81. **Shigeru Yoshida and Tadahiro Iwashige**: Syntheses on Ammonium Compounds of Aminoalkyl Carboxylates. II.[1]

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Syntheses of the ammonium salts of aminoalkyl carboxylates by the rearrangement reaction of ammonium carboxylates were described in the previous paper.[1] In the present series of experiments, the preparation of aminoalkyl carboxylate derivatives by the application of secondary or tertiary amines to ω-haloalkyl carboxylates, especially β-haloethyl carboxylates, was carried out and examinations made on a few side-reactions accompanying this method, and the results are set in the present paper.

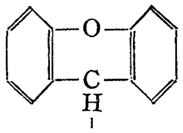
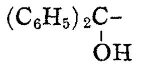
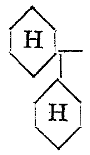
For the preparation of β-haloethyl carboxylates, a reaction of carboxylic halides and ethylenehalohydrin is generally used. Of the carboxylic acids which can be used as the starting material for the aminoalkyl carboxylates possessing antispasmodic actions, xanthene-9-carboxylic chloride is fairly labile and is difficult to be obtained in a pure state while benzilic acid possesses a hydroxyl group which is sensitive to halogenation agent that it seems to be unsuitable for this method.

Therefore, esterification of the carboxylic acid with ethylenehalohydrin, shown by the following formulae, using various catalysts and reaction solvents was examined.

$$\text{R-COOH} + \text{HOCH}_2\text{CH}_2\text{X} \longrightarrow \text{RCOOCH}_2\text{CH}_2\text{X}$$

It was thereby found that β-haloethyl carboxylate would be obtained in a good yield by the use of carbon tetrachloride as a solvent with the addition of a very small amount of conc. sulfuric acid, refluxing this mixture. The results are shown in Table I.

TABLE I. $RCOOCH_2CH_2X$

Compd. No.	R	X	b.p., °C/mm. Hg
(I)		Br	135~139/0.0005
(II)	〃	Cl	150~153/0.01
(III)	 $(C_6H_5)_2C(OH)-$	Br	173~180/0.2
(IV)	$(C_6H_5)_2CH-$	〃	136~140/0.002
(V)	〃	Cl	130~135/0.005
(VI)		〃	120~125/0.02

By the application of a secondary amine to the β-haloethyl carboxylates hereby obtained, as shown by the formulae, several kinds of aminoalkyl carboxylates listed in Table II were obtained. These salts did not depress the melting point of the corresponding salts prepared by the usual method and gave well-agreeing analytical data.

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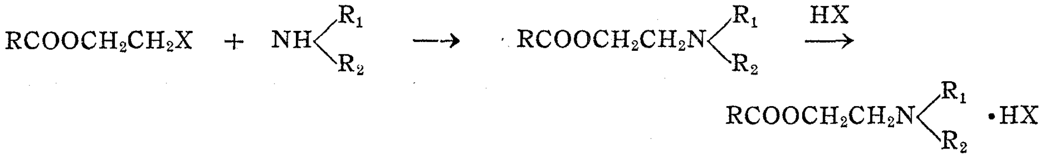
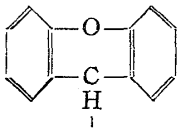
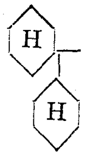
[1] Part I: S. Yoshida, T. Iwashige: J. Pharm. Soc. Japan, 74, 605(1954).

