CX.—*Synthesis of* dl-*Tyrosine and* dl-3 : 4-*Dihydroxyphenylalanine.*

By Henry Stephen and Charles Weizmann.

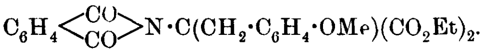
Sörensen (*Zeitsch. physiol. Chem.*, 1905, **44**, 448) has worked out a general method for obtaining α-amino-acids by condensing ethyl phthaliminomalonate with alkyl halogen compounds, and he has prepared, in particular, phenylalanine by using benzyl chloride.

The authors have applied the above method to the synthesis of *dl*-tyrosine and *dl*-3 : 4-dihydroxyphenylalanine by condensing ethyl phthaliminomalonate with *p*-methoxybenzyl bromide and piperonyl bromide respectively.

Tyrosine is formed directly by heating the condensation product with hydrochloric acid in a sealed tube. In the second case the best results were obtained by decomposing the phthalamic acid formed by hydrolysis of the ethyl phthaliminopiperonylmalonate with hydrochloric or hydrobromic acid in acetic acid solution. The *dl*-3 : 4-dihydroxyphenylalanine was found to be unstable in neutral or alkaline solutions, giving in ordinary circumstances a black pigment, as stated by Funk (T., 1911, **99**, 554). We found, however, that the melting point of the amino-acid was 295°, with preliminary decomposition at 281° (Funk gives 263—272°).

Experimental.

Ethyl Phthalimino-p-*methoxybenzylmalonate*,



$$C_6H_4{<}{\substack{CO\\CO}}{>}N{\cdot}C(CH_2{\cdot}C_6H_4{\cdot}OMe)(CO_2Et)_2.$$

30·5 Grams (1 mol.) of ethyl phthaliminomalonate were dissolved in alcohol and added slowly to a solution of 3·9 grams of potassium in absolute alcohol. The bright yellow paste of the potassium compound was freed from alcohol by heating the mixture in an oil-bath at 110° under diminished pressure, and the final traces of alcohol were removed by shaking the yellow cake with dry xylene and removing this by distillation as before, the operation being repeated two or three times.

20·1 Grams (1 mol.) of anisyl bromide (b. p. 110°/10 mm.), prepared by treating *p*-methoxybenzyl alcohol with hydrobromic acid in the cold, or with phosphorus pentabromide in dry ethereal solution (compare Tiffeneau, *Bull. Soc. chim.*, 1911, [iv], **9**, 826), were dissolved in xylene and added to the potassium compound prepared above. The xylene suspension was then heated at 145° for four hours in an oil-bath.

The product was poured into water, and the xylene layer separated, washed several times with dilute potassium hydroxide solution, and finally with water, dried, and the xylene removed by distillation under diminished pressure. The residue, an oil, was dissolved in ethyl alcohol, from which the condensation product crystallised; on recrystallisation from a mixture of benzene and light petroleum, colourless, rhombic prisms were obtained, melting at 83°:

0·2074 gave 0·4786 CO_2 and 0·1010 H_2O. C=64·4; H=5·4.
$C_{23}H_{23}O_7N$ requires C=64·8; H=5·4 per cent.

The hydrolysis of the condensation product just described was effected in two ways, namely, (*a*) according to the method described by Sörensen and Andersen (*Zeitsch. physiol. Chem.*, 1908, **56**, 266), and (*b*) with concentrated hydrochloric acid in a sealed tube at 175° for two hours, which gives the hydrochloride of tyrosine at once.

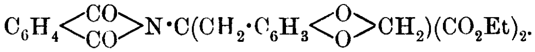
Phthalamino-p-*methoxybenzylmalonic Acid*, $CO_2H\cdot C_6H_4\cdot CO\cdot NH\cdot C(CH_2\cdot C_6H_4\cdot OMe)(CO_2H)_2$.

