Anal. Calcd. for $C_{20}H_{26}O_2N_2$: N, 8.58. Found: N, 8.46.

The monohydrochloride was obtained by the use of the calculated amount of ethereal hydrogen chloride; m.p. 201-202° dec. after recrystallization from acetone.

Anal. Calcd. for $C_{20}H_{27}O_2N_2Cl$: N, 7.72; Cl, 9.77. Found: N, 7.69; Cl, 9.65.

Five grams of the β-dimethylaminoethyl ester hydrochloride was heated in an oil-bath at 210° for 10 minutes. The material was triturated under ether and the insoluble product (1.6 g.) was recrystallized from ethanol–ether; m.p. 201°, mixed m.p. with an authentic sample[15] of diphenyl-(dimethylamino)-methane hydrochloride was 201°. The residue, obtained after removal of the solvent from the ether extract, was sublimed; m.p. 69–70°; the mixed m.p. with an authentic sample[15] of diphenyl-(dimethylamino)-methane was 69–70°.

Ethyl α,β-Diphenylglycidate.—A cooled, stirred mixture of 15.9 g. of benzaldehyde, 29.8 g. of ethyl phenylchloroacetate[16] and 75 cc. of dry ether was treated with 11.6 g. of alcohol-free sodium ethylate at such a rate that the temperature of the mixture could be maintained at 0–4°. After 12 hours at room temperature the ether was removed and the residue was heated on a steam-bath for 1 hour. Ether and dilute acetic acid were added and the mixture was stirred until two clear layers were obtained. The ether layer was separated, washed with sodium bicarbonate solution, dried and distilled; yield 22.8 g. (57%), b.p. 161–163° (2 mm.). m.p. 59–60° after recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.04. Found: C, 75.83; H, 6.04.

The corresponding acid (7.9 g.) was isolated from the bicarbonate wash solution by acidification; m.p. 121–122° dec.[17] after recrystallization from ether–petroleum ether (60–70°).

The methyl ester, prepared by the use of diazomethane, melted at 71–72°[18] after recrystallization from methanol.

α,β-Diphenylglycidic Acid.—The ethyl ester (10.7 g.) was hydrolyzed by the Claisen method.[19] An aqueous solution of the sodium salt obtained (9.7 g., 92%) was acidified; the yield of acid was 8.5 g., m.p. 121–122° dec.[17] after recrystallization from ether–petroleum ether (60–70°).

Anal. Calcd. for $C_{15}H_{12}O_3$: neut. equiv., 240.3. Found: neut. equiv., 242.2.

β-Diethylaminoethyl α,β-Diphenylglycidate Hydrochloride.—This ester was prepared from 2.4 g. of the required acid, 1.4 g. of β-diethylaminoethyl chloride and 35 cc. of chloroform. The hot solution was filtered, the solvent was removed and the residue was recrystallized from chloroform–ether; yield 3.1 g. (82%), m.p. 154–155°.

Anal. Calcd. for $C_{21}H_{26}O_3NCl$: N, 3.73; Cl, 9.43. Found: N, 3.67; Cl, 9.40.

Ethyl α-Methyl-β-phenylglycidate.—Prepared by the method described in the literature,[5a] except that sodamide was employed as the condensation agent, the ester was obtained in 39% yield, b.p. 117–121° (4 mm.).[20]

α-Methyl-β-phenylglycidic Acid.—Hydrolysis of the ethyl ester (15.4 g.) by the Claisen method[19] yielded 13.6 g. of the sodium salt from which the acid was obtained by acidification of its aqueous solution; yield 80%, m.p. 68–69° after recrystallization from petroleum ether (60–70°).

Anal. Calcd. for $C_{10}H_{10}O_3$: neut. equiv., 178.2. Found: neut. equiv., 178.8.

When the acid was heated at 150–160° until gas evolution had ceased (1 hour), it was converted into phenylacetone which was identified by means of its semicarbazone, m.p. 186–187.5°, mixed m.p. with an authentic sample 186–187.5°.

β-Diethylaminoethyl α-Methyl-β-phenylglycidate Hydrochloride.—A mixture of 2.3 g. of the required acid, 1.5 g. of β-diethylaminoethyl chloride and 30 cc. of chloroform was refluxed for 13 hours, filtered, the solvent was removed and the residue was triturated with ether until it solidified; m.p. 115–116° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{16}H_{24}O_3NCl$: N, 4.46; Cl, 11.30. Found: N, 4.36; Cl, 11.39.