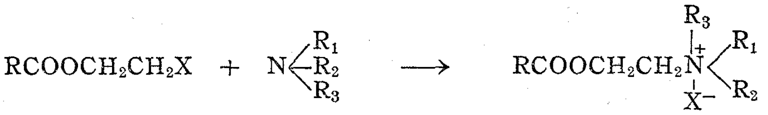


$$RCOOCH_2CH_2X + NH\begin{matrix}R_1\\R_2\end{matrix} \longrightarrow RCOOCH_2CH_2N\begin{matrix}R_1\\R_2\end{matrix} \xrightarrow{HX} RCOOCH_2CH_2N\begin{matrix}R_1\\R_2\end{matrix}\cdot HX$$

TABLE II. $RCOOCH_2CH_2N\begin{matrix}R_1\\R_2\end{matrix}$

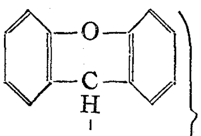
Compd. No.	R	R_1	R_2	b.p., °C/mm. Hg
(VII)		C_2H_5	C_2H_5	140~145/0.002
(VIII)	〃	iso-C_3H_7	iso-C_3H_7	200~210/0.0005(bath temp.)
(IX)	$(C_6H_5)_2CH-$	C_2H_5	C_2H_5	120~125/0.0005
(X)		〃	〃	115~120/0.0001

A few kinds of ammonium salts shown in Table III were obtained by reacting β-haloethyl carboxylate with tertiary amines, sealed in a tube with acetone as a solvent. The melting points and analytical values of these salts agreed with the corresponding ammonium salts prepared by the usual method.



$$RCOOCH_2CH_2X + N\begin{matrix}R_1\\R_2\\R_3\end{matrix} \longrightarrow RCOOCH_2CH_2\overset{R_3}{\underset{X^-}{\overset{+}{N}}}\begin{matrix}R_1\\R_2\end{matrix}$$

TABLE III. $RCOOCH_2CH_2\cdot\overset{R_3}{\underset{X^-}{\overset{+}{N}}}\begin{matrix}R_1\\R_2\end{matrix}$

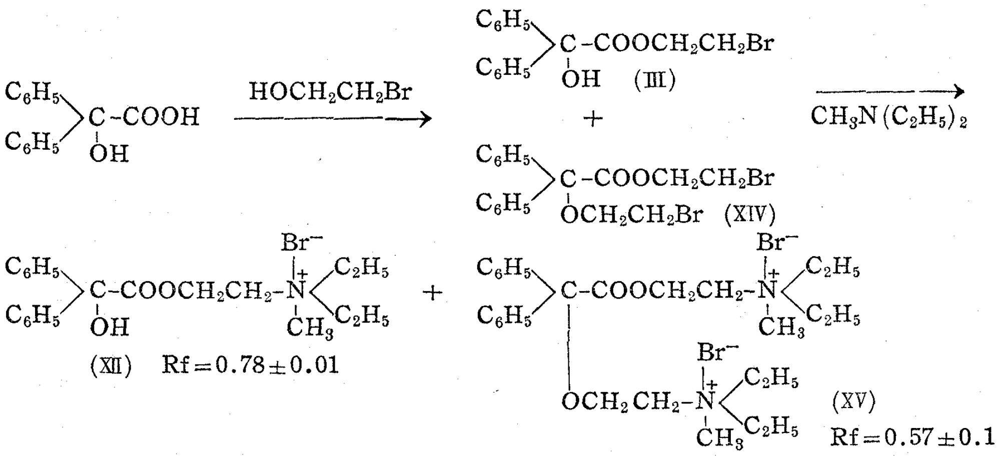
Compd. No.	R	R_1	R_2	R_3	X
(XI)		C_2H_5	C_2H_5	CH_3	Br
(XII)	$(C_6H_5)_2\underset{OH}{C}-$				
(XIII)	$(C_6H_5)_2CH-$				

In the preparation of the foregoing β-bromoethyl benzilate (III), refluxing time of 5~6 hours affords an oil of b.p$_{0.2}$ 173~180° whose analytical values agree with those for (III), with recovery of a small amount of the starting material, benzilic acid. When the time of refluxing is extended beyond this range, there is no recovery of the original acid but the oil of b. p$_{0.001}$ 158~170° obtained gives analytical values not agreeing with those for (III), and the yield becomes smaller.

