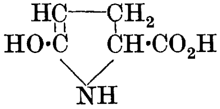
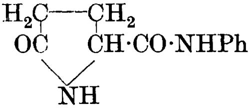
CLXV.—*The Action of Aniline on* d-*Glutamic Acid.*

By WILLIAM HERBERT GRAY.

IT has been stated by Abderhalden and Schwab (*Z. physiol. Chem.*, 1926, **153**, 88) that a new acid, 2-hydroxypyrroline-5-carboxylic acid (I), is formed when *d*-glutamic acid is heated with aniline, and that this, unlike 2-pyrrolidone-5-carboxylic acid, of which it is the enolic form, can be reduced to 2-hydroxypyrrolidine-5-carboxylic acid. Working under the conditions described by these authors, the writer has indeed obtained a substance with the same melting point, and giving the same colour reactions, as attributed by them to 2-hydroxypyrroline-5-carboxylic acid, but this proves to be the anilide of a dehydrated glutamic acid. From the following considerations this dehydrated acid is not the acid (I) : on treatment of the anilide with two atoms of bromine, one atom only is taken up, with formation of the corresponding *p*-bromoaniline derivative; it gives a monoacetyl compound when boiled with a large excess of acetic anhydride; and it is not reduced by hydrogen, with platinum catalyst, under a pressure of two atmospheres. The anilide must have, therefore, the alternative structure (II). It is dextrorotatory, but is found to be the anilide of *l*-2-pyrrolidone-5-carboxylic acid, the same product being obtained by heating this acid with aniline. The racemic anilide is formed to a small extent when glutamic acid is heated with aniline for a comparatively long time. It is much less soluble than the anilide of the *l*-form, so that its absence from the product obtained in the first case indicates that racemisation is slow compared with ring-closure and anilide formation, and this view is borne out by the fact that *dl*-anilide is rapidly formed from *dl*-2-pyrrolidone-5-carboxylic acid under the same conditions.

(I.)





(II.)

Abderhalden and Schwab state that their hydroxypyrrolinecarboxylic acid gives positive Millon and xanthoprotein tests, and is particularly distinguished from the ketonic form by developing a yellow coloration with *p*-dimethylaminobenzaldehyde. The anilide is found to give all these reactions, and 2-pyrrolidone-5-carboxylic acid gives the yellow coloration if a trace of aniline is introduced. In a later paper (Abderhalden and Schwab, *Z. physiol. Chem.*, 1926, **157**, 196) it is mentioned that the same product is obtained when glutamic acid is heated with diphenylamine. On repeating this experiment, the product obtained by the author had in every instance the properties of a 2-pyrrolidone-5-carboxylic acid. Attempts to reduce the substance so prepared were made, in order to be certain that it was not actually the enolic form, possibly indistinguishable from pyrrolidonecarboxylic acid by the other tests applied. In these attempts, hydrogen under a pressure of two atmospheres was used, and either Willstätter's platinum-black as modified by Feulgen (*Ber.*, 1921, **54**, 360), the very active platinum oxide–ferrous salt catalyst of Adams (*J. Amer. Chem. Soc.*, 1922, **44**, 1397), or palladinised barium sulphate, the activity of these being verified in every case by control reduction of quinine or salicylaldehyde, but in no case was hydrogen absorbed. This is additional evidence of the identity of the diphenylamine-treated product with 2-pyrrolidone-5-carboxylic acid, in which, as in other 2-pyrrolidone derivatives, the carbonyl group is resistant to reduction (compare Tafel and Stern, *Ber.*, 1900, **33**, 2226; McCay and Schmidt, *J. Amer. Chem. Soc.*, 1926, **48**, 1933; Ramart-Lucas and Fasal, *Compt. rend.*, 1927, **184**, 1253; and Darapsky, *J. pr. Chem.*, 1927, **116**, 129).

The previous work of Hugounenc, Florence, and Couture (*Bull. Soc. Chim. biol.*, 1924, **6**, 672) appears to have been overlooked. These authors heated *d*-glutamic acid with aniline and obtained a product having practically the same melting point as that found by Abderhalden and Schwab. They correctly called this an anilide but, incorrectly, the anilide of glutamic acid.

EXPERIMENTAL.

1-2-*Pyrrolidone-5-carboxyanilide* (II).—A mixture of *d*-glutamic acid (43·5 g.) and aniline (217 c.c.) was heated under reflux at 205—210° for ½ hour, cooled, and filtered from a small undissolved residue. Ether (130 c.c.) was then added, and the crystalline solid which separated was washed with ether and dried (20·8 g., m. p. 187°). The filtrate was concentrated and treated with ether, giving a further 8·8 g. After one recrystallisation from methyl alcohol the *anilide* was obtained pure, m. p. 191°, $[\alpha]_D^{15^\circ} + 17{\cdot}9^\circ$ in 80% alcohol ($c = 4{\cdot}8$). The foregoing procedure is that of Abderhalden and Schwab; a better yield and a cleaner product are obtained by heating the mixture at 150° instead of 210° and treating the product with acetone in place of ether. Water or ethyl alcohol is equally effective for recrystallisation; the anilide separates from the latter in well-formed, flat tablets with pointed ends, exhibiting a considerable twinning tendency. It is readily soluble in cold glacial acetic acid, β-chloroethyl alcohol, or concentrated hydrochloric acid, moderately easily soluble in methyl and ethyl alcohol, sparingly in cold water but more readily on heating (1 in 7·4), and almost insoluble in benzene (Found: C, 64·7; H, 6·0; N, 13·5. $C_{11}H_{12}O_2N_2$ requires

C, 64·7; H, 5·9; N, 13·7%). On hydrolysis by boiling dilute sodium hydroxide solution it yielded aniline and *d*-glutamic acid.

