dry ether. After 3 days the hygroscopic, crystalline material was purified from dry acetone–ether; yield 1.7 g. (18%).

The corresponding β-diethylaminoethyl ether (Table II, 15) was prepared in the same manner. Hot toluene was added to the crude hydrochloride, the toluene solution was decanted from an insoluble oil and the product was precipitated by the addition of petroleum ether (90–100°). The precipitated oily hydrochloride crystallized from refrigeration under dry ether.

2,2-Diphenyl-5-methyl-5-(β-aminoethyl)-1,3-dioxane Hydrochloride (Table II, 17).—A solution of 6.0 g. of 2,2-diphenyl-5-methyl-5-cyanomethyl-1,3-dioxane in 100 cc. of ether was added, dropwise, to a stirred mixture of 0.78 g. of lithium aluminum hydride in 50 cc. of ether. The mixture was refluxed for 1 hour, then carefully treated with 50 cc. of 10% aqueous sodium hydroxide solution. After separation of the ether layer, the water layer was extracted with ether. The addition of a small amount of ethanol helped to break the emulsion. The ether solution was dried over magnesium sulfate and the solvent was removed. An ethereal solution of the residue was treated with the calculated amount of ethereal hydrogen chloride and then placed in a refrigerator. The precipitated salt was recrystallized from absolute ethanol–diisopropyl ether; yield 5.2 g. (76%).

ANN ARBOR, MICH.

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

Antispasmodics. XV. β-Diethylaminoethyl Esters of β,β-Diphenylglycidic, β,β-Diphenyllactic and β,β-Diphenylglyceric Acids

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

RECEIVED NOVEMBER 25, 1953

It was found that the product obtained from ethyl chloroacetate, benzophenone and sodium ethylate, by the Darzens glycidic ester condensation, was a mixture of ethyl β,β-diphenylglycidate and ethyl diphenylpyruvate. The glycidate was rearranged by heat and acid to the pyruvate. Pure β,β-diphenylglycidic acid was isolated for the first time and converted, by heat, into diphenylacetaldehyde. The preparation of the β-diethylaminoethyl esters of β,β-diphenylglycidic, β,β-diphenyllactic and β,β-diphenylglyceric acids has been described.

Since many basic alkyl esters of diarylhydroxyacetic acids are highly active antispasmodics, it seemed desirable to study basic esters of diphenylhydroxypropionic (β,β-diphenyllactic), diphenyldihydroxypropionic (β,β-diphenylglyceric) and diphenylepoxypropionic (β,β-diphenylglycidic) acids.[3]

β,β-Diphenyllactic acid can be obtained conveniently from diphenylglycidic acid. The only method reported in the literature for the preparation of β,β-diphenylglycidic acid, in the form of its ethyl ester, is the Darzens glycidic ester condensation, but the statements with respect to this ester are confusing and contradictory.

All investigators[4–8] who condensed benzophenone with ethyl chloroacetate, in the presence of a condensation agent, agreed that ethyl β,β-diphenylglycidate was produced. Pointet,[4] as well as Rutowski and Dajew,[6] distilled the crude ester and stated that, after solidification and recrystallization, the glycidate melted at 47°. Troell,[5] Kohler, Richtmyer and Hester[7] and Berger[8] claimed that during attempted purification of the ester by distillation, it rearranged to the isomeric ethyl diphenylpyruvate. The pyruvate was described by Troell and by Berger as an oil but Kohler, *et al.*, obtained it as a solid which melted at 37°.

We found that distillation of the crude reaction product from the Darzens condensation yielded a mixture which consisted mainly of the glycidic ester (m.p. 48–49°) and a small amount of the pyruvate (m.p. 37°), and that these esters, which do not differ greatly in their boiling points, could be separated by recrystallization. The pure glycidic ester does not undergo rearrangement during distillation. However, when the ester was heated in the presence of hydrogen chloride or acetic acid, it rearranged, quantitatively, into the pyruvic ester. In fact, this procedure represents the best process for the preparation of the pyruvate. It was found that methyl β,β-diphenylglycidate and β,β-diphenylglycidamide also rearranged, under the same conditions, into methyl diphenylpyruvate and diphenylpyruvamide, respectively.

When Pointet hydrolyzed the ester (m.p. 47°), which he considered to be ethyl diphenylglycidate, he obtained an acid which, when heated, was transformed into diphenylacetic acid. He did not report the melting point of his initial acid, but if it had been β,β-diphenylglycidic acid it should have been converted, by heat, into diphenylacetaldehyde. Rutowski and Dajow stated that hydrolysis of their ethyl β,β-diphenylglycidate (m.p. 47°) yielded β,β-diphenylglycidic acid which melted at 114–115°.

