by titrating aliquots of the reaction mixtures with hydrochloric acid over a period of approximately 20 hours. These data are compared in Tables III and IV with the relative rates of disappearance of base from the reaction mixtures which are comparable in all other respects except that the hydrogen peroxide has been omitted.

The Preparation of Secondary Alkyl Hydroperoxides and Isoamyl Hydroperoxide.—The secondary alkyl hydroperoxides were prepared under conditions similar to those employed for the preparation of the primary isomers[7]; however, the isolation procedure was modified slightly. The preparations were conducted on a larger scale because of the lower yield of hydroperoxides from secondary alkyl methanesulfonates as compared to the primary isomers.

A one-phase reaction mixture was prepared by adding 10.0 g. (0.090 mole) of 50% aqueous potassium hydroxide to a chilled solution consisting of 40 g. (0.35 mole) of 30% hydrogen peroxide, 0.080 mole of the alkyl methanesulfonate, water and methanol as indicated in Table V. The mixture was then placed in a water-bath at room temperature for the period indicated in Table V. After standing at room temperature, the mixture was cooled in ice and combined with 30 g. of 50% potassium hydroxide. The alkaline solution was extracted with 50 ml. of hexane and then neutralized with hydrochloric acid while being cooled in ice.

The neutralized solution was extracted with six 20-ml. portions of benzene which were combined and extracted with 40 g. of 25% potassium hydroxide. The 2-octyl hydroperoxide was extracted with 80 g. of 12% potassium hydroxide because of the formation of a greasy precipitate in the more concentrated solution. The alkaline solution was neutralized with concentrated hydrochloric acid, with cooling, and the liberated hydroperoxide was extracted with three 15-ml. portions of ether. The ether solution was dried over sodium sulfate, freed of ether under aspirator pressure and then distilled at reduced pressure. The yields, properties and analyses are compiled in Table I.

STANFORD, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Effect of Structure on Reactivity. IX. A Study of the Aminolysis of Esters of Trichloro- and Trifluoroacetic Acids

BY MADELEINE M. JOULLIÉ AND ALLAN R. DAY

RECEIVED JANUARY 6, 1954

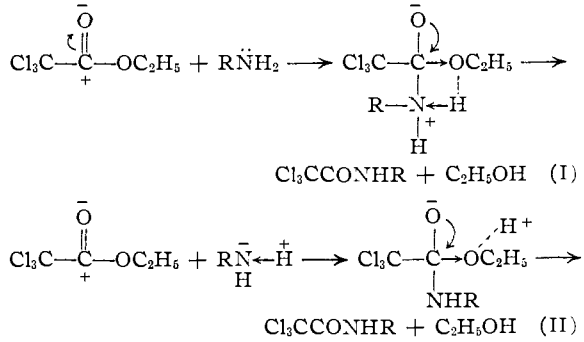
It has been found that esters of trichloroacetic acid and trifluoroacetic acid react in distinctly different ways with primary amines and with secondary amines. With primary amines, cleavage of the carbon-oxygen bond occurs giving the typical end products of an aminolysis reaction, namely, an amide and an alcohol. When 1,2-diamines were used, the ethyl ester of trichloroacetic acid formed derivatives of dihydroimidazole. Ethyl trifluoroacetate, however, reacted with 1,2-diamines to form only the diamide, no dihydroimidazole being formed. Secondary amines reacted with the esters of both trichloroacetic acid and trifluoroacetic acid to give typical haloform reactions. In these cases a carbon-carbon bond was cleaved to form a haloform and a urethan. Mechanisms have been proposed to account for the different behaviors of primary and secondary amines in these reactions.

The cleavage of esters of trichloroacetic acid with alkoxides to form chloroform and alkyl carbonates was reported in 1931.[1] This reaction is very similar to the haloform reaction and probably follows a similar mechanism.

Other anionic reagents, with few exceptions, have not been studied. Concentrated aqueous ammonia converts ethyl trichloroacetate to trichloroacetamide in poor yields.[2] The fact that no chloroform was reported is somewhat surprising since the trichloromethyl group would be expected to cleave very readily. In view of this apparent anomaly, it was decided to study the reactions of ammonia, primary amines and secondary amines with esters of trihalogen substituted acetic acids.

