclic carbonate), 1290 (methoxyl), 1705 $cm^{-1}$ (11-ketone); NMR δ 9.13 (s, 3, 18-$CH_3$), 8.60 (s, 3, 19-$CH_3$), 8.38 (s, 3, 21-$CH_3$), 6.60 (s, 3, 20β-$CH_3O$).

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; $CH_3O$, 7.71. Found: C, 68.84; H, 7.45; $CH_3O$, 7.42.

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-4-en-3-one (9a) with Methanolic Hydrochloric Acid.** To a solution of the chlorocarbonate (1 g) in methylene chloride (50 ml) and methanol (850 ml) was added (without external cooling) water (100 ml) and concentrated hydrochloric acid (200 ml). After 2.5 hr at room temperature methylene chloride (750 ml) was added, and the organic layer was washed successively with cold, dilute sodium hydroxide and water, then concentrated to dryness. Several crystallizations from ethyl acetate provided 560 mg of **17,20α-cyclocarbonyldioxy-20β-chloro-21-hydroxypregn-4-en-3-one (29a)** as rosettes: mp 182–183° dec; [α]D 5.06°; $\lambda_{max}$ 241 nm (ε 16200); $\nu_{max}$ 3440 (hydroxyl), 1825 and 771 $cm^{-1}$ (cyclic chlorocarbonate).

Anal. Calcd for $C_{22}H_{29}O_5Cl$: C, 64.62; H, 7.15. Found: C, 64.83; H, 7.19.

The mother liquor residue was treated with excess acetic anhydride–pyridine for 18 hr. Silica gel chromatography of the reaction mixture resulted in partial separation of two components. From the earlier fractions was obtained 10 mg of **17-*O*-carbomethoxy-21-acetoxypregn-4-ene-3,20-dione (31)** as platelets from methanol: mp 220–222°; [α]D 90.6°; $\lambda_{max}$ 241 nm (ε 15800); $\nu_{max}$ 1750, 1292, and 792 (camylate), 1745 and 1230 $cm^{-1}$ (acetate).

Anal. Calcd for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 67.18; H, 7.59.

**Reaction of 17,20α-Cyclocarbonyldioxy-20β-chloro-21-acetoxypregn-4-ene-3,11-dione (10a) with Methanolic Hydrochloric Acid.** Treatment of the chlorocarbonate (1.5 g) in methylene chloride (75 ml) and methanol (1500 ml) with water (150 ml) and concentrated hydrochloric acid (300 ml) for 2.5 hr was carried out as in the reaction of **9a.** Successive crystallizations from ethyl acetate and methanol gave 1710 mg of **17,20α-cyclocarbonyldioxy-20β-chloro-21-hydroxypregn-4-ene-3,11-dione (30a)** as rosettes: mp 205–207°; [α]D 82.8°; $\lambda_{max}$ 238 nm (ε 15500); $\nu_{max}$ 3440 (hydroxyl), 1828 and 767 (cyclic chlorocarbonate), 1705 $cm^{-1}$ (11-ketone).

Anal. Calcd for $C_{22}H_{27}O_6Cl$: C, 62.48; H, 6.44. Found: C, 62.59; H, 6.47.

Treatment of **30a** with acetic anhydride–pyridine afforded a product identical in all respects with starting material **(10a).**

Acetylation of the mother liquor residue from **30a** and two crystallizations of the product from methanol furnished 500 mg (24%) of **17-*O*-carbomethoxy-21-acetoxypregn-4-ene-3,11,20-trione (32)** as needles: mp 234–236°; [α]D 148°; $\lambda_{max}$ 238 nm (ε 15500); $\nu_{max}$ 1745, 1290, and 790 (camylate), 1745 and 1232 (acetate), 1710 (sh), and 1705 $cm^{-1}$ (11- and 20-ketone).

Anal. Calcd for $C_{25}H_{32}O_8$: C, 65.20; H, 7.01; $CH_3O$, 6.74. Found: C, 65.44; H, 7.11; $CH_3O$, 6.59.

