Carbohydrate Research, 36 (1974) 311–318

SUGAR ORTHOCARBONATES

EDWARD I. STOUT, BARUCH S. SHASHA, DONALD TRIMNELL, WILLIAM M. DOANE, AND CHARLES R. RUSSELL
Northern Regional Research Laboratory, Peoria, Illinois 61604* (*U. S. A.*)
(Received March 4th, 1974; accepted April 4, 1974)

ABSTRACT

A simple procedure is described for preparing sugar orthocarbonates. It is based on treating the corresponding thionocarbonate in pyridine with cupric acetate and an alcohol, such as methanol, ethanol, or isopropyl alcohol. Treatment of 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-thionocarbonate with diols, such as 1,2-ethanediol, 1,2-propanediol, or 1,2:5,6-di-*O*-isopropylidene-D-mannitol, also gave orthocarbonates. Methyl thionocarbonate, *S*-methyl xanthate, and dithiobis(thioformate) derivatives of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose all gave the trimethyl orthocarbonate upon treatment with methanol in the presence of pyridine and cupric acetate. The structure of the orthocarbonates was proved by elemental analysis, n.m.r., and mass spectra, and by treatment with mild acid to form carbonates. Treatment of 1,2:5,6-di-*O*-isopropylidene-3-thio-D-altritol 3,4-thionocarbonate with methanol or ethanol gave the corresponding orthothiocarbonate, but on treatment with 1,2-ethanediol or with sodium ethoxide the 3,4-episulfide resulted.

INTRODUCTION

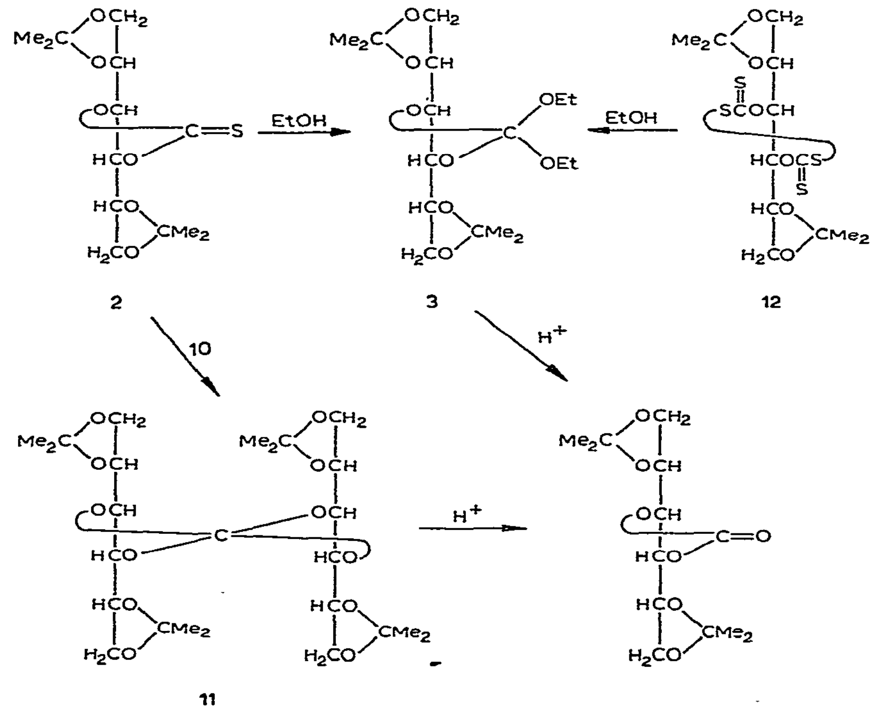
Thionocarbonates are readily prepared from oxidatively coupled xanthates[1] and constitute intermediates from which several types of compounds can be prepared. Reactions of thionocarbonates with trimethyl phosphite give alkenes[2]; with silver nitrate, carbonates[3]; and with potassium iodide, thiolated sugars[4,5]. Methylation of 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-thionocarbonate (**1**) produced 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-(*S*-methyl monothio-orthocarbonate), and benzylation produced the *S*-benzyl analogue[6]. Treatment of **1** with lead tetraacetate yielded bis(1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-orthocarbonyl) disulfide[7]. An orthocarbonate was formed by the reaction of 2,3:5,6-di-*O*-isopropylidene-D-mannitol with thiophosgene in pyridine; it was presumably produced via a cyclic thionocarbonate[8].

