[Chem. Pharm. Bull. 22(1) 201—206 (1974)]

UDC 547.541.04 : 547.421.04

Reaction of N-Haloamide. XIX.[1] Reaction of Acetals with N,N-Dibromobenzenesulfonamide

Yoshiko Kamiya and Shoji Takemura

Faculty of Pharmaceutical Sciences, Kinki University[2]

(Received July 9, 1973)

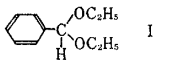
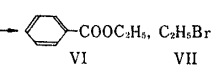
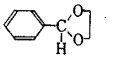
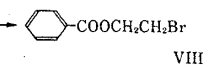
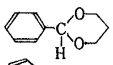
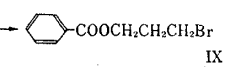
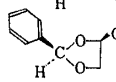
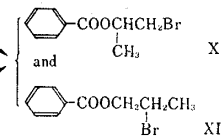
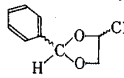
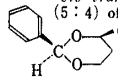
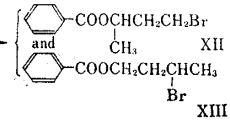
Some oxidative cleavages of acetals with N,N-dibromobenzenesulfonamide (DBBS) have been presented. As a result of oxidative fission of C-O bond and simultaneous bromination, these reaction gave ester and alkyl bromide, or brominated esters (shown in Table I). The reaction mechanism has been discussed on the basis of the experiments and the previous investigation on the reaction of ethers with DBBS.

In the preceding papers from our laboratory it has been reported that N,N-dibromobenzenesulfonamide (DBBS) reacted with ethers under mild conditions; aliphatic ethers[3] gave the corresponding aldehydes and alkyl bromides, and tetrahydrofuran[4] gave *trans*-2-(4'-bromobutoxy)-3-bromotetrahydrofuran in nonaqueous solvent, while in aqueous solvent,[1] aliphatic ether gave the corresponding ester, and cyclic ethers gave the corresponding lactones.

Several works[5] on the reactions of acetals with N-bromosuccinimide (NBS) have been reported. We wish to present here the oxidative cleavage of acetals with DBBS and to discuss the reaction mechanism on the basis of previous investigation[6] and the facts presented in this paper.

Benzaldehyde diethylacetal (I), 2-phenyl-1,3-dioxolane (II), 2-phenyl-1,3-dioxane (III), *cis*-isomer and *cis–trans*-mixture of 2-phenyl-4-methyl-1,3-dioxolane (IV), and *cis*-2-phenyl-4-methyl-1,2-dioxane (V) were made to react, respectively, with DBBS in nonaqueous solvent. These acetals were allowed to react with one half mole of DBBS in dry carbon tetrachloride. In all cases, once the mixture turned red according to the liberation of bromine from DBBS, and the reaction ceased with subsequent rapid consumption of bromine. As a result of oxidative fission of C-O bond and simultaneous bromination, the products were ester and alkyl bromide, or brominated esters as shown in Table I.

Table I. Products of the Reactions of Acetals with DBBS

Acetal	Product	Yield (%)
 I	 VI VII	81.5[a]
 II	 VIII	82.5
 III	 IX	74.9
 *cis*-IV	 and X XI	59[b] 67[b]
 *cis–trans*-mixture (5 : 4) of IV		
 *cis*-V	 and XII XIII	74[b]

[a] yield of VI
[b] yield of the mixture of X and XI or XII and XIII

1) Part XVIII: Y. Kamiya and S. Takemura, *Chem. Pharm. Bull.* (Tokyo), **21**, 1401 (1973).
2) Location: *321, Kowakae, Higashiosaka-shi, Osaka.*
3) S. Takemura, Y. Ando, H. Terauchi, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **15**, 1331 (1967).
4) Y. Kamiya (née Ando), S. Takemura, and Y. Ueno, *Chem. Pharm. Bull.* (Tokyo), **17**, 520 (1969).
5) *a*) J.B. Wright, *J. Am. Chem. Soc.*, **77**, 4883 (1955); *b*) E. N. Marvell and M.J. Joncich, *ibid.*, **73**, 973 (1951); *c*) J.D. Prugh and W.C. McCarthy, *Tetrahedron Letters*, **1966**, 1351.
6) Y. Kamiya and S. Takemura, *Chem. Pharm. Bull.* (Tokyo), **20**, 2471 (1972).

