3.0 g of a yellow syrup that was directly chromatographed on a column of silicic acid using chloroform–methanol (9:1).[38] Following removal of unreacted **19** a crude product (1.35 g) was obtained which was crystallized from ethyl acetate–methanol, giving 450 mg of **21c**. Preparative tlc of the mother liquors followed by crystallization as above gave a further 300 mg (total yield 750 mg, 35%) of pure **21c**: mp 199–201°; λ_{max} (MeOH, H^+) 259 nm (ϵ 16,800); λ_{max} (MeOH, OH^-) 260 nm (ϵ 15,800); $[\alpha]^{23}D$ 30.2° (*c* 0.1, pyridine); ORD (MeOH) $[\Phi]_{280}$ (trough) −5300°, $[\Phi]_{265}$ 0°, $[\Phi]_{240}$ (peak) 11,300°; ν_{max} (KBr) 1740, 1670, 1610 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}N_5O_4I$ (435.18): C, 33.12; H, 3.24; N, 16.09; I, 29.16. Found: C, 33.22; H, 3.34; N, 15.98; I, 29.10.

Registry No. **4a**, 37731-72-9; **4b**, 37731-76-3; **4c**, 42867-59-4; **5**, 7057-48-9; **6**, 73-03-0; **7**, 42867-61-8; **8**, 40627-32-5; **8** 3-*O*-acetyl-2-bromo isomer, 42867-63-0; **9**, 42867-64-1; **11a**, 42867-65-2; **11b**, 42867-66-3; **12a**, 42867-67-4; **12b**, 42867-68-5; **13**, 42867-69-6; **14**, 42867-70-9; **15a**, 5974-93-6; **15b**, 42867-72-1; **15c**, 42867-73-2; **15d**, 42867-74-3; **17**, 42867-75-4; **18**, 19325-92-9; **19**, 42867-77-6; **21a**, 42867-78-7; **21c**, 42867-79-8; chromous acetate, 628-52-4; 2-acetoxyisobutyryl chloride, 40635-66-3; adenosine, 58-61-7; 2-acetoxyisobutyryl bromide, 40635-67-4; uridine, 58-96-8.

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(38) This work-up gave better results than the normal partitioning process where some of the nucleosides became water soluble.

Synthesis and Stereochemistry of Telomers of Vinylene Carbonate as Synthetic Intermediates for Carbohydrates[1]

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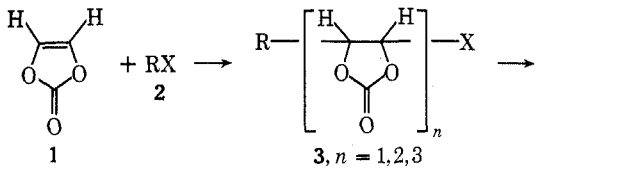
Vinylene carbonate underwent smooth telomerization with various polyhalogenomethanes as telogens in the presence of the radical initiator, BPO or AIBN, to give rise to type **3** telomers which could be synthetic key intermediates for carbohydrates. Isolation and stereochemistry of the lower telomers **3** ($n \leq 3$ or 4) stereoselectively formed were described. Stereochemistry of the $n = 2$ telomers **17a** and **17b** (**18a** and **18b**) was determined as trans,syn,trans and trans,anti,trans configuration by chemical correlation with lyxose and xylose derivatives **31**, and **34**, respectively. Abnormal telomerization involving unusual hydrogen abstraction from telogens by the radicals derived from peroxide was observed in the cases of bromoform and methylene bromide employed as telogens in contrast to those of polychloromethanes.

Apart from chemical modifications of naturally occurring monosaccharides, previously reported syntheses of carbohydrates from simple nonsugar substances mostly involve nonspecific processes at the stage of extension of the carbon chain or introduction of functional groups.[2] This paper deals with the stereoselective synthesis of car-

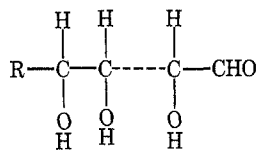
bohydrates starting with simple achiral compounds, vinylene carbonate (1) and polyhalogenomethanes, in two steps (telomerization and hydrolysis).

There have appeared structural and kinetic investigations on the polymers[3] derived from substituted or nonsubstituted vinylene carbonates as well as the chemical reactions involving the photocycloaddition[4] and the Diels–Alder reaction,[5] since the first preparation of parent compound 1 by Newman and coworker in 1953.[6] So far there seems to be no information on the telomerization of vinylene carbonates, which could be of significance in the synthesis of carbohydrates.

Careful control of the telomerization of 1 as a taxogen with polyhalogenomethanes (2) as telogens to give type 3 telomers followed by hydrolysis would provide a novel and facile route to both natural and unnatural polyalcohols, including carbohydrates. Highly stereoselective product formation would be expected owing to the strong tendency of trans radical addition.[7]



1 3, n = 1,2,3



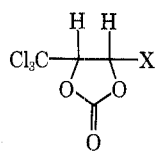
4

In this paper we describe the first radical telomerization of 1 with such polyhalides as carbon tetrachloride, chloroform, carbon tetrabromide, bromoform, dibromomethane, and bromotrichloromethane, as telogens to afford telomers 3, especially lower telomers with n values less than four, which could play an important role as synthetic intermediates for carbohydrates and polyalcohols.

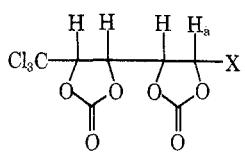
Results and Discussion

Telomerization of Vinylene Carbonate. Carbonate 1 underwent smooth telomerization with polyhalogenomethanes in the presence of benzoyl peroxide (BPO) or azobisisobutyronitrile (AIBN) as radical initiator under a nitrogen atmosphere to give telomers 3 in yields depending on the conditions (Table I). After 1 was almost consumed, treatment of the reaction mixture with hot methylene chloride gave as insoluble portions the higher telomers 3 with average n values of ten or more in addition to soluble products which consisted mainly of the lower telomers 3 with n values less than four. The soluble products could be separated into stereochemically pure telomers 3 (n = 1, 2, 3, and 4) by careful column chromatography on silica gel.[8]

The 1:1 adducts of 1 with carbon tetrachloride and chloroform were identified as 4-chloro-5-trichloromethyl-1,3-dioxolan-2-one (5) and 4-trichloromethyl-1,3-dioxolan-2-one (6), respectively, on the basis of spectral data (ir, nmr) and elemental analyses. Repeated attempts to detect another n = 1 isomer by nmr, tlc, and glpc analyses were unsuccessful.



