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Studies of the Derivatives of Epichlorohydrin. III. A New Method of Preparing γ-Alkoxy-γ-butyrolactones

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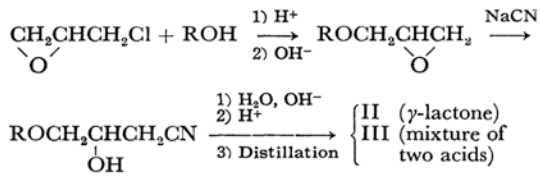
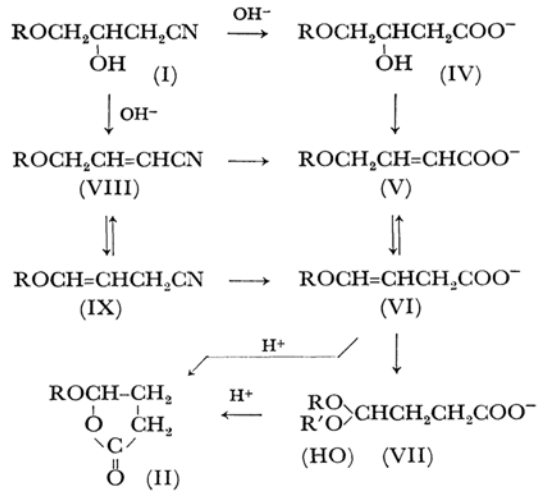
When alkyl glycidyl ethers derived from epichlorohydrin and alcohols were treated with sodium cyanide, the corresponding γ-alkoxy-β-hydroxybutyronitriles (I) were obtained. The hydrolysis of I with aqueous alkali metal hydroxide, followed by acidification and distillation, gave γ-alkoxy-γ-butyrolactones (II). The structure of II was confirmed by chemical and physical means. The reaction paths of I to II were also studied.

In previous papers,[1,2] the synthesis of alkyl glycidyl ammonium salts from epichlorohydrin and amines was described, and their properties as reactive surfactants were discussed. The purpose of this investigation is to develop the study of reactive long-alkyl-chain derivatives of epichlorohydrin. The earlier work[3] on the application of long-alkyl-chain glycidyl ethers prompted the preparation of β-hydroxynitriles, which may be convertible to lactones. Many previous workers have mentioned the lactonization of unsaturated carboxylic acids by the aid of such strong acids as polyphosphoric acid or sulfuric acid.[4] Blout and Elderfield[5] and Newman and Rosher[6] have reported the formation of γ-lactones from β-hydroxycarboxylic acids, the process involving dehydration and subsequent cyclization. Also, Campaigne and Ellis[7] have prepared highly-substituted γ-butyrolactones from unsaturated nitriles. Recently Heiba and Dessau[8] have reported a new radical synthesis of γ-lactones. Although it has been well known that γ-alkoxy-γ-butyrolactones can be prepared from esters of β-formylpropionic acid dialkylacetal, no published investigation has yet described a method of synthesizing γ-lactones directly from β-hydroxynitriles.



The hydrolysis of I yielded predominantly II rather than III. II and III were decided to be, respectively, γ-alkoxy-γ-butyrolactones and a mixture of γ-alkoxy-β-hydroxybutyric acid (IV) and γ-alkoxy-crotonic acid (V), as will be discussed later. From the consideration of these products, it may be predicted that the reaction involves dehydration, the hydrolysis of the cyano group, and a rearrangement of the double bond preceding cyclization. As to the sequence, it was postulated that the course of the reaction may be as is shown in the following scheme:



To confirm this sequence, however, we prepared several presumable intermediates (IV, V, VII, and

1) T. Kuwamura and E. Kameyama, *Kogyo Kagaku Zasshi* (*J. Chem. Soc. Japan, Ind. Chem. Sect.*), **67**, 592 (1964).

2) T. Kuwamura, E. Kameyama and H. Takahashi, *ibid.*, **68**, 2178 (1965).

3) T. Kuwamura, *ibid.*, **63**, 595 (1960).

4) M. F. Ansell and M. H. Palmer, *Quart. Rev.*, **18**, 211 (1964).

5) E. R. Blout and R. C. Elderfield, *J. Org. Chem.*, **8**, 29 (1943).

6) M. S. Newman and R. Rosher, *ibid.*, **9**, 221 (1944).