The oil giving analytical values agreeing with those for (III) showed a marked absorption for the hydroxyl at around 2.9 μ in its infrared absorption spectrum and the absorption in this region was markedly weak in the oil giving different analytical values.

The oil of b. p$_{0.001}$ 158~170° was sealed in a tube with dimethylamine and acetone, and heated from which an oily substance assumed to be an ammonium salt was obtained. Paper partition chromatography of this oil, with β-diethylaminoethyl benzilate methobromide (XII) as a control, gave two spots at Rf 0.57±0.01 and 0.78±

0.01 by the Dragendorff reagent, the latter of which agreed with that of the control (XII). This fact and the foregoing infrared absorption spectral results suggest that, when the period of refluxing lengthens, etherification of benzilic acid, as well as its esterification, occurs, as shown:

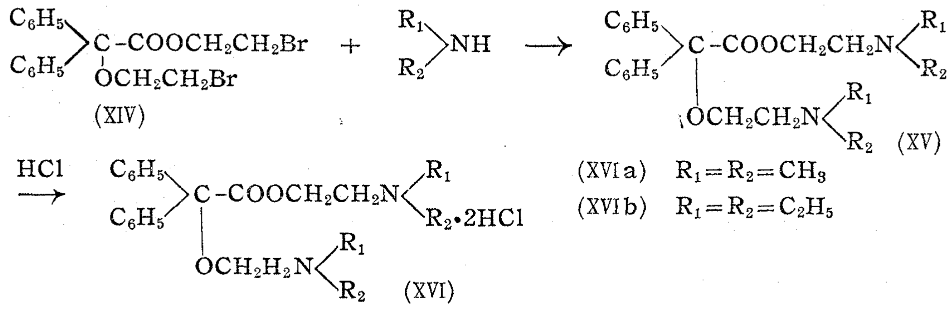


Conditions under which the hydroxyl group in benzilic acid would be etherified to afford β-bromoethyl O-(β'-bromoethyl)benzilate (XIV) in comparatively good yield were examined. It was thereby found that good results would be obtained by the use of carbon tetrachloride as a solvent, conc. sulfuric acid in an amount one-third the amount of benzilic acid, in the presence of an excess of ethylenebromohydrin, and refluxing for around 20 hours. The oil formed by this reaction was repeatedly fractionally distilled and the oil of b. p$_{0.05}$ 173~180° thereby obtained solidified on standing. Recrystallization from ligroine yielded white crystals of m. p. 59~61°, whose analytical values agreed with those for (XIV), and the absorption of the hydroxyl at around 2.9 μ in the infrared spectrum had disappeared in this substance.

Reaction of this compound with diethylmethylamine, with acetone as a solvent, by heating in a sealed tube and recrystallization of the crystalline product from a mixture of ethanol and ether gave the ammonium salt, m. p. ca. 180°, of β-diethylaminoethyl O-(β'-diethylaminoethyl)benzilate dimethobromide (XV). Paper partition chromatography of (XV), as before, gave only one spot at Rf 0.56±0.01 by the Dragendorff reagent and the fact seems to endorse the appropriateness of the foregoing conclusions.

β-Dimethylaminoethyl O-(β'-dimethylaminoethyl)benzilate dihydrochloride (XVIa) and β-diethylaminoethyl O-(β'-diethylaminoethyl)benzilate dihydrochloride (XVIb) were obtained by the respective application of dimethylamine and diethylamine on (XIV).

Recently, Klosa[2)] described the syntheses of various derivatives similar to (XV) and (XVI) by several steps. However, these compounds can be prepared in extreme-

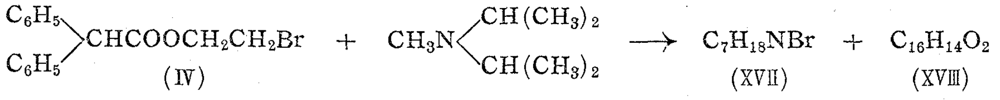


ly short steps by the present method. These compounds, (XV) and (XVI), possess interesting structures in that they combine that of β-diethylaminoethyl benzilate methobromide (XII) possessing comparatively strong antispasmodic action and that of antihistaminic β-dimethylaminomethyl benzhydryl ether hydrochloride. Their pharmacological tests are now being carried out.

