CCXVII.—*αγ-Diamino-β-phenylpropane and Related Compounds of Pharmacological Interest.*

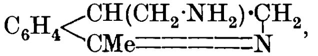
By JOSEPH GILBERT JACKSON and JAMES KENNER.

BOTH ethylenediamine and αε-diaminopentane are characterised pharmacologically by a depressant action on the blood pressure (Cloetta and Wünsche, *Arch. exp. Path. Pharm.*, 1923, **96**, 307; Barger and Dale, *J. Physiol.*, 1920, **41**, 19), and although the behaviour of other polymethylenediamines in this respect does not appear to have been recorded, it may be anticipated that they would exert a similar effect. This is in interesting contrast with the well-known sympathomimetic or pressor influence of β-phenylethylamine and related compounds (Barger and Dale, *loc. cit.*). It therefore seemed worthy of inquiry whether *αγ-diamino-β-phenylpropane*, $CHPh(CH_2{\cdot}NH_2)_2$, would behave as an intensified β-phenylethylamine, or whether its relationship to αγ-triaminopropane would involve more or less complete suppression of any sympathomimetic action.

The base and its NN′-*dimethyl* derivative have therefore been prepared by applying the usual series of reactions to β-*phenylglutardihydrazide*, $CHPh(CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2)_2$, and kindly examined by Dr. S. J. Cowell in the laboratory of Professor E. Mellanby, F.R.S. They were found to produce no appreciable effect upon the blood pressure of a cat, and, further, although Barger and Dale (*loc. cit.*) found that the introduction of hydroxyl groups in the 4- or 3 : 4-positions intensifies the activity of β-phenylethylamine, the hydrobromides of *αγ-diamino-β-4-hydroxyphenylpropane* and of *αγ-diamino-β-3 : 4-dihydroxyphenylpropane* are also reported by Dr. J. H. Burn to be devoid of all but traces of a sympathomimetic action.

The stereochemical considerations previously discussed (Jackson and Kenner, this vol., p. 573) suggest that the intramolecular condensation of diacyl derivatives of αγ-diamino-β-phenylpropane will only result in the formation of one dihydro*iso*quinoline ring, and this was confirmed by experiment.

4-*Aminomethyl*-1-*methyl*-3 : 4-*dihydro*iso*quinoline*,



$$C_6H_4{<}\begin{matrix}CH(CH_2\cdot NH_2)\cdot CH_2\\ CMe{=\!=\!=\!=\!=\!=}N\end{matrix},$$

and the corresponding 1-*phenyl* derivative, thus obtained, may also be considered as compounds in which elements favouring pressor and depressor actions respectively are combined, since, for example, 6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline hydrochloride (Pyman, J., 1908, **95**, 1743), as well as hydrastinine and cotarnine, exerts a depressant action. In the new compounds, however, the two effects are not as nicely balanced as in *αγ*-diamino-β-phenylpropane, since, as Dr. Cowell found, administration of each compound causes definite depression of the blood pressure of a cat.

EXPERIMENTAL.

Ethyl β-*phenylglutarate* is a colourless viscous oil, b. p. 180—184°/14 mm. (Found : C, 68·3 ; H, 7·5. $C_{15}H_{20}O_4$ requires C, 68·2 ; H, 7·6%).

β-*Phenylglutardihydrazide*, prepared from the ester, crystallises from absolute alcohol in long prisms, m. p. 177°, easily soluble in water (Found : N, 24·0. $C_{11}H_{16}O_2N_4$ requires N, 23·8%).

In order to obtain the corresponding *urethane*, amyl nitrite (15 g.) was added to a solution of the dihydrazide (9 g.) in absolute alcohol (500 c.c.) which had been cooled to 25° before treatment with a solution of dry hydrogen chloride (3 g.) in absolute alcohol. After the mixture had been heated until the evolution of nitrogen was complete, the solvent was removed by the aid of steam. By extraction with benzene, the urethane was obtained as a brown syrup (11 g.), from which crystals slowly separated. By crystallisation from benzene–light petroleum, long, colourless needles, m. p. 73—74°, insoluble in water and ligroin, were obtained (Found : N, 9·7. $C_{15}H_{12}O_4N_2$ requires N, 9·5%).