After hydrolysis of ethyl β,β-diphenylglycidate (I, m.p. 48–49°), we obtained an acid (II) which melted at 71° dec., and which was converted by heat into diphenylacetaldehyde (III). We believe that this acid was the true β,β-diphenylglycidic acid which had not been isolated hitherto. In agreement with other investigators,[5,7] we found that hydrolysis of ethyl diphenylpyruvate yielded an acid, diphenylpyruvic acid, which melted at 116–117°.

The glycidic acid II was converted into the β-diethylaminoethyl ester IV by the Horenstein and Pählicke procedure.[9] The basic ester IV was also

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

(3) Only a few basic esters of these acids have been mentioned in the literature. F. F. Blicke and H. M. Kaplan, THIS JOURNAL, **65**, 1967 (1943), described basic esters of β,β-diphenyl-β-hydroxypropionic acid but no mention was made of possible antispasmodic properties. Basic esters of glycidic acids have not been prepared hitherto.

(4) R. Pointet, *Compt. rend.*, **148**, 417 (1909).

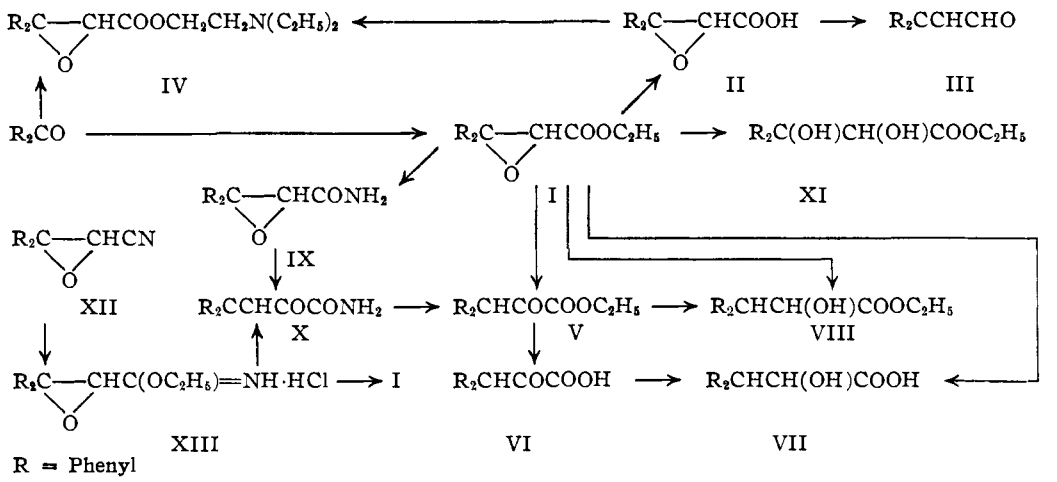
(5) E. Troell, *Ber.*, **61**, 2497 (1928).

(6) B. N. Rutowski and N. A. Dajew, *ibid.*, **64**, 693 (1931).

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

(8) H. Berger, *J. prakt. Chem.*, [2] **152**, 267 (1939).

(9) H. Horenstein and H. Pählicke, *Ber.*, **71**, 1654 (1938).



R = Phenyl

obtained, in low yield, by interaction of benzophenone, β-diethylaminoethyl chloroacetate and sodamide. The oily β-diethylaminoethyl chloroacetate prepared in the form of the hydrochloride from chloroacetyl chloride and β-diethylaminoethanol, changed gradually into a crystalline material which contained ionizable chlorine.[10]

When hydrogen chloride was passed into the glycidic ester I at 200°, it was converted into the isomeric ethyl diphenylpyruvate (V). The pyruvic acid VI, obtained by hydrolysis of the ester, when hydrogenated catalytically, yielded β,β-diphenyllactic acid (VII), a substance which was prepared also by hydrolysis of its ethyl ester VIII, and by reduction of the glycidic ester I with sodium and alcohol; at some stage during the latter process, either the ethyl glycidate or the ethyl diphenyllactate was hydrolyzed to the corresponding acid. Compound VIII was obtained by two procedures: catalytic hydrogenation of the glycidic ester I, and of the pyruvic ester V. The β-diethylaminoethyl ester was prepared by the Horenstein and Pählicke process.[9]

Ethyl β,β-diphenylglycidate (I), treated with concentrated ammonia water, yielded β,β-diphenylglycidamide (IX) which, when heated in the presence of hydrogen chloride, was converted into diphenylpyruvamide (X). The pyruvamide X was produced also when ethyl diphenylpyruvate was allowed to react with ammonia water.