In the preparation of the ammonium salt of aminoalkyl carboxylates by the application of tertiary amines to β-haloethyl carboxylate, straight-chain alkylamines, such as diethylamine, had been used in the foregoing experiments. The use of branched-chain alkylamines, such as diisopropylmethylamine, in this case gave an unexpected result.

A mixture of β-bromoethyl diphenylacetate (IV) and a slight excess of diisoproylmethylamine, with acetone as a solvent, was heated in a sealed tube, as in the case of the preparation of (XI), (XII), and (XIII). It was assumed that, due to the steric hindrance of branched alkyl group in the amine, quaternization would require a longer period than in the case of straight-chain alkyls. Unexpectedly, however, cooling of the mixture after 10 hours' heating separated some crystals whose recrystallization from a mixture of ethanol and ether afforded needle crystals (XVII), m. p. 155~156°, giving positive Beilstein reaction. This substance is easily soluble in water and alkalization of the solution evolved a marked amine odor. The analytical values agreed with those for diisopropylmethylamine hydrobromide.

Concentration of the filtrate, obtained on removal of above crystals, left an oily residue which, after being washed several times with water and extracted with ether, separated ether-insoluble crystals which recrystallized from ethyl acetate to plate crystals (XVIII), m. p. 153~154°. This substance gave negative Beilstein reaction and indistinct reaction to bromine and permanganate tests for a double bond. Its analytical values agree with those for a compound formed by the dehydrobromination of β-bromoethyl diphenylacetate (IV).



$$\underset{\text{(IV)}}{\begin{matrix}C_6H_5\\ C_6H_5\end{matrix}\!>\!CHCOOCH_2CH_2Br} + CH_3N\!<\!\begin{matrix}CH(CH_3)_2\\ CH(CH_3)_2\end{matrix} \longrightarrow \underset{\text{(XVII)}}{C_7H_{18}NBr} + \underset{\text{(XVIII)}}{C_{16}H_{14}O_2}$$

Infrared absorption spectrum of (XVIII) showed a strong absorption at around 6.04 μ that it is not likely to be the anticipated vinyl diphenylacetate. Further examinations on the structure of this substance are now being carried out.

The authors take this opportunity to express their gratitude to Prof. K. Tsuda of the University of Kyushu, Dr. G. Fukuchi, the Director of this Laboratory, and to Mr. Matsui, Vice-Director of the same, for their kind guidance and encouragement, to Messrs. Ito and Shindo for infrared spectral measurements, and to Messrs. Furukawa and Onoe for elementary analyses.

Experimental

Preparation of β-Bromoethyl Xanthene-9-carboxylate (I)—To a solution of 4.0 g. of xanthene-9-carboxylic acid and 9.0 g. of ethylenebromohydrin dissolved in 30 cc. CCl_4, 4~5 drops of conc. H_2SO_4 was added and the mixture was refluxed for about 13 hrs. After cooling, the reaction mixture was washed consecutively with water, 10% Na_2CO_3 solution, and water, dried over Na_2SO_4, and the solvent distilled off. The residue was submitted to low-pressure distillation and 4.7 g. of an oil, b.p$_{0.0005}$ 135~139°, was obtained. *Anal.* Calcd. for $C_{16}H_{13}O_3Br$: C, 57.66; H, 3.93. Found : C, 57.93; H, 3.86.

In the same manner, β-chloroethyl xanthene-9-carboxylate (II), β-bromoethyl benzilate (III), β-bromoethyl diphenylacetate (IV), β-chloroethyl diphenylacetate (V), and β-chloroethyl 1-cyclohexylcyclohexane-1-carboxylate (VI) were prepared with the results shown in Table IV.