ANN ARBOR, MICHIGAN

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[15] M. Sommelet, *Compt. rend.*, **175**, 1149 (1922).

[16] G. Darzens, *ibid.*, **152**, 1601 (1911).

[17] E. P. Kohler and F. W. Brown (THIS JOURNAL, **55**, 4299 (1933)) reported the melting point of one form of this acid as 121°.

[18] Reference 17, m.p. 80° for one form of the ester.

[19] L. Claisen, *Ber.*, **38**, 693 (1905).

[20] Reference 5a, b.p. 153–154° (18 mm.); ref. 5b, b.p. 145.5° (18 mm.).

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. XVIII. Diphenylacetates and *p*-Aminobenzoates of Basic Alkoxyalkanols

BY F. F. BLICKE AND J. H. BIEL[1,2]

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Diphenylacetates, and in some instances *p*-aminobenzoates, of the following alcohols were prepared: 2-(2′-diethylaminoethoxy)-ethanol, 1-dimethylamino-3-methoxy-2-propanol, 2-diethylamino-3-methoxypropanol, 2-methoxy-3-diethylaminopropanol, 1,3-dimethoxy-4-diethylamino-2-butanol and 1-diethylamino-3,4-dimethoxy-2-butanol.

Since it seemed desirable to determine the activity of basic alkoxyalkyl ethers[3] of diphenylacetic acid as antispasmodics, we prepared the diphenylacetates of the following six alcohols: 2-(2′-diethylaminoethoxy)-ethanol (I), 1-dimethylamino-3-methoxy-2-propanol (II), 2-diethylamino-3-methoxypropanol (III), 2-methoxy-3-diethylaminopropanol (IV), 1,3-dimethoxy-4-diethylamino-2-butanol (V) and 1-diethylamino-3,4-dimethoxy-2-butanol (VI). The *p*-nitro- and *p*-aminobenzoates were prepared from alcohols I, II, V and VI, and the benzilate of IV was synthesized.

In order to prepare compound I, 2,2′-dichlorodiethyl ether was heated with sodium acetate whereby 2-(2′-chloroethoxy)-ethyl acetate and 2,2′-diacetoxydiethyl ether were produced. When an alcoholic solution of the former product was heated with diethylamine, compound I was obtained.

The chloride hydrochloride was formed when alcohol I was treated with thionyl chloride. The chloride base cyclized to 1,1-diethylmorpholinium chloride when an attempt was made to distil it; the base also cyclized when it was dissolved in a solvent and the solution was refluxed.

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[1] This paper represents part of a dissertation submitted by J. H. Biel in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1947.

[2] Sterling-Winthrop Fellow.

[3] Very few basic alkoxyalkyl esters have been described in the literature and, with the exception of a series of β-dialkylaminoethoxyethyl *p*-aminobenzoates which were studied by W. H. Horne and R. L. Shriner (THIS JOURNAL, **54**, 2925 (1932); *J. Pharmacol. Exp. Therap.*, **48** 371 (1933)), their pharmacological properties are almost unknown.

Compound II was prepared by interaction of epichlorohydrin with methanol in the presence of sulfuric acid to produce 1-chloro-3-methoxy-2-propanol which was then allowed to react with dimethylamine. Treatment of II with thionyl chloride yielded 1-dimethylamino-2-chloro-3-methoxypropane hydrochloride. When the liberated base was refluxed in isopropyl alcohol, 1,1,4,4-tetramethyl-2,5-di-(methoxymethyl)-piperazinium dichloride was formed.

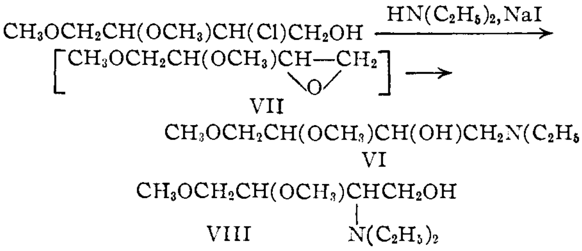
Compound III was synthesized in the following manner. 1-Chloro-3-methoxy-2-propanol was converted into 2-hydroxy-3-methoxypropyl acetate with the aid of sodium acetate. The acetate reacted with phosphorus tribromide to produce 2-bromo-3-methoxypropyl acetate which was transformed into 2-diethylamino-3-methoxypropyl acetate by interaction with diethylamine; hydrolysis of the acetate yielded the alcohol.

