Syntheses from Phthalimido-acids. Part V. Amides of Glycine,* DL-*Alanine, and* L-*Glutamic Acid with Amphetamine, Benzocaine, and Procaine.*

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Phthalylglycyl derivatives of amphetamine (2-phenyl*iso*propylamine) and of procaine (2-diethylaminoethyl *p*-aminobenzoate), and ethyl *p*-(phthalyl-DL-alanylamino)benzoate (phthalyl-DL-alanylbenzocaine) have been synthesised. The reactions of benzocaine and of amphetamine with phthalyl-DL-glutamic anhydride resemble those of ammonia, ethanol, etc. (cf. King and Kidd, *J.*, 1949, 3315; King, Jackson, and Kidd, *J.*, 1951, 243), in yielding γ-compounds. The free amino-acid amides have been prepared from the phthalylated products by treatment with hydrazine.

SIMPLE aminoacyl derivatives of the drugs amphetamine, procaine, and benzocaine were required for pharmacological investigation. The selected amino-acids, *i.e.* glycine, DL-alanine, and L-glutamic acid, were brought into reaction with these amines in the form of their phthalyl compounds, the final stage, namely, removal of the phthalyl group, being accomplished with hydrazine as in previous work of this nature, *e.g.*, Part IV.*

The condensation of phthalylglycyl chloride with amphetamine in chloroform–aqueous alkali gave phthalylglycine 2-phenyl*iso*propylamide (yield 76%), glycylamphetamine being isolated as hydrochloride (66%) after hydrolysis of the phthalyl compound with hydrazine in boiling alcohol. Similarly, procaine gave 2-diethylaminoethyl *p*-(phthalylglycylamino)benzoate (yield of hydrochloride, 84%), from which glycylprocaine was obtained as a dihydrochloride after hydrazine treatment. Ethyl *p*-(phthalyl-DL-alanylamino)benzoate (80%) was prepared from phthalyl-DL-alanyl chloride and benzocaine, the product of its hydrolysis with hydrazine being obtained as a crystalline hydrochloride (69%). Phthalyl-DL-alanylprocaine on the other hand was a sticky solid characterised by its picrate.

Phthalyl-DL-glutamic anhydride reacted with ethyl *p*-aminobenzoate (benzocaine) dissolved in chloroform either at room temperature or at the boiling point, yielding up to 93% of ethyl *p*-(phthalyl-DL-glutamylamino)benzoate. Its representation as the γ-derivative follows from the results of similar experiments with ammonia, glycine, ethyl glutamate, and methanol (King and Kidd, *J.*, 1949, 3315; King, Jackson, and Kidd, *J.*, 1951, 243), and from the ninhydrin analysis of the α-amino-carboxy-group (Van Slyke, MacFadyen, and Hamilton, *J. Biol. Chem.*, 1941, **141**, 671) in the ethyl *p*-DL-glutamylaminobenzoate (yield 68%) obtained by hydrolysis of the aqueous sodium salt with hydrazine at room temperature (King and Kidd, *loc. cit.*). *p*-(Phthalyl-γ-DL-glutamylamino)benzoic acid (84%) was prepared by heating a mixture of phthalyl-DL-glutamic anhydride and *p*-aminobenzoic acid in dioxan. The product of a similar experiment with the anhydride and amphetamine in chloroform was a gum but crystalline DL-glutamic acid γ-2-phenyl*iso*propylamide (overall yield 64%) was obtained when it was hydrolysed in the cold with hydrazine.

EXPERIMENTAL

*Phthalylglycine 2-Phenyliso*propylamide.—2-Phenyl*iso*propylamine sulphate (3 g., 1 mol.) was dissolved in water (30 c.c.) and treated with 40% aqueous sodium hydroxide (3·3 c.c., 4 mols.) and chloroform (30 c.c.), the mixture being stirred during the dropwise addition in 15 min. of a chloroform solution (15 c.c.) of phthalylglycyl chloride (3·64 g., 2 mols.). The chloroform phase was then separated, washed free from alkali, and evaporated to dryness under reduced pressure. The residue of *phthalylglycine 2-phenyliso*propylamide crystallised from aqueous ethanol in rods (4·0 g., 76%), m. p. 167° (Found: C, 70·8; H, 5·4; N, 8·5. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). Alternatively, amphetamine sulphate dissolved in a similar quantity of alkali (4·5%) was vigorously shaken during the addition of a solution of phthalylglycyl chloride (2 mols.) in dioxan. The white crystalline mass was collected and

* Part IV, preceding paper.

crystallised from aqueous ethanol, thereby giving rods (43%), m. p. 167°. In more concentrated alkali (10%) the precipitate first formed redissolved on being shaken, presumably owing to formation of the phthalamic acid. Acidification yielded a gum which, however, crystallised from aqueous alcohol and then had m. p. and mixed m. p. 167°.