Treatment of the 21-acetate **32** (200 mg) in methylene chloride (5 ml) and methanol (85 ml) with water (10 ml) and concentrated hydrochloric acid (20 ml) for 4 hr was followed by the usual workup. The reaction mixture was chromatographed on a Celite column (30% impregnation) in chloroform–isooctane–formamide (500:500:30). From the mobile fraction was obtained 135 mg (74%) of **17-*O*-carbomethoxy-21-hydroxypregn-4-ene-3,11,20-trione (33)** as an amorphous foam: [α]D 123°; $\nu_{max}$ 3450 (hydroxyl), 1745, 1295, and 793 (camylate), 1708 $cm^{-1}$ (11- and 20-ketone). From the polar fraction was recovered 30 mg (16%) of **21-*O*-carbomethoxy-17-hydroxypregn-4-ene-3,11,20-trione (35)** as needles from methanol, mp 222–224°. A mixture melting point with a reference sample[10] showed no depression and their ir spectra were identical.

**35 from 33.** A sample (10 mg) of the 17-*O*-camylate was refluxed in methanol for 18 hr. Concentration of the solution gave 8 mg of prismatic needles, mp 224–225°, identical in all respects with the 21-*O*-camylate **35.**

**Methyl 17,20α-Cyclocarbonyldioxy-20β-chloro-3,11-dioxopregn-4-en-21-oate (36a) from 30a.** To a solution of 17,20α-cyclocarbonyldioxy-20β-chloro-21-hydroxypregn-4-ene-3,11-dione (106 mg, 0.25 mmol) in acetic acid (4.75 ml) was added 100 mg (1 mmol) of chromic anhydride in water (0.25 ml). After 4 days at room temperature the solvent was evaporated and the residue was partitioned between ethyl acetate and dilute sodium bicarbonate solution. Acidification of the aqueous layer with hydrochloric acid and extraction with ethyl acetate furnished the crude acidic fraction (68 mg). Successive treatment with excess diazomethane and silica gel column chromatography gave the methyl ester **36a** (19 mg) as leaflets from methanol: mp 214–215°; [α]D 62.1°; λ 238 nm (ε 15500); $\nu_{max}$ 1835 and 785 (cyclic chlorocarbonate), 1765 and 1285 (carbomethoxy), 1710 $cm^{-1}$ (11-ketone); NMR δ 8.91 (s, 3, 18-$CH_3$), 8.58 (s, 3, 19-$CH_3$), 7.16, 6.99 (d, 2, $J$ = 14 Hz, 12-$CH_2$), 6.05 (s, 3, $CH_3O$).

Anal. Calcd for $C_{23}H_{27}O_7Cl$: C, 61.26; H, 6.04. Found: C, 61.12; H, 5.97.

**Registry No.**—**2a**, 57015-41-5; **2b**, 57015-42-6; **4a**, 57015-43-7; **4b**, 57015-44-8; **7a**, 57015-45-9; **8a**, 57015-46-0; **9a**, 57015-47-1; **9b**, 57015-48-2; **10a**, 57015-49-3; **10b**, 57015-50-6; **11a**, 57015-51-7; **11b**, 57015-52-8; **12a**, 57015-53-9; **15a**, 57015-54-0; **15b**, 57015-55-1; **16a**, 57015-56-2; **16b**, 57015-57-3; **19a**, 57015-58-4; **19b**, 57015-59-5; **20a**, 57015-60-8; **20b**, 57015-61-9; **21**, 57015-62-0; **22**, 57015-63-1; **23**, 57015-64-2; **24**, 57015-65-3; **25a**, 57015-66-4; **26a**, 57031-28-4; **27a**, 57015-67-5; **27b**, 57015-68-6; **28a**, 57015-69-7; **28b**, 57015-70-0; **29a**, 57015-71-1; **30a**, 57015-72-2; **31**, 57015-73-3; **32**, 57015-74-4; **33**, 57015-75-5; **35**, 36623-21-9; **36a**, 57015-76-6; phosgene, 75-44-5.