TABLE II. The NMR Data taken at 60 MHz

	Proton	NMR Chemical shift (ppm), J (cps)	Ratio of integral value
Acetals			
cis-IV	C-4-CH_3	1.32 d. $J=6$	3
	C-4-H	3.33—3.57 m.	1
	C-5-H_2	3.87—4.50 m.	2
	C-2-H	5.70 s.	1
cis-trans-mixture of IV used for the reaction with DBBS	*cis* C-4-CH_3	1.32 d. $J=6$	15
	trans C-4-CH_3	1.28 d. $J=6$	12
	cis C-2-H	5.70 s.	5
	trans C-2-H	5.88 s.	4
cis-V	C-4-CH_3	1.2 d. $J=6$	3
	C-5-H_2	1.3 —1.9 m.	2
	C-4-H, C-6-H_2	3.47—4.26 m.	3
	C-2-H	5.28 s.	1
Reaction products mixture of X and XI obtained by the reaction of cis-IV or *cis–trans*-mixture of IV with DBBS (non distil.)	X C-1-CH_3	1.45 d. $J=6$	9
	XI C-1-CH_3	1.75 d. $J=6$	1
	X C-2-H_2	3.54 d. $J=5$	6
	XI C-2-H, XI C-1-H_2	4.1 —4.55 m.	1
	X C-1-H	5.04—5.55 m.	3
mixture of XII and XIII obtained by the reaction of *cis*-V with DBBS (non distil.)	XII C-1-CH_3	1.38 d. $J=6$	42
	XIII C-3-CH_3	1.75 d. $J=6$	12
	XII C-2-H_2, XIII C-2-H_2	2.0 —2.45 m.	36
	XII C-3-H_2	3.43 q. $J_1=6$, $J_2=8$	28
	XIII C-1-H_2, C-3-H_2	4.1 —4.55 m.	16
	XII C-1-H	5.0 —5.55 m.	14
1-methyl-2-benzenesulfonamino-ethyl benzoate (XIV)	C-1-CH_3	1.35 d. $J=6$	3
	C-2-H_2	3.25 t.	2
	C-1-H, N-H	4.9 —5.4 m.	2
		signal of N-H was quenched and C-2-H_2 appeared as doublet by deuterium exchange	
	aromatic	7.35—8.1	10
mixture of 1-methyl-2-hydroxyethyl benzoate (XV) and 2-hydroxypropyl benzoate (XVI) (non distil.)	XV C-1-CH_3	1.35 d. $J=6$	45
	XVI C-2-CH_3	1.27 d. $J=6$	
	XV and XI O-H	2.87 s. quenched by deuterium exchange	15
	XV C-2-H_2	3.74 d. $J=5$	20
	XVI C-1-H, C-2-H	4.1 —4.32 m.	15
	XV C-1-H	4.95—5.45 m.	10

Thus, the reaction of I with DBBS gave ethyl benzoate (VI) and ethyl bromide (VII) as the main products, which were identified with an authentic samples respectively.

The reactions of cyclic acetals of benzaldehyde, II and III, with DBBS were also examined respectively in the same ways. The reaction of II with DBBS gave 2-bromoethyl benzoate (VIII) of which structure was established by identification with authentic sample by spectroscopic comparison as described in experimental part. III was also allowed to react with DBBS and the product was shown to be 3-bromopropyl benzoate (IX).