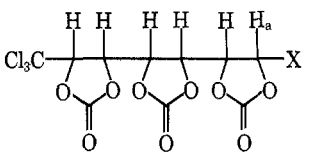
5, X = Cl
6, X = H
12, X = Br



7a,b, X = Cl
8a,b, X = H

Among eight possible isomers two isomeric n = 2 telomers, **7a** and **7b**, were preferentially obtained in the reaction using carbon tetrachloride as telogen and identified as stereoisomers of 5-chloro-5′-trichloromethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione. The nmr spectra of **7a** and **7b** showed doublet signals at δ 6.50 (J = 2 Hz) and 6.55 (J = 2 Hz) due to terminal methine protons and multiplet peaks centered at δ 5.20 and 5.35, with a ratio of 1:3, respectively. Chloroform as a telogen gave as the n = 2 telomers 5-trichloromethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione (**8a** and **8b**), which showed multiplet signals centered at δ 4.90 and 4.85 in the nmr spectra, respectively. Despite an extensive search for the other n = 2 isomers they could not be found in the reaction mixture. This indicates that the reaction proceeded with high stereoselectivity.

As for the n = 3 telomers with 32 possible isomers (carbon tetrachloride as telogen), only three isomeric compounds, **9a**, **9b**, and **9c**, could be selectively isolated in nearly equal amounts. Their nmr spectra, whose pattern was similar to those of **7a** and **7b**, showed two peaks at δ 6.6 and 5.2 in an intensity of 1:5. Further elution on the column gave a small amount of the n = 4 telomer **10**. The n = 3 telomer **11** derived from chloroform was also isolated, presumably in an isomeric mixture.



9a,b,c, X = Cl
11, X = H

Further studies on the distribution of telomers formed showed that the molar ratios 1:7 and 1:25 of 1 to carbon tetrachloride and chloroform gave the best results for the lower telomers ($n \leq 4$), respectively, while the increased ratios of taxogen to telogen resulted in high yields of the higher telomers (Table I). On the contrary, bromotrichloromethane as telogen even in 2 molar equiv gave exclusively the n = 1 adduct **12**, reflecting the large chain transfer constant.[9] This chain transfer reaction was remarkably affected by the ratio of 1 to telogens. Analyses of the higher telomer fractions which were obtained in the telomerization at the molar ratios 1:3, 1:7, and 1:12 of 1 to carbon tetrachloride gave average n values of 15.5, 8.5, and 6.5, respectively. A similar tendency was also observed in the case of chloroform.

The situation was more complicated when poly*bromo*methanes were used as telogens; unusual telomers were obtained in fairly good yields in addition to the normal ones. Thus, the reaction of 1 with methylene bromide free from bromoform and carbon tetrabromide gave four abnormal lower telomers which were identified as 4-dibromomethyl-1,3-dioxolan-2-one (**14**), 4-bromo-5-dibromomethyl-1,3-dioxolan-2-one (**15**), 5-bromo-5′-dibromomethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione (**18a** and **18b**), together with the expected 4-bromo-5-bromomethyl-1,3-dioxolan-2-one (**13**) and 5-bromo-5′-bromomethyl-[4,4′-bi-1,3-dioxolane]-2,2′-dione (**17a** and **17b**).

The isomeric structures of **13** and **14** were established by nmr spectra, which showed doublet peaks at δ 6.48 (J = 1.5 Hz) assignable to the bromomethine proton and δ 5.80 (J = 3.5 Hz) due to the dibromomethine proton, respectively. In the nmr spectra, **17a** and **17b** showed signals due to bromomethylene protons at δ 3.65 and 3.73 as an AB part of an ABX pattern, respectively, while **18a**

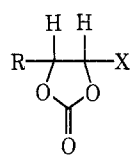
Table I
Isolated Yields (%) of Telomers 3 of Vinylene Carbonate with Polyhalogenomethanes[a]

Mole ratio (telogen/1)	Telogen	Lower telomers: $n = 1$	Lower telomers: $n = 2$	Lower telomers: $n = 3$	Higher telomers[b]
3	CCl_4	4.9 (**5**)	4.2 (**7**)	1.4 (**9**)	43.0 (n = 15.5)[c]
7	CCl_4	28.5 (**5**)	15.6 (**7**)	3.6 (**9**)	15.4 (n = 8.5)[d]
12	CCl_4	45.3 (**5**)	12.2 (**7**)		4.9 (n = 6.5)[e]
8	$CHCl_3$	1.1 (**6**)	1.4 (**8**)		61.0 (n = 17.5)[f]
20	$CHCl_3$	4.8 (**6**)	6.3 (**8**)		4.3 (n = 12.5)[g]
25	$CHCl_3$	15.9 (**6**)	10.3 (**8**)	2.6 (**11**)	5.4 (n = 10.5)[h]
4	$CBrCl_3$	92.0 (**12**)			
15	CH_2Br_2	19.5 (**13, 14, 15**)	4.8 (**17, 18**)		
5	$CHBr_3$	41.0 (**15, 16**)	17.0 (**19**)		
2	CBr_4	35.0 (**16**)			

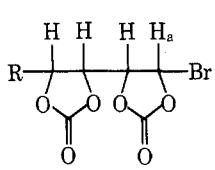
[a] Benzoyl peroxide was used as a radical initiator. [b] Obtained as insoluble products in hot methylene chloride and given in yields (%) based on the average molecular weight determined by elementary analyses. An average of n value was also calculated on the basis of chlorine analyses. [c] Found: C, 41.61; H, 3.88; Cl, 12.92. [d] Found: C, 38.44; H, 3.55; Cl, 20.19. [e] Found: C, 37.46; H, 3.38; Cl, 24.59. [f] Found: C, 42.64; H, 3.89; Cl, 9.36. [g] Found: C, 41.21; H, 3.66; Cl, 15.76. [h] Found: C, 39.19; H, 3.47; Cl, 18.57.

and **18b** gave doublet peaks at δ 5.90 (J = 3 Hz) and 6.05 (J = 3 Hz) assignable to dibromomethine protons, respectively.

