

The Enhancement of Formose Formation with 2-Hydroxyacetophenone. A Mechanism Involving Aldol and Retro-aldol Reactions

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The rapid aldol addition of formaldehyde to 2-hydroxyacetophenone (HAP), an efficient accelerator for formose formation, took place to yield addition products of HAP with one and two molecules of formaldehyde at 35 °C in an aqueous 40% methanol mixture of formaldehyde, HAP, and $\text{Ca}(\text{OH})_2$. No further addition product with more than two molecules of formaldehyde attached to HAP was detected throughout the reaction. On the contrary, benzaldehyde and benzoic acid were formed, accompanied by formose sugars. The initial molar amount of HAP corresponded to the sum of the compounds substituted with the phenyl group including benzaldehyde and benzoic acid. The retro-aldol reaction of the HAP derivatives is likely to be involved in the overall reaction to yield glycolaldehyde or trioses, which are good accelerators for formose formation.

Formose formation in an aqueous mixture of formaldehyde ($\text{C}_{1\text{A}}$) and $\text{Ca}(\text{OH})_2$ at 50–60 °C reveals an autocatalytic feature: an S-shaped profile of the $\text{C}_{1\text{A}}$ conversion *vs.* the reaction time. This characteristic feature arises from the slow dimerization of $\text{C}_{1\text{A}}$ to form glycolaldehyde ($\text{C}_{2\text{A}}$) and a successive rapid aldol addition of $\text{C}_{1\text{A}}$ to $\text{C}_{2\text{A}}$.

It is well known¹⁾ that the introduction of compounds which have the structure of $\text{R}-\text{CO}-\text{CH}_2\text{OH}$ or $\text{R}-\text{CH}(\text{OH})-\text{CHO}$ to the above reaction mixture enhances the formose formation by shortening the induction period and accelerating the successive consumption of $\text{C}_{1\text{A}}$. The initial step has been reported to be the addition of $\text{C}_{1\text{A}}$ to the accelerator.²⁾ The order of efficiencies of accelerators has been evaluated by Langenbeck as follows: 2-hydroxyacetophenone (HAP) > 2-hydroxy-2'-acetonaphthone > 1-hydroxy-2-propanone > 1,3-dihydroxyacetone ($\text{C}_{3\text{K}}$) > $\text{C}_{2\text{A}}$ > 5-hydroxyacetylacenaphthene > D-fructose > D-glucose.³⁾ HAP is a unique accelerator because of its high efficiency and its structure containing a phenyl group. HAP seems to be a good candidate for analyzing the action of the accelerators because it is easy, with the accelerator, to distinguish the addition products of $\text{C}_{1\text{A}}$ from the usual formose sugars by tracing the phenyl group among the products.

In this paper we describe the identification of addition products of $\text{C}_{1\text{A}}$ with HAP and the change in the amounts of the products originated from HAP with the reaction time. No product with more than two molecules of $\text{C}_{1\text{A}}$ attached to HAP was detected. On the contrary, degraded products, such as benzaldehyde and benzoic acid, were formed, accompanied by low-molecular-weight formose sugars. These observations suggest that the C–C bond dissociation of HAP derivatives through retro-aldol reaction is essential for the acceleration.

Experimental

Materials. The reagents, formaldehyde ($\text{C}_{1\text{A}}$), 1,3-dihydroxyacetone ($\text{C}_{3\text{K}}$), HAP, and $\text{Ca}(\text{OH})_2$, were the same as those described previously.⁴⁾ Guaranteed-grade NaOH, CaCl_2 , NaBH_4 , $\text{Si}(\text{CH}_3)_3\text{Cl}$, D-fructose, and hexamethyl-disilazane were used as received from Wako. The pyridine (Wako) was dried with molecular sieve 4A.

The 2,3-dihydroxypropiophenone (DHPP) was prepared according to the method of Cahnmann;⁵⁾ mp 78 °C (lit, 81.5 °C; softening point 78 °C).⁵⁾

Formose-formation Procedure. The reaction was conducted following the "normal procedure" described previously.⁴⁾ An aliquot of the reaction mixture was periodically withdrawn from the flask and was neutralized with a dilute hydrochloric acid to quench the reaction.