---

*Agricultural Research Service, U.S. Department of Agriculture. Mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

We have explored further one reaction of the thiocarbonyl group, especially with thionocarbonates, and report here the preparation of orthocarbonates of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose, and 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose by reaction of thiocarbonyl derivatives of the parent compounds in pyridine with alcohols in the presence of transition-metal salts. Three functional groups containing thiocarbonyl groups were used: $RO\overset{\overset{S}{\|}}{C}OR'$, $(RO\overset{\overset{S}{\|}}{C}S)_2$, and $RO\overset{\overset{S}{\|}}{C}SMe$. All of these groups are fairly stable to acids and quite labile to alkali. In contrast, orthocarbonates are stable to alkali and quite labile to acids.

Heating 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-thionocarbonate (**2**) in pyridine in the presence of ethanol and cupric acetate gave a major component (**3**) having an R_F value higher than that of **2**. The product was isolated and characterized by n.m.r. and mass-spectral data as 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-diethyl orthocarbonate (**3**). A black precipitate deposited from the mixture was assumed to be copper sulfide. When the experiment was repeated but without pyridine, a multicomponent mixture resulted. The n.m.r. spectrum of **3** exhibited a well-defined, 4-protons quartet centred about τ 6.23, and a 6-proton triplet centered



Scheme 1.

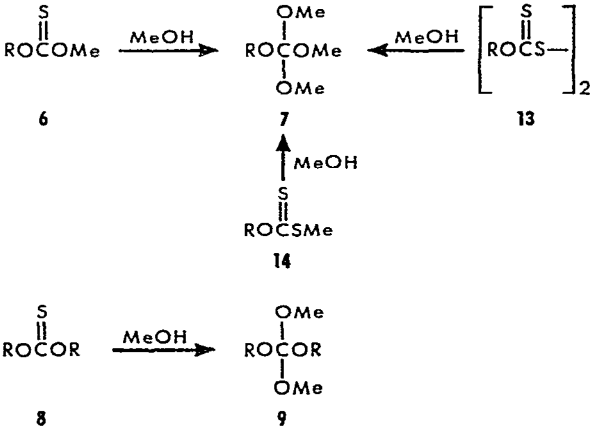
at τ 8.86, assigned to the two ethyl groups. The mass spectrum showed fragments at 347 (M−Me), 317 (M−OEt), and 261 $(M-\overline{OCH_2CH_2OC}Me_2)$. Several of these fragments are characteristic of isopropylidene acetals of sugars[9]. Compound **3** partially decomposed during 5 days to give the known 3,4-cyclic carbonate, which was identified by comparison with an authentic sample (t.l.c. and i.r.).

Preparation of an orthocarbonate has been previously reported by the reaction of a nucleoside thionocarbonate with silver carbonate in ethyl alcohol[10]. However, reaction of **2** under similar conditions gave only the 3,4-cyclic carbonate.

Methyl and isopropyl alcohols readily formed orthocarbonates with **2**, but secondary and tertiary butyl alcohols showed no reaction. We did not observe any distinguishing absorption bands for the orthocarbonate structure in either the i.r. or u.v. spectra. However, treatment of the compounds with mild acid readily converted them into carbonates, which exhibited absorption in the i.r. at 5.6–5.8 μm. This procedure was used to monitor the reactions and detect the presence of orthocarbonates.

As well as cupric acetate, other salts that promoted the formation of orthocarbonates were cupric bromide, cuprous bromide, anhydrous cupric sulfate, and zinc acetate. When zinc acetate was used, the yield of product depended upon the amount of salt. For example, with 0.5 equivalent of zinc acetate the yield was 47%, and with 5 equivalents it was 73%. The presence of water inhibited the reaction.