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2) J. Klosa : Arch. Pharm., **287**, 321 (1954) ; **288**, 75 (1955).

TABLE IV.

Product	Reactants R·COOH (g.)	Reactants $HOCH_2CH_2X$ (g.)	CCl_4 (cc.)	c. H_2SO_4 (drops)	Reflux (hr.)	Yield (g.)	Mol. formula	Anal. (%) Calcd. C	Calcd. H	Found C	Found H
(II)	6.7	9.5 X=Cl	40	5~6	16	6.0	$C_{16}H_{13}O_3Cl$	66.60	4.50	66.26	4.60
(III)	6.0	13.4 X=Br	40	5~6	6	5.7*	$C_{16}H_{15}O_3Br$	57.30	4.47	56.98	4.52
(IV)	6.0	14.0 X=Br	40	4~5	14	7.3	$C_{16}H_{15}O_2Br$	60.2	4.70	59.93	4.71
(V)	9.5	14.4 X=Cl	60	10	18	8.6	$C_{16}H_{15}O_2Cl$	69.95	5.47	69.61	5.39
(VI)	3.3	5.1 X=Cl	30	4~5	20	0.6**	$C_{15}H_{25}O_2Cl$	66.1	9.18	66.05	9.10

* 1.3 g. recovd. ** 2.7 g. recovd.

β-Diethylaminoethyl Xanthene-9-carboxylate (VII)—A mixture of 2.0 g. β-chloroethyl xanthene-9-carboxylate (II) and 1.2 g. of diethylamine was sealed in a tube and heated in a water bath for 14 hrs. The crystals that separated out were collected by filtration and the filtrate was extracted with ether. The ethereal layer was extracted with 10 cc. of 5% HCl, which was basified with Na_2CO_3, and the oil that separated out was extracted with ether. The ether was evaporated after drying over K_2CO_3 and the residue was distilled under a diminished pressure from which 1.6 g. of an oil of $b.p_{0.002}$ 140~145° was obtained. *Anal.* Calcd. for $C_{20}H_{23}O_3N$: C, 73.85; H, 7.08. Found: C, 73.73; H, 7.31.

Under similar conditions as above, reacting the materials in a sealed tube, β-diisopropylaminoethyl xanthene-9-carboxylate (VIII), β-diethylaminoethyl diphenylacetate (IX), and β-diethylaminoethyl 1-cyclohexylcyclohexane-1-carboxylate (X) were prepared with the results shown in Table V.

TABLE V.

Product	Reactants $R \cdot COOCH_2CH_2Cl$ (g.)	Reactants $NH(R)_2$ (g.)	React. temp. (°C)	Heating (hr.)	Yield (g.)	Mol. formula	Anal. (%) Calcd. C	Calcd. H	Found C	Found H
(VIII)	1.0	0.8 R=*iso*-C_3H_7	100~110	18	0.8	$C_{22}H_{27}O_3N$	74.78	7.65	74.54	7.61
(IX)	2.7	1.7 R=C_2H_5	90~100	12	2.3	$C_{20}H_{25}O_2N$	77.20	8.03	76.97	7.98
(X)	1.8	1.5 R=C_2H_5	115~120	12	1.2	$C_{19}H_{35}O_2N$	73.79	11.32	73.17	11.13

β-Diethylaminoethyl Xanthene-9-carboxylate Methobromide (XI)—A solution of 2.3 g. β-bromoethyl xanthene-9-carboxylate (I) and 1.0 g. diethylmethylamine dissolved in 8 cc. acetone was placed in a sealed tube and heated for 10 hrs. at 95~105°. A small amount of ether was added to the reaction mixture, the crystals that separated out were collected by filtration, and recrystallized from a mixture of EtOH, acetone, and ether to 2.1 g. of leaflet crystals, m.p. 173~175°, showing no depression on admixture with (XI) prepared by the usual method. The analytical values also agreed. *Anal.* Calcd. for $C_{21}H_{26}O_3NBr$: C, 60.00; H, 6.19. Found: C, 59.76; H, 6.24.