Product Analyses. The $\text{C}_{1\text{A}}$ and formic acid were determined by the use of a high-performance liquid (HPL) chromatograph, as has been described previously.⁴⁾ The benzoic acid and benzaldehyde were analyzed with an Ohkura 701 gas liquid chromatograph (GLC) equipped with a FID detector and a Silicone Grease (SE-30) column at 130 °C. Biphenyl was used as the internal standard. The other products were determined as trimethylsilyl derivatives after the reduction of the reaction mixture with NaBH_4 ⁶⁾ using the same GLC by increasing the temperature from 100 to 250 °C at the rate of 2 °C min^{−1}. Phenethyl alcohol was added as an internal standard prior to the trimethylsilylation. Several peaks detected in the GL chromatogram were identified by means of GLC-mass spectrometry employing a Hitachi M-52 mass spectrometer. The area of the GL chromatogram of each equimolar amount of $\text{C}_{3\text{K}}$, DL-glyceraldehyde ($\text{C}_{3\text{A}}$), glucose, HAP, and DHPP after the trimethylsilylation was confirmed to be proportional to the molecular weight; accordingly, the amounts of the product appearing in the GL chromatogram were determined on the basis of this proportionality. The amount of $\text{C}_{2\text{A}}$ might be estimated too low, however, because of a partial loss during the evaporation of the reaction mixture.

The conversion of $\text{C}_{1\text{A}}$ to formose (%) is defined by means of Eq. 1;

$$\begin{aligned} \text{C}_{1\text{A}} \text{ conversion to formose (\%)} \\ = \left(1 - \frac{[\text{C}_{1\text{A}}]_{\text{remained}} - [\text{HCOOH}]}{[\text{C}_{1\text{A}}]_{\text{initial}}} \right) \times 100. \end{aligned} \quad (1)$$

The recovery of $\text{C}_{1\text{A}}$ (%) is defined by Eq. 2:

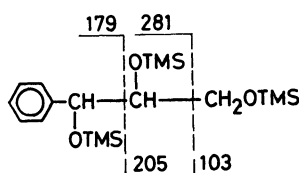
$$\begin{aligned} \text{Recovery of C}_{1\text{A}} (\%) \\ = \{ ([\text{C}_{1\text{A}}]_{\text{remained}} + [\text{HAPC}_1] + 2[\text{HAPC}_2] \\ + \sum_{n=2}^7 n[\text{C}_n] - 6[\text{Fru}]_{\text{initial}} + [\text{HCOOH}]) / [\text{C}_{1\text{A}}]_{\text{initial}} \} \\ \times 100, \end{aligned} \quad (2)$$

where HAPC_1 and HAPC_2 represent the addition products of one and two molecules of $\text{C}_{1\text{A}}$ respectively with HAP, where C_n represents the carbohydrates of *n* carbon atoms, and where Fru represents D-fructose.

Results and Discussion

A typical GL chromatogram of the reaction mixture after reduction and trimethylsilylation is shown in Fig. 1. The four peaks indicated by arrows appeared exclusively in the presence of HAP. The other peaks are those found in the usual $\text{Ca}(\text{OH})_2$ -catalyzed formose formation. The peaks are resolved for trimethylsilylated sugar alcohols according to the differences in carbon numbers and in either a straight (s) or branched (b) carbon skeleton of sugar alcohols. Therefore, the peaks are denoted as C_{4s} and so on, where C_{4s} represents tetroses with a straight carbon chain.

The four peaks originating from HAP were identified by means of GLC-mass spectrometry. Characteristic mass fragments measured for the peaks indicated as HAPC_1 , $\text{HAPC}_2(\text{s})$, and $\text{HAPC}_2(\text{b})$ in the GLC are tabulated in Table 1. The presence of strong fragments of $m/e=103$, 205, and 307 has been reported to indicate $-\text{CH}_2\text{OTMS}$, $-\text{CH}(\text{OTMS})-\text{CH}_2\text{OTMS}$, and $-\text{C}(\text{OTMS})(-\text{CH}_2\text{OTMS})_2$ respectively, where OTMS stands for $\text{OSi}(\text{CH}_3)_3$.⁷⁾ The peak denoted as HAPC_1 was identical to the sample derived from DHPP. The characteristic main fragments of $m/e=281$, 205, 179, and 103 are in accordance with the bond scissions shown below, as well as the fragment of $m/e=295$ ($\text{M}-\text{OTMS}$).



