BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 550—553 (1973)

Synthetic Studies by the Use of Carbonates. II.[1] An Easy Method of Preparing Cyclic Carbonates of Polyhydroxy Compounds by Transesterification with Ethylene Carbonate

Hajime KOMURA, Teruo YOSHINO, and Yoshiharu ISHIDO

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo

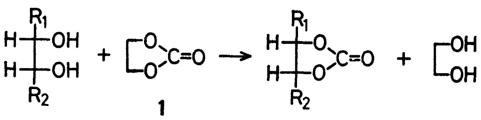
(Received June 14, 1972)

Transesterification reactions of polyhydroxy compounds, such as 1-*O*-*p*-nitrobenzoyl-, 1-*O*-benzylglycerols, 1,2;3,4-di-*O*-, 3,4-*O*-isopropylidene-D-mannitols, 1,2-*O*-isopropylidene-α-D-glucofuranose, uridine, 1,2;5,6-di-*O*-isopropylidene-D-mannitol, and D-mannitol, by ethylene carbonate were attempted; the corresponding products were obtained in good yields except in the case of uridine, which gave 2,2′-anhydro-1-β-D-arabinofuranosyluracil.

Since the synthesis of α-D-glucofuranose 1,2;5,6-dicarbonate from D-glucose and phosgene, although in a considerably low yield, was reported,[2] a number of sugar carbonates have been prepared for the purpose of investigating the partial blocking of hydroxy groups of carbohydrates by the use of phosgene, alkyl or aryl chloroformates, diphenyl carbonate under basic conditions, by the use of carbonyl diimidazole, or by changing the *O*-methylene group into carbonate through oxidation with permanganate.[3] In contrast with such blocking groups as alkylidene and arylidene groups, the carbonate group can easily be removed under basic conditions, and it has been widely used in the field of carbohydrate chemistry with due regard to its properties.

Results and Discussion

In view of the glycidol[4] and glycerol 1,2-carbonate[5] syntheses involving the reaction of ethylene carbonate (**1**) with glycerol, the present authors investigated the preparation of cyclic carbonates of polyhydroxy compounds, taking the stability and wieldiness of **1** into consideration. The starting materials were selected on the basis of the following categories: i) 1-*O*-*p*-nitrobenzoyl-(**2**), 1-*O*-benzylglycerols(**3**), 1,2;3,4-di-*O*-(**4**), 3,4-*O*-isopropylidene-D-mannitols(**5**), and 1,2-*O*-isopro-



Scheme I.

---

1) T. Yoshino, S. Inaba, H. Komura, and Y. Ishido, This Bulletin, in contribution.

2) C. F. Allpress and W. N. Haworth, *J. Chem. Soc.*, **1924**, 1223.

3) W. N. Haworth and W. Maw, *ibid.*, **1926**, 1751; L. Hough and J. E. Priddle, *ibid.*, **1961**, 581; W. Schroeder, U. S. 3284438; O. T. Schmidt, A. Distelmaier, und H. Reinhard, *Chem. Ber.*, **86**, 741 (1953).

4) H. A. Bruson and T. W. Reiner, *J. Amer. Chem. Soc.*, **74**, 2100 (1952).

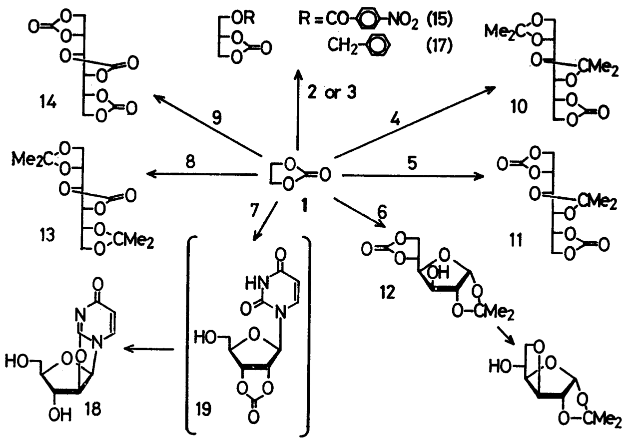
5) J. B. Bell, V. A. Currier, and J. D. Malkemus, U. S. 2915529; *Chem. Abstr.*, **54**, 6552 (1960).