The glycidate I was converted into the glycerate XI when it was heated with water which contained a small amount of hydrochloric acid; a similar process had been used previously by Kohler, *et al.*[7] Hydrolysis of XI yielded the glyceric acid which was used for the preparation of β-diethylaminoethyl β,β-diphenylglycerate.

β,β-Diphenylglycidonitrile (XII) was prepared from benzophenone, chloroacetonitrile and sodium ethylate, and it was then converted into ethyl β,β-diphenylglycidimino ether hydrochloride (XIII). The salt was heated in the hope that it might be transformed into β,β-diphenylglycidamide; however, instead of this substance, diphenylpyruvamide (X) was obtained. The imino ether salt, when dissolved in water, was converted into ethyl β,β-diphenylglycidate.

Tested on the isolated intestine which had been antagonized with acetylcholine, it was found at the Sterling–Winthrop Research Institute that the maximum effective dilution for the β-diethylaminoethyl esters of the glycidic, glyceric and lactic acids was about 1:1,000,000. The maximum effective dilution for atropine is about 1:50,000,000.

Experimental

Methyl and Ethyl β,β-Diphenylglycidate (I).—To a cooled, stirred mixture of 91 g. of benzophenone, 61.6 g. of ethyl chloroacetate and 150 cc. of dry ether, there was added 38 g. of powdered, alcohol-free sodium ethylate at such a rate that the temperature of the reaction mixture could be maintained at 0–4°. The mixture was stirred at room temperature for 12 hours, the ether was removed and the residue was stirred at 100° for 6 hours. The cooled mass was acidified with 20 cc. of acetic acid, poured into 400 cc. of ice-water and the insoluble oil was extracted with ether. The extract was washed with water and sodium bicarbonate solution until the extract was neutral.

Fractionation of the crude product yielded 27.5 g. of unchanged benzophenone and 89 g. of a yellow oil, b.p. 151–160° (1 mm.). The oil, when cooled, solidified almost completely. The mixture of oil and crystals was dissolved in 50 cc. of hot ethanol; 64 g. (48%) of the crystalline glycidic ester precipitated from the cooled solution; m.p. 48–49°.[11] The pure ester boiled at 152–153° (1 mm.) and at 190–193° (11 mm.).[11]

Distillation of the alcoholic mother liquor from the recrystallization of the crude glycidic ester yielded 19 g. of an oil, b.p. 153–159° (1 mm.), from which there was obtained, by hydrolysis (the procedure is described in the preparation of compound VI), 9.9 g. (54%) of sodium diphenylpyruvate. Upon acidification of an aqueous solution of this salt, 7.2 g. of diphenylpyruvic acid monohydrate, m.p. 85–87°, precipitated; after dehydration and recrystallization from chloroform–petroleum ether (60–70°), the pyruvic acid melted at 116–117°.[12]

From 36.4 g. of benzophenone, 21.7 g. of methyl chloroacetate, 200 cc. of dry ether and 8.2 g. of sodamide there was obtained 7.0 g. (14%) of methyl β,β-diphenylglycidate; b.p. 165–167° (5 mm.), m.p. 53–54° after recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.35 H, 5.24.

β,β-Diphenylglycidic Acid (II).—Ethyl β,β-diphenylglycidate (18.8 g.) was dissolved in a cold solution of sodium

(10) The amount of ionizable chlorine found in this substance corresponded to that which would be found in the product obtained by cyclization, namely, 4-ethyl-2-morpholone ethochloride. However, it was not established that the morpholone actually was formed. E. Fourneau, *Bull. soc. chim.*, [4] **3**, 1141 (1908), stated that the α-methyl-α-ethyl-β-dimethylaminoethyl ester of phenylbromoacetic acid cyclized spontaneously to a morpholone.

(11) Reference 4, m.p. 47°, b.p. 202–204° (12 mm.); ref. 6, m.p. 47° b.p. 210–215° (25 mm.).

(12) Reference 5, m.p. 116°.

ethylate, which had been prepared from 1.6 g. of sodium and 50 cc. of absolute ethanol, and 1.3 cc. of water was added. After the mixture had remained at room temperature for 12 hours, the precipitated sodium salt (16 g., 87%) was filtered. A cold (about −5°), stirred aqueous solution of 5.2 g. of the salt was covered with ether, and dilute hydrochloric acid was added until the aqueous layer was acidic. From the dried ethereal layer 3.9 g. (81%) of the glycidic acid was obtained, m.p. 70–71° dec. Even at room temperature, this crystalline compound soon became gummy. The analytical sample was dried at 0° under 0.1 mm. pressure.