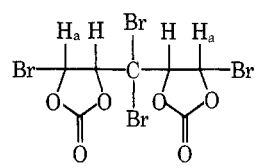
Bromoform as a telogen gave three unusual lower telomers, 4-bromo-5-tribromomethyl-1,3-dioxolan-2-one (**16**) and dibromomethylene-4,4′-bis(5-bromo-1,3-dioxolan-2-one) (**19a** and **19b**) in addition to **15** with no formation of the expected **18a** and **18b**. The addition of carbon tetrabromide to 1 afforded **16** in 35% yield. Failure to convert



13, R = CH_2Br; X = Br **20**, R = OCOPh; X = Cl
14, R = $CHBr_2$; X = H **21**, R = OCOPh; X = H
15, R = $CHBr_2$; X = Br **22**, R = OCOPh; X = Br
16, R = CBr_3; X = Br **23**, R = $C(CH_3)_2CN$; X = Br



17a,b, R = CH_2Br
18a,b, R = $CHBr_2$

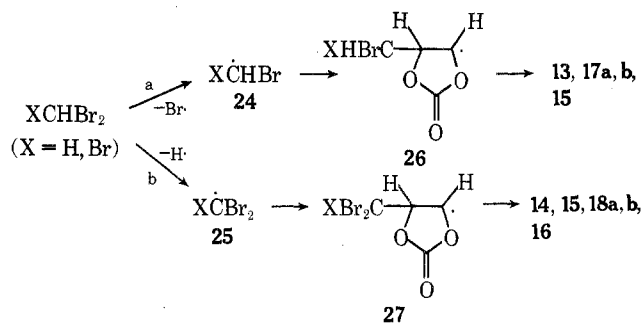


19a,b

13 into **15** and **15** into **16** in the presence of BPO and polybromomethanes would preclude **13** and **15** as the possible intermediates in the reaction. The nmr spectra of **19a** and **19b**, which closely resemble that of **16**, showed two doublets at δ 6.55 (J = 2.5 Hz) and 5.25 (J = 2.5 Hz) and δ 6.60 (J = 2.5 Hz) and 5.30 (J = 2.5 Hz), respectively, indicative of the symmetrical structures. Treatment of **1** with **16** in the presence of BPO gave a mixture of **19a** and **19b** in a ratio of 5:4 (75% yield).

The additional products, **20**, **21**, **22**, and **23**, which were undoubtedly derived from the direct participation of the decomposed radicals of BPO and AIBN, were isolated in low yields.

Reaction Pathways. First, mention should be made of the formation of unusual telomers in the reactions using poly*bromo*methanes as telogens.[7] Bromine and hydrogen abstractions (paths a and b) from polybromides by the radicals, PhCOO· and/or Ph· derived from an initiator BPO could take place in the radical reactions described above and result in the formation of radicals **24** and **25**, which could account for the isolated products **13**–**18** *via* the ethylene carbonate radicals **26** and **27**. Path b, which was further supported by a fair yield of benzoic acid formed in the telomerization of **1** with methylene bromide and bromoform, provides a unique example of hydrogen abstraction by radicals derived from peroxide with one precedent of similar type of unusual telomerization of polyhaloethylenes.[10]



The initial formation of trichloromethyl radicals from carbon tetrachloride and chloroform by BPO or AIBN followed by the telomerization with **1** would explain all the isolated products derived from polychloromethanes as telogens.

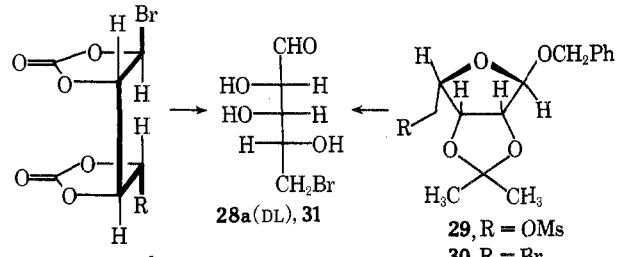
The products **19a** and **19b** are formed by radical addition of **16** to **1** as disclosed in the separate experiment.

Stereochemistry of Lower Telomers. Steric effects are most important in the highly stereoselective formation of telomers during radical telomerizations;[7] products of trans configuration might be expected to be formed preferentially in the rather nonflexible cyclic carbonate system, because the eclipsing approach of telogens to the halogenomethyl substituents (radicals) in the product-forming step of the chain process is energetically very disfavored.[11]

Just as predicted on the basis of mechanistic considerations, the expected trans stereochemistry of the n = 1 products **5**, **12**, **13**, **15**, and **16** as well as of the adducts **20**, **22**, and **23** was substantiated by the small coupling constants ($J_{vic} \cong$ 2.0 Hz) of the vicinal protons on the carbonate rings[12,14] which are in good accord with the value, J_{vic} = 2.0 Hz, of monochloroethylene carbonate, attributable to trans coupling[14,15] (Table II). Such small values for **5** and its analogs, unlike the large coupling constant J_{vic} = 6.0 Hz (presumably trans) for **6**, may reflect the significant steric effects of electronegative substituent groups on conformation.[15]

Application of this general tendency in the n = 1 series to the stereoselectively formed n = 2 telomers would make it possible to assign the trans,syn,trans and trans,anti,trans structures to **17a** (**18a**) and **17b** (**18b**),

which on hydrolysis of the carbonate groups give 5-substituted 5-deoxy-DL-lyxose and -xylose, respectively. Such a stereochemistry was unequivocally proven by selective reduction of **18a** and **18b** with nickel carbonyl in tetrahydrofuran[16] to **17a** and **17b** followed by their successful conversion into 5-bromo-5-deoxy-DL-lyxose (**28a**) and -xylose (**28b**), respectively.[2] The authentic sugar derivatives **31** and **34** were obtained as syrups by simultaneous removal of protecting groups of benzyl 5-bromo-5-deoxy-2,3-*O*-isopropylidene-α-D-lyxofuranoside (**30**) and 5-bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (**33**) which were prepared from the corresponding mesylate **29**[17] and tosylate **32**,[18] respectively. Identity of the hydrolyzates **28a** and **28b** with the authentic specimens **31** and **34** was established, respectively, except for the optical activity by paper chromatography and gas chromatographic analysis (as trimethylsilates).



trans,syn,trans form

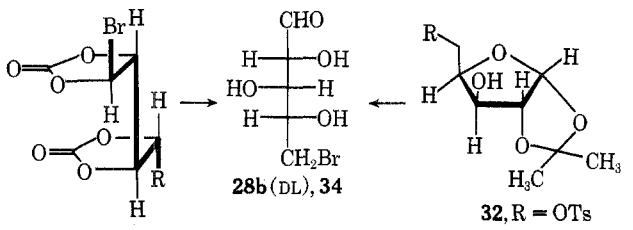
17a, R = CH_2Br

18a, R = $CHBr_2$

28a(DL), **31**

29, R = OMs

30, R = Br



trans,anti,trans form

17b, R = CH_2Br

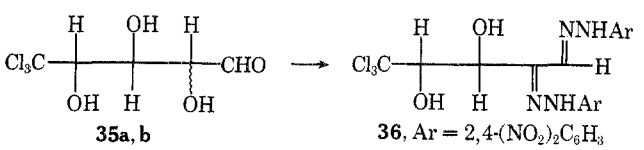
18b, R = $CHBr_2$

28b(DL), **34**

32, R = OTs

33, R = Br

All of the n = 2 and 3 telomers isolated except 8 and 11 which gave intricate nmr spectra showed well-defined doublet peaks due to H_a protons with small coupling constants (J_{vic} = 2.0 Hz) (Table III), which were comparable to those of the n = 1 products and hence suggested trans-substituted 1,3-dioxolan-2-one structures, though the complexity of the spectra prevented further assignments of configuration. On the other hand, acid hydrolysis of **7a** and **7b** gave high yields of 5-deoxypentoses **35a** and **35b**, which afforded identical 2,4-dinitrophenylosazones (**36**), indicative of a configurational difference only at C-2. These findings strongly suggest trans,syn,trans and trans,anti,trans configurations or their homologs for **7a** and **7b** and **19a** and **19b** in analogy with **17a,b** and **18a,b**.