When the cyclic thionocarbonate **1** was treated in pyridine with ethanol and cupric acetate, a multicomponent mixture was obtained. As the 3,5,6-orthothiocarbonate is formed[6] from **1**, protecting the 3-position should simplify the reaction. Indeed, when the 3-acetate (**4**) of **1** was treated with ethanol and cupric acetate, the diethyl orthocarbonate (**5**) was the major product, as expected.



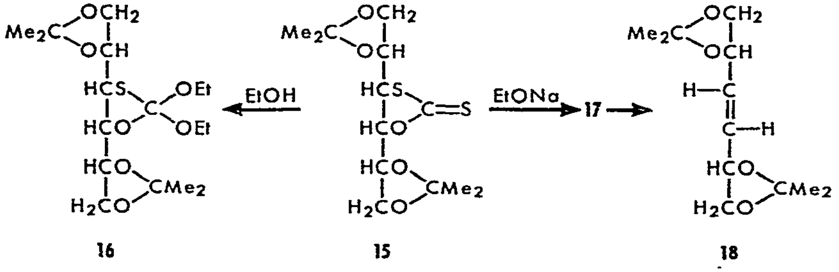
R = 6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-yl

Scheme 2

The acyclic thionocarbonate, 1,2:3,4-di-*O*-isopropylidene-6-*O*-(methoxythiocarbonyl)-α-D-galactopyranose (**6**), readily reacted with methanol to give the corresponding sugar trimethyl orthocarbonate (**7**). Similarly, bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) 6,6′-thionocarbonate (**8**) gave bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) dimethyl orthocarbonate (**9**).

Compound **2** reacted with 1,2-ethanediol, 1,2-propanediol, and 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**10**) to give crystalline orthocarbonates. These orthocarbonates were identified by elemental analyses and n.m.r. spectra. For orthocarbonate **11** prepared from **10** and **2**, mass-spectral data were also obtained. The spectrum showed the expected fragments: M—Me and $M-\overline{OCH_2CH_2OC}Me_2$.

To determine the generality of the conversion of thiocarbonyl groups into orthocarbonates, compounds containing such structures as $(RO\overset{\overset{S}{\|}}{C}S)_2$ and $RO\overset{\overset{S}{\|}}{C}SR'$ were subjected to similar reaction conditions. Thus 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-dithiobis(thioformate) (**12**) gave **3**, and bis(1,2:3,4-di-*O*-isopropylidene α-D-galactopyranose) dithiobis(thioformate) (**13**) yielded the corresponding orthocarbonate **7**. Reaction of the *S*-methyl xanthate (**14**) of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose under similar conditions also gave **7**. The cyclic ester, 1,2:5,6-di-*O*-isopropylidene-3-thio-D-altritol dithiocarbonate (**15**), was converted into the corresponding diethyl orthocarbonate (**16**) by reaction with ethanol. The product decomposed on storage to give a multicomponent mixture.



Scheme 3

When compound **15** in pyridine was heated with cupric acetate in the presence of 1,2-ethanediol, the yield of orthocarbonate was low (i.r. and n.m.r.), and instead a major component (**17**) was isolated and characterized as a 3,4-episulfide. The configuration of this new derivative is not yet fully established. Heating **15** in pyridine alone or in the presence of cupric acetate failed to give any significant amount of **17**, but dissolution of **15** in diethyl ether in the presence of sodium ethoxide produced **17**. Compound **17** was identified by elemental analysis and by mass-spectral and n.m.r. data. The n.m.r. spectrum revealed a doublet at τ 7.1, assigned to the 2 protons of the episulfide ring and confirmed by decoupling experiments. Treatment of **17** in ethanol with Raney nickel gave the known alkene, *trans*-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-hex-3-enitol[2]. This reaction indicates that the episulfide has a *trans* configuration about C-3, C-4, as the elimination of episulfide under these conditions occurs with retention of configuration[11].