7) E. Campaigne and R. L. Ellis, *Chem. Commun.*, **1966**, 140.

8) E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.*, **89**, 2238 (1967).

TABLE 1. PROPERTIES AND YIELDS OF ALKYL GLYCIDYL ETHERS

R	Bp °C/mmHg (lit.)[3]	n_D^{21}	[O] %*		Yield %
			Found	Calcd	
C_2H_5	123—128 (126.5—127.5)	1.4108	15.2	15.6	70
n-C_4H_9	72—74/25 (74—75/26)	1.4190	12.2	12.3	80
n-C_8H_{17}	120—125/20 (140.0—141.5/30)	1.4349	8.4	8.5	70

* [O]% of oxirane determined by the acetic acid-HBr method.
(Ref. Report of the F.A.C. subcommittee on oxirane oxygen, 1956, *J. Am. Oil Chemist's Soc.*, **34**, 476 (1957)).

VIII) (indicated above) and established that they did indeed exist in the reaction mixture. Furthermore, evidence was obtained that they all afford II. Then the proceeding of the reaction was followed up by measuring the nitrogen content and the hydroxyl number in the reaction mixture in order to establish the reaction path preferred. Unfortunately, however, we had only rough information because of technical difficulties.

Experimental and Results

Preparation of Alkyl Glycidyl Ethers. According to a method described in a previous report,[3] these ethers were prepared from epichlorohydrin and alcohols. Ethyl, butyl, and octyl derivatives were prepared. Their purity, as checked by gas-liquid chromatography (GLC), was satisfactory. The properties and yields are shown in Table 1.

Preparation of γ-Alkoxy-β-hydroxybutyronitriles. Alkyl glycidyl ether (1 mol) was dissolved in an equivalent volume of ethanol containing a few drops of a thymol blue solution as the indicator. Into the resulting solution, a 30% aqueous solution of sodium cyanide (1 mol) was, drop by drop, added with stirring at 30—40°C over a period of about 90 min. During the reaction, the mixture was kept at pH 7.0—7.5 by the drop-by-drop addition of a 30% aqueous solution of acetic acid. After all the sodium cyanide had been added to the reaction mixture, stirring was continued for an additional 3—6 hr at 40—50°C. When the reaction mixture no longer exhibited a color change, it was cooled. Then the separated organic layer and the ether extract of the water layer were gathered and dried over magnesium sulfate. After the ether had been removed, I was isolated by distillation and then purified using a concentric-type fractionator. Their purities were checked by GLC. Table 2 shows their properties and yields. The IR spectrum of the C-2 homologue of I is indicated in Fig. 1. The characteristic absorption band at 2240 cm^{-1} can be ascribed to the $-C\equiv N$ group.

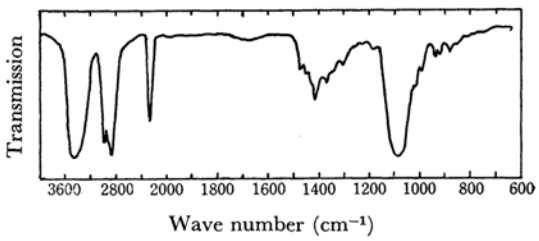


Fig. 1. IR spectrum of γ-ethoxy-β-hydroxybutyronitrile.

Preparation and Identification of II. *a) Hydrolysis of I.* A solution of I (1 mol) in an equivalent volume of ethanol was mixed with a concentrated aqueous solution of sodium hydroxide (1.1 mol). The resulting mixture was heated under reflux for 24—30 hr and then evaporated to dryness. During the first 30 min, ammonia was liberated from the reaction mixture. The residue was then made into a slurry with a small amount of water and acidified to pH 3—4 with a 50% aqueous solution of mineral acid. The separated organic layer and the ether extract from the water layer were combined and dried over magnesium sulfate. After the solvent had then been removed, the residue was distilled under reduced pressure. The substance first distilled out, II, was fractionated and its purity determined by GLC. The one distilled out next, III, was also redistilled, but it did not show a mono peak on the GLC chart. Table 3

TABLE 2. PROPERTIES AND YIELDS OF γ-ALKOXY-β-HYDROXYBUTYRONITRILE

R	Bp °C/mmHg	N%		n_D^{18}	Yield %
		Found	Calcd		
C_2H_5	138.5—139.0/26.5	10.8	10.9	1.4393	87
n-C_4H_9	148.0—148.5/18	8.5	8.9	1.4455	77
n-C_8H_{17}	150—153/5	6.3	6.5	1.4490	58