35a, b

36, Ar = 2,4-$(NO_2)_2C_6H_3$

Similar considerations regarding the stereochemistry of **9a–c** would assign to these substances three configurations among four isomeric structures **37**, **38**, **39**, and **40**, hydrolysis of which would give glycero-manno-, glycero-gluco-, glycero-gulo, and glycero-idoheptose derivatives.

Table II
Vicinal Coupling Constants for 4,5-Disubstituted 1,3-Dioxolan-2-ones (3, n = 1)[a]

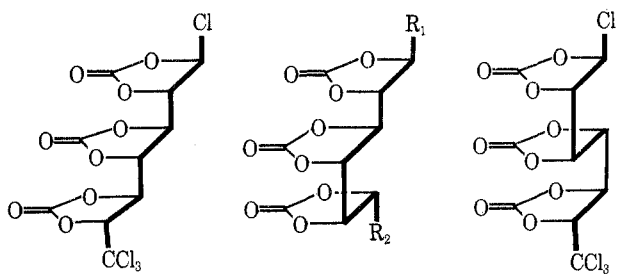
Compd	R	X	J_{vic}, Hz	Solvent
3 (n = 1)	H	Cl	2.0, 5.5	$CDCl_3$
5	CCl_3	Cl	2.0	CCl_4
6	CCl_3	H	6.0, 7.5	$CDCl_3$
12	CCl_3	Br	2.0	$CDCl_3$
13	CH_2Br	Br	1.5	CCl_4
15	$CHBr_2$	Br	2.5	CCl_4
16	CBr_3	Br	2.0	CCl_4
20	OCOPh	Cl	0	$CDCl_3$
21	OCOPh	H	3.0, 5.5	$CDCl_3$
22	OCOPh	Br	0	CCl_4
23	$C(CH_3)_2CN$	Br	3.0	CCl_4

[a] All spectra were obtained at 60 MHz.

Table III
Nmr Data on the n = 2 and 3 Telomers[a]

Compd	X	H_a δ, ppm	H_a J, Hz
7a	Cl	6.50	2.0
7b	Cl	6.65	2.0
9a	Cl	6.60	2.0
9b	Cl	6.65	2.0
9c	Cl	6.65	2.0
17a	Br	6.75	2.0
17b	Br	6.75	2.0
18a	Br	6.65	2.0
18b	Br	6.85	2.0
19a[b]	Br	6.55	2.5
19b[b]	Br	6.60	2.5

[a] Spectra were obtained in CH_3CN at 60 MHz. [b] In $CDCl_3$.



37

38, R_1 = Cl; R_2 = CCl_3

39, R_1 = CCl_3; R_2 = Cl

40

Telomerization of **1** described above, which could be appreciably controlled with regard to the length of carbon chain by simple alteration of the ratios of **1** to telogens, provides an interesting potential for stereoselective synthesis of carbohydrates and polyalcohols.

Experimental Section

All melting points were taken in a Yanaco micro melting point apparatus and are uncorrected. Ir spectra were determined on a Nihon Bunko Model DS-402G spectrophotometer. Nmr spectra were recorded on a Nihon Denshi Model JMN-3H-60 spectrometer using TMS as an internal standard. Determination of molecular weight was performed with a Hitachi Perkin-Elmer Model 115 vapor pressure osmometer. Glc analysis was carried out with a Yanaco G800-T gas chromatograph using a 10% SE-30 (A) or a 15% PEGS (B) column (2 m × 3 mm). Tlc plates coated with silica gel (Camag D-5) were used.

Polyhalogenomethanes. Commercially available halides, carbon tetrachloride, chloroform, bromoform, carbon tetrabromide, and bromotrichloromethane were purified by distillation or recrystallization immediately before use. Bromoform-free methylene bromide was prepared by the literature methods[19] and purified by repeated distillation.

Vinylene Carbonate (1). Ethylene carbonate (88 g, 1 mol) was placed in a 300-ml three-necked flask equipped with a thermometer and gas inlet and exhausting tubes and chlorine gas was bub-

bled through the liquefied carbonate at 100–105°, while BPO (0.1 g) was added at 1.5-hr intervals. After the chlorination for 6 hr, the gas chromatogram (column A at 120°) indicated that the reaction products consisted of dichloroethylene carbonate, ethylene carbonate, and monochloroethylene carbonate in a ratio of 1:1:8. Fractional distillation under reduced pressure gave monochloroethylene carbonate, nmr ($CDCl_3$) δ 6.72 (1 H, d, d, J = 2.0 Hz, J' = 5.5 Hz), 4.88 (1 H, d, d, J = 5.5 Hz, J' = 10 Hz), 4.57 (1 H, d, d, J = 2.0 Hz, J' = 10 Hz), bp 105–110° (9 mm) [lit.[6] bp 106–107° (10–11 mm)], in 70% yield (85 g) in addition to a small amount of 1,2-dichloroethylene carbonate, bp 78–80° (20 mm). According to Newman's method,[6] vinylene carbonate (1) was prepared from monochloroethylene carbonate by action of triethylamine in 45%, bp 73° (30 mm) [lit.[6] bp 73–74° (32 mm)].

General Procedure for Telomerization. A solution of 1 in telogens was placed in a four-necked flask equipped with thermometer, condenser, and tubes for nitrogen gas and warmed under stirring in a slow stream of nitrogen. Radical initiator, BPO or AIBN, was added every *ca.* 4 hr and the reaction was checked by glpc (column A, at 120°). After removal of unchanged telogens and 1 by distillation, the products were separated by column chromatography on silica gel.