The urethane syrup (70 g.) was boiled with hydrobromic acid (b. p. 125° ; 700 c.c.) for 6 hours, and the major portion of the acid was then removed from the hot filtered solution by distillation. β-Phenylglutaric acid (10 g.) was recovered from the residual liquor by extraction with ether. Evaporation of the aqueous solution to a syrupy consistency furnished *αγ-diamino*-β-*phenylpropane hydrobromide* (32 g.), which separated from alcohol–ether in colourless prisms, melting at 252° and decomposing at 272° (Found : Br, 51·3. $C_9H_{14}N_2,2HBr$ requires Br, 51·3%). The free *base*, b. p. 150°/15 mm., is miscible with water in all proportions, giving an alkaline solution, and is rapidly converted in the atmosphere into its carbonate, m. p. 172° (decomp.). The *picrate* separates from alcohol in yellow prisms, m. p. 247° (decomp.) (Found : N, 19·0. $C_{21}H_{20}O_{14}N_8$ requires N, 18·5%). The *diacetyl* derivative crystallises from benzene in stout prisms, m. p. 153—154°, easily soluble in water, alcohol and hot benzene (Found : N, 12·1. $C_{13}H_{18}O_2N_2$ requires N, 12·0%). The *dibenzoyl* derivative separates from alcohol in colourless needles, m. p. 179°, easily soluble in alcohol, but very sparingly soluble in water (Found : N, 7·9. $C_{23}H_{22}O_2N_2$ requires N, 7·8%). The pp'-*ditoluenesulphonyl* derivative crystallises from alcohol in slender prisms, m. p. 91° (Found : N, 6·2. $C_{23}H_{26}O_4N_2S_2$ requires N, 6·1%), and was easily converted by means of methyl sulphate into NN'-*dimethyl*-NN'-*di*-p-*toluenesulphonyl*-αγ-*diamino*-β-*phenylpropane*, m. p. 60°, which could not be crystallised and was therefore purified by pouring its solution in cold concentrated sulphuric acid into water (Found : N, 5·7. $C_{25}H_{30}O_4N_2S_2$ requires N, 5·8%). Hydrolysis occurred when a solution of the methyl derivative (5 g.) in sulphuric acid (20 c.c.) and glacial acetic acid (10 c.c.) was maintained at 100° for 8 hours. The mixture was then made strongly alkaline, and the base removed in steam. From the distillate, NN'-*dimethyl*-αγ-*diamino*-β-*phenylpropane hydrochloride* was prepared in the usual manner; it crystallised from alcohol–ether in prisms, m. p. 249° (Found : Cl, 28·1. $C_{11}H_{18}N_2,2HCl$ requires Cl, 28·2%).

γ-*Amino*-β-*phenylbutyric acid hydrobromide*, isolated when the filtrate from the preparation of phenyldiaminopropane hydrobromide was evaporated, separated from benzene in colourless, irregular plates, m. p. 114° (Found : N, 5·5. $C_{10}H_{13}O_2N,HBr$ requires N, 5·4%). On treatment with cold 10% aqueous potassium hydroxide solution, 4-*phenyl*-2-*pyrrolidone* was obtained, which crystallised from benzene–light petroleum in colourless, hexagonal prisms, m. p. 60° (Found : N, 8·9. $C_{10}H_{11}ON$ requires N, 8·7%). Its *acetyl* derivative separated from alcohol in hexagonal plates, m. p. 63° (Found : C, 70·5, 70·8; H, 6·8, 7·2; N, 7·4, 7·6. $C_{12}H_{13}O_2N$ requires C, 71·0; H, 6·4; N, 6·9%). The *benzoyl* derivative crystallised from benzene–light petroleum in colourless prisms, m. p. 145° (Found : C, 76·7, 77·2; H, 5·6, 5·4; N, 5·3. $C_{17}H_{15}O_2$ requires C, 77·0; H, 5·7; N, 5·3%).