When ethyl trichloroacetate in dry ethanol was treated with dry ammonia, good yields of trichloroacetamide were obtained. Primary amines under anhydrous conditions behaved similarly and formed N-alkyl trichloroacetamides in good yields. If the trichloromethyl group had cleaved, chloroform and a substituted urethan would have been formed but these products were not found. The course of these reactions was not changed by the presence of strong base catalysts such as the ethoxide ion. It would appear that as long as two hydrogen atoms are attached to the nitrogen of the amine, aminolysis of the ester group occurs as the only reaction.

Two possible mechanisms may be written for the reaction with primary amines.

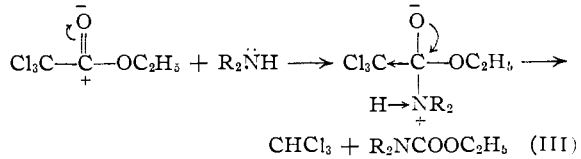


$$Cl_3CCONHR + C_2H_5OH \quad (I)$$

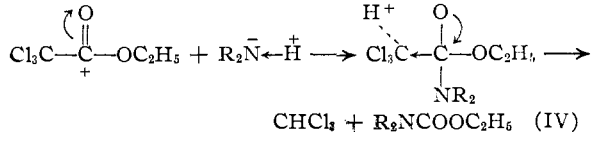
$$Cl_3CCONHR + C_2H_5OH \quad (II)$$

The two mechanisms are very similar, differing only in the time at which the proton is transferred.

Secondary amines reacted with ethyl trichloroacetate in a different manner, giving a typical haloform cleavage with the formation of chloroform and a N-substituted urethan. Here again two possible mechanisms may be written.



$$CHCl_3 + R_2NCOOC_2H_5 \quad (III)$$



$$CHCl_3 + R_2NCOOC_2H_5 \quad (IV)$$

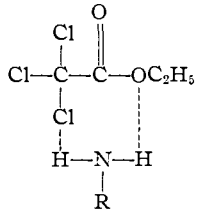
(1) H. Meerwein and H. Sönke, *Ber.*, **64**, 2375 (1931).

(2) M. A. Clermont, *Compt. rend.*, **133**, 737 (1901).

This marked difference in behavior, between primary and secondary amines, indicates a difference in the mechanism involved. It is difficult to see how variations in base strength or in steric factors could account for the differences noted since the reactions are mutually exclusive. Another possibility to be considered is the fact that the N–H bond in a secondary amine is less acidic (decreased tendency for proton transfer) than the corresponding bond in a primary amine. If one assumes that mechanism III holds for secondary amines, a reasonable explanation is available. In the intermediate in this case, the trichloromethyl group, being more electron attracting than the ethoxide group, cleaves and the resulting carbanion (base) facilitates the removal of the hydrogen (as a proton) from the N–H bond.

If mechanism II is assumed to hold for primary amines due to the greater acidity of the N–H bond, an explanation for the cleavage of the ethoxide bond is available also. In the intermediate in this case, the ethoxide group has increased electron-attracting power due to the coördination of the proton with the ethoxide–oxygen atom. Thus the carbon–ethoxide bond is cleaved with the formation of an amide.

The attachment of two hydrogen atoms to nitrogen in the case of primary amines could make possible a type of cyclic hydrogen-bonding not possible with secondary amines. A hydrogen-bonded intermediate such as



would also appear to offer an explanation for the cleavage of the carbon–ethoxide bond. Such an intermediate should result in increasing the nucleophilic activity of the nitrogen as well as facilitating the cleavage of the carbon–ethoxide bond. Cyclic hydrogen-bonded intermediates have been postulated for other cases of ammonolysis and aminolysis with primary amines.[3]

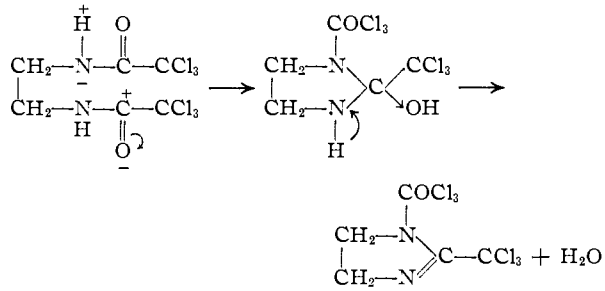
Ethyl trifluoroacetate reacted even more energetically with primary and secondary amines to give even better yields of the same products.