Reaction of 1 with Carbon Tetrachloride. A typical run was provided as follows. A mixture of 1 (17.2 g, 0.2 mol) and carbon tetrachloride (216 g, 1.4 mol) was refluxed in the presence of BPO (0.1 g) under a nitrogen atmosphere and the radical initiator (0.1 g) was added every 3 hr. Within 28 hr 1 was completely consumed. After removal of the low-boiling materials, the residue was repeatedly extracted with hot methylene chloride (300 ml). The insoluble products were purified by reprecipitation with acetone and *n*-hexane to give the higher telomers (3.2 g) as a colorless, amorphous powder. The combined extracts and washings were evaporated *in vacuo* to leave the oily residue (32.9 g), which was dissolved in methylene chloride and placed on a column containing silica gel (250 g). The column was eluted with successive solvents of *n*-hexane–benzene, benzene, benzene–methylene chloride, methylene chloride, and methylene chloride–acetone and fractions of 100 ml each were collected. Elution with *n*-hexane–benzene (7:3) and benzene gave **5** (13.7 g) and **20** (0.16 g) as crystalline products, respectively, in addition to a mixture (0.19 g) of **5** and **20**. Further elution with benzene gave **7a** (2.3 g) and **7b** (2.2 g), which were readily crystallized on standing, together with a solid (0.58 g) as a mixture of **7a** and **7b**. The n = 3 telomers **9a** (0.27 g), **9b** (0.25 g), and **9c** (0.27 g) were obtained from the pooled fractions eluted with methylene chloride–acetone (98:2). The fractions eluted with methylene chloride–acetone (9:2) gave a solid **10** (0.18 g) identified as the n = 4 telomer on the basis of elementary analysis. Mixed fractions of the components were rechromatographed on silica gel with the same solvent systems as above and total yields were summarized in Table I. The physical and spectral data of the products follow.

5: mp 53–54° from *n*-hexane as colorless needles; ir (KBr) 1840 cm^{-1}; nmr (CCl_4) δ 6.40 (1 H, d, J = 2 Hz), 5.20 (1 H, d, J = 2 Hz). *Anal.* Calcd for $C_4H_2O_3Cl_4$: C, 20.03; H, 0.84; Cl, 59.12. Found: C, 19.77; H, 1.11; Cl, 59.85.

20: mp 109–110° from *n*-hexane; ir (KBr) 1855 and 1740 cm^{-1}; nmr ($CDCl_3$) δ 8.00 (2 H, m), 7.50 (3 H, m), 6.83 (1 H, s), 6.28 (1 H, s). *Anal.* Calcd for $C_{10}H_7O_5Cl$: C, 49.51; H, 2.91; Cl, 14.61. Found: C, 49.32; H, 3.00; Cl, 15.08.

7a: mp 185–186° from CCl_4; ir (KBr) 1825 and 1805 cm^{-1}; nmr (CH_3CN) δ 6.50 (1 H, d, J = 2 Hz), 5.20 (3 H, m). *Anal.* Calcd for $C_7H_4O_6Cl_4$: C, 25.80; H, 1.24; Cl, 43.51; mol wt, 326. Found: C, 25.94; H, 1.21; Cl, 43.72; mol wt, 345.

7b: mp 159–160° from CCl_4; ir (KBr) 1845, 1830, and 1810 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.35 (3 H, m). *Anal.* Calcd for $C_7H_4O_6Cl_4$: C, 25.80; H, 1.24; Cl, 43.51; mol wt, 326. Found: C, 25.75; H, 1.38; Cl, 43.49; mol wt, 354.

9a: mp 244° dec from CH_2Cl_2; ir (Nujol) 1840 and 1820 cm^{-1}; nmr (CH_3CN) δ 6.60 (1 H, d, J = 2 Hz), 5.15 (5 H, m). *Anal.* Calcd for $C_{10}H_6O_9Cl_4$: C, 29.16; H, 1.47. Found: C, 29.24; H, 1.83.

9b: mp 225–230° dec from CH_2Cl_2; ir (Nujol) 1845, 1825, and 1805 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.25 (5 H, m). *Anal.* Calcd for $C_{10}H_6O_9Cl_4$: C, 29.16; H, 1.47; Cl, 34.18. Found: C, 29.16; H, 1.84; Cl, 34.08.

9c: mp 290° dec from CH_2Cl_2; ir (Nujol) 1830–1810 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.25 (5 H, m). *Anal.* Calcd for $C_{10}H_6O_9Cl_4$: C, 29.16; H, 1.47. Found: C, 29.16; H, 1.64.

10: mp 280° dec from CH_2Cl_2; ir (Nujol) 1845–1810 cm^{-1}. *Anal.* Calcd for $C_{13}H_8O_{12}Cl_4$: C, 31.35; H, 1.62; Cl, 28.47. Found: C, 31.59; H, 1.84; Cl, 29.02.

Reaction of 1 with Chloroform. A solution of 1 (17.2 g, 0.2 mol) in chloroform (600 g, 5 mol) was refluxed in the presence of BPO for 59 hr in a similar way to that described for the reaction with carbon tetrachloride. After removal of the excess telogen, the unreacted 1 (8.9 g) was recovered by distillation. On treatment of the residue with hot methylene chloride, the higher telomers as insoluble products (0.51 g) were obtained in addition to the soluble lower telomers, of which separation was achieved by careful chromatography on silica gel, analogously to the telomers with carbon tetrachloride, and the products **6** (3.4 g), **21** (0.07 g), **8a** (0.83 g), **8b** (0.64 g), and **11** (0.24 g) were obtained in pure forms. Telomers obtained had the following properties.

6: mp 98–99° from *n*-hexane; ir (Nujol) 1810 and 1800 cm^{-1}; nmr ($CDCl_3$) δ 5.25 (1 H, d, d, J = 7.5 Hz, J' = 6.0 Hz), 4.75 (2 H, m). *Anal.* Calcd for $C_4H_3O_3Cl_3$: C, 23.39; H, 1.47; Cl, 51.77. Found: C, 23.66; H, 1.50; Cl, 51.49.

21: mp 112–113° from CCl_4; ir (KBr) 1827, 1808, and 1735 cm^{-1}; nmr ($CDCl_3$) δ 7.97 (2 H, m], 7.55 (3 H, m), 6.95 (1 H, d, d, J = 6 Hz, J' = 3 Hz), 4.7 (2 H, m). *Anal.* Calcd for $C_{10}H_8O_5$: C, 57.69; H, 3.87; Found: C, 56.96; H, 3.98.

8a: mp 185–186° from benzene; ir (Nujol) 1840, 1820, 1800, and 1785 cm^{-1}; nmr (CH_3CN) δ 5.35–4.45 (m). *Anal.* Calcd for $C_7H_5O_6Cl_3$: C, 28.84; H, 1.73; Cl, 36.49. Found: C, 29.38; H, 2.12; Cl, 36.71.

8b: mp 152° from benzene; ir (Nujol) 1840–1784 cm^{-1}; nmr (CH_3CN) δ 5.40–4.30 (m). *Anal.* Calcd for $C_7H_5O_6Cl_3$: C, 28.84; H, 1.73. Found: C, 28.95; H, 1.91.

11: mp 227–235° dec from CH_2Cl_2; ir (Nujol) 1830–1810 cm^{-1}. *Anal.* Calcd for $C_{10}H_7O_9Cl_3$: C, 31.82; H, 1.87. Found: C, 31.50; H, 1.91.