By the similar method, β-diethylaminoethyl benzilate methobromide (XII) and β-diethylaminoethyl diphenylacetate methobromide (XIII) were prepared with results shown in Table VI.

TABLE VI.

Product (m.p., °C)	Reactants R·COO-CH_2CH_2Br (g.)	Reactants CH_3N-$(C_2H_5)_2$ (g.)	Acetone (cc.)	React. temp. (°C)	Time (hr.)	Yield (g.)	Mol. formula	Anal. (%) Calcd. C	Calcd. H	Found C	Found H
(XII) 169~170	(III) 3.7	1.6	10	90~100	12	3.4	$C_{21}H_{28}O_3NBr$	59.71	6.63	59.52	6.39
(XIII) 75~78	(IV) 2.0	1.0	8	90~100	15	1.6	$C_{21}H_{28}O_2NBr \cdot \frac{1}{2}H_2O$	60.86	7.00	61.02	6.98

Examination of the Oil obtained on β-Bromoethylation of Benzilic Acid by extended Reflux Time—To a solution of 6.0 g. of benzilic acid and 13.3 g. of ethylenebromohydrin dissolved in 35 cc. CCl_4, 10 drops of conc. H_2SO_4 was added and the mixture was refluxed for 13 hrs. This was worked up as in the case of (III) and an oil of $b.p_{0.001}$ 158~170° was obtained.

To 2.2 g. of the oil thereby obtained, 0.9 g. of diethylmethylamine and 8 cc. acetone were added, sealed in a tube, and heated in a water bath for 14 hrs. The oily substance thereby obtained, assumed to be the ammonium salt, was submitted to paper partition chromatography by the following conditions, and spots were detected at Rf 0.78±0.01 and 0.57±0.01. Method: One-dimensional, ascending. Filter paper: Toyo Roshi No. 50. Developer: BuOH:EtOH:H_2O= 4:1:2. Time: 13 hrs. Temp.: 26°±1°. Detection reagent: Dragendorff reagent.

β-Bromoethyl O-(β'-Bromoethyl)benzilate (XIV)—A solution of 20.0 g. benzilic acid and 43 g. ethylenebromohydrin, dissolved in 130 cc. CCl_4 and added with 7 g. conc. H_2SO_4, was refluxed for 20 hrs., cooled, and treated as in the case for (III). The crude oil thereby obtained was distilled under a reduced pressure and the oil of b.$p_{0.05}$ 160~180° was fractionated twice. The oil of b.$p_{0.05}$ 173~180° obtained here solidified on standing for some time. Its recrystallization from ligroine yielded 18 g. of white crystals melting at 59-61°. *Anal.* Calcd. for $C_{18}H_{18}O_3Br_2$: C, 48.90; H, 4.07. Found : C, 48.69; H, 3.91.

β-Diethylaminoethyl O-(β'-Diethylaminoethyl)benzilate Dimethobromide (XV)—A solution of 1.8 g. of (XIV) and 1.3 g. of diethylmethylamine dissolved in 5 cc. of acetone was heated in a sealed tube at 80~90° for 8 hrs. The oil that separated out crystallized on being left over night. The solvent was removed by decantation, the crystals were washed with a small amount of acetone, and recrystallized from a mixture of EtOH and ether to 1.3 g. of white crystals, m.p. ca. 180°. *Anal.* Calcd. for $C_{28}H_{44}O_3N_2Br_2 \cdot H_2O$: C, 52.99; H, 7.26. Found : C, 52.30; H, 7.71.