It seemed to be interest to examine the effect of the introduction of methyl group to an adjacent carbon of oxygen in stereoisomeric cyclic acetals and to see the direction of ring fission and to compare the ratio of the products which may provide some information on the reaction mechanism. The reactions of 2-phenyl-4-methyl-1,3-dioxolane (IV) and 2-phenyl-4-methyl-1,3-dioxane (V) with DBBS were examined. In the reaction of *cis–trans*-mixture of IV[7] with DBBS, the products were 1-methyl-2-bromoethyl benzoate (X) and 2-bromopropyl benzoate (XI), which resulted from fission of C_5-O or C_4-O bond respectively. The molar ratio of the products (X: XI) was estimated as 9: 1 judging from the integral values of the signals in the nuclear magnetic resonance (NMR) spectrum of the mixture (Table II). (The sample for measurement was not distilled to avoid any artificial effect of fractionation.) Elemental analysis of the distillate from the product gave reasonable composition, $C_{10}H_{11}O_2Br$, as a mixture of X and XI. The reaction of *cis*-IV[8] with DBBS gave essentially no change in the ratio of products, X and XI, comparing with that of *cis–trans*-mixture. This suggests that the mechanism involves an intermediate having plane structure as discussed below. In the reaction of *cis*-V[9] with DBBS, the product was a mixture of 1-methyl-3-bromopropyl benzoate (XII) and 3-bromobutyl benzoate (XIII) which were afforded by fission of C_6-O or C_4-O bond, and its ratio was found to be 7 to 2. The elemental analysis of a distilled sample supported that the product was a mixture of the isomer of composition, $C_{11}H_{13}O_2Br$. Such ratio of ester products from reaction of IV and V with DBBS may be determined by steric hindrance in the stage of attack of the bromide ion to an intermediate as discussed below.

A minor product, 1-methyl-2-benzenesulfonaminoethyl benzoate (XIV), $C_{16}H_{17}O_4NS$, mp 75—77°, was also isolated as colorless crystals from the reaction mixture of IV with DBBS.

In order to obtain additional supports of the reaction mechanism, the reaction of IV with DBBS was quenched by addition of sodium hydroxide when the reaction mixture turned

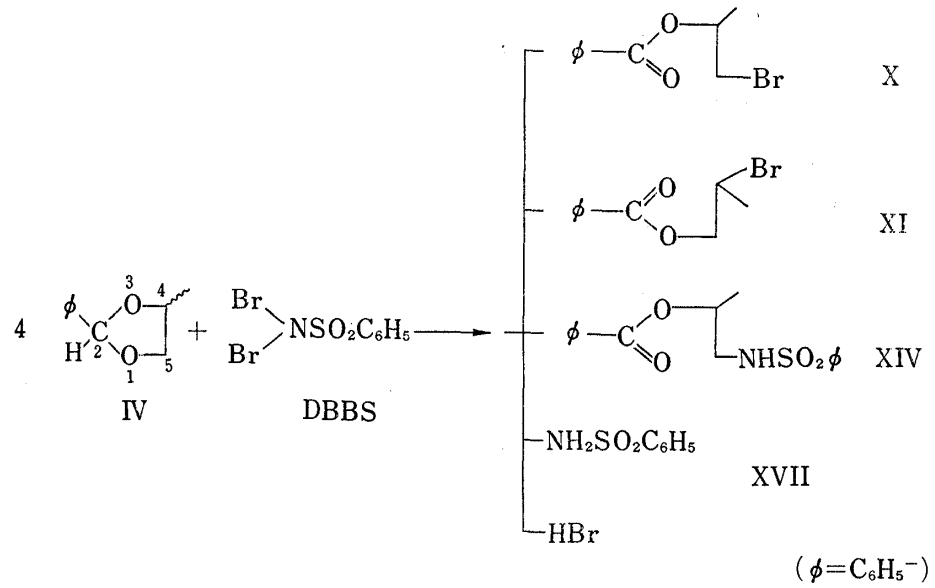


Chart 1

7) *cis–trans*-mixture of IV: IV prepared in the usual way was shown to be a mixture of 5: 4 molar ratio of *cis* and *trans* isomer, which was calculated on the integral values of NMR signals (Table II).
8) N. Bagget, J.M. Duxhury, A.B. Foster, and J.M. Webber; *J. Chem. Soc.* (*C*), **1966**, 208.
9) No evidence that this material is a mixture of giometrical isomers was found by showing simplicity in thin-layer and gas chromatographies and NMR (Table II). From the synthetic route, acid catalyzed condensation of benzaldehyde with glycol, it is assumed to be a *cis*-isomer in which both phenyl and methyl groups are equatorial.

red with liberation of bromine. An oil, bp 131° (3 mmHg), $C_{10}H_{12}O_3$, (IR: ν_{OH} 3400 cm^{-1}, ν_{COOR} 1710 cm^{-1}), was obtained as the main product in this case. This oil was a mixture of 1-methyl-2-hydroxyethyl benzoate (XV) and 2-hydroxypropyl benzoate (XVI) by showing distinguishable signals in NMR spectrum (Table II).