There seemed to be a remote possibility that the differences noted might not be due to differences between primary and secondary amines but rather to differences in the behavior of N-alkyl trichloroacetamides and N-dialkyl trichloroacetamides. N-Isopropyl trichloroacetamide and N-dimethyl trichloroacetamide were prepared and each treated with one equivalent of sodium ethoxide. In both cases good yields of the corresponding urethans were obtained as a result of haloform cleavages. These data suggest that the actions of primary and secondary amines on ethyl trichloroacetate do not give similar intermediates, for if such were the case urethan formation would be expected in both cases. These facts are consistent with the mechanisms proposed for the reactions of ethyl trichloroacetate with primary and secondary amines.

t-Butyl trichloroacetate was treated with one primary amine, isopropylamine, and one secondary amine, piperidine. It was hoped that the *t*-butyl group because of its bulk and the fact that it is a strong electron-repelling group might play a role in determining the position where cleavage occurs. The end-products, however, were the same as those obtained from the ethyl ester. The reactions were less exothermic and the yields were lower.

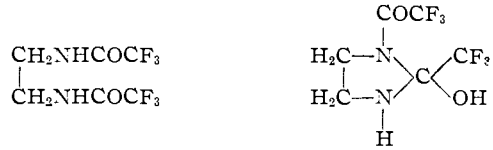
The reactions of ethyl trichloroacetate with a series of primary amines were studied, including such hindered amines as isopropylamine and *t*-butylamine. Aminolysis to the corresponding amide occurred in every case. When secondary amines were used, the haloform cleavage took place with such relatively unhindered amines as morpholine, piperidine, pyrrolidine and dimethylamine. Diethylamine and α-methylpiperidine did not react, presumably because of steric hindrance.

Ethylenediamine and propylenediamine behaved like primary amines as far as the point of cleavage is concerned. The reactions did not stop at the diamide stage, however. The diamide apparently undergoes a rapid ring closure to form a substituted dihydroimidazole. Such ring closures are well known but usually do not proceed as readily as the examples observed during the present investigation.



Propylenediamine reacted similarly to give the corresponding 5-methyl derivative. When 1,3-diaminopropanol-2 was used, the reaction stopped with the formation of the diamide.

It was expected that ethyl trifluoroacetate would react with ethylenediamine in a similar manner. A very vigorous reaction took place but no dihydroimidazole was formed. The diamide was isolated in excellent yields. Actually the analytical data fit the calculated values for both the diamide and the corresponding tetrahydroimidazole.



It has not been possible to differentiate between the two structures to date. Presumably it is possible that ring closure could take place without losing the elements of water. The strong electron attraction of the trifluoromethyl group might prevent the splitting out of a molecule of water. The stability

(3) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **71**, 1245 (1949); E. McC. Arnett, J. G. Miller and A. R. Day, *ibid.*, **72**, 5635 (1950).

of compounds such as chloral hydrate and alloxan hydrate has been attributed to similar effects. The fact that the product is hydrolyzed by heating with hydrochloric acid does not distinguish between the two since both would be expected to hydrolyze. The corresponding dihydroimidazole, however, probably would not be hydrolyzed, since it was found that 1 - trichloroacetyl - 2 - trichloromethyldihydroimidazole did not react under similar conditions.

Experimental

Preparation of Ethyl Trichloroacetate.—This ester was prepared according to previously reported directions[2,4]; yields 68–72%, b.p. 166.5–167°.

Preparation of Ethyl Trifluoroacetate.—This ester was prepared essentially by the method of Henne, Aldersen and Newman[5]; yield 88%, b.p. 60.5–61°.

Preparation of *t*-Butyl Trichloroacetate.—This ester was prepared from isobutylene and trichloroacetic acid by the method of Scovill, Burk and Lankelma[6]; m.p. 25–26°, b.p. 42.5° at 3 mm.

Reactions of Ethyl Trichloroacetate with Ammonia and Primary Amines. Preparation of Trichloroacetamide.—Clermont's procedure[2] was first tried but gave very low yields, only 2 g. of trichloroacetamide from 19.1 g. of ester, so anhydrous conditions were tried. Ethyl trichloroacetate (19.1 g., 0.1 mole) was dissolved in 60 ml. of dry ethyl alcohol and cooled in an ice-bath. The solution was saturated with dry ammonia. After standing overnight, the excess alcohol was removed on the steam-bath. The residue in the flask crystallized. An 81% yield of pure product was obtained after recrystallization from absolute ethyl alcohol, m.p. 140–141°.