β-Dimethylaminoethyl O-(β'-Dimethylaminoethyl)benzilate Dihydrochloride (XVIa)—A mixture of 2.0 g. of (XIV) and 6 g. of 26% EtOH solution of Me_2NH was sealed in a tube and heated at 80~90° for 9 hrs. On cooling, the solvent was evaporated on a water bath, ether was added to the residue, and the crystals that separated out were collected by filtration. The ethereal filtrate was washed with 10 cc. of 5% HCl, the acid layer was basified with K_2CO_3, and the oil that separated out was taken up in ether. After drying over K_2CO_3, ether was evaporated and the residue was submitted to low-pressure distillation, affording 1.2 g. of oil, b.$p_{0.05}$ 150~155°. It formed a dihydrochloride of m.p. ca. 80° from HCl-ether mixture. *Anal.* Calcd. for $C_{22}H_{30}O_3N_2$ (Free base) : C, 71.35; H, 8.11. Found : C, 71.03; H, 7.67. *Anal.* Calcd. for $C_{22}H_{30}O_3N_2 \cdot 2HCl \cdot 2H_2O$ (dihydrochloride) : C, 55.11; H, 7.51. Found : C, 54.68; H, 7.43.

β-Diethylaminoethyl O-(β'-Diethylaminoethyl)benzilate Dihydrochloride (XVIb)—A mixture of 2.0 g. of (XIV) and 2.4 g. of diethylamine was sealed in a tube and heated in a water bath. After about 30 mins. of heating, crystals began to separate out so that the heating was stopped and the mixture was allowed to stand over night. The crystals that separated out were collected by filtration and the filtrate was treated as for (XVIa), from which 1.4 g. of oil, b.$p_{0.02}$ 155-156°, was obtained. It formed a dihydrochloride of m.p. 213~214° from HCl-ether mixture. *Anal.* Calcd. for $C_{26}H_{38}O_3N_2$(Free base) : C, 73.24; H, 8.92. Found : C, 73.05; H, 8.42. *Anal.* Calcd. for $C_{26}H_{38}O_3N_2 \cdot 2HCl$(Dihydrochloride) : C, 62.50; H, 8.02. Found : C, 62.40; H, 7.64.

Reaction of β-Bromoethyl Diphenylacetate (IV) and Diisopropylmethylamine—A solution of 4.0 g. of β-bromoethyl diphenylacetate (IV) and 2.3 g. of diisopropylmethylamine dissolved in 8 cc. of acetone was sealed in a tube and heated in a water bath for 10 hrs. On cooling, the crystals that separated out were collected by filtration and recrystallized from EtOH-ether mixture to 1.2 g. of needles, m.p. 155~156°. *Anal.* Calcd. for $C_7H_{18}NBr$: C, 42.80; H, 9.18; N, 7.15. Found : C, 43.16; H, 9.12; N, 7.35.

The foregoing acetone filtrate was evaporated, the residue was washed several times with water, and a small amount of ether added whereby sparingly soluble crystals separated out. These were recrystallized from ethyl acetate to 1.1 g. of plate crystals melting at 153~154°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88. Found : C, 80.55; H, 5.81.

Summary

1) β-Haloethyl esters of carboxylic acid was formed by the reaction of a carboxylic acid with ethylenehalohydrin in carbon tetrachloride, with a few drops of sulfuric acid as a catalyst. The β-haloethyl carboxylates thereby obtained were reacted with secondary or tertiary amines and several kinds of aminoalkyl carboxylate derivatives possessing antispasmodic action were prepared.

2) In the esterification of benzilic acid with ethylenehalohydrin, only the esterification occurs when the amount of sulfuric acid catalyst is small but in the presence of a large amount of the acid, concurrent etherification was found to occur. This was utilized in preparation of β-bromoethyl O-(β'-bromoethyl)benzilate (XIV) which was reacted with a secondary or tertiary amine and some novel derivatives of aminoalkyl carboxylate were obtained.

3) Application of tertiary amines with branched alkyl chain, such as diisopropylmethylamine, to β-bromoethyl diphenylacetate (IV) failed to cause the anticipated quaternization.

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