β,β-Diphenylglycidamide (IX).—A mixture of 4 g. of ethyl β,β-diphenylglycidate, 40 cc. of ethanol and 25 cc. of 28% ammonia water was allowed to remain at room temperature for 3 days. The mixture was cooled, saturated with ammonia and, after 24 hours, was concentrated. The precipitated amide was recrystallized from ethanol; yield 2 g. (56%), m.p. 148–149°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.86. Found: N, 5.83.

Diphenylpyruvamide (X). (a).—The glycidamide (IX, 0.2 g.) was heated at 175° for 5 minutes in a slow stream of hydrogen chloride. The material, which solidified when cooled, was recrystallized from ethanol; yield 0.15 g. (75%), m.p. 167–168°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.86. Found: N, 5.78.

(b).—A solid began to separate almost immediately when 25 cc. of 28% ammonia water was added to 4 g. of ethyl diphenylpyruvate dissolved in 25 cc. of ethanol. After 12 hours, the precipitated amide was recrystallized from ethanol; yield 3.2 g. (89%), m.p. 167–168°, mixed m.p. 167–168°.

(c).—When ethyl β,β-diphenylglycidimino ether hydrochloride (XIII) (described below) was heated at 120–140° until the gas evolution had ceased (5–10 minutes), it was converted into diphenylpyruvamide, m.p. 167–168° after recrystallization from ethanol, mixed m.p. 167–168°.

Ethyl β,β-Diphenylglycerate (XI) and β,β-Diphenylglyceramide.—Ethyl β,β-diphenylglycidate (5.4 g.) was suspended in 70 cc. of water, which had been acidified with hydrochloric acid, and the suspension was stirred and refluxed for 1 hour. The suspended oil solidified when the mixture was cooled; yield 5.5 g. (91%), m.p. 130–131°[20] after recrystallization from methanol.

The corresponding amide was obtained when 2.9 g. of the ester XI, 14 cc. of 28% ammonia water and 50 cc. of ethanol were allowed to remain at room temperature for 10 days; the solvent was removed and the residue was recrystallized from ethyl acetate–petroleum ether (60–70°). The amide (1 g., 38%) melted at 173–174°.

(20) Reference 7, m.p. 130°.

Anal. Calcd. for $C_{15}H_{15}O_3N$: N, 5.45. Found: N, 5.29.

β,β-Diphenylglyceric Acid.—A mixture of 12 g. of ethyl β,β-diphenylglycerate, 9 g. of sodium carbonate and 100 cc. of water was stirred and refluxed for one-half hour, cooled and then filtered. The alkaline filtrate was clarified by ether extraction and then acidified. The precipitated acid (4.9 g., 45%) melted at 177–178° dec. after recrystallization from dil. ethanol.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46; neut. equiv., 258.3. Found: C, 69.91; H, 5.55; neut. equiv., 259.3.

β-Diethylaminoethyl β,β-Diphenylglycerate Hydrochloride.—The glyceric acid (3.5 g.), 1.8 g. of β-diethylaminoethyl chloride and 35 cc. of isopropyl alcohol were allowed to react in the usual manner[9]; yield 3.6 g. (70%), m.p. 194–195° dec.

Anal. Calcd. for $C_{21}H_{28}O_4NCl$: N, 3.56; Cl, 9.02. Found: N, 3.47; Cl, 8.94.

β,β-Diphenylglycidonitrile (XII).—Benzophenone (72.9 g.), 30.2 g. of chloroacetonitrile, 150 cc. of dry ether and 28 g. of sodium ethylate were allowed to react in the manner described for the preparation of ethyl β,β-diphenylglycidate. The nitrile boiled at 124–126° (0.01 mm.), yield 74 g. (84%).

Ethyl β,β-Diphenylglycidimino Ether Hydrochloride (XIII).—A mixture of 2.21 g. of the nitrile (XII), 0.46 g. of absolute ethanol, 0.37 g. of hydrogen chloride and 45 cc. of absolute ether was allowed to remain in a refrigerator for 5 hours. The precipitate was washed with dry ether; yield 1.4 g. (46%), m.p. 108–109° dec.