Reaction of 1 with Methylene Bromide. A mixture of 1 (17.2 g, 0.2 mol), methylene bromide (522 g, 3 mol), and BPO was heated at 90° in a similar manner to that described above. After excess methylene bromide was removed *in vacuo*, the distillation gave a recovery of the unchanged 1 (1.6 g). The residue was chromatographed on silica gel to afford the lower telomers in pure forms. The unusual adduct **15** (4.68 g) was first eluted with benzene–*n*-hexane (3:7) and was indistinguishable from the normal n = 1 telomer in the reaction of bromoform as a telogen. Subsequent elution with the same solvent gave the n = 1 adduct **13**, bp 100° (0.1 mm), 4.46 g, as a viscous oil and a crystalline isomer **14** (0.34 g) recrystallized from carbon tetrachloride as colorless needles, mp 68–69°, which showed distinct difference in the nmr spectral data as given below. A small amount of **22** was also isolated. Subsequent fraction eluted out with benzene–chloroform (1:1) gave the unusual n = 2 telomers **18a** (0.22 g) and **18b** (1.07 g) which were recrystallized from carbon tetrachloride to give colorless needles, mp 147–148 and 131–132°, respectively. On the continuing elution the normal n = 2 telomers, **17a** (0.04 g) and **17b** (0.39 g), were obtained, which afforded colorless prisms, mp 170–171 and 126–128°, on recrystallization from chloroform, respectively. Further elution with chloroform–acetone (10:1) gave an amorphous powder (7.09 g), presumably the higher telomers.

When AIBN was used in the place of BPO under the same conditions as described above, the identical products **13** (1.5 g, 5.7%), **15** (1.3 g, 3.8%), **17a** (50 mg, 0.2%), **17b** (101 mg, 0.4%), **18a** (65 mg, 0.3%), and **18b** (180 mg, 0.7%) were isolated in addition to the recovered **1** (8.6 g) and the adduct **23** (138 mg, 0.6%), mp 80–81° (from CCl_4). No formation of **14** was observed. Data on the spectra and combustion analyses were as follows.

13: ir (neat) 1845 and 1825 cm^{-1}; nmr (CCl_4) δ 6.48 (1 H, d, J = 1.5 Hz), 5.20 (1 H, m), 3.65 (2 H, m). *Anal.* Calcd for $C_4H_4O_3Br_2$: C, 18.49; H, 1.55. Found: C, 18.84; H, 1.58.

14: ir (Nujol) 1825 and 1800 cm^{-1}; nmr ($CDCl_3$) δ 5.80 (1 H, d, J = 3.5 Hz), 4.95 (1 H, m), 4.55 (2 H, m). *Anal.* Calcd for $C_4H_4O_3Br_2$: C, 18.49; H, 1.55; Br, 61.50. Found: C, 18.74; H, 1.57; Br, 61.43.

18a: ir (Nujol) 1845, 1820, and 1795 cm^{-1}; nmr (CH_3CN) δ 6.65 (1 H, d, J = 2 Hz), 5.90 (1 H, d, J = 3 Hz), 5.00 (3 H, m). *Anal.* Calcd for $C_7H_5O_6Br_3$: C, 19.78; H, 1.19. Found: C, 20.03; H, 1.22.

18b: ir (Nujol) 1840–1815 cm^{-1}; nmr (CH_3CN) δ 6.85 (1 H, d, J = 2 Hz), 6.05 (1 H, d, J = 3 Hz), 5.35 (3 H, m). *Anal.* Calcd for $C_7H_5O_6Br_3$: C, 19.78; H, 1.19. Found: C, 20.36; H, 1.20.

17a: ir (Nujol) 1835 and 1795 cm^{-1}; nmr (CH_3CN) δ 6.75 (1 H, d, J = 2 Hz), 4.60–5.20 (3 H, m), 3.65 (2 H, m). *Anal.* Calcd for $C_7H_6O_6Br_2$: C, 24.30; H, 1.75; Br, 46.20. Found: C, 24.35; H, 1.85; Br, 45.60.

17b: ir (Nujol) 1845 and 1795 cm^{-1}; nmr (CH_3CN) δ 6.75 (1 H, d, J = 2 Hz), 4.60–5.50 (3 H, m), 3.73 (2 H, m). *Anal.* Calcd for $C_7H_6O_6Br_2$: C, 24.30; H, 1.75. Found: C, 24.30; H, 1.85.

23: ir (Nujol) 2280 (vw), 1845, and 1825 cm^{-1}; nmr ($CDCl_3$) δ 1.50 (6 H, s), 4.83 (1 H, d, J = 3.0 Hz), 6.05 (1 H, d, J = 3.0 Hz). *Anal.* Calcd for $C_7H_8NO_3Br$: C, 35.90; H, 3.44; N, 5.97; Br, 33.29. Found: C, 35.91; H, 3.46; N, 5.73; Br, 33.75.

Reaction of 1 with Carbon Tetrabromide. The mixture of 1 (6.88 g, 0.08 mol), carbon tetrabromide (53 g, 0.16 mol), and BPO (0.2 g) was heated at 90° under an atmosphere of nitrogen for 5 hr. Removal of the excess carbon tetrabromide gave a crystalline product (11.68 g) which was recrystallized from *n*-hexane to give **16** as colorless needles: 35% yield; mp 85–86°; ir (KBr) 1883, 1826, and 1790 cm^{-1}; nmr (CCl_4) δ 6.42 (1 H, d, J = 2 Hz), 5.38 (1 H, d, J = 2 Hz). *Anal.* Calcd for $C_4H_2O_3Br_4$: C, 11.49; H, 0.48; mol wt, 418. Found: C, 12.13; H, 0.63; mol wt, 424.

Reaction of 1 with Bromoform. A solution of 1 (9.46 g, 0.11 mol) and bromoform (140 g, 0.55 mol) was heated at 90° under an atmosphere of nitrogen for 18 hr, while BPO (0.1 g) was occasionally added. Excess bromoform was removed by distillation *in vacuo* and a part (15.4 g) of the residue (30.1 g) was chromatographed on silica gel to give a small amount of benzoic acid in addition to the telomers. Separation of the lower telomers was achieved by eluting the column with a mixture of *n*-hexane and benzene in the ratio of 2:1 to 1:2. Elution with benzene–*n*-hexane (1:2) gave **16**, mp 85–86° (3.23 g), which was identical with the n = 1 telomer in the reaction of carbon tetrabromide as a telogen with respects to melting points and ir and nmr spectra. Subsequent elution with the same solvent gave **15** (5.27 g) and a small amount of **22** (0.15 g) which were purified by distillation under diminished pressure and recrystallization, respectively. A mixture of benzene–*n*-hexane (2:1) as an eluting solvent gave the n = 2 unusual telomers **19a** (1.93 g) and **19b** (1.33 g). An amorphous solid (5.0 g) was obtained by elution with more polar solvent (chloroform–methanol, 10:1).