By modification of the processes described in the patent literature,[4,5] compound IV was prepared from allyl alcohol. This alcohol was converted, successively, into 2-methoxy-3-acetoxymercuri-, 2-methoxy-3-bromomercuri- and 2-methoxy-3-iodopropanol; the last-mentioned substance reacted with diethylamine to produce the desired alcohol. 2-Methoxy-3-diethylaminopropyl chloride, obtained from IV, showed no tendency to undergo cyclization.

In order to obtain compound V, 1,2-epoxy-3-butene (butadiene monoxide) was allowed to react with methanol and sodium to form 1-methoxy-3-buten-2-ol as described by Kadesch.[6] Interaction of the alcohol with mercuric acetate and methanol produced 1,3-dimethoxy-4-acetoxymercuri-2-butanol which was not isolated but was converted, by reaction with potassium iodide, into 1,3-dimethoxy-4-iodomercuri-2-butanol. This butanol reacted with iodine to form 1,3-dimethoxy-4-iodo-2-butanol which, without isolation, was transformed into 1,3-dimethoxy-4-diethylamino-2-butanol by the use of diethylamine.

Compound VI was prepared in the following manner. Kadesch[6] found that 1,2-epoxy-3-butene reacted with methanol and sulfuric acid to form 2-methoxy-3-buten-1-ol. We converted this alcohol into the sodium derivative which reacted with methyl iodide to yield 1,2-dimethoxy-3-butene. By the action of benzenesulfonic acid, acetic acid and *tert*-butyl hypochlorite, the butene was converted into 2-chloro-3,4-dimethoxybutanol. The nature of this substance as a primary alcohol was shown by its oxidation by nitric acid to 2-chloro-3,4-dimethoxybutyric acid.[7] When 2-chloro-3,4-dimethoxybutanol was treated with a mixture of sodium iodide and diethylamine, 1-diethylamino-3,4-dimethoxy-2-butanol (VI) was produced.

Incidentally, a portion of the 2-chloro-3,4-dimethoxybutanol was converted into 1,2-epoxy-3,4-dimethoxybutane by treatment of the chlorohydrin with sodium methylate. We believe that the epoxy compound VII may have been formed as an intermediate during the preparation of VI and that, in view of the manner in which numerous epoxy compounds have been reported to react with ammonia or an amine, alcohol VI possesses the assigned structure, 1-diethylamino-3,4-dimethoxy-2-butanol, and not that of the isomeric alcohol VIII.



$$CH_3OCH_2CH(OCH_3)CH(Cl)CH_2OH \xrightarrow{HN(C_2H_5)_2,NaI}$$

$$\left[\begin{array}{l}CH_3OCH_2CH(OCH_3)\underbrace{CH—CH_2}_{O}\end{array}\right] \longrightarrow$$

VII

$$CH_3OCH_2CH(OCH_3)CH(OH)CH_2N(C_2H_5)_2$$

VI

$$CH_3OCH_2CH(OCH_3)\underset{\displaystyle N(C_2H_5)_2}{\underset{|}{CH}}CH_2OH$$

VIII

Tested on the isolated rabbit intestine against acetylcholine-induced spasm, the following data was obtained in the Sterling–Winthrop Research Institute Laboratories for the diphenylacetates listed in Table I; maximum effective dilution: compound 1, 1:1,500,000; 2, 1:150,000; 3, 1:300,000; 4, 1:1,500,000; 5, 1:300,000.

Experimental

2-(2′-Chloroethoxy)-ethyl Acetate.—A mixture of 429.0 g. of 2,2′-dichlorodiethyl ether, 168.0 g. of fused sodium acetate and 3 cc. of diethylamine was stirred and heated in an oil-bath at 190° for 13 hours. The mixture was filtered, the inorganic material was washed with ether and the filtrate was fractionated through a 10-inch Vigreux column. There were obtained 185 g. of unchanged ether, b.p. 67–95° (11 mm.), 160.0 g. (47%) of the acetate, b.p. 95–97° (11 mm.)[8] and 70.0 g. of 2,2′-diacetoxydiethyl ether, b.p. 120–122° (12 mm.).[9]