4-*Aminomethyl*-1-*methyl*-3 : 4-*dihydro*iso*quinoline* resulted when a solution of diacetylphenyldiaminopropane (5 g.) in toluene (150 c.c.) was boiled with phosphoric oxide (30 g.) for 12 hours, and for a further 8 hours after addition of more pentoxide (5 g.). The decanted solution was treated with water, toluene removed in steam, and the residue rendered alkaline; the *base* (1·5 g.) then separated. It crystallised from benzene in colourless, hexagonal plates, m. p.

182°, easily soluble in alcohol and dilute acids (Found: C, 75·6; H, 8·4; N, 16·0. $C_{11}H_{14}N_2$ requires C, 75·8; H, 8·0; N, 16·1%), and its *hydrochloride* separated from a mixture of alcohol and ether in slender prisms, m. p. 222°, very soluble in water.

4-*Aminomethyl*-1-*phenyl*-3 : 4-*dihydro*iso*quinoline*.—The benzoyl derivative (7 g.) of this base was obtained by boiling a solution of dibenzoylphenyldiaminopropane (10 g.) in toluene (500 c.c.) with phosphoric oxide (40 g.) for 26 hours, and separated when the acid solution of the reaction products was almost neutralised. The free *base* (0·1 g.) and unchanged dibenzoyl derivative (0·2 g.) were recovered when the liquors were rendered alkaline. The *benzoyl* derivative crystallised from alcohol in long prisms, m. p. 114° (Found: N, 8·5. $C_{25}H_{20}ON_2$ requires N, 8·2%), and was converted, by boiling 50% sulphuric acid, into the free base. This separated from aqueous alcohol in colourless leaflets, m. p. 169° (Found: C, 81·6; H, 7·1; N, 12·1. $C_{16}H_{16}N_2$ requires C, 81·4; H, 6·8; N, 11·8%). Its *dihydrochloride* formed colourless prisms, m. p. 291°.

Ethyl p-*methoxyphenylpropane*-ααγ-*tricarboxylate* was produced when ethyl malonate (214 g.) and ethyl *p*-methoxycinnamate (280 g.) were mixed with a solution of sodium (30 g.) in absolute alcohol (500 g.), the whole being kept at the ordinary temperature for 14 days. The ester (275 g.) was a yellow, viscous oil, b. p. 225—240°/12 mm. (Found: C, 62·5; H, 7·0. $C_{19}H_{26}O_7$ requires C, 62·4; H, 7·1%). Hydrolysis readily ensued when the ester (60 g.) was mixed with a solution of sodium hydroxide (40 g.) in water (50 c.c.) and alcohol (21 c.c.). After the reaction had subsided, and the product had been dissolved in water (200 c.c.), methoxycinnamic acid (3 g.) was precipitated by partial acidification. After concentration of the solution to 100 c.c., and further acidification, the crude tricarboxylic acid was removed by ether and converted at 130° into the dicarboxylic acid. After crystallisation from hot water, β-p-*methoxyphenylglutaric acid* (35 g.) was obtained in colourless prisms, m. p. 165° (Found: C, 60·6; H, 6·2; equiv., 121·5. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%; equiv., 119). It was characterised by its *anhydride*, slender prisms, m. p. 152° (Found: C, 65·2; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%), its *methyl* ester, slender prisms, m. p. 42°, b. p. 205—210°/20 mm. (Found: C, 63·1; H, 6·6. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%), its *ethyl* ester, b. p. 206—210°/14 mm. (Found: C, 64·9; H, 7·5. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%), and its *dihydrazide*, needles, m. p. 190° (Found: C, 54·2; H, 6·8. $C_{12}H_{18}O_3N_4$ requires C, 54·2; H, 6·8%). The corresponding *diurethane* separated from aqueous alcohol in slender prisms, m. p. 99—100° (Found: C, 59·2; H, 7·8. $C_{16}H_{24}O_5N_2$

requires C, 59·3; H, 7·4%). Hydrolysis with boiling hydrobromic acid (*d* 1·45) was accompanied by demethylation.