## References and Notes

(1) This research was supported wholly by a grant, AM 01255, 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) Address correspondence to Department of Medicine, Crozer-Chester Medical Center, Chester, Pa. 19013.
(3) M. L. Lewbart, *J. Org. Chem.*, **38**, 2328 (1973).
(4) The preparation of this previously undescribed monoketal was made possible by our observation that the presence of a 17$\alpha$-acetoxy group prevents ketalization at C-20. Thus treatment of 17$\alpha$-acetoxypregn-4-ene-3,20-dione (5.0 g) in benzene (250 ml) and ethylene glycol (40 ml) with *p*-TSA (150 mg) for 8 hr by the Bernstein procedure gave 5.2 g (93%) of leaflets from ethyl acetate: mp 230–233°; $[\alpha]D$ −17.4°. Reported[5] for **17-acetoxypregn-5-ene-3,20-dione 3-ethylene ketal:** mp 241–243°; $[\alpha]D$ −62° (chloroform). Saponification of the acetoxy ketal (4.16 g) in a mixture of methylene chloride (100 ml) and methanol (250 ml) with aqueous 1 *N* sodium hydroxide (50 ml) was carried out for 2 hr on a steam bath. The product crystallized spontaneously from the concentrated solution. Recrystallization of the crude material from ethyl acetate afforded **17-hydroxypregn-5-ene-3,20-dione 3-ethylene ketal** as leaflets in a total yield of 2.54 g (68%): mp 244–246°; $[\alpha]D$ −58.9°; $\nu_{max}$ 3490 (hydroxyl), 1705 (sh), 1695 (20-ketone), 1100 cm$^{-1}$ (ketal). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.91; H, 9.26. Deketalization of the saponification product in acetone–*p*-TSA gave a product identical in all respects with **17-hydroxyprogesterone.**
(5) J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson, and J. A. Campbell, *Chem. Ind. (London)*, 1002 (1958).
(6) As far as we are aware the monoketal **6** has not been described previously. The reaction sequence, as in the preparation of the 11-deoxy analogue **5**, follows. Forced acetylation of 21-deoxycortisone (3.0 g) in acetic acid (120 ml) and acetic anhydride (24 ml) in the presence of *p*-TSA (2.4 g) was carried out for 1.25 hr at room temperature. The crude product, recovered in the usual manner, was chromatographed on a silica gel column. Crystallization of the mobile component from methanol gave 800 mg (21%) of **3,17-diacetoxypregna-3,5-diene-11,20-dione** as prisms: mp 163–165°; $[\alpha]D$ −79.5°; $\lambda_{max}$ 234 nm ($\epsilon$ 19500); $\nu_{max}$ 1735, 1250, and 1220 (acetate), 1706 (11- and 20-ketone), 1671 and 1638 cm$^{-1}$ ($\Delta^{3,5}$). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53; $CH_3CO$, 20.09. Found: C, 69.90; H, 7.64; $CH_3CO$, 19.45. Crystallization of the major, polar fraction from methanol furnished 2.0 g (59%) of **17-acetoxypregn-4-ene-3,11,20-trione** as platelets: mp 205–207°; $[\alpha]D$ 143°; $\lambda_{max}$ 238 nm ($\epsilon$ 16100); $\nu_{max}$ 1733 and 1255 (acetate), 1710 cm$^{-1}$ (11- and 20-ketone). Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; $CH_3CO$, 11.14. Found: C, 71.38; H, 7.86; $CH_3CO$, 10.70. Ketalization of the 17-acetate by the Bernstein procedure afforded **17-acetoxypregn-5-ene-3,11,20-trione 3-ethylene ketal** (75% yield) in the form of prisms from ethyl acetate: mp 207–211°; $[\alpha]D$ 0.85°; $\nu_{max}$ 1733 and 1255 (acetate), 1705 (11- and 20-ketone), 1100 cm$^{-1}$ (ketal). Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.64; H, 7.96. Saponification of the acetoxy ketal as in the preparation of the 11-deoxy analogue afforded in 41% yield **17-hydroxypregn-5-ene-3,11,20-trione 3-ethylene ketal (6)** as prisms from ethyl acetate: mp 208–212°; $[\alpha]D$ −41.4°; $\nu_{max}$ 3460 (hydroxyl), 1705 (11- and 20-ketone), 1098 cm$^{-1}$ (ketal). Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.88; H, 8.34.
(7) M. L. Lewbart, *J. Org. Chem.*, **38**, 2335 (1973).
(8) N. S. Bhacca and D. H. Williams, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 57.
(9) The author is deeply indebted to Dr. Byron Arison of the Merck Institute for the determination and interpretation of all NMR spectra included in this paper.
(10) M. L. Lewbart, *J. Org. Chem.*, **37**, 3892 (1972).
(11) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).