2-(2′-Diethylaminoethoxy)-ethanol (I).—2-(2′-Chloroethoxy)-ethyl acetate (33.2 g.) 44.0 g. of diethylamine and 50 cc. of ethanol were heated in an autoclave at 120–125° for 16 hours. The alcohol was removed, the residue was dissolved in water and the solution was made strongly alkaline. The product was extracted with ether, the extract was dried, the solvent was removed and the residue fractionated; b.p. 90–92° (7 mm.)[10]; yield 28.0 g. (68%). The *p*-nitrophenylurethan hydrochloride melted at 148–150°.[11]

When 25 g. of the alcohol and 25 g. of acetic anhydride were refluxed for 6 hours and the mixture was then fractionated, 15 g. (50%) of the acetate was obtained; b.p. 98–99° (7 mm.).

Anal. Calcd. for $C_{10}H_{21}O_3N$: N, 6.87. Found: N, 6.98.

2-(2′-Diethylaminoethoxy)-ethyl Chloride Hydrochloride.—After a solution of 24.2 g. of the alcohol I in 100 cc. of chloroform had been saturated with hydrogen chloride, 36.0 g. of thionyl chloride was added gradually. The mixture was refluxed for 4 hours and the solvent and excess thionyl chloride were removed under diminished pressure. The oily residue crystallized when it was rubbed under ether. The hygroscopic hydrochloride melted at 54–57°; yield 29.0 g. (91%).

Anal. Calcd. for $C_8H_{19}NCl_2$: Cl, 16.43. Found: Cl, 16.54.

1,1-Diethylmorpholinium Chloride.—A solution of 2.0 g. of the chloride base in 30 cc. of toluene was refluxed for 1 hour, the solvent was removed, the residue was dissolved in isopropyl alcohol and refluxed with Norite for 0.5 hour. The Norite was removed by filtration through Super-Cel, and acetone was added to the filtrate until it became turbid. The quaternary salt precipitated when the mixture was

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(4) German Patent 446,324; *Frdl.*, **15**, 1452.

(5) German Patent 420,447; *Frdl.*, **15**, 1450.

(6) R. G. Kadesch, THIS JOURNAL, **68**, 41 (1946).

(7) This compound was characterized by conversion into the *p*-bromoanilide.

(8) K. Freundenberg and L. Acker (*Ber.*, **74**, 1400 (1941)), b.p. 94–95° (11 mm.).

(9) L. H. Cretcher and W. H. Pittenger (THIS JOURNAL, **47**, 164 (1925)), b.p. 148° (26 mm.).

(10) H. W. Horne and R. L. Shriner (*ibid.*, **54**, 2925 (1932)), b.p. 92–95° (7 mm.).

(11) Reference 10, m.p. 152–153° (cor.).

cooled. The water-soluble, ether-insoluble product melted at 283–285° dec., yield 1.4 g. (70%).

Anal. Calcd. for $C_8H_{18}ONCl$: Cl, 19.72. Found: Cl, 19.58.

1-Dimethylamino-3-methoxy-2-propanol (II).—1-Chloro-3-methoxy-2-propanol[12] (26.0 g.), 28.4 g. of dimethylamine and 100 cc. of absolute ethanol were heated in a citrate bottle on a steam-bath for 24 hours. The solvent and excess dimethylamine were removed, the residue was dissolved in 50 cc. of ether and the solution was treated with hydrogen chloride. The ether layer was decanted from the precipitated oily hydrochloride, the salt was dissolved in 50 cc. of water, the solution was made strongly alkaline with solid sodium hydroxide, and the base was extracted with ether. The extract was dried over anhydrous potassium carbonate. The alcohol boiled at 69–70° (11 mm.), yield 18.0 g. (65%).

Anal. Calcd. for $C_6H_{15}O_2N$: N, 10.52. Found: N, 10.43.

1-Dimethylamino-2-chloro-3-methoxypropane Hydrochloride.—The propanol (20.0 g.) was allowed to react with 36 g. of thionyl chloride in the manner described above. The crude chloride hydrochloride was recrystallized from isopropyl alcohol; yield 23.0 g. (80%), m.p. 153–154°.

Anal. Calcd. for $C_6H_{15}ONCl_2$: Cl, 37.44. Found: Cl, 37.76.

The chloride base boiled at 59–61° (14 mm.).

Anal. Calcd. for $C_6H_{14}ONCl$: N, 9.24. Found: N, 9.29.