Anal. Calcd. for $C_{17}H_{18}O_2NCl$: N, 4.61. Found: N, 4.56

When 0.1 g. of the imino ether salt was dissolved in 7 cc. of water, 0.05 g. (57%) of ethyl β,β-diphenylglycidate precipitated; m.p. 47–49° after recrystallization from ethanol, mixed m.p. 47–49°.

ANN ARBOR, MICHIGAN

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

Antispasmodics. XVI. β-Diethylaminoethyl Esters of Substituted Lactic and Acrylic Acids

BY F. F. BLICKE AND J. A. FAUST[1,2]

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The preparation of β-diethylaminoethyl esters of α-methyl-β,β-diphenyllactic, α,β,β-triphenyllactic, α,β,β-triphenylacrylic and α-bromo-β,β-diphenylacrylic acids has been described.

Since basic alkyl esters of diphenyl- and diphenylhydroxyacetic acids are highly active antispasmodics, it was decided to prepare basic esters of phenyl-substituted lactic and acrylic acids.

α-Methyl-β,β-diphenyllactic acid (m.p. 167–168.5°) was obtained by reaction between diphenylpyruvic acid[3] and methylmagnesium iodide. An acid, m.p. 167°, was obtained by Bardon and Ramart[4] by hydrolysis of the ester[5] formed by the interaction of methylmagnesium iodide with an ester stated by them to be ethyl β,β-diphenylglycidate.[6] They assumed that their acid was β-methyl-β,β-diphenyllactic acid since its properties were different from those of the isomeric α-methyl-β,β-diphenyl-β-hydroxypropionic acid,[7] and because they expected the epoxy group in their ester to react in the same manner as ethylene oxide with a Grignard reagent. It was shown by Kohler and associates[8] that this assumption is unwarranted. Since the melting point of the acid obtained by us and that of the acid prepared by Bardon and Ramart are practically identical, we believe that these investigators may actually have obtained α-methyl-β,β-diphenyllactic acid instead of β-methyl-β,β-diphenyllactic acid, possibly due to the fact that, unwittingly, they had

(1) 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 wish to express our indebtedness to the Sterling-Winthrop Research Institute for assistance during this investigation.

(3) E. Troell, *Ber.*, **61**, 2497 (1928).

(4) Bardon and Ramart, *Compt. rend.*, **183**, 214 (1926).

(5) The ester, m.p. 73°, was considered to be ethyl β-methyl-β,β-diphenyllactate by Bardon and Ramart. However, since we found that ethyl α-methyl-β,β-diphenyllactate melts at 73–74°, we believe that these investigators actually hydrolyzed the last-named ester.

(6) Bardon and Ramart did not mention either the source or the properties of this ester.

(7) H. Rupe, H. Steiger and F. Fiedler, *Ber.*, **47**, 63 (1914).

(8) E. P. Kohler, N. K. Richtmyer and W. F. Hester, THIS JOURNAL **53**, 205 (1931).

isomerized their ethyl β,β-diphenylglycidate, probably during its isolation and purification,[9] to ethyl diphenylpyruvate.[10] The latter ester then reacted with methylmagnesium iodide in the manner stated above.

Esterification of α-methyl-β,β-diphenyllactic acid with methanol, ethanol or β-diethylaminoethyl chloride yielded the methyl, ethyl and β-diethylaminoethyl esters, respectively.

By the use of diphenylpyruvic acid and phenylmagnesium bromide, α,β,β-triphenyllactic acid was prepared. This acid was converted into the methyl and β-diethylaminoethyl esters.

α,β,β-Triphenyllactic acid, when heated to 245°, was transformed into α,β,β-triphenylacrylic acid[11] which was then converted into the β-diethylaminoethyl ester.

