The hydrochloride was prepared by the addition of a slight excess of ethereal hydrogen chloride to an ethereal solution of the base; m.p. 155–156° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{21}H_{26}O_2NClBr$: N, 3.19; Cl^-, 8.06. Found: N, 3.07; Cl^-, 7.99.

The methobromide, obtained in 55% yield by interaction of the base and methyl bromide in alcoholic solution, melted at 90.5–92° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{22}H_{27}O_2NBr_2$: N, 2.82; Br , 16.07. Found: N, 2.75; Br^-, 16.08.

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

Antispasmodics. XVII. β-Diethylaminoethyl Esters of Substituted Acetic and Glycidic Acids

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Esters of the general formula $C_6H_5CHXCOOCH_2CH_2N(C_2H_5)_2$, in which X represents chlorine, bromine, dimethylamino, piperidino or morpholino, were prepared. In addition, β-diethylaminoethyl esters of the following acids were synthesized: diphenylchloroacetic, diphenylbromoacetic, diphenylethoxyacetic, diphenyl-(dimethylamino)-acetic, α,β-diphenylglycidic and α-methyl-β-phenylglycidic acids.

The antispasmodic activity of β-diethylaminoethyl phenylacetate is enhanced to a great extent by the introduction of a second substituent, such as phenyl, cyclohexyl or thienyl, into the acyl radical of the ester. The effect of the introduction of substituents which are not hydrocarbon radicals has not been studied very extensively. During this investigation we prepared esters of the general formula $C_6H_5CHXCOOCH_2N(C_2H_5)_2$ in which X represents chlorine, bromine, dimethylamino, piperidino or morpholino.

Furthermore, it was of interest to determine the effect of the replacement of the hydroxyl group in the highly active β-diethylaminoethyl diphenylhydroxyacetate by such groups as bromine, ethoxy and dimethylamino. Hence the β-diethylaminoethyl esters of diphenylbromo-, diphenylethoxy and diphenyl-(dimethylamino)-acetic acids were prepared; in addition, the β-dimethylaminoethyl ester of the last-named acid was synthesized.

Interaction of phenylbromoacetyl bromide with β-diethylaminoethanol yielded β-diethylaminoethyl phenylbromoacetate hydrobromide. The oily ester base partially solidified after two days at room temperature. Since the solid portion of the material was water-soluble, and contained ionizable bromine, it may have been the quaternary salt, 3-phenyl-4-ethyl-2-morpholone ethobromide, formed by cyclization of the ester.

β-Diethylaminoethyl phenylbromoacetate reacted with dimethylamine, piperidine and morphine to form the salts of the β-diethylaminoethyl esters of phenyldimethylamino-, phenylpiperidino- and phenylmorpholinoacetic acids, respectively.

β-Dimethylaminoethyl and β-diethylaminoethyl diphenylchloroacetate hydrochlorides were prepared by treatment of the corresponding diphenylhydroxyacetate (benzilate) hydrochlorides with thionyl chloride. The β-diethylaminoethyl ester hydrochloride, which was obtained also from β-diethylaminoethanol and diphenylchloroacetyl chloride, was converted, very rapidly and practically quantitatively in aqueous solution, into β-diethylaminoethyl benzilate hydrochloride.[3]

Treatment of β-diethylaminoethyl diphenylhydroxyacetate hydrochloride with hydrogen bromide converted the compound into β-diethylaminoethyl diphenylbromoacetate hydrobromide. The bromo derivative reacted with ethanol and with dimethylamine, respectively, to form the β-diethylaminoethyl esters of diphenylethoxy- and diphenyl-(dimethylamino)-acetic acids.

β-Dimethylaminoethyl diphenyl-(dimethylamino)-acetate hydrochloride was heated at 210° for 10 minutes; diphenyl-(dimethylamino)-methane and its hydrochloride were isolated as products of pyrolysis.

Even though β-diethylaminoethyl β,β-diphenylglycidate[4] did not prove to be a highly active compound, it seemed desirable to study basic esters of other glycidic acids for antispasmodic activity. Accordingly, the β-diethylaminoethyl esters of α,β-diphenylglycidic and α-methyl-β-phenylglycidic acids were prepared. Condensation of benzaldehyde with ethyl phenylchloroacetate and with ethyl α-chloropropionate, respectively, yielded ethyl α,β-diphenylglycidate and α-methyl-β-phenylglycidate.[5] Each glycidate was hydrolyzed to the corresponding glycidic acid which was then esterified with β-diethylaminoethyl chloride to form the basic ester.

The basic esters were tested for antispasmodic activity at the Sterling–Winthrop Research Institute. All of the esters, tested against acetylcholine-induced spasm in an isolated intestinal strip, were ineffective in a dilution greater than 1:1,000,000 with two exceptions: β-diethylaminoethyl diphenylchloroacetate hydrochloride and the corresponding bromo derivative. The former ester was active in a dilution of 1:50,000,000, the latter in a dilution of 1:63,000,000. When the two last-mentioned compounds were tested, we were not aware of the speed with which the chloro derivative reacts

(1) A portion of this paper represents part of a dissertation submitted by J. A. Faust in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1949.