Preparation of N-Methyl Trichloroacetamide.—This compound was prepared by the method of Franchimont and Klobbie[7]; yield 77%, m.p. 104.5–106°.

Preparation of N-Isopropyl Trichloroacetamide from Ethyl Trichloroacetamide from Ethyl Trichloroacetate. General Procedure.—Ethyl trichloroacetate (38.2 g., 0.2 mole) was treated gradually with 11.8 g. (0.2 mole) of isopropylamine, the mixture allowed to stand overnight and the product removed by filtration. The product was recrystallized from hexane. Most of the reactions of the ester with amines were highly exothermic and the solutions became yellow to orange on standing.

Preparation of N-*n*-Butyl Trichloroacetamide.—*n*-Butylamine was the reagent in this case. After standing overnight, the solution was fractionally distilled *in vacuo*. N-*n*-Butyl trichloroacetamide was also prepared from isopropyl trichloroacetate under similar conditions and equally good yields were obtained. Chloroform could not be detected in any of these reactions; therefore the haloform cleavage did not take place to a measurable extent.

Preparation of *t*-Butyl Trichloroacetamide.—The *t*-butylamine used in this experiment was prepared from *t*-butylurea.[8] The crude product was recrystallized from toluene.

Preparation of N-Nonyl Trichloroacetamide.—The nonylamine used in this case was 3,5,5-trimethylhexylamine. The product was fractionally distilled *in vacuo*.

Preparation of N-β-Phenylethyl Trichloroacetamide.—β-Phenylethylamine was used for this preparation. The product was recrystallized from benzene.

Preparation of N-3-Dimethylaminopropyl Trichloroacetamide.—3-Dimethylaminopropylamine was the reagent used in this experiment. The crude product was fractionally distilled *in vacuo*. The free base was converted to a hydrochloride by treating its dry alcohol–ether solution with dry hydrogen chloride. The salt was recrystallized from dry ethyl alcohol, m.p. 189–190°.

Preparation of N-Isopropyl Trichloroacetamide from *t*-Butyl Trichloroacetate.—Isopropylamine (0.2 mole) was added gradually to 0.1 mole of *t*-butyl trichloroacetate. After standing for four days, the excess isopropylamine was removed by distillation from a steam-bath and the solid residue was recrystallized from hexane; yield 40%, m.p. 82.5–84°.

Preparation of N-β-Phenylethyl Trifluoroacetamide from Ethyl Trifluoroacetate.—An extremely exothermic reaction took place when β-phenylethylamine was added to the ester. The crude amide was obtained either by removing any remaining ester or amine *in vacuo* or by precipitating the amide by the addition of petroleum ether. It was recrystallized from carbon tetrachloride–petroleum ether.

Reactions of Ethyl Trichloroacetate with Secondary Amines. Preparation of N-Carbethoxypiperidine ("Piperidine Urethan").—Piperidine was the reagent used in this experiment. After standing overnight, the solution was filtered and fractionally distilled *in vacuo*. When ethyl trifluoroacetate was used even better yields of the urethan were obtained (97%). In all of the reactions with secondary amines, chloroform was obtained, but no attempt was made to isolate it in a quantitative way.

Preparation of N-Carbethoxymorpholine ("Morpholine Urethan").—Morpholine was used in this preparation. The crude product was fractionally distilled *in vacuo*.

Preparation of N-Carbethoxypyrrolidine ("Pyrrolidine Urethan").—Carefully purified pyrrolidine was used. The crude product was fractionally distilled *in vacuo*.

Preparation of N-Carbethoxydimethylamine ("N-Dimethyl Urethan").—Ethyl trichloroacetate (39 g.) was dissolved in 20 ml. of dry methyl alcohol. Dry dimethylamine was passed into the solution, slowly at first because of the exothermic nature of the reaction, then rapidly until the solution was saturated. The solution was allowed to stand in a pressure bottle for two days at room temperature. The solution was filtered and the filtrate was fractionally distilled *in vacuo*.