EXPERIMENTAL

General. — I.r. spectra were recorded for solutions and films with a Perkin–Elmer Model 137 spectrophotometer. U.v. spectra were determined with a Perkin–Elmer Model 202 spectrophotometer. N.m.r. spectra were recorded with a Varian HA-100 n.m.r. spectrometer, with chloroform-*d* or pyridine-*d* as solvents and tetramethylsilane (τ 10.0) as the internal reference standard. Spin-decoupling experiments were performed with a Model 200AV Hewlett–Packard audio-frequency oscillator. Melting points were determined in sealed capillaries and are uncorrected. Optical rotations were measured with a Rudolph polarimeter. Silica Gel G was the adsorbent for t.l.c. and sulfuric acid (5%) in methanol, the spraying reagent. Desorption chromatography was conducted with silicic acid (Mallinckrodt, 100 mesh) or basic alumina (Fisher, 80–200 mesh) as stationary phase and hexane–ethyl acetate as eluent. The following compounds were prepared as reported earlier: 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-thionocarbonate[1] (**2**), 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-thionocarbonate[1] (**1**), and the 3-*O*-acetyl analogue[6] (**4**) of **1**, 1,2:3,4-di-*O*-isopropylidene-6-*O*-(methoxythiocarbonyl)-α-D-galactopyranose[12] (**6**), bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) 6,6′-thionocarbonate[13] (**8**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol[14] (**10**), 1,2:5,6-di-*O*-isopropylidene-D-mannitol 3,4-dithiobis(thioformate)[15] (**12**), bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose) dithiobis(thioformate)[7] (**13**), the *S*-methyl xanthate of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[16] (**14**), and 1,2:5,6-di-*O*-isopropylidene-3-thio-D-altritol 3,4-thionocarbonate[15] (**15**). The following general procedure was used to prepare orthocarbonates and orthothiocarbonate: 100 mg of sample was dissolved in pyridine (2 ml). Cupric acetate (200 mg) and the monohydroxy alcohol (3 ml) were then added and the mixture was heated on a steam bath. The reaction was monitored by t.l.c. and usually was stopped after 20 min. The mixture was cooled, treated with sodium hydroxide solution (5M, 3 ml), and extracted with hexane or hexane–ethyl ether (1:1, v/v). The extract was washed with water and analyzed. Orthocarbonates prepared from monohydroxy alcohols, which did not crystallize, decomposed on storage. Elemental analyses were unacceptable for almost all of these orthocarbonates, and yields varied according to reaction conditions.

*Reaction of compound **2** with alcohols.* — *A. Ethanol.* The hexane extract showed (t.l.c.) some **10**, in addition to 1,2:5,6-di-*O*-isopropylidene-D-mannitol diethyl orthocarbonate (**3**). The sample was purified by desorption chromatography from silicic acid. Hexane containing 1–25% of ethyl acetate was the eluent. Compound **3** was obtained as a colorless syrup, $[\alpha]_D^{25}$ 0° (*c* 2, acetone); n.m.r.: τ 6.23 (4-proton quartet), 8.86 (6-proton triplet) (two OEt groups); mass spectrum (major fragments): *m*/*e* 347, 317, 273, 261, 144, 143 (base peak), 111, and 101.

Anal. Calc. for $C_{17}H_{30}O_8$: C, 56.3; H, 8.3. Found: C, 55.9; H, 8.2.

B. Methanol. The hexane extract was fairly pure (t.l.c.) and upon evaporation of the hexane the product crystallized, m.p. 64–65°, $[\alpha]_D^{25}$ 0° (*c* 1, chloroform); n.m.r.: τ 6.58 (6-proton singlet, OMe).

Anal. Calc. for $C_{15}H_{26}O_8$: C, 53.9; H, 7.8. Found: C, 53.8; H, 7.9.

C. Isopropyl alcohol. The hexane extract was fairly homogeneous (t.l.c.) but attempts to purify it further were unsuccessful. The n.m.r. spectrum was concordant with the assigned structure.

D. Compound **10**. To a solution of **2** (200 mg) in pyridine (1 ml) were added cupric acetate (300 mg) and **10** (500 mg). The mixture was kept for 15 min on a steam bath. After cooling, the mixture was treated with sodium hydroxide (5M, 2 ml) and extracted with hexane (25 ml). The hexane extract was washed with water (25 ml). On cooling, compound **11** (100 mg) crystallized from the hexane solution. The product was recrystallized from hexane to give pure **11** (75 mg, 22%), m.p. 171–172°, $[\alpha]_D^{25}$ −9° (*c* 1, chloroform); mass spectrum (major fragments): *m/e* 517, 431, 247, 189, 144, 143 (base peak), 131, 129, 111, 102, and 101.