1,1,4,4-Tetramethyl-2,5-di-(methoxymethyl)-piperazinium Dichloride.—The propane (7.3 g.) was dissolved in 50 cc. of isopropyl alcohol, the solution was refluxed for 7 hours, the solvent was removed and the residue was recrystallized from acetone and then from acetone–isopropyl alcohol; yield 2.2 g., m.p. 194° dec.

Anal. Calcd. for $C_{12}H_{28}O_2N_2Cl$: Cl^-, 23.43. Found: Cl, 23.32.

2-Hydroxy-3-methoxypropyl Acetate.—1-Chloro-3-methoxy-2-propanol[12] (122.0 g.) and 41.0 g. of fused sodium acetate were heated in an oil-bath at 210° for 4 hours. After filtration, the filtrate was fractionated through a column; yield 56.0 g., b.p. 98–99°.

2-Bromo-3-methoxypropyl Acetate.—To a stirred solution of 53.2 g. of the hydroxy acetate in 50 cc. of chloroform, 32.5 g. of phosphorus tribromide was added during a period of 1 hour. The mixture was stirred for 18 hours at room temperature and then heated at 70° for 2 hours. The chloroform solution was washed thoroughly with water and then with sodium bicarbonate solution. The product boiled at 56–58° (2 mm.), yield 49.0 g. (65%).

Anal. Calcd. for $C_6H_{11}O_3Br$: Br, 37.87. Found: Br, 38.51.

2-Diethylamino-3-methoxypropyl Acetate.—A mixture of 75.6 g. of the bromo compound, 129.0 g. of diethylamine and 180 cc. of benzene was refluxed for 46 hours. The solvent and excess diethylamine were removed from the filtered mixture. The residue was dissolved in hydrochloric acid, the solution was extracted with ether and the ether extract was discarded. The base was liberated by the addition of solid sodium hydroxide and then extracted with ether. The product boiled at 83–86° (7 mm.), yield 28.0 g. (39%).

Anal. Calcd. for $C_{10}H_{21}O_3N$: N, 6.99. Found: N, 7.03.

2-Diethylamino-3-methoxypropanol (III).—The acetate (10.2 g.), 5.6 g. of potassium hydroxide and 50 cc. of 80% aqueous methanol were refluxed for 7 hours. After removal of the solvent, the residue was extracted with ether and the extract dried; the product boiled at 78–80° (10 mm.), yield 8.0 g. (90%).

Anal. Calcd for $C_8H_{19}O_2N$: N, 8.70. Found: N, 8.59.

2-Methoxy-3-bromomercuripropanol.[13]—To a mixture of 74.0 g. of mercuric acetate and 50 cc. of methanol there was added 11.6 g. of allyl alcohol dissolved in 40 cc. of methanol. After 30 minutes, ionic mercury could no longer be detected. The methanol was distilled and the residue was dissolved in 200 cc. of water. The solution was neutralized with 34 g. of sodium bicarbonate, filtered and 28.0 g. of potassium bromide was added to the filtrate while the temperature of the mixture was maintained at 10–15°. The oily brown precipitate crystallized after the material had been kept in a refrigerator. The product was filtered and washed with water; yield 64.0 g. (86%). A small portion was recrystallized from ethyl acetate; m.p. 69–71°.

2-Methoxy-3-diethylaminopropanol (IV).—Iodine (104.0 g.) was added to a mixture of 131.0 g. of the crude bromomercuri compound and 400 cc. of chloroform and the mixture was stirred and refluxed for 20 minutes. After filtration and the addition of 500 cc. of 95% ethanol to the filtrate, the brown color was removed by treatment with 10 g. of sodium bisulfite. The solution was concentrated to a volume of 200 cc. and, after filtration, 79.0 g. of diethylamine was added. After 12 hours at room temperature, the mixture was refluxed for 12 hours. Ethanol and excess diethylamine were removed by distillation under reduced pressure and the oily residue was dissolved in 150 cc. of water. After the addition of 15 cc. of concd. hydrochloric acid, the solution was extracted with ether to remove any neutral material. The acidic solution was made strongly alkaline with solid sodium hydroxide and then extracted with ether. The extract was dried over anhydrous potassium carbonate. The product boiled at 76–77° (5 mm.),[14] yield 37.0 g. (78%).