(2) We are indebted to the Sterling-Winthrop Research Institute for support during this investigation.

(3) See F. E. King and D. Holmes, *J. Chem. Soc.*, 164 (1947).

(4) F. F. Blicke and J. A. Faust, THIS JOURNAL, **76**, 3156 (1954).

(5) (a) G. Darzens, *Compt. rend.*, **142**, 214 (1906); (b) G. Richard, *ibid.*, **199**, 71 (1934).

with water.[6] It seems very probable now that, after solutions of the salts were made, both the chloro- and bromoacetates were converted into the benzilate, and that the high activity found was due to the presence of this ester.

Experimental

β-Diethylaminoethyl Phenylbromoacetate Hydrobromide.—A solution of 6.9 g. of β-diethylaminoethanol in 50 cc. of dry ether was added to a stirred solution of 16.3 g. of phenylbromoacetyl bromide[7] in 150 cc. of ether at such a rate that the mixture could be maintained at 25°. After the mixture had been stirred for 1 hour, the solid (20 g., 86%) was recrystallized four times from ethanol–ether; m.p. 105–107°.

Anal. Calcd. for $C_{14}H_{21}O_2NBr_2$: N, 3.55; Br, 40.45. Found: N, 3.58; Br, 40.88.

β-Diethylaminoethyl phenylbromoacetate, which had been obtained from 5 g. of the hydrobromide, partially solidified after 2 days at room temperature. The water-soluble, solid portion was washed with ether, dissolved in ethanol and the solution treated with Norite, and the material was then recrystallized from ethanol–ether; yield 1.2 g. (30%), m.p. 191–192°.

Anal. Calcd. for $C_{14}H_{20}O_2NBr$[8]: N, 4.46; Br^-, 25.43. Found: N, 4.55; Br^-, 25.18.

β-Diethylaminoethyl Phenyl-(dimethylamino)-acetate Dihydrochloride.—A mixture of 8.0 g. of β-diethylaminoethyl phenylbromoacetate, 10 g. of anhydrous dimethylamine and 50 cc. of chloroform was heated in a citrate bottle on a steam-bath for 5 hours. The solvent was removed, the residue was treated with water and the insoluble oil was extracted with ether. The ethereal solution was washed with water, dried and distilled; yield 4.7 g. (67.5%), b.p. 104–107° (0.1 mm.).

The dihydrochloride was obtained by the addition of ethereal hydrogen chloride to an ethereal solution of the base; m.p. 194–195° dec. after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{16}H_{28}O_2N_2Cl_2$: N, 7.98; Cl, 20.18. Found: N, 7.98; Cl, 20.29.

β-Diethylaminoethyl Phenylpiperidinoacetate Dihydrochloride.—The ester base was obtained from 6.3 g. of the bromoacetate, 10 g. of piperidine and 50 cc. of chloroform in the manner described above; yield 5.0 g. (78%), b.p. 132–136° (0.01 mm.).

The dihydrochloride melted at 194–195° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{19}H_{32}O_2N_2Cl_2$: N, 7.16; Cl, 18.12. Found: N, 7.20; Cl, 18.18.

β-Diethylaminoethyl Phenylmorpholinoacetate Dihydrochloride.—When 10.5 g. of morpholine was added to 8.0 g. of the bromoacetate, dissolved in 50 cc. of chloroform, a solid separated almost immediately. The mixture was heated for 5 hours on a steam-bath, water was added, the chloroform layer was separated, the solvent was removed and the residue distilled; yield 7.0 g. (86%), b.p. 129–132° (0.01 mm.).

The dihydrochloride melted at 170–171° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{18}H_{30}O_3N_2Cl_2$: N, 7.12; Cl, 18.03. Found: N, 7.25; Cl, 17.77.

The methobromide was obtained when a mixture of 3.2 g. of the ester base, 0.95 g. of methyl bromide and chloroform was allowed to remain at room temperature for 2 days. After removal of the solvent, the oily residue was triturated with ether and then recrystallized from isopropyl alcohol–ether; yield 2.6 g., m.p. 144–146°.

Anal. Calcd. for $C_{19}H_{31}O_3N_2Br$: N, 6.75; Br, 19.24. Found: N, 6.84; Br, 19.89.