From above results, a stoichiometry of the reaction of IV with DBBS is probably shown as follows;

The reaction of acetal with DBBS could proceed without irradiation and without any initiator such as 2,2′-azobisisobutyronitrile (AIBN) while the reaction with NBS[5c] requires these conditions. The appearance of the reaction was quite similar to that of ethers with DBBS, that is, the reaction consists of two stages, first stage involving bromine-liberation from DBBS and subsequent stage of bromine consuming. In our previous paper[7] the mechanism of reaction of tetrahydrofuran with DBBS has been proposed on the basis of kinetic study. The reaction has been explained by the formation of two intermediates, an ylid-like complex and an oxonium ion.

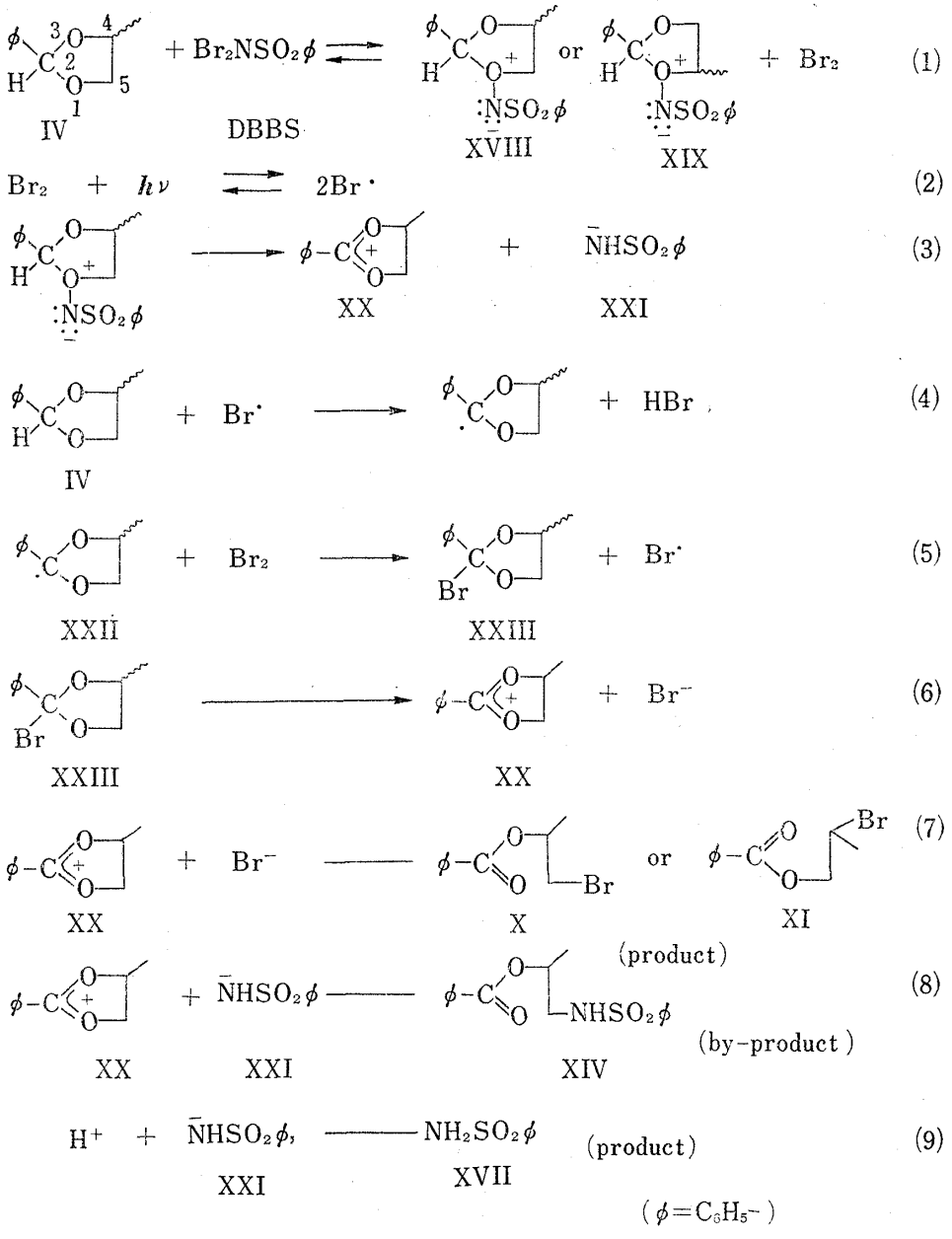


Chart 2

Therefore, the above mentioned observations on the reaction of IV with DBBS may be explained by the following steps, equations (1)—(9).

The reaction of acetal with DBBS starts with bromine-liberation and formation of ylid-like complex (XVIII or XIX), simultaneously. Subsequently, an ion pair of XX and XXI may be given with β-elimination of benzenesulfonium anion from the complex. If a radical reaction with bromine on this oxonium ion occurrs at 4 or 5 position in the next bromine-consuming step, the molar ratio of the isomeric esters, X/XI, should be smaller than 1, because the predominant attack of bromine can be expected to occur at tertiary carbon, C-4 rather than at C-5. Actually, however, the ratio of the two esters is 9: 1, so one explanation for this may be drawn considering a chain mechanism shown by equations (4) and (5) which gives 2-bromoacetal (XXIII).[10] The oxonium ion (XX) may also be formed from XXIII by elimination of bromide ion (eq. (6)). The brominated esters, X and XI, the final products, may be formed with the fission of C-O bond and nucleophilic attack of bromide ion to XX as shown in eq. (7). The ratio of X to XI, 9: 1, may be attributed to the steric hindrance of methyl group for approach of bromide ion.