Ethyl β,β-diphenyl-β-hydroxypropionate, prepared from benzophenone, ethyl bromoacetate and zinc,[12] was heated in a stream of hydrogen chloride whereby it was converted into ethyl β,β-diphenylacrylate. The acrylic acid, obtained by hydrolysis of the ester, was converted by the use of β-diethylaminoethyl chloride into β-diethylaminoethyl β,β-diphenylacrylate hydrochloride.[13]

It was found that β,β-diphenylacrylic acid could be obtained also by dehydration of β,β-diphenyl-β-hydroxypropionic acid with phosphorus pentoxide.

β-Diethylaminoethyl β,β-diphenylacrylate hydrochloride reacted with bromine to form a substance, presumably a hydrohalide salt of β-diethylaminoethyl α-bromo-β,β-diphenylacrylate. The bromine atom in this ester seemed to be very unreactive since the ester base did not cyclize to a morpholone when it was heated, nor would it react with dimethylamine to form an α-dimethylamino derivative.

The hydrochlorides of the β-diethylaminoethyl esters of α-methyl-β,β-diphenyllactic and α-bromo-β,β-diphenylacrylic acids were tested against spasms induced in the isolated intestine by acetylcholine in the Sterling–Winthrop Research Institute. The maximum effective dilution for the former ester was about 1:3,000,000, and for the latter ester about 1:1,000,000.

Experimental

α-Methyl-β,β-diphenylacetic Acid.—A solution of methylmagnesium iodide, prepared from 2.8 g. of magnesium, 15.6 g. of methyl iodide and 100 cc. of ether, was added to a cooled, stirred solution of 9.6 g. of diphenylpyruvic acid in 140 cc. of ether at such a rate that the temperature of the mixture could be maintained at 10–15°. After the mixture had been stirred at room temperature for 1 hour, and acidified with dilute hydrochloric acid, the ether layer was separated, washed with water and dried. The ether was removed and the solid residue (8.0 g.) was recrystallized from chloroform–petroleum ether (60–70°); m.p. 167–168.5°.[14]

The methyl ester was prepared by interaction of 1.0 g. of the acid, 33 cc. of absolute methanol and 2.5 g. of hydrogen chloride; yield 0.7 g. (69%), m.p. 88–89°[15] after recrystallization from methanol.

The ethyl ester, obtained in 47% by the same general method, melted at 73–74°[16] after recrystallization from ethanol.

β-Diethylaminoethyl α-Methyl-β,β-diphenylacetate Hydrochloride.—This compound was prepared by interaction of 3.85 g. of the required acid, 2.05 g. of β-diethylaminoethyl chloride and 40 cc. of isopropyl alcohol in the manner which has been described[17]; yield 4.5 g. (59%), m.p. 140–141° after recrystallization from ethanol–ether.

Anal. Calcd. for $C_{22}H_{30}O_3NCl$: N, 3.57; Cl, 9.05. Found: N, 3.68; Cl, 9.14.

α,β,β-Triphenyllactic Acid.—This acid was prepared in the same general manner as α-methyl-β,β-diphenyllactic acid from a solution of phenylmagnesium bromide, obtained from 2.4 g. of magnesium, 15.7 g. of bromobenzene, 115 cc. of ether and 9.6 g. of diphenylpyruvic acid dissolved in 160 cc. of ether; yield 9.9 g. (78%), m.p. 235–236° dec.[18] after recrystallization from acetone–petroleum ether (60–70°).

The methyl ester, prepared in 56% yield by direct esterification, melted at 183–184°[19] after recrystallization from ethanol.

β-Diethylaminoethyl α,β,β-Triphenyllactate Hydrochloride.—This ester was prepared from 3.2 g. of the required acid, 1.4 g. of β-diethylaminoethyl chloride and 100 cc. of isopropyl alcohol; yield 2.7 g. (60%), m.p. 193–194° after recrystallization from ethanol.

Anal. Calcd. for $C_{27}H_{32}O_3NCl$: N, 3.09; Cl, 7.81. Found: N, 3.11; Cl, 8.01.