Table 3. Properties and yields of II

R	Bp (°C/mmHg)	Anal. C% Found / Calcd*	Anal. H% Found / Calcd*	Mol wt Found / Calcd*	n_D^{18}	d_4^{18}	Yield %
C_2H_5	112—113/25	55.0 / 55.4	7.6 / 7.7	115 / 130	1.4336	1.093	50
n-C_4H_9	93—94/2.5	60.7 / 60.7	8.4 / 8.9	156 / 158	1.4380	1.032	65—70
n-C_8H_{17}	102—105/1	66.9 / 67.2	10.5 / 10.4	—	1.4459***	0.969***	35
n-C_4H_9**	90—91/3	—	—	—	1.4387	—	40

* Calculated for γ-alkoxy-γ-butyrolactone.
** The authentic substance prepared by the routine method.
*** They were measured at 20°C.

shows the properties and yields of II.

b) *IR Spectra.* The IR spectra of II exhibit the characteristic absorption band at 1790 cm^{-1}, indicating the presence of the γ-butyrolactone carbonyl group. Its chart is given in Fig. 2.

c) *Identification of II.* γ-Butoxy-γ-butyrolactone, the authentic substance, was prepared by a well-known method[9] and then compared with II. β-Formylpropionitrile (1 mol) was dissolved in butyl alcohol (400 m*l*) containing a small amount of hydrochloric acid. The reaction mixture was heated at 110°C for 3 hr and then allowed to stand at room temperature for several hours. After neutralization with an aqueous solution of potassium carbonate, the corresponding butyl acetal was obtained by distillation; bp 104—106°C/1 mmHg (lit.,[9] 122—123°C/3.4 mmHg). β-Formylpropionitrile butyl acetal was then hydrolyzed in the presence of an alkaline catalyst. The salt thus obtained was purified and acidified. On distilling, carboxylic acid of the acetal type formed γ-butoxy-γ-butyrolactone immediately. The properties and yields are listed in Table 3. The best evidence for the identity of II with this γ-alkoxy-γ-butyrolactone is the fact that the IR spectrum and the GLC retention time of II agreed entirely with the values of the authentic sample. They are shown in Fig. 2.

d) *NMR Spectra.* The NMR spectra of II provided further information for the structual consideration. In Fig. 3, A and B represent the normal spectra of the C-4 and C-2 homologues of II, while C and D show the spin-spin decoupled spectra of B. As may be seen in the spectrum B, four bands are found, at τ 4.45, and 8.8 and in the regions of τ 6.1—6.6, and 7.4—7.9. The relative heights of the integrated spectrum give the number of protons as in the following ratio in the spectrum B from the low to the high field; 1:2:4:3. The band at

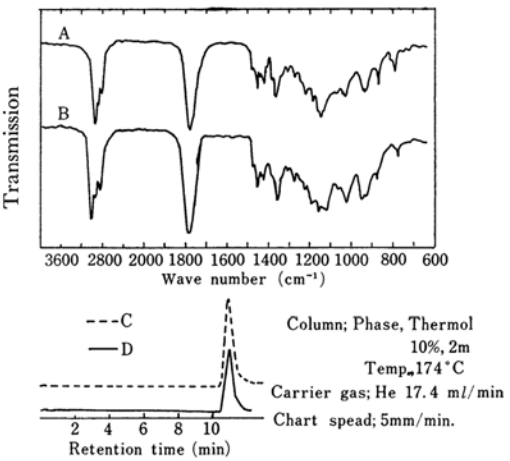


Fig. 2. IR spectra and GLC charts.
A and B; IR spectra of the authentic γ-butoxy-γ-butyrolactone and C_4-II.
C and D; GLC charts of the authentic γ-butoxy-γ-butyrolactone and C_4-II.

