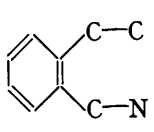
195. *Phthalocyanines and Related Compounds. Part XVII. Intermediates for the Preparation of Tetrabenzporphins: Acids derived from Phthalimidine.*

By R. P. Linstead and G. A. Rowe.

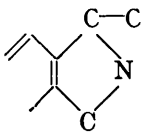
Iminophthalimidine condenses with malonic ester and acetoacetic ester to yield unsaturated derivatives of phthalimidine. From the product with malonic ester, 3-carboxymethylenephthalimidine has been obtained. The " dihydrate " of this substance is the monohydrate of *o*-carbamylbenzoylacetic acid.

The reduction of both these substances leads to 3-carboxymethylphthalimidine or the corresponding open-chain compound, β-hydroxy-β-*o*-carbamylphenylpropionic acid.

Recent work (Helberger, *Annalen*, 1937, **529**, 205, and subsequent papers; Dent, J., 1938, 1; Barrett, Linstead, and Tuey, J., 1939, 1809) has shown the importance of substances containing the skeleton (I) or (II) as intermediates for the preparation of compounds of the tetrabenzporphin group. Two substances of particular interest from this point of view are the acids (III) and (IV). These have received a variety of names in the past: to avoid any possible ambiguity we shall call them 3-carboxymethylenephthalimidine (III) and 3-carboxymethylphthalimidine (IV) respectively. This paper is concerned with the preparation of these substances and with certain aspects of their chemistry.



(I.)



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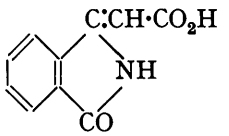

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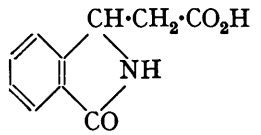
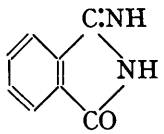
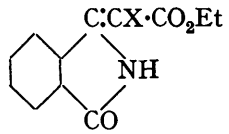


(IV.)

We find that iminophthalimidine (V) (Braun and Tcherniac, *Ber.*, 1907, **40**, 2709) condenses with malonic and acetoacetic esters.* With the latter, condensation occurred in the absence of catalyst at 140°, with the evolution of ammonia and heat; the *product* (VI, X = CO·CH_3) was formed in good yield. The reaction with malonic ester went less readily but in the same way to give 3-dicarbethoxymethylenephthalimidine (" phthalimidylmalonic ester "; VI, X = CO_2Et).

(V.) 

$\xrightarrow{CH_2X\cdot CO_2Et}$


(VI.)

Iminophthalimidine may be considered as an internally acylated benzamidine. The condensation is of a type which seems to be new in benzamidine chemistry.

The condensation products were shown to be of type (VI) and not to have the isomeric hydrindone or open-chain (*o*-cyanobenzoyl) structure by the fact that both were readily oxidised to phthalimide in excellent yield. Vigorous hydrolysis of 3-dicarbethoxymethylenephthalimidine (VI, X = CO_2Et) with aqueous alcoholic baryta yielded a monobasic acid, $C_{10}H_7O_3N$. Products containing some dibasic acid were obtained under other

* These experiments were suggested by a discovery by Mr. N. H. Haddock in the Laboratories of the Dyestuffs Group of Imperial Chemical Industries, Ltd., details of which will be published later.

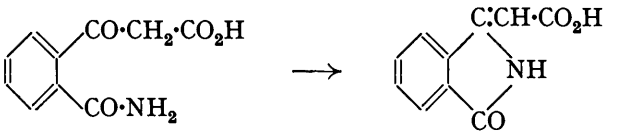
conditions, but the malonic acid corresponding to (VI) could not be isolated in the pure condition. The monobasic acid has been proved to be 3-carboxymethylenephthalimidine (III). It can be crystallised from boiling water, separates in the anhydrous form, and melts at 220°. On oxidation with permanganate it gives phthalimide readily and quantitatively. On treatment with diazomethane, it yields a *methyl* ester, m. p. 125°, which also is readily oxidised. Reduction of the acid yields 3-carboxymethylphthalimidine (IV).