Anal. Calc. for $C_{25}H_{40}O_{12}$: C, 56.4; H, 7.5. Found: C, 56.1; H, 7.6.

E. 1,2-Ethanediol. To a solution of **2** (200 mg) in pyridine (1 ml) were added 1,2-ethanediol (0.5 ml) and cupric acetate (500 mg). The mixture was heated for 10 min on a steam bath, cooled, treated with sodium hydroxide (5M, 2 ml), and extracted with ether. Evaporation of the ether gave a crystalline product (200 mg), which was recrystallized from 4:1 hexane–carbon disulfide to give the pure product, m.p. 140–141°; n.m.r.: τ ~6.02 (4-proton singlet, glycol moiety).

Anal. Calc. for $C_{15}H_{24}O_8$: C, 53.2; H, 7.2. Found: C, 53.2; H, 6.9.

F. 1,2-Propanediol. Compound **2** was treated with 1,2-propanediol under the same conditions as in section *E* to give the orthocarbonate (160 mg), m.p. 79–81°, $[\alpha]_D^{25}$ −0.04° (*c* 1, acetone); n.m.r.: τ 8.82 (3-proton doublet, methyl group of the propanediol moiety).

Anal. Calc. for $C_{16}H_{26}O_8$: C, 55.5; H, 7.5. Found: C, 55.8; H, 7.8.

Effect of salt concentration. — To a solution of **2** (150 mg) in pyridine (1 ml) and methanol (2 ml), various amounts of zinc acetate were added. The mixtures were heated for 15 min on a steam bath, treated with sodium hydroxide (5M, 1 ml), and extracted with hexane. The extracts were washed with water and evaporated to constant weight.

Zinc acetate used (mg): 10, 50, 108, 216, 314.

Yield of product in mg: Trace, 78, 97, 108, 120.

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose 6-(trimethyl orthocarbonate) (**7**). — To a solution of **6** (100 mg) in pyridine (1 ml) were added methanol (1 ml) and cupric acetate (200 mg). The mixture was kept for 10 min on a steam bath, and then cooled and extracted with hexane. T.l.c. of the extract showed one component, **7**. The compound was characterized by n.m.r.: τ 6.68 (9-proton singlet, OMe).

The procedure was repeated with **13** or **14** in place of **6** and gave **7** each time. The products were identified by t.l.c., and by i.r. and n.m.r. spectroscopy.

3-O-Acetyl-1,2-O-isopropylidene-α-D-glucofuranose 5,6-diethyl orthocarbonate (**5**). — Conditions similar to those used when **7** was prepared from **6** were used with 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-thionocarbonate in the presence of ethanol. The n.m.r. spectrum of the product showed a 4-proton quartet at τ 6.36 (methylene groups of the two ethyl substituents).

Bis(1,2:3,4-di-O-isopropylidene-α-D-galactopyranose) dimethyl orthocarbonate (**9**). — To a solution of **8** (200 mg) in pyridine (2 ml) were added cupric acetate (400 mg) and methanol (3 ml). The mixture was kept for 20 min on a steam bath, cooled, treated with sodium hydroxide (5M, 2 ml), and extracted with ether. After evaporation of the ether, the colorless syrup was extracted with hexane. T.l.c. showed one major component. The hexane solution was extracted again with sodium hydroxide solution (5%). Evaporation of the hexane yielded a colorless syrup. T.l.c. showed a single component. The n.m.r. spectrum of the syrup showed a singlet at τ 6.70 (6 protons, attributed to OMe groups).