Glycine 2-Phenylisopropylamide Hydrochloride.—A solution of phthalylglycine 2-phenyl-*iso*propylamide (12·88 g.) in ethanol (400 c.c.) was heated with aqueous hydrazine (4 c.c., 33·2%, 1·04 equivs.) under reflux for 1 hr. The solution, which became faintly yellow and deposited a small quantity of white solid, was evaporated to dryness under reduced pressure and the residue extracted with N-hydrochloric acid (100 c.c.) and finally with a little water. The combined extracts were evaporated at 45° (reduced pressure) and the crystalline residue, after being dried in a vacuum-desiccator, was dissolved in the minimum of ethanol. Addition of anhydrous ether precipitated glistening plates of *glycine 2-phenylisopropylamide hydrochloride* (6 g., 66%), m. p. 180°, raised by two crystallisations from *iso*propanol–light petroleum (b. p. 80—100°) to 192—193° (Found: C, 57·9; H, 7·2; N, 12·4. $C_{11}H_{16}ON_2$,HCl requires C, 57·6; H, 7·4; N, 12·3%).

2-Diethylaminoethyl p-(*Phthalylglycylamino*)*benzoate.*—A solution of 2-diethylaminoethyl *p*-aminobenzoate (4·74 g.) in chloroform (20 c.c.) at 0° was stirred during the addition in 1 hr. of a chloroform solution (50 c.c.) of phthalylglycyl chloride (4·46 g.). Solid slowly separated, and next morning the product was collected and crystallised from 2-ethoxyethanol, thus giving *2-diethylaminoethyl* p-(*phthalylglycylamino*)*benzoate hydrochloride* as plates (7·7 g., 84%), m. p. 224—228° (Found: C, 60·5; H, 5·8; N, 9·2. $C_{23}H_{25}O_5N_3$,HCl requires C, 60·1; H, 5·7; N, 9·1). Mixing aqueous solutions of sodium picrate and of the hydrochloride gave the *picrate* which crystallised from ethanol or aqueous ethanol as yellow needles, m. p. 220° (decomp.) (Found: C, 52·8; H, 4·4; N, 12·9. $C_{23}H_{25}O_5N_3$,$C_6H_3O_7N_3$ requires C, 53·3; H, 4·3; N, 12·9%). The addition of aqueous sodium carbonate to the hydrochloride liberated an oil which soon solidified and crystallised from methanol, giving prisms consisting of the *2-diethylaminoethyl* p-(*phthalylglycylamino*)*benzoate monohydrate*, m. p. 144—146° (Found: C, 62·7; H, 6·0; N, 9·8; loss, 4·1. $C_{23}H_{25}O_5N_3$,H_2O requires C, 62·5; H, 6·1; N, 9·5; loss, 4·1%).

2-Diethylaminoethyl p-*Glycylaminobenzoate Dihydrochloride.*—A solution of 2-diethylaminoethyl *p*-(phthalylglycylamino)benzoate monohydrate (3·8 g.) in ethanol (100 c.c.) was heated under reflux with aqueous hydrazine (33·2%, 0·9 c.c.) for 1 hr. Evaporation and treatment with 2N-hydrochloric acid precipitated phthalhydrazide which was removed after several hours at 0°. The gum left on evaporation of the filtrate was dissolved in ethanol and obtained solid by precipitation with ether. Crystallisation from ethanol–light petroleum (b. p. 60—80°) yielded *2-diethylaminoethyl* p-*glycylaminobenzoate dihydrochloride* as plates, m. p. 234° (decomp.) (Found: C, 49·0; H, 6·8; N, 11·1; Cl, 19·0. $C_{15}H_{23}O_3N_3$,2HCl requires C, 49·2; H, 6·9; N, 11·5; Cl, 19·4%).

Ethyl p-(*Phthalyl*-DL-*alanylamino*)*benzoate.*—Ethyl *p*-aminobenzoate (7·3 g., 2 mols.), dissolved in chloroform (30 c.c.), was stirred and slowly treated with a chloroform solution (30 c.c.) of phthalyl-DL-alanyl chloride (5·2 g., 1 mol.). When the solvent had been evaporated and the residue washed with 2N-hydrochloric acid, the product crystallised from ethanol as rods, m. p. 178°, consisting of *ethyl* p-(*phthalyl*-DL-*alanylamino*)*benzoate* (6·49 g., 80%) (Found: C, 65·5; H, 5·0; N, 7·4. $C_{20}H_{18}O_5N_2$ requires C, 65·6; H, 4·9; N, 7·6%).

Ethyl p-DL-*Alanylaminobenzoate Hydrochloride.*—Ethyl *p*-(phthalyl-DL-alanylamino)-benzoate (3·66 g.) in ethanol (100 c.c.) was heated with aqueous hydrazine solution (1 c.c., 33·2%) and the solution evaporated and freed from phthalhydrazide by treatment with 2N-hydrochloric acid in the usual way. The aqueous solution was evaporated and the product dried azeotropically, after which the *ethyl* p-DL-*alanylaminobenzoate hydrochloride* crystallised from *iso*propanol–light petroleum (b. p. 60—80°) as prisms (1·89 g., 69%), m. p. 224—225° (Found: C, 52·8; H, 6·4; N, 10·3. $C_{12}H_{16}O_3N_2$,HCl requires C, 52·8; H, 6·25; N, 10·3%).