τ 4.45, indicating one proton, is attributable to the γ-position proton, which may be the lowest field since it is deshielded by the adjacent oxygen atoms. The two protons appearing in the region of τ 6.1—6.6 may correspond to methylene protons in the substituted ethoxy group, and their chemical shift may be lowered by the adjacent oxygen atom. The band in the region of τ 7.4—7.9 comes from the four protons at the α- and β-methylene groups. They appear as a group of bands, since they are nearly, but not exactly, equivalent protons and split each other complicatedly. The three protons of the methyl group in the side chain resonate at τ 8.8 and are split into a triplet. Spin-spin decoupling was carried out to support these assignments. In the spectrum C, decoupling the multiplet at τ 6.45 causes the triplet at τ 8.8 to collapse to a singlet and somewhat simplifies the multiplet

9) S. Motoki, S. Satsumabayashi and I. Tajima, This Bulletin, **37**, 646 (1964).

in the region of τ 7.4—7.9. On the other hand, decoupling the triplet at τ 8.8, although its spectrum is not shown here, causes a partial collapse in two regions, τ 6.1—6.6 and 7.4—7.9. As the spectrum D indicates, decoupling the multiplet at τ 4.45 partially collapses the multiplet in the region of τ 7.4—7.9, whereas the alternative decoupling in the region of τ 7.4—7.9 serves to simplify the pattern at τ 4.45. As a result, it is apparent that the relative positions of protons in the molecule deduced above are reasonable, and that the complex patterns resulted not only from a simple coupling, but also from a long-range coupling. Therefore, it was not easy to interpret them in a simple way.

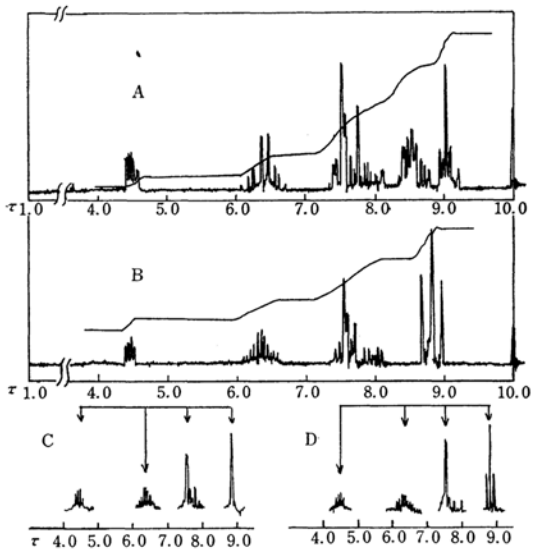


Fig. 3. NMR spectra of γ-alkoxy-γ-butyrolactone.
A: γ-Butoxy-γ-butyrolactone.
B: γ-Ethoxy-γ-butyrolactone.
C and D: Spin-spin decoupling spectra of γ-ethoxy-γ-butyrolactone.

e) *Characteristic Reaction of II.* Fife has kinetically studied the hydrolysis of γ-alkoxy-γ-butyrolactone to β-formylpropionic acid and alcohol.[10] In the present work, the C-4 homologue of II was hydrolyzed without any catalyst. The products were detected by GLC under various conditions. The acid product thus obtained was then conveniently converted to its 2,4-dinitrophenylhydrazone, mp 206—207°C. The authentic γ-alkoxy-γ-butyrolactone was treated similarly and gave a derivative with the same melting point. No depression of the melting point was observed when the two samples were mixed. The IR spectrum is shown in Fig. 4. The absorptions at 1715 cm^{-1}, at 1620 cm^{-1}, at 1530 and 1340 cm^{-1}, and at 1080 and 825 cm^{-1} are associated with –C=O, –C=N–, –NO_2, and 1,2,4-substituted phenyl groups respectively.

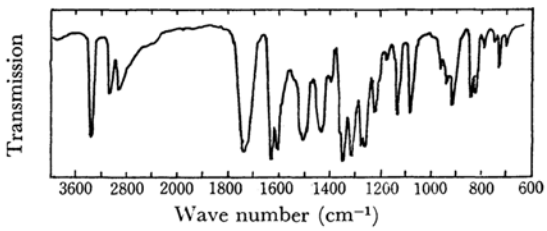


Fig. 4. IR spectrum of 2,4-dinitrophenylhydrazone of β-formylpropionic acid.

Determination of III. The determination of III, obtained as a by-product upon the hydrolysis of I, is helpful in considering the overall reaction. III was regarded as a mixture of IV and V because of its low OH number and its rather high acid value in comparison with IV alone, the separation of the two acids in III was difficult and not completed. Therefore, the mixture was esterified and fractionated effectively. The properties of the esters of IV and V thus isolated agreed with those of the authentic substances listed in Table 4.