The pathway presented in chart 2 is not only reasonable for the formation of considerable amount of by-product (XIV) (eq. (8)) but also that of hydroxy esters (XV and XVI) which resulted by treatment of the reaction mixture with sodium hydroxide, in the stage of bromine-accumulation.

The above mechanism involving O-N ylid, XVIII or XIX, as an intermediate may also be supported by the studies on the insertion reaction of ethoxycarbonylnitrene into cyclic ethers reported by T. Shingaki, *et al.*,[11] and K. Takeuchi, *et al.*,[12] who proposed the O-N ylid intermediate, although no evidence of successive insertion reaction was found in our case. It probably due to the presence of bromine simultaneously formed.

Experimental[13]

Preparation of Acetals——I was prepared from benzaldehyde with orthoformic acid ester.[14] II, III, *cis–trans*-mixture of IV, and *cis*-V[9] were synthesized by condensation of benzaldehyde with appropriate glycols in the presence of toluenesulfuric acid in benzene. *cis*-IV was obtained by the method of N. Bagget, *et al.*,[8]; the condensed-ring compound of 3-chloropropane-1,2-diol with benzaldehyde was treated with potassium *t*-butoxide, and the resultant 4-methylene-2-phenyl-1,3-dioxolane was reduced catalytically to *cis*-IV. Boiling points of the acetals were I: 86—87° (10 mmHg), II: 225—227°, III: 108—111° (5 mmHg), *cis–trans*-mixture of IV: 97° (8 mmHg), *cis*-IV: 103—107° (15 mmHg), and *cis*-V: 113° (7 mmHg). NMR spectra of *cis*-IV, *cis–trans* mixture of IV and *cis*-V were listed on Table II.