Physical and spectral data of the products isolated were as follows.

15: bp 105° (0.03 mm); ir (neat) 1825 cm^{-1}; nmr (CCl_4) δ 6.55 (1, H, d, J = 2.5 Hz), 5.75 (1 H, d, J = 3.5 Hz), 5.20 (1 H, q, J = 2.5 Hz, J' = 3.5 Hz). *Anal.* Calcd for $C_4H_3O_3Br_3$: C, 14.17; H, 0.89; mol wt, 339. Found: C, 14.70; H, 0.93; mol wt, 342.

22: mp 87–88° from *n*-hexane; ir (Nujol) 1850 and 1730 cm^{-1}; nmr (CCl_4) δ 8.00 (2 H, m), 7.50 (3 H, m), 6.87 (1 H, s), 6.40 (1 H, s). *Anal.* Calcd for $C_{10}H_7O_5Br$: C, 41.83; H, 2.47; mol wt, 287. Found: C, 41.66; H, 2.42; mol wt, 283.

19a: mp 147–148° from CCl_4; ir (KBr) 1840, 1827, and 1790 cm^{-1}; nmr ($CDCl_3$) δ 6.55 (1 H, d, J = 2.5 Hz), 5.25 (1 H, d, J = 2.5 Hz). *Anal.* Calcd for $C_7H_4O_6Br_4$: C, 16.68; H, 0.81; Br, 63.46; mol wt, 504. Found: C, 16.82; H, 0.87; Br, 63.74; mol wt, 504.

19b: mp 131–132° from CCl_4; ir (KBr) 1855, 1820, and 1790 cm^{-1}; nmr ($CDCl_3$) δ 6.60 (1 H, d, J = 2.5 Hz), 5.30 (1 H, J = 2.5 Hz). *Anal.* Calcd for $C_7H_4O_6Br_4$: C, 16.68; H, 0.81; Br, 63.46; mol wt, 504. Found: C, 16.73; H, 0.75; Br, 64.46; mol wt, 515.

Reaction of 1 with Bromotrichloromethane. The mixture of 1 (17.2 g, 0.2 mol), bromotrichloromethane (162 g, 0.82 mol), and BPO was kept at 90° in a slow stream of nitrogen overnight. Evaporation of the solvent *in vacuo* left the pale yellow residue, which was crystallized on trituration with *n*-hexane. Recrystallization from *n*-hexane gave the 1:1 adduct **12** (52.0 g, 91.4%) as colorless prisms: mp 51–52°; ir (Nujol) 1860 cm^{-1}; nmr ($CDCl_3$) δ 6.55 (1 H, d, J = 2 Hz), 5.37 (1 H; d, J = 2 Hz). *Anal.* Calcd for $C_4H_2O_3BrCl_3$: C, 16.87; H, 0.70. Found: C, 17.11; H, 0.68.

Reaction of 1 with 16. The mixture of 1 (1.72 g, 0.02 mol), **16** (21.31 g, 0.05 mol), and BPO was dissolved in benzene (50 ml) and refluxed under nitrogen for 20 hr, whereupon glpc indicated that 1 was almost consumed. The benzene was removed *in vacuo* and the residue was chromatographed on silica gel to give **19a** (2.02 g) and **19b** (1.74 g), which were identical with the isomeric telomers prepared by the reaction of 1 with bromoform described above. The starting material **16** was recovered (17.23 g) and a total yield of **19a** and **19b** was 75% based on the unrecovered **16**.

Benzyl 5-Bromo-5-deoxy-2,3-*O*-isopropylidene-α-D-lyxofuranoside (30). The mixture of benzyl 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-α-D-lyxofuranoside (**29**, 7.2 g, 0.2 mol) prepared from D-mannose according to the Brimacombe method,[17] lithium bromide (10.5 g), and hexamethylphosphoric triamide (21.48 g) was refluxed in dry toluene (500 ml) for 2 hr. The mixture, after cooling in an ice bath, was washed with water (80 ml) three times. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give a syrup (10.09 g) from which chromatography on alumina (*n*-hexane–benzene, 1:1) gave the crude product **30** (4.9 g) in addition to **29** (2.97 g). Distillation under diminished pressure gave **30** (3.9 g, 97% based on the unrecovered **29**) as a colorless liquid: bp 130° (0.03 mm); $[\alpha]^{20}D$ +91.6° (c 1.31, MeOH); ir (neat) 1610, 1590, 1385, 740,and 700 cm^{-1}; nmr ($CDCl_3$) δ 7.32 (5 H, s), 5.15 (1 H, s), 4.49 (2 H, q, J = 12 Hz, J' = 24 Hz), 3.52 (2 H, m), 1.52 (3 H, s), 1.36 (3 H, s). *Anal.* Calcd for $C_{15}H_{19}O_4Br$: C, 52.49; H, 5.58; Br, 23.28. Found: C, 52.59; H, 5.59; Br, 22.81.

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (33). The mixture of 1,2-*O*-isopropylidene-5-*O*-p-toluenesulfonyl-α-D-xylofuranose (**32**, 10.0 g, 0.03 mol) prepared from D-xylose by the method of Levin,[18] lithium bromide (16 g), and hexamethylphosphoric triamide (32 g) was refluxed in dry toluene (600 ml) for 2 hr. Analogous treatment of the mixture to that described for **30** gave the crude product, which was purified by recrystallization from *n*-hexane to give **33** (6.87 g, 93%) as colorless needles: mp 93–94°; $[\alpha]^{20}D$ −22.2° (c 1.58, MeOH); ir (Nujol) 3420 and 1385 cm^{-1}; nmr ($CDCl_3$) δ 5.95 (1 H, d, J = 4 Hz), 3.55 (2 H, m), 1.56 (3 H, s), 1.36 (3 H, s). *Anal.* Calcd for $C_8H_{13}O_4Br$: C, 37.96; H, 5.18; Br, 31.57. Found: C, 38.02; H, 5.29; Br, 31.07.

5-Bromo-5-deoxy-D-lyxose (31). A suspension of **30** (686 mg) in 2 *N* sulfuric acid (40 ml) was heated at 100° for 4 hr. A homogeneous solution resulted and then was neutralized with barium carbonate. The precipitate was removed by a centrifugation and the clear supernatant was evaporated *in vacuo* to leave an oil which was washed with five 5-ml portions of benzene and extracted with dry ethanol. The extracts were decolorized with charcoal and evaporated to give **31** (440 mg) as a colorless syrup. This compound gave a single pink spot (R_f 0.69) on the paper chromatogram[20] and a single peak with a retention time of 6 min for the trimethylsilyl derivative by gas chromatographic analysis.[21]

5-Bromo-5-deoxy-D-xylose (34). Compound **33** (506 mg) was treated with 0.3 *N* sulfuric acid (20 ml) at 90° for 2.5 hr. The solution was neutralized with barium carbonate and centrifuged. The supernatant decolorized was evaporated *in vacuo* to leave a syrup. The ethanol solution was centrifuged to remove insoluble materials and evaporated to give a quantitative yield of **34** (420 mg) as a colorless syrup, which gave a pink spot (R_f 0.65) and a peak with a retention time of 7.0 min for the trimethylsilyl ether on paper[20] and gas[21] chromatograms, respectively.