Table 1. Preparations of carbonates by transesterification reaction with ethylene carbonate (**1**)

Starting Material	Reaction Conditions		Product	
			Yield	IR Absorption[a]
1-*O*-*p*-Nitrobenzoylglycerol (**2**)	130—140°C/20—30 mmHg	2 hr	30%[b]	1785 cm^{-1}
1-*O*-Benzylglycerol (**3**)	150/15	1[c]	80	1790
1,2;3,4-Di-*O*-isopropylidene-D-mannitol (**4**)	160/40	1	90	1790
3,4-*O*-Isopropylidene-D-mannitol (**5**)	150—160/30	1	65	1785, 1800
1,2-*O*-Isopropylidene-α-D-glucofuranose (**6**)	140—145/40	1	71	1785, 1800
Uridine (**7**)	140—145/15	1.5	71[d]	—
1,2;5,6-Di-*O*-isopropylidene-D-mannitol (**8**)	160/40	1	76	1785
D-Mannitol (**9**)	150/20	6	65	1790, 1820

a) The absorption bands stand for those of five-membered cyclic carbonate. b) In this reaction, ethylene glycol di-*O*-*p*-nitrobenzoate(**16**) was obtained in 16% yield as a by-product. c) A catalytic amount of sodium bicarbonate was applied in this case. d) This product was identified with 2,2′-anhydro-1-β-D-arabinofuranosyluracil(**18**).

pylidene-α-D-glucofuranose(**6**) as involving vicinal primary and secondary hydroxyl groups, and ii) uridine (**7**) and 1,2;5,6-di-*O*-isopropylidene-D-mannitol(**8**) as involving vicinal secondary hydroxyl groups. iii) D-Mannitol was, in addition, used because it involved both types of vicinal hydroxyl groups. These compounds were heated with 3—4 mol of **1** under reduced pressure to remove the ethylene glycol co-produced in the course of the reactions. Moreover, the reactions were carried out in a Pyrex-glass flask to avoid the decomposition of the carbonate once formed, in view of the results reported by Reist *et al.*,[6] and by Hall and Hough.[7] The results are demonstrated in Table 1. In the cases of **4**, **5**, **6**, **8**, and **9**, the corresponding cyclic carbonates, *i.e.*, 1,2;3,4-di-*O*-isopropylidene-D-mannitol 5,6-carbonate(**10**), 3,4-*O*-isopropylidene-D-mannitol 1,2;5,6-dicarbonate(**11**), 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-carbonate(**12**),[8] 1,2;5,6-di-*O*-isopropylidene-D-mannitol 3,4-carbonate(**13**), and D-mannitol 1,2;3,4;5,6-tricarbonate(**14**), were obtained in 90, 65, 71, 76, and 65% yields respectively. On the other hand, different results were obtained in the cases of **2**, **3**, and **7**. The reaction with **2** gave a mixture of the corresponding 1,2-carbonate(**15**) and di-*p*-nitrobenzoate of ethylene glycol(**16**) in 30 and 16% yields respectively. These results may be explained in terms of the susceptibility of the carbonyl carbon of the *p*-nitrobenzoyl group to the nucleophilic attack of the hydroxyl group of ethylene glycol. Since the reaction with **3** was confirmed by means of tlc to leave a small amount of **3** in the reaction mixture, even after 2 hr, the reaction was carried out in the presence of sodium bicarbonate as a catalyst to afford 1-*O*-benzylglycerol 2,3-carbonate(**17**) in an 80% yield. Moreover, contrary to expectations, **7** afforded 2,2′-anhydro-1-β-D-arabinofuranosyluracil(**18**) selectively. **18** was considered to be produced *via* the 2′,3′-carbonate of **7** (**19**); *i.e.*, the 2′-carbon of **19** was subjected to the intramolecular nucleophilic substitution reaction by the carbonyl group of the 2-position to produce **18**; this result may be ascribed to the nucleophilicity of the carbonyl group being larger than that of the hydroxyl group of ethylene glycol. The structures of the products obtained here were confirmed by elemental analyses, and by a study of the IR, NMR, and UV spectra.



Scheme II.

On the basis of these results, it can be concluded that **1** can also be used in the preparation of the five-membered cyclic carbonate of polyhydroxy compounds.

Experimental

All the melting points are uncorrected. The IR spectra were taken with a Hitachi EPI-2S apparatus. The UV spectrum was measured on a Hitachi EPS-3T in distilled water. The NMR spectra were taken with a Varian XL-100 apparatus.