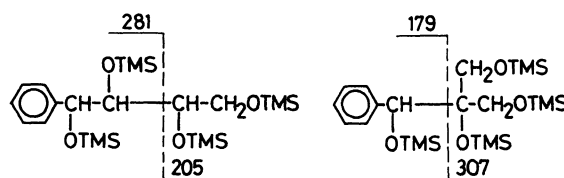
The peaks denoted as $\text{HAPC}_2(\text{s})$ and $\text{HAPC}_2(\text{b})$ showed a mass fragment of $m/e=383$ ($\text{M}-\text{CH}_2\text{OTMS}$). The former has mass fragments of 281 and 205, similar to

TABLE 1. MASS FRAGMENTS OF REDUCED AND TRIMETHYLSILYLATED DHPP, HAPC_1 , $\text{HAPC}_2(\text{s})$, AND $\text{HAPC}_2(\text{b})$

Mass fragment in m/e		
HAPC_1 , DHPP	$\text{HAPC}_2(\text{s})$	$\text{HAPC}_2(\text{b})$
—	383 (w)	383 (w)
—	382 (w)	382 (w)
—	308 (w)	308 (w)
—	—	307 (st)
295 (st)	295 (w)	—
281 (m)	281 (st)	—
—	—	280 (m)
—	—	218 (st)
205 (st)	205 (m)	—
—	—	204 (m)
179 (st)	179 (m)	179 (st)
149 (m)	149 (m)	149 (m)
116 (m)	116 (m)	—
—	—	115 (m)
103 (m)	103 (w)	103 (st)
90 (w)	90 (m)	—
73 (m)	73 (m)	73 (m)

st: Strong, m: medium, w: weak.

those of the HAPC_1 peak. On the contrary, the latter is characterized by the main fragments of 307 and 179, together with a strong fragment of 218 ($307-\text{OTMS}$). These fragmentations are in accordance with the respective bond scissions of the straight and branched structures, as is shown below:



$\text{HAPC}_2(\text{s})$ Peak

$\text{HAPC}_2(\text{b})$ Peak

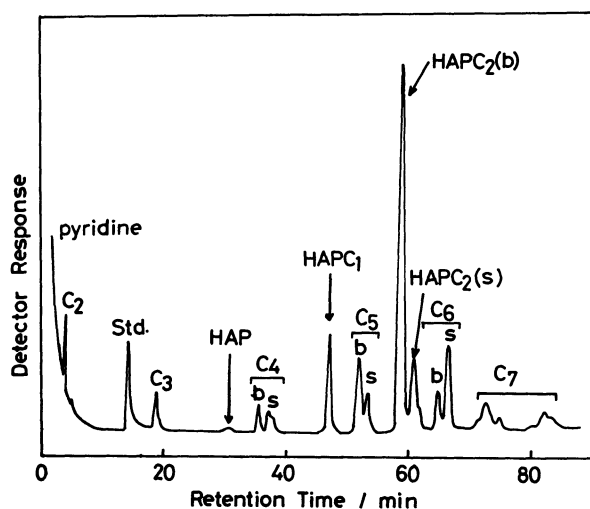


Fig. 1. A typical GL chromatogram of the products at the reaction time of 10 min after reduction with NaBH_4 and trimethylsilylation. 35°C , 40 vol % $\text{CH}_3\text{OH}-\text{H}_2\text{O}$, $\text{Ca}(\text{OH})_2$; 0.10 mmol cm^{-3} , C_{1A} ; 1.0 mmol cm^{-3} , HAP; 0.20 mmol cm^{-3} .

These characteristic fragmentations lead to the identifications of the $\text{HAPC}_2(\text{b})$ peak and $\text{HAPC}_2(\text{s})$ peak with tetrakis-*O*-trimethylsilyl-1-phenylerythritol and tetrakis-*O*-trimethylsilyl-1-phenyl-2-(hydroxymethyl)glycerol respectively. These results show that the addition products of C_{1A} with HAP belong to three classes of compounds which give 1-phenylglycerol, 2-(1-hydroxybenzyl)glycerol, and 1-phenyl-erythritol by reduction with NaBH_4 . HAPC_1 , $\text{HAPC}_2(\text{s})$, and $\text{HAPC}_2(\text{b})$ are, therefore, mixtures of phenyl-substituted sugars with the straight or branched carbon skeleton mentioned above.

The absence of compounds having a branched carbon skeleton for HAPC_1 in the product is worth notice.