Preparation from 1-2-*pyrrolidone*-5-*carboxylic acid*. This acid, prepared by the method of Menozzi and Appiani (*Gazzetta*, 1894, **24**, 373), is advantageously purified by extraction with acetone, in which the *dl*-acid is very sparingly soluble, and recrystallisation of the acetone-soluble material from alcohol. For preparation of the anilide, the acid was heated at 150° with five parts of aniline for 6 hours. On removal of a portion of the excess of aniline in a vacuum, the anilide crystallised. It had the same melting point and rotation as that described above.

1-2-*Pyrrolidone*-5-*carboxy*-p-*bromoanilide*.—*l*-Pyrrolidonecarboxyanilide (1 g.), dissolved in 50% aqueous acetone (15 c.c.), was treated with bromine water (2 at. Br). This was immediately decolorised, and colourless needles separated (1·2 g.), m. p. 212°; these crystallised from alcohol in large prisms (Found: Br, 28·2. $C_{11}H_{11}O_2N_2Br$ requires Br, 28·2%). The substance is insoluble in cold concentrated hydrochloric acid. On hydrolysis, it yielded *p*-bromoaniline.

1-*Acetyl*-2-*pyrrolidone*-5-*carboxyanilide*.—The anilide (5 g.) was boiled with acetic anhydride (25 c.c.; 11 mols.) for 1½ hours, the excess of anhydride removed by distillation, and the oil treated with ether (30 c.c.). A small quantity of solid which separated was rejected, and a solution of the remainder in alcohol was treated with water until turbid; colourless needles then separated (1·2 g.) which, after recrystallisation from boiling water, had m. p. 166° (Found: C, 63·2; H, 5·5; N, 11·4. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·7; N, 11·4%).

1-*Dibenzyl*-2-*pyrrolidone*-5-*carboxyanilide*.—*l*-Pyrrolidonecarboxyanilide (5·5 g.), benzyl chloride (14·7 c.c.), and powdered sodium hydroxide (1·7 g.) were mixed, treated with a drop of pyridine, and heated for 7 hours at 100°. The acidified reaction-mixture yielded to ether 1·1 g. of crystalline material, which separated from ligroin in fern-like crystals, or from aqueous acetone in large, colourless plates, m. p. 158°. It was insoluble in water, sparingly soluble in ligroin, and readily in acetone (Found: C, 78·1; H, 6·25; N, 7·4. $C_{25}H_{24}O_2N_2$ requires C, 78·1; H, 6·3; N, 7·3%).

Attempted Reduction of 1-2-*Pyrrolidone*-5-*carboxyanilide*.—The anilide (1 g.), dissolved in glacial acetic acid (30 c.c.), with addition of active platinum oxide (0·01 g.), and ferric chloride solution (0·11 c.c containing 0·0007 g.), were shaken with hydrogen under a pressure of 2 atmospheres for 27 hours. No hydrogen was absorbed, and the original substance was recovered unchanged.

dl-2-*Pyrrolidone*-5-*carboxyanilide*.—*dl*-2-Pyrrolidone-5-carboxylic acid (4 g.), prepared by the method of Haitinger (*Monatsh.*, 1882, **3**, 228), was heated with aniline (20 c.c.) under reflux at 205—210° for ½ hour. When cool, the solid product was washed with ether, leaving undissolved 4·1 g. of a colourless solid, m. p. 204°, unchanged by recrystallisation from water, the *anilide* then forming elongated, striated plates. It is considerably less soluble than the *d*-form (1 in 24, approximately, in water at 100°) and is almost insoluble in ethyl alcohol or aqueous acetone. β-Chloroethyl alcohol dissolves it fairly readily (Found : C, 64·45; H, 5·9. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

Heating d-*Glutamic Acid with Diphenylamine.*—A mixture of *d*-glutamic acid (18·6 g.) and diphenylamine (93 g.) was heated at 205—210° for ½ hour. The dark-coloured product was extracted with boiling ether, leaving 14·2 g. undissolved. 3 G. of this were extracted with cold water, and the insoluble tar was rejected. The almost colourless remainder gave, on recrystallisation from alcohol, 0·8 g., m. p. 186° (Found : C, 46·6; H, 5·7. $C_5H_7O_3N$ requires C, 46·5; H, 5·5%). The same substance was obtained by recrystallising the crude product from methyl alcohol. It does not decolorise bromine or permanganate solution appreciably. Bromine is dissolved by an aqueous solution of the substance to a considerably greater extent than by water, but is removed entirely in a vacuum, leaving the original substance, m. p. 188° (Found : C, 46·2; H, 5·4. Calc. : C, 46·5; H, 5·5%). For the attempted hydrogenation by the catalysts mentioned on p. 1265, glacial acetic acid, water, or alcohol was used as solvent. From the mother-liquor of the above substance a small quantity of *l*-pyrrolidonecarboxylic acid, m. p. 160°, $[\alpha]_D^{15^\circ}$ −10·36° in water, was isolated.

As it is stated in general terms by Abderhalden and Schwab (*Z. physiol. Chem.*, 1926, **157**, 196) that the time of heating has an influence on the nature of the product, the preceding preparation was repeated, heating at the same temperature being prolonged to 2½ hours. The same product was obtained. The effect of higher and lower reaction-temperatures was tried; at 240°, only tarry products, and at 155—165° a higher proportion of *l*-pyrrolidonecarboxylic acid, were obtained.

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