The literature relating to the acid (III) shows some discrepancies. It had previously been prepared (Gabriel and Michael, *Ber.*, 1877, **10**, 1551) by the action of aqueous ammonia on phthalylacetic acid, followed by acidification, and was originally taken to be phthalylacetamide, on the basis of the erroneous formulation of phthalylacetic acid as a derivative of hydrindene. Subsequently Roser (*Ber.*, 1884, **17**, 2623) showed it to be an acid and suggested it was a double-bond isomeride of (III); finally Gabriel (*Ber.*, 1885, **18**, 2451) gave it the present formula. Gabriel and Michael state that it can be crystallised from hot water, is anhydrous, and melts at 200°. On the other hand Dent (*loc. cit.*), by the same reaction, obtained the acid as a " dihydrate " which was decomposed by boiling water and melted at 120°.

We have repeated this work and confirmed both sets of observations. The essential difference lies in the temperature of acidification. If the acid is liberated with ice-cooling the " dihydrate " described by Dent is obtained; if without special precautions, then the product is anhydrous carboxymethylenephthalimidine. This substance melts at 220° and is identical with that prepared from the condensation product of iminophthalimidine and ethyl malonate. It seems probable that Gabriel's material, m. p. 200°, contained some of the 120° acid. The position of the double bond proposed by Gabriel is proved by the behaviour on oxidation already mentioned.

What, then, is the structure of the " dihydrate," m. p. 120°? When its solution in alkali is acidified at room temperature, the 220° acid is precipitated. On the other hand it is not possible to convert the 220° acid into the 120° form by any treatment with water or by acidification of ice-cold solution of its salts. It is, therefore, evident that some at least of the " water of hydration " is chemically combined. Esterification with diazomethane yielded a *methyl* ester, m. p. 117°, which depressed the m. p. of 3-carbomethoxymethylenephthalimidine (m. p. 125°). The new ester was much more soluble in water than the latter and had the molecular formula $C_{11}H_{11}O_4N$, *i.e.*, the molecule was larger by *one* element of water. No water was eliminated by heating the ester at 110°, whereas the parent acid (m. p. 120°) lost water readily at 80°. The dehydration was not quantitative, being accompanied by secondary decomposition. The " dehydrated " material yielded the same methyl ester, m. p. 117°, as the original acid, and not the cyclic ester of m. p. 125°.

It thus became evident that the 120° acid was the monohydrate of an acid $C_{10}H_9O_4N$, and not the dihydrate of one $C_{10}H_7O_3N$. It does not contain the phthalimidine ring, but is o-*carbamylbenzoylacetic acid* (VII). Its easy conversion into 3-carboxymethylenephthalimidine involves the cyclodehydration of the enolic form.



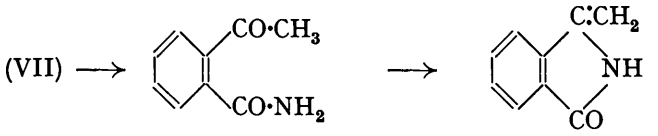
(VII), monohydrate, m. p. 120°. (III), m. p. 220°.

Precisely the same cyclisation occurs with the methyl ester of (VII), which yields the methyl ester of (III) when its aqueous solution is acidified.

The absence of a double bond in the 120° acid is shown by its resistance to oxidation with alkaline permanganate, even at 100°. Acidification of the resulting solution at room temperature yielded the unsaturated acid (III) by the cyclisation of unoxidised keto-acid (VII). This recovery of a compound, itself oxidised with great ease, after a process of vigorous oxidation is an interesting paradox. There is clearly no tendency for the cyclisation (VII ⟶ III) in alkaline solution. The methyl ester of the keto-acid (VII) failed

to yield ketonic derivatives owing to the ease of cyclisation in faintly acid solution: even treatment with semicarbazide acetate gave the cyclic ester, m. p. 125°. The keto-acid gave an immediate orange precipitate with 2 : 4-dinitrophenylhydrazine, but the derivative has not been obtained analytically pure.

The formulation of the 120° acid as a substituted benzoylacetic acid also explains its easy decarboxylation in boiling water, as against the comparative stability of the 220° acid. The product is 3-methylenephthalimidine (IX) (Dent, *loc. cit.*), which is possibly formed through the enolic modification of the amide of acetophenone-*o*-carboxylic acid:



(VIII), as enol. (IX.)

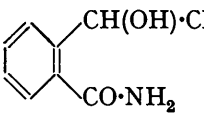
The mechanism of this change cannot, however, be regarded as settled, because Helberger, von Rebay, and Hevér (*Annalen*, 1938, **533**, 197) have isolated a substance which appears to be the amide (VIII), and this is stable to boiling water.