Anal. Calcd. for $C_{15}H_{12}O_3 \cdot H_2O$: C, 69.76; H, 5.46. Found: C, 69.84; H, 5.32.

Diphenylacetaldehyde (III).—β,β-Diphenylglycidic acid (3.9 g.) was heated at 110–110° until the evolution of carbon dioxide had ceased (15 minutes). Upon distillation, 2.4 g. (75%) of the aldehyde was obtained, b.p. 170–174° (16 mm.)[13]; the semicarbazone melted at 160–161°.[14]

β-Diethylaminoethyl Chloroacetate.—This compound, required for a following experiment, was obtained as described below.

β-Diethylaminoethanol (36.3 g.), dissolved in 50 cc. of benzene, was added, during a 45-minute period, to a stirred solution of 33.9 g. of chloroacetyl chloride in 150 cc. of benzene which was maintained at 10–20°. After the mixture had been stirred for 1 hour at room temperature, it was diluted with 100 cc. of dry ether and then filtered. The very hygroscopic hydrochloride was dried in a desiccator; yield 66 g. (96%).

In order to obtain the base, 23 g. of the crude hydrochloride was added to a stirred mixture of 15 cc. of 50% aqueous sodium hydroxide and 25 cc. of ether which was cooled to 10°. After separation of the ether layer and extraction of the aqueous layer with ether, the ether solution was dried, the solvent removed and the product distilled; b.p. 74–76° (2 mm.), yield 5 g. (26%).

The oily ester (5 g.), after 4 days at room temperature, had become a semi-solid mass. It was heated at 100° for 1 hour, dissolved in hot isopropyl alcohol and the solution was cooled. Two grams of crystalline product, possibly 4-ethyl-2-morpholone ethochloride, precipitated, m.p. 198–199° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_8H_{16}O_2NCl$ (the ethochloride): Cl, 18.31. Found: Cl, 18.39.

β-Diethylaminoethyl β,β-Diphenylglycidate Hydrochloride (IV). (a).—β,β-Diphenylgycidic acid, obtained from 7.9 g. of the sodium salt, was dissolved in dry ether and added to an ethereal solution of β-diethylaminoethyl chloride which had been isolated from 6.9 g. of the chloride hydrochloride. After the ether had been removed by distillation, 85 cc. of isopropyl alcohol was added, the mixture was refluxed for 12 hours and the solvent was then removed. The oily residue was triturated with ether whereupon it solidified; m.p. 155–156° after recrystallization from acetone–ethanol; yield 3.5 g. (31%).

Anal. Calcd. for $C_{21}H_{26}O_3NCl$: N, 3.73; Cl, 9.43. Found: N, 3.71; Cl, 9.59.

(b).—A stirred mixture of 3.5 g. of benzophenone, 3.7 g. of β-diethylaminoethyl chloroacetate and 50 cc. of dry ether was cooled in an ice-bath and 0.75 g. of sodamide was added, in portions, during a period of one-half hour. After 24 hours at ordinary temperature, water was added, and the ether layer was separated and dried. Upon the addition of ethereal hydrogen chloride, an oil precipitated which became crystalline after trituration under dry ether; yield 0.9 g. (13%), m.p. 152–154° after recrystallization from acetone–ethanol; mixed m.p. 152–154°.

Methyl and Ethyl Diphenylpyruvate (V). (a).—Methyl β,β-diphenylglycidate (0.70 g.) was heated at 200° for 45 minutes while a slow stream of hydrogen chloride was passed through the molten ester. The oil solidified when cooled, and the methyl ester was recrystallized from methanol; yield 0.45 g. (64%), m.p. 69–70°.[15]

(b).—A mixture of 1.2 g. of diphenylpyruvic acid and 1.0 g. of hydrogen chloride dissolved in 25 cc. of absolute methanol was refluxed for 3 hours. The solution was concentrated to a volume of about 3 cc., cooled and the precipitated methyl ester filtered; yield 0.7 g. (55%), m.p. 69–70°, mixed m.p. 69–70°.