Reactions with Diprimary Amines. Preparation of 1-Trichloroacetyl-2-trichloromethyldihydroimidazole.—Ethylenediamine (6.0 g., 0.1 mole) was mixed with 38.2 g. (0.2 mole) of ethyl trichloroacetate. A highly exothermic reaction took place and colorless crystals appeared until the whole solution finally appeared to solidify. The product was broken up and removed by filtration. The crude product was crystallized from methyl cellosolve. Better yields could be obtained by carrying out the reaction in dry ethyl alcohol. For example, when the above reaction was carried out in 50 ml. of dry ethyl alcohol a yield of 84% was obtained.

Preparation of 1-Trichloroacetyl-2-trichloromethyl-5-methyldihydroimidazole.—Propylenediamine was used for this preparation. After standing overnight, the crude product was removed by filtration and recrystallized from ethyl cellosolve.

Preparation of 1,3-Di-(trichloroacetamido)-propanol-2.—1,3-Diaminopropanol-2 (9 g., 0.1 mole) was added gradually to 38.2 g. (0.2 mole) of ethyl trichloroacetate in 20 ml. of dry ethyl alcohol. After standing overnight, the product was removed by filtration. Partial evaporation of the filtrate resulted in more product. It was purified by recrystallization from ethyl alcohol; yield 80%, m.p. 161–164°. The exact melting point was difficult to determine because the melt remained cloudy over a range of three degrees before it cleared.

Anal. Calcd. for $C_7H_8O_3N_2Cl_6$: C, 22.08; H, 2.11; N, 7.35; Cl, 55.86. Found: C, 22.20; H, 2.27; N, 7.50; Cl, 55.83.

Preparation of Symmetrical Di-(trifluoroacetyl)-ethylenediamine.—Ethylenediamine (6 g., 0.1 mole) was added gradually to 30 g. (0.21 mole) of cold ethyl trifluoroacetate. This reaction was highly exothermic and the mixture solidified. After standing for several hours, the mass was broken up and transferred to a suction funnel. The product was recrystallized from hot absolute ethyl alcohol followed by washing with a small amount of dry ether until the product melted constantly at 201.5–202.5°, yield 87%.

Anal. Calcd. for $C_6H_6O_2N_2F_6$: C, 28.59; H, 2.39; N, 11.12. Found: C, 28.58; H, 2.39; N, 11.15.

To further distinguish the product from the dihydroimidazole derivative obtained from ethyl trichloroacetate a sample was hydrolyzed with hydrochloric acid. Two grams of the diamide was mixed with 20 ml. of concentrated hydrochloric acid and refluxed for three hours. The di-

(4) L. Spiegel and P. Spiegel, *Ber.*, **40**, 1730 (1907).

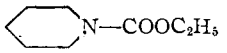
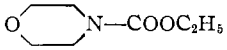
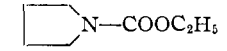
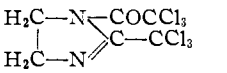
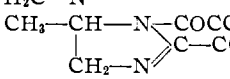
(5) A. L. Henne, T. Aldersen and M. S. Newman, THIS JOURNAL, **67**, 918 (1945).

(6) W. E. Scovill, R. E. Burk and H. P. Lankelma, *ibid.*, **66**, 1039 (1944).

(7) A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **6**, 234 (1887).

(8) D. E. Pearson, J. F. Baxter and K. N. Carter, THIS JOURNAL, **70**, 2290 (1948).

TABLE I

	M.p. or b.p. (mm.), °C.	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
Amides										
$Cl_3CCONHC_3H_7$-*i*	82.5–84	83	29.38	29.32	3.94	3.99	6.85	6.84	52.04	51.89
$Cl_3CCONHC_4H_9$-*n*	29–30	71–77	32.98	33.00	4.61	4.51	6.41	6.48	48.68	48.53
	96 (1)									
$Cl_3CCONHC_4H_9$-*t*	108–110	54	32.98	32.94	4.61	4.64	6.41	6.36	48.68	48.65
$Cl_3CCONHC_9H_{19}$	34–35	66	45.78	45.72	6.98	6.81	4.85	4.85	36.85	36.75
	133 (2)									
$Cl_3CCONHCH_2CH_2C_6H_5$	118–119[a]	94	45.07	45.14	3.78	3.89	5.26	5.29	39.89	39.72
$Cl_3CCONH(CH_2)_2CH_2N(CH_3)_2 \cdot HCl$	189–190	57	29.62	29.71	4.93	5.00	9.87	9.83	49.95	49.77
$F_3CCONHCH_2CH_2C_6H_5$	56–57	80–85	55.30	55.44	4.64	4.64	6.45	6.36		
Urethans										
	56 (1)[b]	65–70	61.12	61.04	9.61	9.53	8.91	8.98		
	60 (1)	73	52.61	52.55	8.19	8.03	8.76	8.45		
	63 (2)	50–60	58.71	58.66	9.14	9.32	9.78	9.72		
$(CH_3)_2N\text{-}COOC_2H_5$	74 (80)[c]	43	51.28	51.33	9.46	9.43	11.97	11.99		
Dihydroimidazoles										
	206–207	84	21.66	21.51	1.21	1.56	8.42	8.43	63.91	63.66
	196–197	91	24.25	24.14	1.74	1.94	8.09	8.03	61.34	61.43