2-Diethylaminoethyl p-(*Phthalyl*-DL-*alanylamino*)*benzoate.*—The material obtained from chloroform solutions of procaine and phthalyl-DL-alanyl chloride was soluble in alcohol and water but could not be crystallised. In aqueous solution with sodium picrate it gave *2-diethylaminoethyl* p-(*phthalyl*-DL-*alanylamino*)*benzoate picrate* which crystallised from moist ethanol in yellow needles, m. p. 203° (Found: C, 54·0; H, 4·7; N, 12·8. $C_{24}H_{27}O_5N_3$,$C_6H_3O_7N_3$ requires C, 54·1; H, 4·5; N, 12·6%).

Ethyl p-(*Phthalyl*-γ-DL-*glutamylamino*)*benzoate.*—A suspension of phthalyl-DL-glutamic anhydride (11·7 g.) in a solution of ethyl *p*-aminobenzoate (7·46 g.) in chloroform (120 c.c.) was stirred at room temperature. The anhydride gradually dissolved and when the nearly clear solution was filtered and set aside *ethyl* p-(*phthalyl*-γ-DL-*glutamylamino*)*benzoate* slowly separated.

It crystallised from aqueous ethanol in prisms (14·8 g., 77%), m. p. 189—190° (Found: C, 62·2; H, 4·4; N, 6·4. $C_{22}H_{20}O_7N_2$ requires C, 62·3; H, 4·7; N, 6·6%). When the mixture was heated under reflux solid material began to separate in 10 min. After further refluxing (total 1 hr.) the solution was set aside overnight at room temperature; the crystalline ester (93%), m. p. 187—188°, formed rectangular prisms, m. p. 189—190°, when recrystallised from aqueous ethanol.

p-(*Phthalyl-γ-*DL-*glutamylamino*)*benzoic Acid.*—*p*-Aminobenzoic acid (2·74 g.) and phthalyl-DL-glutamic anhydride (5·18 g.) were heated under reflux for 50 min. in dry dioxan (60 c.c.), and the solution was then evaporated. Hot water dissolved the gummy residue which later separated as a crystalline solid and formed nearly colourless prisms of p-(*phthalyl-γ-*DL-*glutamylamino*)*benzoic acid* (6·65 g., 84%), m. p. 237—238°, when crystallised from aqueous ethanol (Found: C, 60·3; H, 4·1; N, 7·3. $C_{20}H_{16}O_7N_2$ requires C, 60·6; H, 4·1; N, 7·1%). Recrystallisation (charcoal) raised the m. p. to 240—240·5°.

Ethyl p-(*γ-*DL-*Glutamylamino*)*benzoate.*—Ethyl *p*-(phthalyl-DL-glutamylamino)benzoate (12·72 g.) was dissolved in water (100 c.c.) containing sodium carbonate (3·48 g.) and treated with aqueous hydrazine (33·2%, 3 c.c.). The mixture was set aside at room temperature for three days, the solution becoming yellow and a white solid gradually separating. The solution was strongly acidified with hydrochloric acid and after an hour the phthalhydrazide was collected, the filtrate then being brought to pH 5·5 with aqueous sodium carbonate. The white precipitate of *ethyl* p-(*γ-*DL-*glutamylamino*)*benzoate* crystallised from aqueous ethanol in plates (6·0 g. 68%), m. p. 203·5° (Found: C, 57·2; H, 6·0; N, 9·3; carboxyl-N, 4·52. $C_{14}H_{18}O_5N_2$ requires C, 57·1; H, 6·2; N, 9·5; carboxyl-N, 4·76%). The ester gave a deep magenta colour with ninhydrin reagent.

DL-*Glutamic Acid γ-2-Phenyl*iso*propylamide.*—Powdered phthalyl-DL-glutamic anhydride (17·1 g.) slowly dissolved in a solution of amphetamine (8·9 g.) in pure dry chloroform (200 c.c.) with slight evolution of heat. The product failed to crystallise and it was therefore dissolved in water (250 c.c.) containing sodium carbonate (7·7 g.) and treated with aqueous hydrazine (6·6 c.c., 33·2%) during three days at room temperature. Acidification with hydrochloric acid (62·5 c.c.; 10N) and removal in due course of phthalhydrazide followed by the addition of sodium carbonate to pH 5·5 precipitated DL-*glutamic acid γ-2-phenyl*iso*propylamide* which crystallised from water as plates (10 g.), m. p. 216° (decomp.); the total yield with a further quantity (1·2 g.), m. p. 215—216° (decomp.), obtained by concentration of the mother-liquors, was 64% (Found: C, 63·9; H, 7·6; N, 10·7; carboxyl-N, 5·32. $C_{14}H_{20}O_3N_2$ requires C, 63·6; H, 7·6; N, 10·6; carboxyl-N, 5·30%). The pure compound gave a deep magenta colour with ninhydrin reagent.

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