The change in the amounts of HAP and its derivatives during the reaction is shown in Fig. 2. The rapid formation of HAPC_1 is the initial step of the reaction, followed by the formation of $\text{HAPC}_2(\text{b})$, presumably through a successive addition of C_{1A} to HAPC_1 . Both HAPC_1 and $\text{HAPC}_2(\text{b})$ reach their maxima within

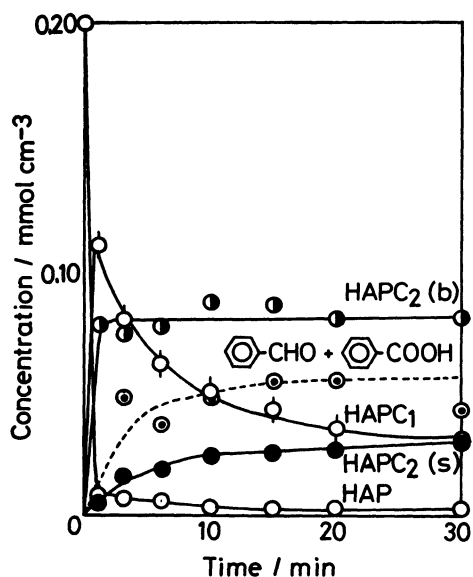


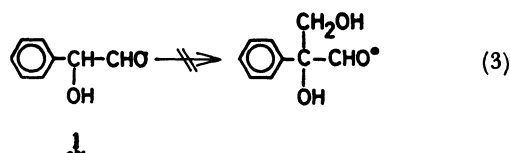
Fig. 2. Consumption of HAP and formations of HAPC₁, HAPC₂ (b), and HAPC₂ (s), and benzaldehyde + benzoic acid. 35 °C, 40 vol % CH₃OH-H₂O, Ca(OH)₂; 0.10 mmol cm⁻³, C_{1A}; 2.45 mmol cm⁻³, HAP; 0.20 mmol cm⁻³.

1 min after the addition of HAP to the mixture of Ca(OH)₂ and C_{1A}. The amount of HAPC₁ gradually decreases thereafter, but that of HAPC₂(b) is kept at *ca.* 0.8 mmol cm⁻³. The formation of HAPC₂(s) appears to be slow, but its amount continues to increase as the reaction proceeds. As HAPC₁ decreases and HAPC₂(s) increases, benzaldehyde, benzoic acid, and low-molecular-weight formose sugars are formed in the reaction mixture. The summation over the molar amounts of HAP, HAPC₁, HAPC₂(s), HAPC₂(b), benzaldehyde, and benzoic acid was in agreement with the molar amount of HAP initially introduced.

The above observations suggest successive C_{1A} additions to HAP to form phenyl-substituted carbohydrates. However, no HAP derivative with more than two molecules of C_{1A} added to HAP was detected throughout the reaction. The occurrence of benzaldehyde and benzoic acid, accompanied by the simultaneous production of low-molecular-weight formose sugars, suggests the important role of the retro-aldol reaction of the phenyl-substituted carbohydrates. Benzaldehyde is expected to change to benzoic acid under the present reaction conditions, as will be discussed later.

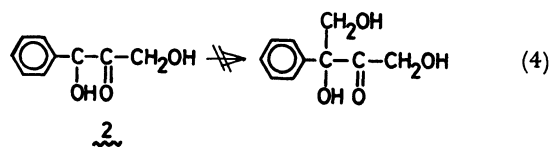
A reaction scheme is drawn in Fig. 3 based on the aldol addition, retro-aldol reaction, and Lobry de Bruyn-Alberda van Ekenstein (LA) transformation, to which HAP and its derivatives are susceptible under basic conditions. In this scheme, HAPC₁ corresponds to either DHPP, **2**, and/or **3**; HAPC₂(s) corresponds to either **5**, **6**, **7**, and/or **8**, and HAPC₂(b) corresponds to either **4** and/or **9**.