β-Diethylaminoethyl α,β,β-Triphenylacrylate Hydrochloride.—This compound was obtained from 1.5 g. of α,β,β-triphenylacrylic acid (m.p. 209–213°),[15] 0.7 g. of β-diethylaminoethyl chloride and 35 cc. of isopropyl alcohol; yield 1.5 g. (69%), m.p. 201–202° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{27}H_{30}O_2NCl$: N, 3.21; Cl, 8.13. Found: N, 3.39; Cl, 8.25.

Ethyl β,β-Diphenylacrylate.—β,β-Diphenyl-β-hydroxypropionate[12] (50 g.) was heated on a steam-bath for 3 hours while a slow stream of hydrogen chloride was passed through the molten ester. The water, which had formed, was separated from the oil and the latter was distilled; yield 45 g. (96%), b.p. 152–155° (1–2 mm.).[20]

β,β-Diphenylacrylic Acid (a).—A mixture of 45 g. of the ethyl ester, 22.4 g. of potassium hydroxide and 300 cc. of methanol was refluxed for 12 hours and the solvent was then removed. The residue was dissolved in water, the solution was filtered and the filtrate acidified; the precipitated acid weighed 38 g. (95%), m.p. 157–158°.[21]

(b).—A mixture of 4.8 g. of β,β-diphenyl-β-hydroxypropionic acid,[12] 5 g. of Super-Cel and 120 cc. of dry benzene was stirred vigorously at 40° and 5 g. of phosphorus pentoxide was added. After the mixture had been stirred and refluxed for one-half hour, it was filtered and the filtrate was evaporated to dryness. The residue was dissolved in dilute sodium carbonate solution, the solution was treated with Norite, filtered and the filtrate was acidified. The precipitated acid (2 g., 45%) melted at 156–158°, mixed m.p. 156–158°.

β-Diethylaminoethyl α-Bromo-β,β-diphenylacrylate.—A solution of 12.5 g. of β-diethylaminoethyl β,β-diphenylacrylate hydrochloride[13] in 70 cc. of chloroform was treated with 5.6 g. of bromine and then allowed to remain at room temperature for 27 hours. After removal of the solvent, the residue was covered with ether, treated with a solution of 1 g. of sodium bisulfite in 200 cc. of water and the mixture was stirred until two clear layers were obtained. The mixture was made alkaline, and the ether layer was washed with water, dried, the solvent removed and the residue distilled; yield 11 g. (78%), b.p. 172–176° (0.01 mm.).

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

(10) From their study of the reaction between Grignard reagents and glycidic esters, Kohler, *et al.* (ref. 8), also concluded that the supposed glycidic ester described by Bardon and Ramart was actually the pyruvic ester.

(11) This process had been used previously by E. P. Kohler and N. Weiner, THIS JOURNAL, **56**, 434 (1934).

(12) H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907).

(13) R. R. Burtner and J. W. Cusic, THIS JOURNAL, **65**, 262 (1943).

(14) Bardon and Ramart (ref. 4) reported 167° as the melting point of an acid believed by them to be β-methyl-β,β-diphenyllactic acid.

(15) E. P. Kohler and N. Weiner, THIS JOURNAL, **56**, 434 (1934).

(16) Bardon and Ramart (ref. 4) stated that an ester, considered by them to be ethyl β-methyl-β,β-diphenyllactate, melted at 73°.

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

(18) Reference 15, m.p. 243–245° dec.

(19) Reference 15, m.p. 186°; J. Wegmann and H. Dahn (*Helv. Chim. Acta*, **29**, 415 (1946)) reported 174–175°.

(20) W. Schlenk and E. Bergmann (*Ann.*, **463**, 1 (1928)) reported 207° (17 mm.).

(21) E. P. Kohler and R. M. Johnstin (*Am. Chem. J.*, **33**, 35 (1905)) found 155°; ref. 12, m.p. 162°.

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).