Ten grams of the condensation product were dissolved in ethyl alcohol, and 18 grams of crystallised barium oxide dissolved in hot water were added, the mixture being boiled on the steam-bath for one hour. The alcohol was then removed in a current of steam, and the residue filtered while hot, the barium salt being washed several times with hot water. The salt was dried, finely powdered, and digested with cold dilute hydrochloric acid. The free acid thus obtained was filtered from barium chloride in solution, boiled with water until free from barium chloride, and finally crystallised from acetic acid, from which it separated in small, colourless needles, melting and decomposing at 210°:

0·1233 gave 0·2649 CO_2 and 0·0466 H_2O. C=58·6; H=4·2.
$C_{19}H_{17}O_8N$ requires C=58·88; H=4·4 per cent.

The phthalamino-compound described above was dissolved in glacial acetic acid, and the solution treated with concentrated hydrochloric acid, and warmed on the steam-bath for three hours, further quantities of hydrochloric acid being added from time to time. The solution was afterwards diluted with water, and, when cold, a large part of the phthalic acid formed had separated, and the remaining portion was removed by extracting several times with ether. The aqueous solution was then decolorised by boiling with animal charcoal, and afterwards evaporated under diminished pressure. The hydrochloride of the base was dissolved in water and neutralised with ammonia, when tyrosine was obtained, which crystallised from hot water and possessed all the properties of the synthetic substance.

Ethyl Phthaliminopiperonylmalonate,



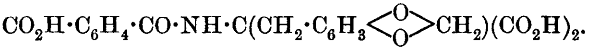
$$C_6H_4{<}{\genfrac{}{}{0pt}{}{CO}{CO}}{>}N{\cdot}C(CH_2{\cdot}C_6H_3{<}{\genfrac{}{}{0pt}{}{O}{O}}{>}CH_2)(CO_2Et)_2.$$

This was obtained similarly by condensing piperonyl bromide and ethyl phthaliminomalonate. After recrystallisation from benzene and light petroleum, it melted at 89°. This substance was hydrolysed according to method (*b*) described above:

0·2128 gave 0·4876 CO_2 and 0·0878 H_2O. C = 62·5; H = 4·6.

$C_{23}H_{21}O_8N$ requires C = 62·8; H = 4·7 per cent.

Phthalaminopiperonylmalonic Acid,



$$CO_2H{\cdot}C_6H_4{\cdot}CO{\cdot}NH{\cdot}C(CH_2{\cdot}C_6H_3{<}{\genfrac{}{}{0pt}{}{O}{O}}{>}CH_2)(CO_2H)_2.$$

This acid was obtained by hydrolysis of the above ester with barium hydroxide; it crystallises from acetic acid in small, colourless needles, melting and decomposing at 234—236°.

0·1632 gave 0·3383 CO_2 and 0·0514 H_2O. C = 56·55; H = 3·7.

0·2131 „ 6·4 c.c. N_2 (moist) at 15° and 764 mm. N = 3·5.

$C_{19}H_{15}O_9N$ requires C = 56·85; H = 3·7; N = 3·47 per cent.

The above acid on treatment with hydrochloric or hydrobromic acid in acetic acid solution, as already described, gave the hydrochloride or hydrobromide of 3:4-dihydroxyphenylalanine, which crystallised from methyl alcohol in colourless, thin plates, melting and decomposing at 246° and 212° respectively.

Hydrochloride:

0·1001 gave 0·1653 CO_2 and 0·0479 H_2O. C = 45·77; H = 5·33.

0·1690 „ 0·1016 AgCl. Cl = 14·77.

$C_9H_{11}O_4N,HCl$ requires C = 46·25; H = 5·14; Cl = 14·7 per cent.

Hydrobromide:

0·1404 gave 0·0936 AgBr. Br = 28·4.
$C_9H_{11}O_4N,HBr$ requires Br = 28·70 per cent.

The above salts, on treatment with ammonia sufficient for neutralisation, gradually became dark; the change was more rapid in alkaline solution or on boiling with water; it was thus found impossible to obtain a pure sample of the dihydroxyphenylalanine, owing to the oxidation in neutral or alkaline solutions. The best sample was obtained by allowing a hot aqueous solution to cool in a vacuum; the substance separated in pale brown flakes, which began to decompose at 281°, and melted and decomposed completely at 295°:

0·1608 gave 0·3244 CO_2 and 0·0764 H_2O. C = 54·30; H = 5·25.
$C_9H_{11}O_4N$ requires C = 55·10; H = 5·20 per cent.

THE UNIVERSITY,
MANCHESTER.