HAP can undergo LA transformation, yielding 2-phenylglycolaldehyde (**1**) as has been reported previously,⁴⁾ and can undergo aldol addition, yielding DHPP. The results of GLC-mass spectrometry exclude the aldol addition of C_{1A} to **1** to form products possessing a



branched carbon skeleton, as is shown above. HAPC₁ and DHPP coincided exactly in the results of GLC and mass fragmentation data on reduction and trimethylsilylation. DHPP will isomerize to two isomers, 1-phenyl-1,3-dihydroxyacetone (**2**) and 3-phenylglyceraldehyde (**3**), through LA transformation and will undergo aldol addition with C_{1A} to yield 2-benzoylglycerol (**4**). The last compound can not add further C_{1A} because no hydrogen is available at the α-carbon atom to the carbonyl group. The retro-aldol reaction of DHPP can not be disregarded because a small amount of HAP remained throughout the reaction, as is shown in Fig. 2.

One of the tautomers of DHPP, **2**, which does not undergo retro-aldol reaction, adds C_{1A}, leading to 1-phenyl-2-ketotetrose (**6**). The product, **6**, can isomerize to three isomers; 1-benzoylglycerol (**5**), 4-phenyl-2-ketotetrose (**7**), and 4-phenylaldotetrose (**8**) and can undergo the retro-aldol reaction to yield C_{1A} and **2**. Compounds **5**, **7**, and **8** can degrade to C_{2A} and HAP, C_{3K} and benzaldehyde, C_{2A} and **1**, respectively, through retro-aldol reactions. The aldol addition of C_{1A} at the carbon atom adjacent to a phenyl group can be excluded in line with the fact that Eq. 3 scarcely proceeds.



The last tautomer of DHPP, **3**, decomposes to yield C_{2A} and benzaldehyde through retro-aldol reaction and undergoes aldol addition with C_{1A}, yielding a product, **9**, which can not be distinguished from **4** on reduction and trimethylsilylation. Compound **9** decomposes to C_{3A} and benzaldehyde through the retro-aldol reaction.

The rapid formation of HAPC₁ and HAPC₂(b) suggests that the entities of HAPC₁ and HAPC₂(b) in the early stage of the reaction (less than 1 min) are DHPP and 2-benzoylglycerol (**4**) respectively. The aldol addition of C_{1A} to the carbon atom next to the carbonyl group seems to proceed quickly. The compound, **4**, is a terminal product in respect to the aldol addition, and its amount can be equilibrated by means of a retro-aldol reaction. The slow decrease in [HAPC₁] is accounted for by the loss of the tautomers of DHPP, **2** and **3**, due to the aldol additions and the retro-aldol reaction.

It is uncertain at present which is the main path for the production of benzaldehyde among retro-aldol reactions of **3**, **7**, and **9**. Benzaldehyde will be oxidized to benzoic acid under the present reaction conditions. The ratio of [benzaldehyde] to [benzoic acid] decreased from 1 : 9 in the early stage to 0.5 : 9.5 in the later stage. The absence of benzyl alcohol indicates that

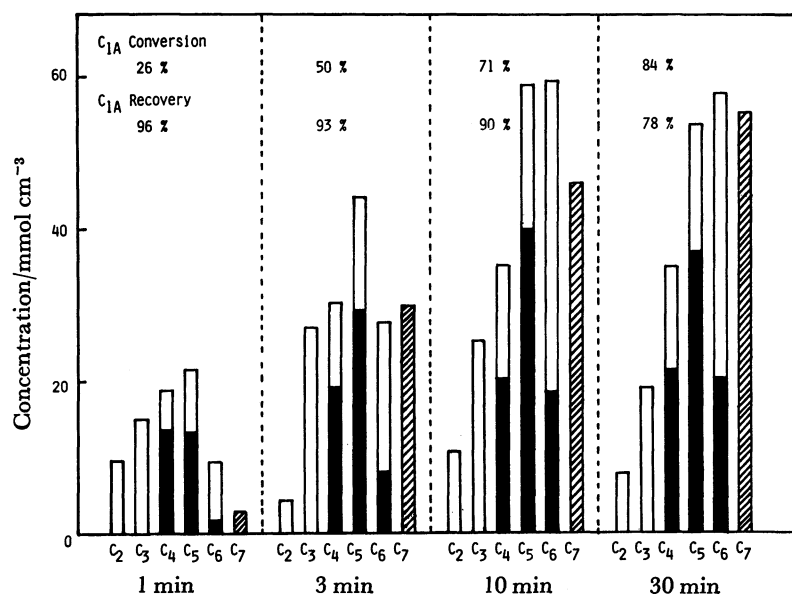


Fig. 5. C-number distributions in amounts of formose sugars and sugar alcohols obtained in the reaction accelerated by HAP. Reaction conditions; same as indicated in Fig. 2. C_n represents formose sugars and sugar alcohols having n carbon atoms. ■ or □ denotes branched chain or straight chain carbon skeleton, respectively.