# Nucleosides. XCIV. Synthesis of Some C Nucleosides by 1,3-Dipolar Cycloadditions to 3-(Ribofuranosyl) Propiolates[1]

Federico G. De Las Heras, Steve Y-K. Tam, Robert S. Klein, and Jack J. Fox*

*Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021*

*Received July 18, 1975*

Condensation of 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranosyl chloride (**3**) with the silver acetylide of methyl (or ethyl) propiolate **4a** (or **4b**) gives fair yields of the $\beta$-D-ribofuranosyl propiolate **5a** (or **5b**). 1,3-Dipolar cycloaddition of **5a** with trimethylsilyl azide gives directly the deblocked 1,2,3-triazole ester **7** which on treatment with methanolic ammonia affords amide **8**. 1,3-Dipolar cycloaddition of **5a** (or **5b**) with diazomethane gives the fully blocked 4-ribosylated pyrazole ester **9a** (or **9b**) in good yields along with the *N*-methyl derivative **10a** (or **10b**). Compound **9a** (or **9b**) can be readily deblocked to the corresponding 4-ribosylpyrazole ester **13a** (or **13b**) or treated with ammonia to give the blocked pyrazole amide **11**. A similar cycloaddition reaction of **5a** with ethyl diazoacetate (**15**) affords the 4-ribofuranosylpyrazole-3,5-dicarboxylate **16** as the major product and some 3-ribofuranosylpyrazole-4,5-dicarboxylate **17**. These two products have been unequivocally identified by comparing them with the products (**16** and **19**) obtained from the cycloaddition reaction of **5b** with methyl diazoacetate (**18**).

A relatively new group of naturally occurring nucleosides[2] exhibiting important biological activities has been isolated recently. They are the C-nucleoside antibiotics formycin, formycin B, showdomycin, and pyrazomycin. Also belonging to this class of compounds is the most recently isolated oxazinomycin,[3] a close analogue of pseudouridine.[4] All, except pseudouridine, possess antibiotic properties and many exhibit anticancer and antiviral activities. These biological properties, together with their unique structural feature (a C–C linkage between the heterocycle and the sugar), have elicited many efforts directed toward the synthesis of such compounds or analogues thereof.

The methods described for the synthesis of C nucleosides can be classified into three general types. The first involves the conversion of some available C nucleosides to prepare new ones. 6-Azapseudouridine, for example, has been synthesized[5] from pseudouridine. Oxazinomycin has been converted to pseudouridine[3c] and formycin has been obtained from formycin B.[6] The second approach, direct condensation of suitably blocked sugar derivatives with appropriate heterocyclic bases (usually as metalated derivatives), has been utilized for the preparation of pseudouridine[7] or some of its sugar analogues,[8] 5-ribosylcytosine[9] and 1-deazauridine.[10] The third and most fruitful approach to date has been the multistep elaboration of the desired heterocycle