Some Aspects of the Reaction Paths. *a*) *Preparation of Intermediates.* As has previously been pointed out, the four intermediates presumed on the reaction paths were synthesized by the following routine methods. I was manipulated with a large excess of ethanol saturated with hydrogen chloride to give the ethyl ester of IV without any significant dehydration.[11] The acetylation of the β-hydroxyl group in I and the subsequent pyrolysis of the acetate over potassium acetate yielded V.[12] According to Wohl's method,[13] the ethyl esters of VII were obtained from β-formylpropionitrile in three steps. Their properties and yields are summarized in Table 4. Their IR spectra are given in Fig. 5. All these products indicated a mono peak on the GLC chart except for the thermally unstable VII.

b) *Determination of Components in the Reaction Mixture.* The C-2 homologue of I was hydrolyzed in the same way as has been described above. The reaction mixture was neutrallized by the use of carbon dioxide and then evaporated to dryness. The residue was then recrystallized from ethanol. The sodium salt thus obtained was treated with an equivalent portion of ethyl iodide in a large amount of ethanol under reflux for 15 hr; this gave the corresponding ethyl ester. However, the esterified product distilled out at 90—120°C/20 mmHg and could not be fractionated. The GLC of this distillant indicates the presence of II and ethyl esters

10) T. H. Fife, *J. Am. Chem. Soc.*, **87**, 271 (1960).

11) C. F. Koelsh, *ibid.*, **65**, 2460 (1943).

12) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, **1949**, 3098.

13) A. Wohl and H. Schweizer, *Ber.*, **39**, 890 (1906).

Table 4. Properties and yields of intermediates

	Bp °C/mmHg	n_D^{20}	S.V. Found	S.V. Calcd	Anal. Found	Anal. Calcd	Yield %
					OH %		
C_2-IV*	119—120/17***	1.4315	314	318	9.8	9.7	70
C_4-IV*	95—102/1.5	1.4355	271	275	8.5	8.4	85
C_2-V*	87.0—88.5/17***	1.4343	355	354	—	—	44
C_4-V*	119—120/15	1.4375	301	301	—	—	70
C_2-VII*	103—104/15***	1.4182***	276	274	—	—	54
C_4-VII*	124—127/12	1.4328	209	216	—	—	47
					N%		
C_4-VIII	102—105/13	1.4417	—	—	9.4	10.1	80
C_4-IV**	107/3	1.4357	275	275	—	—	—
C_4-V**	111.5—112.0/12	1.4373	295	301	—	—	—

* Obtained as ethyl esters.
** Ethyl esters derived from III.
*** C_2-IV,* bp 120—121°C/13mmHg: C_2-V,* bp 95—96°C/19mmHg (R. Lespieau, *Comp. rend.*, **140**, 436, 726 (1904)); C_2-VII,* bp 111—116°C/16mmHg, n_D^{20} 1.4180 (A. M. Acheson, *J. Chem. Soc.*, **1956**, 4232).

of IV, V, and VII, for their retention times correspond to those of authentic substances. A similar attempt to establish their presence was made. Thus, the C-4 homologue of I was hydrolyzed in butyl alcohol containing a suitable amount of ethanol to avoid the separation of water and was subsequently esterified to give the corresponding ethyl esters of the intermediates. The results gave evidence of the presence of C-4 homologues of IV, V, VII, and II in the reaction mixture. As is shown in Fig. 5, the IR spectrum of the ester obtained from the reaction mixture can be interpreted. Namely, it was found in the spectrum D that the four characteristic absorption bands near 3580 cm^{-1}, 1790 cm^{-1}, 1680 cm^{-1}, and 1060 cm^{-1}, referrable to the OH, γ-lactone C=O, C=C, and C–O–C–O–C groups respectively, indicate the presence of IV, II, V, and VII in the reaction mixture just before the acidification.

Table 5. Results of the preparation of γ-alkoxy-γ-butyrolactone from intermediates

	Catalyst (mol ratio)	Temp. °C	Time hr	Yield* %	Recovery** %
IV***	1.1	110—120	18	8	70
V***	1.1	110—120	15	22	65
V***	1.2	110	10	62	28
VIII	1.2	110	10	80	—
VIII	1.1	110—120	20	70	—

* Obtained as γ-alkoxy-γ-butyrolactone.
** Obtained as free carboxylic acid.
*** Ethyl ester was used as the starting material.

c) Preparation of γ-Lactone from Intermediates. The experimental procedure was analogous to that used in preparing II from I. The results are summarized in Table 5.