$\alpha\gamma$-Diamino-β-p-hydroxyphenylpropane dihydrobromide crystallised from alcohol–ether in irregular prisms, m. p. 316°, easily soluble in water and furnishing a violet coloration with ferric chloride (Found: Br, 49·3. $C_9H_{14}ON_2,2HBr$ requires Br, 48·8%). The *tribenzoyl* derivative crystallised from alcohol in nodules of irregular prisms, m. p. 206—207° (Found: C, 75·0; H, 5·6. $C_{30}H_{26}O_4N_2$ requires C, 75·2; H, 5·4%).

3 : 4-*Dimethoxybenzylidenemalonic acid* (3·5 g.) resulted with 3 : 4-dimethoxycinnamic acid (10 g.) when veratraldehyde (15 g.), malonic acid (15 g.), and alcoholic ammonia (4*N*, 50 c.c.) were heated at 100° for 6 hours. The acid crystallised from water in light yellow prisms, m. p. 208° (decomp.) (Found: C, 57·3; H, 4·9. $C_{12}H_{12}O_6$ requires C, 57·2; H, 4·8%).

Ethyl β-3 : 4-dimethoxyphenylpropane-$\alpha\alpha\gamma$-tricarboxylate was prepared in a similar manner to the monomethoxy-derivative. The reaction mixture set almost solid, but after 14 days the crude product, b. p. 225—250°/16 mm., consisted to the extent of only 84% of the desired ester. This after further fractionation boiled at 245—248°/14 mm., was very viscous, and exhibited a faint green fluorescence (Found: C, 60·4; H, 7·2. $C_{20}H_{28}O_8$ requires C, 60·6; H, 7·1%). Alkaline hydrolysis, as in the previous case, was almost instantaneous, and dimethoxycinnamic acid was removed by rendering the solution of the crude sodium salt just acid.

3 : 3′-*Dimethoxydiphenylglutaric acid* separated from water in colourless prisms, which melted in the hydrated condition (Found: H_2O, 6·3. $C_{13}H_{16}O_6,H_2O$ requires H_2O, 6·3%) at 125—130°, and when anhydrous at 184° (Found: C, 58·6; H, 6·1. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%). It was characterised by its *anhydride*, hexagonal prisms, m. p. 124° (Found: C, 62·4; H, 5·6. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%), its *methyl* ester, needles, m. p. 73° (Found: C, 61·0; H, 6·9. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%), its *ethyl* ester, b. p. 226—229°/15 mm. (Found: C, 62·7; H, 7·5. $C_{17}H_{24}O_6$ requires C, 63·0; H, 7·4%), and its *dihydrazide*, needles, m. p. 182° (Found: C, 53·1; H, 6·8. $C_{13}H_{20}O_4N_4$ requires C, 52·7; H, 6·8%). The syrupy urethane prepared from the last compound could not be obtained in the solid condition, and was therefore directly hydrolysed in 24 hours by boiling hydrobromic acid (*d* 1·45). Dealkylation also occurred and *$\alpha\gamma$-diamino-β-3 : 4-dihydroxyphenylpropane dihydrobromide* was obtained in stout, hydrated prisms (Found: H_2O, 5·2. $C_9H_{14}O_2N_2,2HBr,H_2O$ requires H_2O, 5·0%). In the anhydrous condition, the salt melted at 294° (Found: N, 8·0; Br, 46·4. $C_9H_{14}O_2N_2,2HBr$ requires N, 8·1;

Br, 46·6%). The *tetrabenzoyl* derivative separated from alcohol in small prisms, m. p. 217° (Found : C, 74·5; H, 5·1; N, 5·1. $C_{27}H_{30}O_6N_2$ requires C, 74·3; H, 5·0; N, 5·9%).

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