[a] This compound, prepared by a different method, was reported to melt at 112–113° (J. v. Braun, F. Jostes and W. Munch, *Ann.*, **453**, 144, 1927). [b] Prepared by a different method, it was reported to boil at 211° at atmospheric pressure (C. Schotten, *Ber.*, **15**, 425, 1882). [c] Prepared by a different method, it was reported to boil at 147° at atmospheric pressure.[7]

amide gradually dissolved. The solution was then evaporated to dryness and 1.2 g. of a crystalline substance was obtained. The product was recrystallized from ethyl alcohol and water (10 ml. of ethyl alcohol and 3 ml. of water). The recrystallized product darkened at 300° and decomposed at about 327° without melting. The analytical results showed the compound to be ethylenediamine dihydrochloride.

Anal. Calcd. for $C_2H_{10}N_2Cl_2$: C, 18.06; H, 7.57; N, 21.07. Found: C, 18.17; H, 7.54; N, 20.99.

In contrast to the behavior of the above diamide with hydrochloric acid, the dihydroimidazole derivative obtained from ethylenediamine and ethyl trichloroacetate did not react with hydrochloric acid under similar conditions.

PHILADELPHIA, PENNSYLVANIA

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

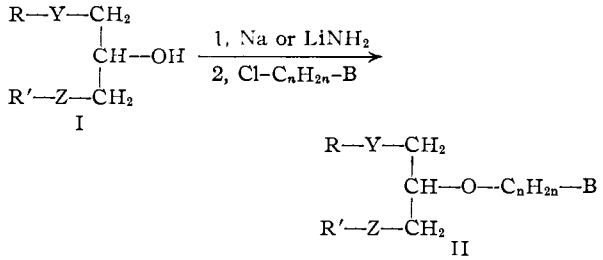
Glycerol Ethers. I. Alkaminoalkyl Ethers of 1,3-Bis-(aryloxy)-2-propanols and Related Compounds

BY WILLIAM F. MINOR, RICHARD R. SMITH AND LEE C. CHENEY

RECEIVED JANUARY 30, 1954

By the condensation of an alkali salt of a 1,3-diether of glycerol with an alkaminoalkyl chloride, a novel series of basic ethers has been prepared for pharmacological investigation. 2-[(1,3-Diphenoxy)-2-propoxymethyl]-imidazoline was obtained by heating ethyl [(1,3-diphenoxy)-2-propoxy]-acetate with ethylenediamine. Certain members of the group exhibit pronounced local anesthetic activity.

A series of glycerol triethers wherein the central alkoxy moiety bears an alkamine function (general formula II) has been prepared for biological investigation.



R, R′ = alkyl, aryl or substituted aryl groups
Y, Z = O or S; B = dialkylamino, piperidyl or imidazolyl

The intermediate symmetrical 1,3-bis-(aryloxy)-2-propanols (I) were prepared by a slight modification of the excellent method of Marple and Evans[1] (method A), utilizing the interaction of the appropriate phenol, sodium hydroxide and epichlorohydrin in a medium of dioxane. The yields varied from 61 to 95% with but four exceptions (Table I). Obviously this procedure was suitable only when R and R′ of I were the same. In the instances where they differed, methods B, C and D were employed.

The evidence that the ring openings in basic media of unsymmetrical epoxides by alcohols,[2] phe-

(1) K. E. Marple and T. W. Evans, U. S. Patent 2,351,025 (1944), Example V; *C. A.*, **38**, 5224 (1944).

(2) D. Swern, G. N. Billen and H. B. Knight, THIS JOURNAL, **71**, 1152 (1949).