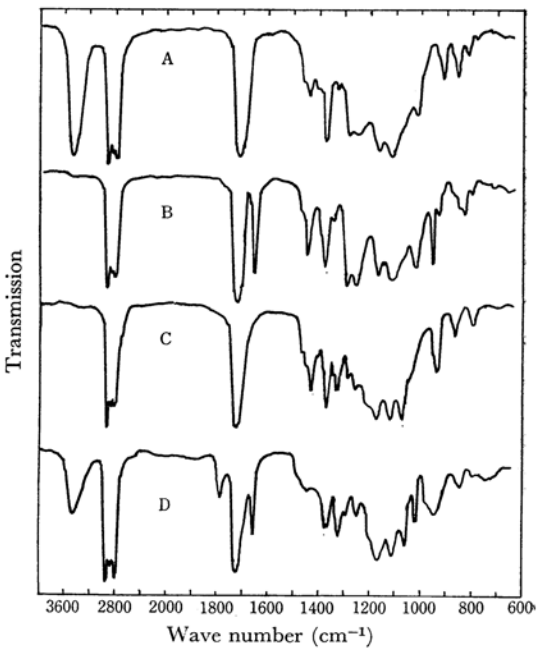


Fig. 5. IR spectra of ethyl esters of intermediates and reaction mixture.
A: γ-Ethoxy-β-hydroxybutyric acid.
B: γ-Ethoxycrotonic acid.
C: γ,γ-Diethoxybutyric acid.
D: Reaction mixture.

The products II obtained were checked by GLC, and their properties were determined. From these results, it seems likely that the predominance of VIII rather than V in the yield of γ-lactone may be attributable to its advantage in the rearrangement of the double bond, since the contribution of the resonance of the conjugate base $(-\ddot{C}H-CH=CH-CN \longleftrightarrow -CH=CH-\ddot{C}H-CN)^-$ must be larger than

that of V.

d) *Tracing of the Process of the Reaction.* The process of the reaction was followed by measuring the OH number and the N%. The sample submitted to analysis was pretreated to exclude difficulties. The neutralization of the alkaline catalyst and of the liberated ammonia with diluted hydrochloric acid, and the removal of the resulting salt and solvent, were carried out carefully. In spite of these cautions, however, there remained some doubt about the values obtained, because the loss of the species to be analyzed, which were assumed to be present, could not be avoided during the procedure. Aside from the point of whether or not the data indicates the absolute values, however, information about the estimated situation was obtained. That is, the decrease in the N% in the sample is relatively faster than that of the OH number. About 5 hr after reflux, 80—90% of the N content with respect to the theoretical amount was consumed. However, the consumption of OH was not so great. Moreover, the rate of the decrease in N% in the hydrolysis of γ-alkoxycrotonitrile is comparable to that of I. Therefore, the comparison between the consumption of OH and that of the N content gives information about the relative rates of the I to VIII and I to IV paths respectively.

Summary

The principal purpose of this investigation, the development of a new route for the synthesis of γ-alkoxy-γ-butyrolactone from epichlorohydrin, has been achieved. The identity of the products obtained with authentic substances prepared by well-known methods, and some proofs for the structure have been indicated by GLC, IR, NMR, and other appropriate procedures. In the experiments concerning the reaction paths, it was confirmed that some of the presumed intermediates indeed exist in the reaction mixture and that these intermediates, treated in the same condition to that of the hydrolysis of I, give γ-alkoxy-γ-butyrolactone. These results suggest that all the postulated paths in a scheme presented early in this paper are possible. To decide the most favorable path, however, was difficult on the basis of the results obtained in the present work. It may still be guessed that the attack on the cyano group is preferrable to the competing elimination of the hydroxyl group. As the sequence, the I→IV→V→VI→(*via* VII)→II path may eventually come to be significant, even though the rearrangement of VIII to IX is more likely than that of V to VI, as has been mentioned. The outline of the synthesis has already been published as a letter to the editor.[14]

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14) T. Kuwamura, H. Takahashi and S. Tomidokoro, *Kogyo Kagaku Zasshi* (*J. Chem. Soc. Japan, Ind. Chem. Sect.*), **70**, 1051 (1967).