1-O-p-Nitrobenzoylglycerol (2). According to the method of Hennis,[9] glycerol α-monochlorohydrin (11 g,

---

[6] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, **23**, 1958 (1958) [Mp 231—233°C (dec.) (**12**); Mp 52—54°C, $[\alpha]^{26}_{D}$ +30.5° (1%, H_2O) (3,6-anhydro derivative of **6**)].

[7] L. D. Hall and L. Hough, *J. Chem. Soc.*, **1963**, 5301 [Mp 224—225°C (sublimation: 210°C), $[\alpha]_D$ −31.8° (*c* 0.5, Me_2CO) (**12**); Mp 53.2—54.6°C, $[\alpha]_D$ +28.7° (*c* 1.6, H_2O) (3,6-anhydro derivative of **6**)].

[8] W. N. Haworth and C. R. Porter, *ibid.*, **1929**, 2796 [Mp 223—224°C (dec.), $[\alpha]^{20}_{5780}$ −36°]; A preparation of this compound by the same procedure was recently reported in a paper (P. A. Gent, R. Gigg, and R. Conant, *J. Chem. Soc. Perkin Trans. I.*, **1972**, 248) as a part of an investigation on phenyloxazoline derivative of aminosugars.

[9] H. E. Hennis, J. P. Easterly, Jr., L. R. Collins, and L. R. Thompson, *Ind. Eng. Chem.*, **6**, 193 (1967); H. E. Hennis, L. R. Thompson, and J. P. Long, *ibid.*, **7**, 96 (1968).

100 mmol) and sodium *p*-nitrobenzoate (19 g, 100 mmol) were suspended in dimethylformamide (150 ml), together with tetraethylammonium iodide (TEAI) (13 g, 50 mmol); the mixture was then heated at 130—140°C for 2 hr with stirring. After cooling, acetone (100 ml) was added to the resultant mixture, and the solvents were evaporated *in vacuo* to give a sirup after the filtration of the unchanged TEAI. After the sirup had been dissolved in hot ethyl acetate (50 ml) and left to stand overnight in a refrigerator, pale yellow crystals of **2** (12.7 g, 52.7%) were obtained. Mp 107—107.5°C. IR(KBr): 1720 cm^{-1} (ester C=O). Found: C, 49.31; H, 4.72; N, 5.72%. Calcd for $C_{10}H_{11}O_6N$: C, 49.79; H, 4.60; N, 5.81%.

3-O-p-Nitrobenzoylglycerol 1,2-Carbonate (15). 1-*O*-*p*-Nitrobenzoylglycerol (**2**) (7.2 g, 30 mmol) was heated, together with ethylene carbonate (**1**) (9.0 g, 105 mmol), at 130—140°C/20—30 mmHg for 2 hr, and finally again at 140°C/10 mmHg, until the distillation of **1** stopped. The residue was chromatographed on a column (diameter: 5 cm) of silica gel (100 g), with chloroform–ethyl acetate (99:1) used for the elution, after which the effluent was fractionated into a volume of 10 ml. The concentration of Fractions No. 41—75 *in vacuo*, followed by recrystallization from ethyl acetate, gave ethylene glycol di-*p*-nitrobenzoate (**16**) (1.7 g, 16%). Mp 142—143.5°C. Found: C, 53.08; H, 3.08; N, 7.89%. Calcd for $C_{16}H_{12}O_8N_2$: C, 53.34; H, 3.36; N, 7.78%. The concentration of Fractions No. 88—214 *in vacuo*, followed by recrystallization from ethyl acetate, gave **15** (2.4 g, 30%). Mp 149.5—150°C. Found: C, 49.30; H, 3.16; N, 5.31%. Calcd for $C_{11}H_9O_7N$: C, 49.44; H, 3.40; N, 5.24%. IR(KBr): 1785 (five-membered cyclic carbonate), 1720 (ester C=O), 1270, 1170 (ester C–O–C), 1520, and 1345 (NO_2) cm^{-1}.

1-O-Benzylglycerol 2,3-Carbonate (17). The transesterification reaction was carried out by the same procedure as above, using 1-*O*-benzylglycerol (**3**) (5.4 g, 30 mmol) and **1** (9.0 g, 105 mmol) together with a catalytic amount of sodium bicarbonate (0.1 g), at 150°C/15 mmHg for 1 hr. After the filtration of the precipitated crystals and the washing of the crystals with ethyl acetate (5 ml), the filtrate and washings were combined; the mixture was then concentrated *in vacuo* to give a heavy liquid. The residue was distilled to give **17** (5.6 g, 80%) boiling at 146—147°C/0.17 mmHg (Found: C, 63.53; H, 5.53%).[10] IR(NaCl): 1790 cm^{-1} (five-membered cyclic carbonate). Without sodium bicarbonate, it was necessary to prolong the reaction to 2.5 hr in order to afford an almost equal yield of the product.