2-Methoxy-3-diethylaminopropyl Chloride.—Prepared in the manner described above, 22.7 g. of the alcohol and 37.6 g. of thionyl chloride yielded 27.0 g. (89%) of the chloride hydrochloride; m.p. 104–106° after recrystallization from acetone–ether.

Anal. Calcd. for $C_8H_{19}ONCl_2$: Cl, 16.44. Found: Cl, 16.32.

The crude chloride hydrochloride was dissolved in water and the base was liberated by the addition of solid sodium hydroxide; b.p. 69–70° (6 mm.).

Anal. Calcd. for $C_8H_{18}ONCl$: N, 7.80; Cl, 19.77. Found: N, 7.38; Cl, 19.72.

1,3-Dimethoxy-4-iodomercuri-2-butanol.—1-Methoxy-3-buten-2-ol[6] (102.0 g.), 320 g. of mercuric acetate and 1.5 l. of methanol were shaken vigorously for 30 minutes. The excess methanol was removed by distillation under reduced pressure. The oily residue was shaken with 500 cc. of water, 84 g. of sodium bicarbonate and Super-Cel, filtered, the filtrate was cooled to 5° and 150 g. of potassium iodide, dissolved in 150 cc. of water, was added. The oily, yellow precipitate became crystalline after it had been cooled for 6 days in a refrigerator. The filtered material was recrystallized from a mixture of 200 cc. of acetone and 100 cc. of water; yield 143.0 g. (31%), m.p. 62–66°. A small portion was recrystallized from aqueous acetone; m.p. 68–71°.

Anal. Calcd. for $C_6H_{13}O_3IHg$: Hg, 43.56. Found: Hg, 43.25.

1,3-Dimethoxy-4-diethylamino-2-butanol (V).—A mixture of 50.8 g. of iodine, 92.0 g. of crude 1,3-dimethoxy-4-iodomercuri-2-butanol and 150 cc. of chloroform was stirred rapidly and heated at 35–40° for 1.5 hours. It was then refluxed until the mixture became colorless. The precipitated mercuric iodide was filtered and the chloroform was removed from the filtrate by distillation under reduced pressure. Diethylamine (44.0 g.) was added to the residue and, after 12 hours, the material was refluxed for 8 hours. After removal of the excess diethylamine by distillation, 100 cc. of absolute ethanol and 75 cc. of 2.67 *N* alcoholic potassium hydroxide solution was added. The precipitated potassium iodide was filtered and the alcohol was removed from the filtrate. The residue was dissolved in 100 cc. of dry ether and 53 cc. of 3.46 *N* ethereal hydrogen chloride was added. The precipitated oil was washed thoroughly with ether, then dissolved in 100 cc. of absolute alcohol and 40 cc. of 3.3 *N* alcoholic potassium hydroxide added. The precipitated potassium chloride was filtered and the alcohol was removed from the filtrate; b.p. 97–98° (6 mm.), yield 25.0 g. (54%).

Anal. Calcd. for $C_{10}H_{23}O_3N$: N, 6.83. Found: N, 6.54.

1,2-Dimethoxy-3-butene.—Sodium powder (46.6 g.) was suspended in 200 cc. of ether, stirred and 207.0 g. of 2-methoxy-3-buten-1-ol[6] was added at such a rate that the mix-

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[12] E. Fourneau and I. Ribas, *Bull. soc. chim.*, **39**, 1584 (1926). We found that this compound boils at 169–172° (740 mm.).

[13] This process represents a modification of that found in the patent literature ref. 5.

[14] Reference 5, b.p. 62–63° (1.2 mm.).

ture boiled. The stirring was continued and 332 g. of methyl iodide was added. After the mixture had been stirred and refluxed for 2 hours, the sodium iodide was filtered and washed with ether. After removal of the solvent, the product boiled at 117–119° (740 mm.), yield 163.0 g. (70%).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.06; H, 10.34. Found: C, 61.81; H, 10.23.

2-Chloro-3,4-dimethoxybutanol.—*t*-Butyl hypochlorite[15] (145 g.) was added to a stirred mixture of 115.0 g. of 1,2-dimethoxy-3-butene, 149 g. of acetic acid, 1 g. of benzenesulfonic acid and 1,400 cc. of water during a 5-hour period and the mixture was kept at 0–3°. After 12 hours, the mixture was neutralized with 210 g. of sodium bicarbonate. After the addition of ammonium sulfate to decrease the solubility of the chlorohydrin, the mixture was extracted with ether and the extract dried with magnesium sulfate. After removal of the solvent, the product boiled at 97–108° (8 mm.), yield 165.0 g. (70%).