Reactions of 1,2:5,6-di-O-isopropylidene-3-thio-D-altritol 3,4-thionocarbonate (**15**). — *A. 1,2-Ethanediol.* To a solution of **15** (200 mg) in pyridine (1 ml) were added 1,2-ethanediol (0.5 ml) and cupric acetate (500 mg). The mixture was kept for 10 min on a steam bath, cooled, and extracted with hexane. Evaporation of the hexane gave a yellow syrup (**17**, 100 mg), which was purified by desorption from silicic acid; $[\alpha]_D^{25}$ −87° (*c* 1, chloroform); n.m.r.: τ 7.1 (doublet), 2 protons of the episulfide ring; mass spectrum (major fragments): *m/e* 260 (M), 245 (M−15), 187, 145, 127, 115, 111, 102, 101 (base peak), and 99.

Anal. Calc. for $C_{12}H_{20}O_4S$: C, 55.4; H, 7.7; S, 12.3. Found: C, 55.3; H, 7.7; S, 12.5.

B. Sodium ethoxide. A mixture of **15** (250 mg), ethanol (3 ml), and sodium hydroxide (12.5M, 3 ml) was warmed for several min on a steam bath until two clear phases formed. The mixture was diluted with ice–water (20 ml) and neutralized with sulfuric acid (M, 20 ml). Several extractions with hexane and evaporation of the hexane extract left impure **17**. Purification was achieved by repeated chromatography from basic alumina, with hexane–ethyl acetate as the eluent. Evaporation of the solvents gave crystalline **17** (90 mg, 44%), m.p. 42–44°.

C. Ethanol. The conditions used were similar to those used for the preparation of **3**. The n.m.r. spectrum revealed a quartet centered about τ 6.13. Apparently some impurity was present, as the quartet was only of 3-proton intensity instead of the expected 6 protons.

trans-*3,4-dideoxy-1,2:5,6-di-O-isopropylidene-*D-threo-*hex-3-enitol* (**18**). — To a solution of **17** (88 mg) in ethanol (10 ml) was added excess Raney nickel. The mixture was refluxed for 1 h, cooled, and filtered. After evaporation of ethanol, the residue was extracted with hexane. The title compound **18** crystallized upon evaporation of the hexane to yield 88 mg (85%), which was identified by comparison with an authentic sample (t.l.c., i.r., and m.p.).

ACKNOWLEDGMENTS

We thank Larry W. Tjarks for n.m.r. spectral measurements, and Mrs. Bonita R. Heaton and Mrs. Clara E. McGrew for the microanalyses.

REFERENCES

1 B. S. Shasha, W. M. Doane, C. R. Russell, and C. E. Rist, *Carbohyd. Res.*, 3 (1966) 121.
2 A. H. Haines, *Carbohyd. Res.*, 1 (1965) 214; R. S. Tipson and A. Cohen, *ibid.*, 1 (1965) 338.
3 W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, 30 (1965) 162.
4 F. N. Jones and S. Andreades, *J. Org. Chem.*, 34 (1969) 3011.
5 D. Trimnell, W. M. Doane, C. R. Russell, and C. E. Rist, *Carbohyd. Res.*, 17 (1971) 319.
6 B. S. Shasha, W. M. Doane, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, 30 (1965) 2324.
7 W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, 30 (1965) 3071.
8 W. M. Doane, B. S. Shasha, C. R. Russell, and C. E. Rist, *J. Org. Chem.*, 32 (1967) 1080.
9 D. C. DeJongh and K. Biemann, *J. Amer. Chem. Soc.*, 86 (1964) 67.
10 W. V. Ruyle, T. Y. Shen, and A. A. Patchett, *J. Org. Chem.*, 30 (1965) 4353.
11 J. F. McGhie, W. A. Ross, F. J. Julietti, B. E. Grimwood, G. Usher, and N. M. Waldron, *Chem. Ind.* (London), (1962) 1980.
12 B. S. Shasha, W. M. Doane, C. R. Russell, and C. E. Rist, *Carbohyd. Res.*, 18 (1971) 251.
13 B. S. Shasha, W. M. Doane, and C. R. Russell, *Carbohyd. Res.*, 24 (1972) 202.
14 L. F. Wiggins, *J. Chem. Soc.*, (1946) 13.
15 B. S. Shasha, D. Trimnell, W. M. Doane, and C. R. Russell, *Carbohyd. Res.*, 32 (1974) 349.
16 K. Freudenberg and A. Wolf, *Ber.*, 60 (1927) 232.