5-Bromo-5-deoxy-DL-lyxose (28a). The mixture of **17a** (215 mg) and 1 *N* sulfuric acid (10 ml) was kept under stirring at 90° for 16 hr. After neutralization with barium carbonate, the reaction mixture was centrifuged in order to remove the insoluble compounds, and treatment of the supernatant with charcoal followed by evaporation *in vacuo* gave a syrup which was dissolved in absolute ethanol and filtered. The filtrate was evaporated to give **28a** as a syrup quantitatively. This product was identical with an authentic sample **31** with respect to R_f value (0.69)[20] and retention time (6.0 min).[21]

5-Bromo-5-deoxy-DL-xylose (28b). A suspension of **17b** (346 mg) and 1 *N* sulfuric acid (15 ml) was stirred on heating at 90° for 16 hr. The homogeneous mixture was treated in an analogous manner for **28a** to afford **28b** as a colorless syrup, which was identical with the authentic compound **34** on behavior to paper and gas chromatography (R_f 0.65,[20] retention time 7.0 min[21]).

5-Trichloro-5-deoxypentoses (35a and 35b). Telomers **7a** (0.65 g) and **7b** (0.22 g) were treated with 2 *N* HCl (20 ml) at 80° for 10 hr. Thorough removal of the solvent gave syrupy products **35a** [0.38 g, ir (neat) 3400 and 1780 cm^{-1}] and **35b** [0.14 g, ir (neat) 3400 and 1735 cm^{-1}], respectively, which were positive against the Fehling reagent. 2,4-Dinitrophenylosazones, mp 253–254° (from AcOEt), prepared from **35a** and **35b** were identical with regard to melting point, tlc, and ir spectra (KBr). *Anal.* Calcd for $C_{17}H_{13}N_8O_{10}Cl_3$: N, 18.81; Cl, 17.85. Found: N, 19.16; Cl, 17.93.

Registry No. 1, 872-36-6; 3 (n = 1, R = H, X = Cl, 3967-54-2; **5**, 39010-29-2; **6**, 42854-66-0; **7a**, 42854-67-1; **7b**, 42854-68-2; **8**, 42854-69-3; **9**, 42854-70-6; **10**, 42854-71-7; **11**, 42854-72-8; **12**, 38987-59-6; **13**, 42854-74-0; **14**, 42854-75-1; **15**, 42854-76-2; **16**, 39189-28-1; **17a**, 42854-78-4; **17b**, 42854-79-5; **18a**, 42854-80-8; **18b**, 42854-81-9; **19a**, 42854-82-0; **19b**, 42854-83-1; **20**, 42854-84-2; **21**, 42854-85-3; **22**, 42854-86-4; **23**, 42854-87-5; **28a**, 36663-35-1; **28b**, 36663-36-2; **29**, 20689-04-7; **30**, 42854-91-1; **31**, 42854-92-2; **32**, 20513-95-5; **33**, 42854-94-4; **34**, 42854-95-5; **35a**, 42854-96-6; **35b**, 42854-97-7; **36**, 42854-98-8; ethylene carbonate, 96-49-1; 1,2-dichloroethylene carbonate, 3967-55-3; carbon tetrachloride, 56-23-5; chloroform, 67-66-3; methylene bromide, 74-83-9; carbon tetrabromide, 558-13-4; bromoform, 75-25-2; bromotrichloromethane, 75-62-7.

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Preparation and Use of Benzhydrylamine Polymers in Peptide Synthesis. II. Syntheses of Thyrotropin Releasing Hormone, Thyrocalcitonin 26–32, and Eledoisin[1]

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Three procedures have been developed for the synthesis of a benzhydrylamine polymer for the preparation of C-terminal amide peptides by solid-phase synthesis. From a common keto intermediate, prepared by acylation of polysterene–1% divinylbenzene with benzoyl chloride, the desired product can be obtained directly by the Leukart reaction, by reduction of an oxime intermediate, or by ammonolysis of the benzhydryl bromide intermediate. The application of this support to the syntheses of the wide range of peptide hormones possessing a C-terminal amide is illustrated by the syntheses of TRH, the C-terminal heptapeptide fragment of thyrocalcitonin, and the endecapeptide, eledoisin.

The original synthesis of a biologically active peptide hormone was that of oxytocin by du Vigneaud.[5] Both oxytocin and antidiuretic hormone are of neurohypophyseal origin and are characterized by the presence of the C-terminal amide group. Recent advances in endocrinology have led to the isolation and sequence analysis of a number of other peptides which are also characterized by the presence of the C-terminal amide group. The presence of the masked carboxyl function may serve to protect these peptides from degradation by exopeptidases with carboxypeptidase specificity. Examples of such physiologically important peptides would be thyrotropin releasing hormone (TRH) and follicle stimulating hormone-luteinizing hormone-releasing hormone (FSH-LH-RH) from the hypothalamus,[6] gastrin,[7] cholecystokinin–pancreozymin and secretin from the gastrointestinal tract,[8] thyrocalcitonin from the thyroid,[9] and substance **P**, which was also isolated from the hypothalamus.[10]

Concurrent advances in peptide synthesis have seen the development of the solid-phase method.[11] As originally outlined by Merrifield[12] and most commonly employed, the solid-phase method utilizes a polymeric benzyl ester for carboxyl protection. Cleavage of this link to the polymeric support by ammonolysis either with NH_3–CH_3OH or NH_3–dimethylformamide[13-15] or with liquid ammonia[16] to give the desired peptide amide has been reported. Minor difficulties with the side reaction of transesterification or with hindered release of product have been noted.[17-20] A more serious consideration is the problem of protection of side chain carboxyl groups such as those of glutamic or aspartic acid residues. Restriction of side chain protection to the labile *tert*-butyl esters which are resistant to ammonolysis imposes concomitant restraints on the choice of amino group protection to ones even more labile.

In order to circumvent these problems when the desired product possesses a C-terminal amide function, we have conceived of a new type of polymeric carboxyl protecting group.[21] In this case, the covalent link to the support is through an amide bond between the C-terminal amino acid residue and the amine function of the polymer. Selective cleavage of the bond between the amino group and the support allows the peptide to be cleaved with the C-terminal amide function intact. The benzhydrylamine (diphenylmethylamine) support is the first of such supports which allow the selective placement of the amide function. Three methods[22] for the preparation of this sup-