General Procedure for Reaction of Acetal with DBBS——Acetal was allowed to react with one half mole of DBBS in dry CCl_4 on cooling under stirring. During the reagent was added in small portions, the reaction mixture turned red by bromine liberated from DBBS and subsequently the bromine was consumed. After the total amount of reagent was added, the mixture was refluxed for about 30 to 60 minutes until it turned colorless. The resulting crystals were filtered off and these crystals were identified with the authentic sample of benzenesulfonamide (XVII) by mixed melting point determination and the comparison of infrared (IR)

10) The mechanism of the reaction of O-benzylidene sugars with NBS has been presented by S. Hanessian and N. R. Plessas, [*J. Org. Chem.*, **34**, 1035 (1969)]. They assumed a reaction step between a radical-like intermediate from acetal and Br. However our step (5) involving a reaction between acetal radical and molecular bromine looks like more reasonable than the interradical reaction. The liberation of molecular bromine which they observed too may also support our presumpsion. our Presumpsion.

11) T. Shingaki, M. Inagaki, N. Torimoto, and M. Takebayashi, *Chemistry Letters*, **1972**, 297.

12) K. Takeuchi, T. Okada, M. Mitani, T. Tuchida, and K. Koyama; The 28th Annual Meeting of Spring of the Chemical Society of Japan, Tokyo, April, 1973, Abstract papers, p. 1223.

13) Melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a type EPI-S2 Hitachi infrared spectrophotometer (nujol or oil), and NMR spectra were measured on a type R-20B 60 MHz Hitachi Perkin-Ermer spectrometer using TMS as an internal standard. N,N-Dibromobenzenesulfonamide (DBBS) was prepared as described previously; Y. Ueno, S. Takemura, Y. Ando, and H. Terauchi, *Chem. Pharm. Bull.* (Tokyo), **15**, 1193 (1967).

14) L. Claisen, *Ber.*, **40**, 3903 (1907).

spectra. The filtrate was washed with 40% aq. $NaHSO_3$ and saturated aq. NaCl, and dried over anhyd. Na_2SO_4. The dried CCl_4 solution was distilled under reduced pressure. Products and yields of these reactions were shown in Table I and NMR spectra of these products were noted on Table II.

Ethyl Benzoate (VI) and Ethyl Bromide (VII)——The mixture resulted of the reaction of I (18 g, 0.1 mole) with DBBS (15.8 g, 0.05 mole) was treated as described in the general procedure. The washed and dried CCl_4 solution separated from benzenesulfonamide was applied to gas chromatography, and the peaks of ethyl bromide (VII) and ethyl benzoate (VI) were detected. The analysis was carried out under the following conditions: sample, 1 μl; column, DEGS chromosorb w (60—80 mesh), 2 m, 3 ϕ, glass column, 49°; carrier gas, H_2. t_R: VI, 1.4 min; VII, 4 min. An oil obtained by distillation of the CCl_4 solution, bp 66° (4 mmHg), was VI (12.2 g, 81.5%) showing identical IR spectrum of authentic sample.

2-Bromoethyl Benzoate (VIII)——The reaction of II (15 g, 0.1 mole) with DBBS (15.8 g, 0.05 mole) gave XVII and an oil (18.9 g, 82.5%), bp 125° (3 mmHg), VIII, whose IR and NMR spectra were superimposable on those of the authentic sample prepared by the reaction of benzoyl chloride with ethylene bromohydrine. IR (liquid) ν_{max} cm^{-1}: 1720 (Ar-COOR), 1600, 1580 (aromatic). NMR δ_{ppm} in $CDCl_3$: 3.56 (2H, t., J=6 cps, C_2-H), 4.62 (2H, t., J=6 cps, C_1-H).

3-Bromopropyl Benzoate (IX)——The reaction of III (16.4 g., 0.1 mole) with DBBS (15.8 g, 0.05 mole) gave XVII and an oil (18.2 g, 74.9%), bp 153—156° (4 mmHg), which was proved to be IX by giving following data. IR (liquid) ν_{max} cm^{-1}: 1720 (Ar-COOR), 1600, 1580 (aromatic). NMR δ_{ppm} in $CDCl_3$: 2.23 (2H, m, C_2-H), 3.50 (2H, t., J=6.5 cps, C_3-H), 4.40 (2H, t., J=6 cps, C_1-H).