*1,2-O-Isopropylidene-α-D-glucofuranose 5,6-Carbonate (**12**).* 1,2-*O*-Isopropylidene-α-D-glucofuranose (**6**)[11] (22 g, 100 mmol) and **1** (30 g, 350 mmol) were fused at 140—145°C/40 mmHg for 1 hr, and the **1** was finally removed by reducing the pressure to 17 mmHg. The residual crystals were recrystallized from ethanol to give **12** (17 g, 71%).[6,7,8] Mp 219—220°C (dec.); 223—224°C (measured in a capillary tube of Hario-glass: decomposed after fusion without coloration). $[\alpha]^{22}_{D}$ −29° (*c* 1.0, Me_2CO). IR(KBr): 1785 and 1800 cm^{-1} (five-membered cyclic carbonate). NMR (acetone-d_6, TMS): δ 5.94 (H–1, d, $J_{1,2}=3.3$ Hz), 4.50 (H-2, d, $J_{2,3}=0$ Hz), 4.29 (H-3, q, $J_{3,4}=3.5$ Hz), 4.46 (H-4, sex., $J_{4,5}=3.2$ Hz), 5.05 (H-5, octet, $J_{5,6}=8.7$ Hz and $J_{5,6'}=6.4$ Hz), 4.46 (H-6, t, $J_{6,6'}=8.7$ Hz), 4.53 (H-6′, q), 4.71 (HO-3, q, $J_{3,OH}=4.5$ Hz and $J_{4,OH}=1.0$ Hz), 1.25 and 1.40 (Me, two s, unassignable). On the use of a usual commercial flask in the above reaction, 3,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose was obtained in an 80% yield by treating the resultant reaction mixture with distilled water (300 ml), by the subsequent extraction of the aqueous solution with ether (200 ml ×4), followed by washing with water (200 ml), by the evaporation of the solvent *in vacuo* to a semicrystalline sirup after drying with anhydrous sodium sulfate, and by the recrystallization of the residue from light petroleum ether. Mp 44—46°C.[6,7,12,13]

2,2′-Anhydro-1-β-D-arabinofuranosyluracil (18). A transesterification reaction was similarly carried out in this case by treating uridine (**7**) (2.5 g, 10 mmol) and **1** (3.0 g, 35 mmol) at 140—145°C/15 mmHg for 1.5 hr. After about 1 hr, the crystallization of the product occurred; the crystals were, after cooling, treated with methanol (5 ml). They were filtered and recrystallized from 25% aqueous methanol to give **18** (1.6 g, 71%). Mp 238—244°C (dec.). $[\alpha]^{22}_{D}$ −22.2° (*c* 1.0, H_2O). $\lambda^{H_2O}_{max}$ 224 (ε 7860) and 251 nm (ε 7600). $\lambda^{H_2O}_{min}$ 236 nm (ε 5940). A slight shoulder was observed at about 270 nm.[14]

*1,2;3,4-Di-O-isopropylidene-D-mannitol 5,6-Carbonate (**10**).* The transesterification was carried out by treating 1,2;3,4-di-*O*-isopropylidne-D-mannitol (**4**)[15] (1.3 g, 5 mmol) and **1** (1.5 g, 17.5 mmol) at 160°C/40 mmHg for 1 hr; the residual crystals were then recrystallized from ethanol to give colorless crystals of **10** (1.3 g, 90%). Mp 111—112°C. $[\alpha]^{22}_{D}$ −50° (*c* 0.97, Me_2CO). IR (KBr): 1790 cm^{-1} (five-membered cyclic carbonate). Found: C, 54.08; H, 6.88%. Calcd for $C_{13}H_{20}O_7$: C, 54.16; H, 6.99%. Without recrystallization, the product was already analytically pure enough.