Anal. Calcd. for $C_6H_{13}O_3Cl$: Cl, 21.07. Found: Cl, 21.28.

1,2-Epoxy-3,4-dimethoxybutane.—Sodium (2.3 g.) was added gradually (through the condenser) to 16.8 g. of 2-chloro-3,4-dimethoxybutanol dissolved in 50 cc. of methanol. The solvent was removed from the filtered mixture and the residue was distilled; b.p. 59–62° (10 mm.) or 74–76° (25 mm.), yield 6.0 g. (40%).

Anal. Calcd. for $C_6H_{12}O_3$: C, 54.40; H, 9.09. Found: C, 54.22; H, 9.01.

2-Chloro-3,4-dimethoxybutyric Acid.—To 67 g. of concd. nitric acid, which was stirred and heated to 105°, there was added 24 g. of 2-chloro-3,4-dimethoxybutanol during a period of 1 hour. As soon as oxides of nitrogen were evolved, the temperature was allowed to drop to 70–75° and then maintained there until all of the chlorohydrin had been added. The mixture was stirred for 2 hours at 70° and for 3 hours at room temperature. The nitric acid was removed under reduced pressure and the residue was fractionated; b.p. 115–117° (2 mm.), yield 11 g. (42%).

Anal. Calcd. for $C_6H_{11}O_4Cl$: Cl, 19.40; neut. equiv., 182. Found: Cl, 18.94; neut. equiv., 183.

2-Chloro-3,4-dimethoxybutyr-*p*-bromoanilide.—A mixture of 1.0 g. of the butyric acid and 2 cc. of thionyl chloride was refluxed for 30 minutes, the excess thionyl chloride was removed under reduced pressure and 2.0 g. of *p*-bromoaniline, dissolved in 30 cc. of benzene, was added to the residue. After the material had been refluxed for 2 minutes, the precipitated *p*-bromoaniline hydrochloride was filtered. The filtrate was washed successively with 5% hydrochloric acid and 5% aqueous sodium hydroxide solution. After removal of the benzene, the residue was recrystallized from 50% methanol with the use of Norite; yield 0.5 g., m.p. 89–92°.

Anal. Calcd. for $C_{12}H_{15}O_3NClBr$: N, 4.16; total halogen, 34.30. Found: N, 4.12; total halogen, 34.00.

1-Diethylamino-3,4-dimethoxy-2-butanol (VI).—A mixture of 40.0 g. of 2-chloro-3,4-dimethoxybutanol, 71.0 g. of sodium iodide, 70.0 g. of diethylamine and 125 cc. of absolute ethanol was heated in a citrate bottle at 100° for 24 hours. The alcohol and excess amine were removed by distillation under reduced pressure and the residue was dissolved in water. The solution was made strongly alkaline with solid sodium hydroxide and then extracted with ether. The dried extract was treated with ethereal hydrogen chloride and the ether layer was decanted from the oily precipitate. The oil was washed with ether, dissolved in water and the aqueous solution was made alkaline. After extraction with ether, the extract was dried and the solvent removed; b.p. 72–73° (2 mm.), yield 29.0 g. (60%), $n^{21}{}_D$ 1.4442.

Anal. Calcd. for $C_{10}H_{23}O_3N$: N, 6.83. Found: N, 6.81.

Diphenylacetate Hydrochlorides.—Diphenylacetyl chloride[16] (0.083 mole), dissolved in 40 cc. of ether, was stirred and 0.083 mole of the required alcohol (I, II, III or IV), dissolved in 40 cc. of the same solvent, was added gradually (through the condenser). The mixture was refluxed for 1 hour, cooled in an ice-bath, the precipitate was filtered and recrystallized.

When alcohol V was employed, 50 cc. of benzene was used instead of ether. When the ester was prepared from VI, benzene was used as the solvent and the reaction mixture was refluxed for 24 hours.

***p*-Nitrobenzoate Hydrochlorides.**—A mixture of 0.06 mole of *p*-nitrobenzoyl chloride, 0.06 mole of the required alcohol and 80 cc. of ether was refluxed for 1 hour and then cooled in an ice-bath.