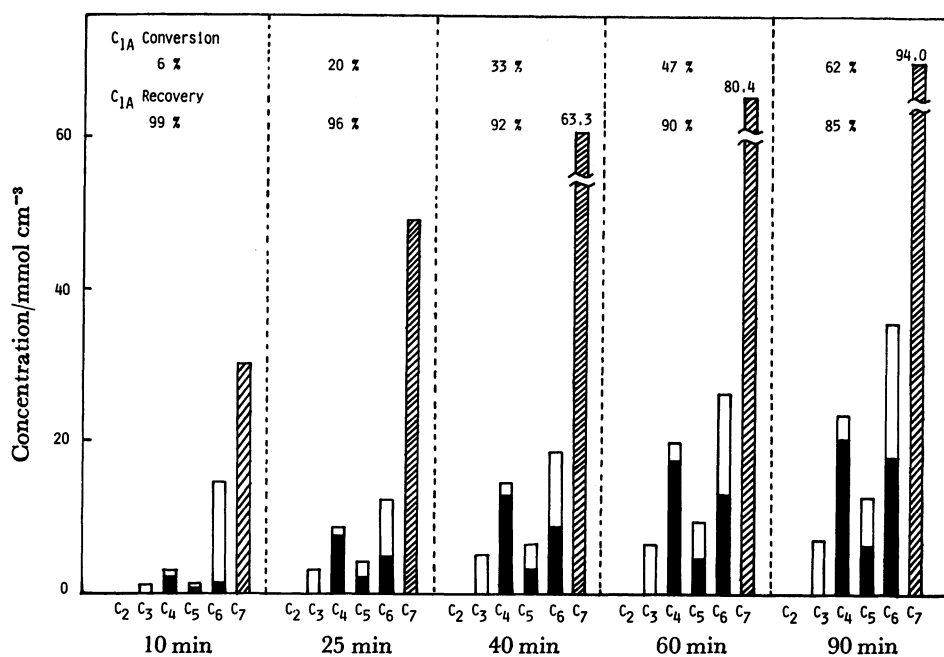


Fig. 6. C-number distributions in amounts of formose sugars and sugar alcohols obtained in the reaction accelerated by D-fructose. 45 °C, water, NaOH; 0.20 mol cm⁻³, CaCl₂; 0.10 mmol cm⁻³, C_{1A}; 2.0 mmol cm⁻³, D-fructose; 0.05 mmol cm⁻³.

analogous distributions for the fructose-accelerated reaction are illustrated in Fig. 6. These are determined from the GL chromatograms; therefore, the amount of C_{2A} is likely to have been evaluated too low as a result of evaporation loss during pretreatment. The amounts of C₂ and C₃ carbohydrates for the HAP-accelerated reaction are larger than those for the fructose-accelerated reaction. Moreover, the predominant carbohydrates for

the fructose-accelerated reaction are aldo- and keto-heptuloses, which were presumably produced by the aldol addition of C_{1A} to D-fructose. The low efficiency of D-fructose is attributable to the low reactivity of D-fructose and/or heptuloses toward retro-aldol reactions.

References

- 1) T. Mizuno and A. H. Weiss, *Adv. Carbohydr. Chem. Biochem.*, **29**, 173 (1974).
 - 2) H. Ruckert, E. Pfeil, and G. Scharf, *Chem. Ber.*, **98**, 2558 (1965).
 - 3) W. Langenbeck, *Angew. Chem.*, **61**, 186 (1949).
 - 4) T. Sakai, M. Ishizaki, K. Kobayashi, and M. Goto, *Bull. Chem. Soc. Jpn.*, **54**, 2083 (1981).
 - 5) H. Cahnmann, *Bull. Soc. Chim. Fr., Ser. 5*, **4**, 226 (1937); *Chem. Abstr.*, **31**, 3893 (1937).
 - 6) C. C. Sweely, R. Bentley, M. Makita, and W. W. Wells, *J. Am. Chem. Soc.*, **85**, 2497 (1963).
 - 7) R. D. Partridge, A. H. Weiss, and D. Todd, *Carbohydr. Res.*, **24**, 29 (1972).
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