When 18.8 g. of ethyl β,β-diphenylglycidate was treated as described in method a, there was obtained 16.5 g. (88%) of ethyl diphenylpyruvate, b.p. 152–155° (1 mm.). The oily ester crystallized when inoculated with a crystal of the ethyl ester which had been obtained from the silver salt of the pyruvic acid and ethyl iodide; m.p. 36–37°.[16] The phenylhydrazone melted at 101–102°.[16]

Diphenylpyruvic Acid (VI).—Ethyl diphenylpyruvate (43.7 g.) and 3.5 cc. of water were added to a cold solution of sodium ethylate prepared from 4.0 g. of sodium and 150 cc. of absolute ethanol. After 4 hours in an ice-bath, the precipitated sodium diphenylpyruvate was dissolved in 600 cc. of water and the solution was acidified. The precipitated diphenylpyruvic acid monohydrate (38 g., 87%) was recrystallized from water; m.p. 85–87°; neut. equiv., calcd. for $C_{15}H_{14}O_4$, 258.3; found 255.2.

In order to obtain the anhydrous acid, the monohydrate was dissolved in 100 cc. of chloroform and the solution was refluxed for 15 minutes. After distillation of the solvent, the residue was recrystallized from chloroform–petroleum ether (60–70°); m.p. 116–117°; neut. equiv., calcd. for $C_{15}H_{12}O_3$, 240.3; found 242.1.

Recrystallization of the anhydrous acid from water converted it into the monohydrate. The phenylhydrazone melted at 208° dec.[17] Distillation under reduced pressure converted the acid into diphenylacetic acid, m.p. 143–145°.

β,β-Diphenyllactic Acid (VII). (a).—Diphenylpyruvic acid (1.2 g.), dissolved in 50 cc. of ethanol, was hydrogenated in the presence of a palladium–charcoal catalyst under an initial pressure of 40 pounds for 4 hours. After removal of the solvent and the catalyst, the residue melted at 158–159°.[18]

(b).—A mixture of 3.3 g. of ethyl β,β-diphenyllactate (described below), 1.4 g. of potassium hydroxide and 35 cc. of methanol was refluxed for 4 hours, the solvent was removed, the residue was dissolved in water and the solution was acidified. The precipitated, oily acid soon solidified; yield 2.7 g. (95%), m.p. 158–159° after recrystallization from water.

(c).—Sodium (4 g.) was added in portions, during a period of one-half hour, to a refluxing solution of 5.4 g. of ethyl β,β-diphenylglycidate in 75 cc. of absolute ethanol. The alcohol was removed, the residue was treated with water and the mixture was acidified. The oily material was stirred with sodium carbonate solution and the insoluble portion was extracted with ether. Acidification of the aqueous solution yielded 1.3 g. (27%) of the lactic acid, m.p. 153–155°. Upon evaporation of the solvent from the ether extract, 2 g. of an unidentified oil was obtained.

Ethyl β,β-Diphenylacetate (VIII). (a).—Ethyl β,β-diphenylglycidate (2.7 g.), dissolved in 40 cc. of absolute ethanol, was hydrogenated in the presence of Raney nickel catalyst, at room temperature, under an initial pressure of 48 pounds. The reduction was completed in 1 hour. After removal of the solvent and the catalyst, the oily residue soon solidified; m.p. 65–66°[19] after recrystallization from petroleum ether (60–70°); yield 2.6 g. (96%).

(b).—Ethyl diphenylpyruvate (16 g.), dissolved in 80 cc. of absolute ethanol, was hydrogenated in the manner described above; however, after 6 hours it was necessary to add fresh catalyst and the hydrogenation required 14 hours. The ester melted at 66–67° after recrystallization; yield 16 g. (99%).

β-Diethylaminoethyl β,β-Diphenyllactate Hydrochloride.—The lactic acid (VII, 2.7 g.), β-diethylaminoethyl chloride, which had been obtained from 3.4 g. of the chloride hydrochloride, and 40 cc. of isopropyl alcohol were allowed to react in the usual manner.[9] After recrystallization from ethanol–ether, there was obtained 3.0 g. (72%) of the ester hydrochloride, m.p. 141–142°.

Anal. Calcd. for $C_{21}H_{28}O_3NCl$: N, 3.71; Cl, 9.38. Found: N, 3.47; Cl, 9.48.

(13) S. Daniloff and E. Venus-Danilova, *Ber.*, **59**, 1032 (1926), b.p. 193–195° (33 mm.).

(14) Reference 13, m.p. 160.5°.

(15) Reference 7, m.p. 75°.

(16) It has been reported (ref. 7) that the ester, obtained by the use of the silver salt, melted at 37°; the phenylhydrazone melted at 99–100°.

(17) Reference 5, m.p. 189° dec.; reference 7, m.p. 210° or 245° dec. depending on the rate at which the material was heated.

(18) W. G. M. Weise, *Ann.*, **248**, 34 (1888), prepared the acid from diphenylacetaldehyde; m.p. 159°.

(19) Reference 18, m.p. 66°.

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).