*3,4-O-Isopropylidene-D-mannitol 1,2;5,6-Dicarbonate (**11**).* 3,4-*O*-Isopropylidene-D-mannitol (**5**)[15] (1.1 g, 5 mmol) and **1** (1.5 g, 17.5 mmol) were heated together at 150—160°C/30 mmHg for 1 hr, and the residue was, after cooling, dissolved in ethanol (*ca.* 10 ml). After the solution had then been allowed to stand at room temperature, colorless needles of **11** (0.9 g, 65%) were obtained. This product was analytically pure enough without recrystallization (Found: C, 48.15; H, 5.19%). Mp 205—207°C. $[\alpha]^{22}_{D}$ −16.3° (*c* 1.0, Me_2CO).[16]

*1,2;5,6-Di-O-isopropylidene-D-mannitol 3,4-Carbonate (**13**).* 1,2;5,6-Di-*O*-isopropylidene-D-mannitol (**8**)[17] (1.3 g, 5 mmol) and **1** (1.5 g, 17.5 mmol) were heated at 160°C/40 mmHg for 1 hr. The raw crystals, obtained in the same manner as above, were recrystallized from ethanol to give colorless crystals of **13** (1.1 g, 76%). Mp 144—145°C.[18] $[\alpha]^{22}_{D}$ −111° (*c* 0.97, Me_2CO). IR (KBr): 1785 cm^{-1} with a shoulder at

---

10) J. Cunningham and R. Gigg, *J. Chem. Soc.*, **1965**, 1553 [Bp 150°C/0.08 mmHg (**17**)].

11) O. T. Schmidt, "Methods in Carbohydrate Chemistry," Vol. II, ed. by R. L. Whistler, M. L. Wolfrom, and J. N. BeMiller, Academic Press Inc., New York (1963), pp. 321—322.

12) NMR data of this compound is completely agreed with those reported by Abraham *et al.* (R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLanchlan, *J. Chem. Soc.*, **1962**, 3699.).

13) H. Ohle, C. Vargha, und H. Erlbach, *Ber.*, **61**, 1211 (1928), [Mp 56—57°C, $[\alpha]^{20}_{D}$ +29.3° (*c* 3.1, H_2O)].

14) J. J. Fox and I. Wempen, *Tetrahedron Lett.*, **1965**, 643 ($\lambda^{H_2O}_{max}$ 223 and 249 nm with a slight shoulder at 270 nm, Mp 246—248°C); A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966) (Mp 238—244°C).

15) L. F. Wiggins, *J. Chem. Soc.*, **1946**, 13.

16) G. Hannisch und G. Henseki, *Chem. Ber.*, **100**, 3225 (1967), [Mp 214°C, $[\alpha]_D$ −21° (*c* 1, Me_2CO)].

17) E. Baer, *J. Amer. Chem. Soc.*, **67**, 338 (1945).

18) B. R. Baker and H. S. Sachder, *J. Org. Chem.*, **28**, 2135 (1963), [Mp 147°C, $[\alpha]^{25}_{D}$ +8.0° (0.9%) (**13**)]; L. Hough, J. E. Priddle, and R. S. Theobald, *J. Chem. Soc.*, **1961**, 1934 [Mp 146.5—147°C, $[\alpha]^{20}_{D}$ +14.9° (*c* 1.8, Me_2CO) (**13**); Mp 233–234°C (dec.), $[\alpha]^{20}_{D}$ +31.9° (*c* 2.1, Me_2CO) (**14**)].

* A part of this paper was presented at the 26th Annual Meeting of the Chemical Society of Japan (April, 1972; Hiratsuka).

1810 cm^{-1} (five-membered cyclic carbonate).

D-*Mannitol 1,2;3,4;5,6-Tricarbonate (**14**).* D-Mannitol (**9**) (1.8 g, 10 mmol) and **1** (9.0 g, 105 mmol) were heated together at 150°C/20 mmHg for 6 hr. The residue was dissolved in ethanol (*ca.* 10 ml), and the resultant crystals, obtained on standing at room temperature, were recrystallized from glacial acetic acid to give **14** (1.7 g, 65%) (colorless needles). Mp 228—229°C. $[\alpha]^{22}_{D}$ +33.2° (*c* 1.0, Me$_2$CO).[18] IR (KBr): 1790 and 1820 cm^{-1} (five-membered cyclic carbonate).

The authors are grateful to the Ministry of Education, Japanese Government, for a Scientific Research Grant-in-Aid, and to the Kurata Foundation for a grant. Moreover, they also wish to thank Dr. Masatsune Kainosho, Central Research Lab., Ajinomoto Co., Inc., for the assignment of the NMR spectra, and the members of the Laboratory of Organic Analysis, Department of Chemistry, Tokyo Institute of Technology.