β-Diethylaminoethyl and β-Dimethylaminoethyl Diphenylchloroacetate Hydrochlorides. (a).—A solution of 15.0 g. of β-diethylaminoethyl benzilate hydrochloride[9] and 6.1 g. of thionyl chloride in 100 cc. of chloroform was refluxed for 3 hours, the solvent was removed under reduced pressure and the residue was washed with ether; m.p. 152–153°[10] after recrystallization from acetone

(b).—A solution of 7.2 g. of β-diethylaminoethanol in 20 cc. of benzene was added, dropwise, over a period of 30 minutes to a stirred solution of 16.1 g. of diphenylchloroacetyl chloride,[11] dissolved in 100 cc. of benzene, while the temperature of the mixture was maintained at 25–35°. The solvent was removed and the oily residue was triturated under acetone whereupon it became solid. In order to purify the product, it was necessary to liberate the ester base, dissolve it in ether and wash the ethereal solution several times with water. The dried ethereal solution was then treated with hydrogen chloride and the precipitated salt was recrystallized from acetone[12]; m.p. 152.5–153.5°.

A solution of 1.0 g. of β-diethylaminoethyl diphenylchloroacetate hydrochloride in 50 cc. of water was allowed to remain at room temperature for 5 minutes. Sodium chloride (10 g.) was added and the precipitate was extracted with chloroform. The solution was dried over magnesium sulfate and the solvent was removed. The residue (0.8 g.) was recrystallized from chloroform–ether; m.p. 178–179°.[13] A mixed melting point with an authentic sample of β-diethylaminoethyl benzilate hydrochloride showed no depression.

In order to obtain the β-dimethylaminoethyl ester, a mixture of 22.8 g. of β-dimethylaminoethyl benzilate hydrochloride,[14] 10.1 g. of thionyl chloride and chloroform was refluxed for 10 hours and then treated in the described manner; m.p. 183–184° after recrystallization from chloroform–ether.

Anal. Calcd. for $C_{18}H_{21}O_2NCl_2$: N, 3.95; Cl, 20.00. Found: N, 3.90; Cl, 19.82.

β-Diethylaminoethyl Diphenylbromoacetate Hydrobromide.—A suspension of 3.6 g. of diethylaminoethyl benzilate hydrochloride[9] in 35 cc. of chloroform was cooled in an ice-bath and saturated with hydrogen bromide. After 19 hours at 0–10° and 10 hours at room temperature, the solvent was removed. The residue was recrystallized from chloroform–ether; yield 4.3 g. (91%), m.p. 164–165°.

Anal. Calcd. for $C_{20}H_{25}O_2NBr_2$: N, 2.97; Br, 33.92. Found: N, 3.12; Br, 34.20.

β-Diethylaminoethyl Diphenylethoxyacetate Hydrobromide.—A solution of 2.3 g. of the bromoacetate hydrobromide in 50 cc. of absolute ethanol was refluxed for 1 hour. The solution was then concentrated and diluted with ether. The precipitate weighed 1.9 g., m.p. 150–151°.

Anal. Calcd. for $C_{22}H_{30}O_3NBr$: N, 3.21; Br, 18.32. Found: N, 3.15; Br, 18.28.

β-Diethylaminoethyl and β-Dimethylaminoethyl Diphenyl-(dimethylamino)-acetate Hydrochlorides and Methobromide.—β-Diethylaminoethyl diphenylbromoacetate (3.3 g.), 8.0 g. of anhydrous dimethylamine and 50 cc. of chloroform were heated in a citrate bottle on a steam-bath for 10 hours; yield 1.7 g. (68%), b.p. 152–153° (0.01 mm.).

The monohydrochloride, obtained by the use of the calculated amount of ethereal hydrogen chloride, melted at 182–183° dec. after recrystallization from acetone.

Anal. Calcd. for $C_{22}H_{31}ON_2Cl$: N, 7.17; Cl, 9.08. Found: N, 7.09; Cl, 9.15.

The methobromide melted at 190–192° dec. after recrystallization from acetone.

Anal. Calcd. for $C_{23}H_{33}O_2N_2Br$: N, 6.24; Br, 17.78. Found: N, 6.28; Br, 17.53.

The β-dimethylaminoethyl ester was prepared in the described manner from 15.0 g. of β-dimethylaminoethyl diphenylchloroacetate, 19.1 g. of dimethylamine and chloroform; yield 10.2 g. (73.5%), b.p. 160° (0.01 mm.).

(6) In view of the ease with which this reaction takes place, it is not surprising to note that identical antispasmodic, antihistamine and toxicity data have been reported for the β-diethylaminoethyl esters of diphenylchloroacetic and benzilic acids (R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943)).

(7) J. B. Cohen, *J. Chem. Soc.*, **99**, 1058 (1911).

(8) Calcd. for 3-phenyl-4-ethyl-2-morpholone ethobromide.

(9) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1644 (1938).

(10) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943), m.p. 149–151°.

(11) H. Bickel, *Ber.*, **22**, 1537 (1889).

(12) This method had been used previously (ref. 10) but no experimental details were reported and it was stated that the salt could not be recrystallized.

(13) Reference 9, m. p. 173–174.5°; ref. 10, m. p. 177–178°.

(14) F. F. Blicke and H. M. Kaplan, THIS JOURNAL, **65**, 1967 (1943).

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.

(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.

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.

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

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

ANN ARBOR, MICHIGAN

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

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

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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.

(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.