Benzene was used as a solvent for the preparation of the ester from V and the mixture was refluxed for 2 hours.

In order to obtain the ester from VI, 0.10 molar amounts of the reactants in 35 cc. of benzene were refluxed for 36 hours. The benzene was removed, the residue was dissolved in dry acetone, the solution was treated with Norite, filtered and the filtrate clarified with Super-Cel; ether was added to the solution until it became turbid.

***p*-Aminobenzoate Hydrochlorides.**—The *p*-nitrobenzoate hydrochloride (0.03 mole), dissolved in 125 cc. of water, was hydrogenated in the presence of 1 g. of palladium–carbon catalyst[17] under an initial pressure of 3 atmospheres. The catalyst was filtered in a nitrogen atmosphere and the water was removed under reduced pressure. The product was dissolved in isopropyl alcohol and the solution was decolorized with Norite.

In the case of the *p*-nitrobenzoate obtained from V, the solvent was 100 cc. of absolute ethanol and the catalyst was 0.5 g. of platinum oxide

2-Methoxy-3-diethylaminopropyl Benzilate.—2-Methoxy-3-diethylaminopropyl chloride (12.0 g.), 15.3 g. of benzilic acid and 150 cc. of dry isopropyl alcohol were refluxed for 42 hours, the alcohol was removed and the residue was dissolved in water. The solution was made alkaline with sodium carbonate and then extracted with ether. From the extract 8.5 g. (34%) of the ester was obtained, b.p. 186–188° (0.2 mm.).

Anal. Calcd. for $C_{22}H_{29}O_4N$: N, 3.77. Found: N, 3.60.

The ester base (6.8 g.), dissolved in 50 cc. of ether, was mixed with 5.8 cc. of 25% alcoholic hydrogen bromide. The oily precipitate crystallized after several days in a refrigerator; m.p. 119–121° after recrystallization from acetone–ether.

Anal. Calcd. for $C_{22}H_{30}O_4NBr$: N, 3.10; Br, 17.68. Found: N, 3.30; Br, 17.95.

TABLE I

DIPHENYLACETATE HYDROCHLORIDES

Compounds 1, 3, 4, 5, 6, 9 and 10 were recrystallized from acetone–ether, 8 and 14 from acetone, 2 from alcohol–ether, 12 from isopropyl alcohol, 13 from isopropyl alcohol–acetone.

	Prepared from	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	I	82–84	80	$C_{22}H_{30}O_3NCl$	3.57	3.50	9.10	9.29
2	II	163–165	78	$C_{20}H_{26}O_3NCl$	3.86	4.01	9.78	10.06
3	III	95–97	30	$C_{22}H_{30}O_3NCl$	3.57	3.49	9.07	9.29
4	IV	120–121	70	$C_{22}H_{30}O_3NCl$	3.57	3.43	9.07	8.97
5	V	112–114	50	$C_{24}H_{34}O_4NCl$	3.23	3.10	8.15	8.20
6	VI	112–114	50	$C_{24}H_{34}O_4NCl$	3.23	3.19	8.15	8.14
				p-Nitrobenzoate hydrochlorides				
7	I	128–129[a]						
8	II	164–165	57	$C_{13}H_{19}O_5N_2Cl$			11.14	11.13
9	V	122–123	74	$C_{17}H_{27}O_6N_2Cl$			9.09	9.22
10	VI	119–122	72	$C_{17}H_{27}O_6N_2Cl$			9.07	9.20
				p-Aminobenzoate hydrochlorides				
11	I	152–153[b]						
12	II	159–161	95	$C_{13}H_{21}O_3N_2Cl$	9.70	9.92	12.29	12.39
13	V	183–184	86	$C_{17}H_{29}O_4N_2Cl$	7.77	7.62	9.85	9.83
14	VI	167–168	78	$C_{17}H_{29}O_4N_2Cl$	7.77	7.65	9.85	9.97

[a] A. J. W. Headlee, A. R. Collett and C. L. Lazzell, THIS JOURNAL, **55**, 1066 (1933), m.p. 128.5°. [b] Through an oversight this compound was not analyzed.

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[15] W. E. Hanby and H. N. Rydon, *J. Chem. Soc.*, 114 (1946).

[16] H. Staudinger and K. Clar, *Ber.*, **44**, 1622 (1911).

[17] W. H. Hartung, THIS JOURNAL, **50**, 3372 (1928).