1-Methyl-2-bromoethyl Benzoate (X) and 2-Bromopropyl Benzoate (XI)——By the above mentioned manner, *cis–trans*-mixture of IV (3.2 g, 0.02 mole) was allowed to react with DBBS (3.2 g, 0.01 mole) and the reaction mixture was treated as described in general procedure. The resulting CCl_4 solution was applied to measurement of NMR spectrum to know the molar ratio of the brominated esters (X: XI) (listed in Table II). The most part of the CCl_4 solution including X and XI, was distilled at 106° (3 mmHg), yield 3.2 g, 67%. *Anal.* Calcd. for $C_{10}H_{11}O_2Br$: C, 49.40; H, 4.57; Br, 32.86. Found: C, 49.38; H, 4.45; Br, 33.13. IR ν_{max} cm^{-1} 1720 (Ar-COOR), 1600, 1580 (aromatic). The volatile reaction products of *cis*-IV (3 g, 0.018 mole) with DBBS (2.86 g, 0.009 mole), the mixture of X and XI, were shown to be produced in the similar ratio, yield, 2.6 g, 59%.

1-Methyl-3-bromopropyl Benzoate (XII) and 3-Bromobutyl Benzoate (XIII)——*cis*-V (3.6 g, 0.02 mole) was made to react with DBBS (3.2 g, 0.01 mole) to give an oil, a mixture of XII and XIII. The molar ratio of the compornents was judged to be 7: 2 from NMR spectrum (see Table II). This oil was distilled at 124—125° (2 mmHg), yield 3.8 g, 74%. *Anal.* Calcd. for $C_{11}H_{13}O_2Br$: C, 51.37; H, 5.11; Br, 31.07. Found: C, 51.54; H, 5.24; Br, 30.89. IR ν_{max} cm^{-1}; 1720 (Ar-COOR), 1600, 1580 (aromatic).

1-Methyl-2-benzenesulfonaminoethyl Benzoate (XIV)——After the volatile products of the reaction of IV (3.2 g, 0.02 mole) with DBBS (3.2 g, 0.01 mole) was distilled off, the residue was dissolved in ether. Addition of *n*-hexane to this solution gave crystals. The purification from CCl_4 gave colorless crystals (XIV), mp 75—77°, 110 mg (3.5%), *Anal.* Calcd. for $C_{16}H_{17}O_4NS$: C, 60.18; H, 5.37; N, 4.39. Found: C, 60.10; H, 5.47; N, 4.49. NMR spectrum was shown in Table II. IR ν_{max} cm^{-1}: 3300 (N-H), 1720 (Ar-COOR), 1600, 1580 (aromatic).

1-Methyl-2-hydroxyethyl Benzoate (XV) and 2-Hydroxypropyl Benzoate (XVI)——DBBS (3.2 g, 0.02 mole) was added to IV (3.2 g, 0.01 mole) in 30 ml of $CHCl_3$. At the maximum of the liberation of bromine (judged by the comparison of the color with standard solution of Br_2 (0.8 g) in $CHCl_3$ (15 ml)), the reaction mixture was poured into 20 ml of ice-cooled 10% aq. NaOH and the mixture was stirred vigorously and extracted with $CHCl_3$. The extract was chromatographed on a silicagel column eluting with $CHCl_3$. After a small amount of a mixture of X and XI was eluted, fractions giving one spot on thin-layer chromatography were collected. It was shown to be still a mixture of two components (XV and XVI) as the analysis by NMR. The mixture was distilled at 131° (3 mmHg). Yield 1.6 g, 44.5%. *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.55; H, 6.96. NMR spectrum was shown in Table II. IR $\nu_{max}$$cm^{-1}$: 3400 (OH), 1710 (Ar-COOR), 1600, 1580 (aromatic).

Acknowledgement We wish to express our gratitude to Prof. Y. Tamura of Osaka University for his hearty encouragement and discussion. We are grateful to Dr. B. Yasui for his useful discussion throughout this work. We also thank assistant Prof. K. Otsuki and Mr. M. Takeuchi of this Faculty, for the NMR spectral measurements and for the gas chromatographic measurement, respectively.