There are many analogies for the formation of an open-chain keto-compound from phthalylacetic acid. Gabriel (*Ber.*, 1885, **18**, 2451) obtained the keto-methylamide, corresponding to (VII), by the action of aqueous methylamine, and noticed its dehydration by means of acid to the *N*-methyl derivative of (III). Other similar observations have been made with benzylidenephthalide, and in the work of Mertens (*Ber.*, 1886, **19**, 2367).

3-*Carboxymethylphthalimidine* (With F. G. RUNDALL).—Reduction of 3-carboxymethylenephthalimidine in aqueous alkali with sodium amalgam yielded the corresponding dihydro-acid, $C_{10}H_9O_3N$, m. p. 180°, in 90% yield. The saturated acid gives a *methyl* ester, m. p. 140°. The acid is identical with that prepared by the action of alkali on *o*-cyanocinnamic acid (Edwards, J., 1926, 816), which was shown by Rowe, Haigh, and Peters to be *iso*indolinone-3-acetic acid (3-carboxymethylphthalimidine) (J., 1936, 1101). Material prepared by this method gave an identical methyl ester. The structure is proved by the new preparation from a compound which undoubtedly contains the *iso*indole ring, and by the fact that decarboxylation over copper bronze yielded 3-methylphthalimidine, identical with authentic material.

Whereas reduction of the unsaturated acid (III) gave 3-carboxymethylphthalimidine under all the conditions tried, the reduction of the keto-acid, m. p. 120°, by sodium amalgam gave two products. If both the reduction in aqueous solution and the subsequent acidification were carried out at room temperature, the product was 3-carboxymethylphthalimidine. If all the operations were performed at 0°, the product, although very similar in solubility and appearance, and having practically the same melting point, had the composition $C_{10}H_{11}O_4N$, *i.e.*, the molecule was larger by H_2O. The same "hydrated" material was formed by reduction in methanol at 50°, followed by acidification at 0°.

We believe that the new acid is the open-chain secondary alcohol (X) corresponding to the keto-acid (VII) and not a simple monohydrate of (IV). The principal reasons are: (*a*) The method of preparation, and the fact that the "hydrated" acid is not obtained from the reduction of the unsaturated acid. (*b*) The fact that the water can only be eliminated *irreversibly*. The "hydrated" acid loses a molecule of water without secondary decomposition when heated at 110°, but it has not been found possible to induce the cyclic acid (IV) to take up water. The same cyclisation (X ⟶ IV) is brought about by treatment with dilute acid at the boiling point but not at room temperature. (*c*) The "hydrated" acid is slowly oxidised by permanganate, unlike the cyclic acid (IV). The "hydrated" acid, $C_{10}H_{11}O_4N$, is therefore regarded as β-*hydroxy*-β-*o*-*carbamylphenylpropionic acid.*



(X.)

A contradictory fact is that treatment of (X) with diazomethane yields the methyl ester of (IV), m. p. 140°. This would suggest that the new acid is merely a monohydrate

of (IV), were it not that the rest of the evidence points so strongly in the other direction. We have not succeeded in preparing a simple ester of the hydroxy-acid.

The production of the saturated cyclic acid (IV) by the reduction of the keto-acid (VII) resembles that of benzylphthalimidine from *o*-carbamyldeoxybenzoin (Gabriel, *Ber.*, 1885, **18**, 2434). The cyclisation probably accompanies the liberation of the acid on the acidification of the strongly alkaline solution. The simple reduction of the keto-acid to the secondary alcohol (X) parallels precisely the behaviour of the corresponding methylamide, which yields the *N*-methyl homologue of (X). This can be converted into 2-methyl*iso*indolinone-3-acetic acid by heat (Gabriel and Giebe, *Ber.*, 1896, **29**, 2524).

o-Cyanocinnamic acid has been mentioned above as an intermediate in one synthesis of 3-carboxymethylphthalimidine. Its reduction by means of sodium amalgam in methanol has been found by Mr. G. A. P. Tuey to give β-*o*-cyanophenylpropionic acid in excellent yield. The product is identical with that obtained by Edwards (*loc. cit.*) by electrolytic reduction of the corresponding *allo*-acid. The *methyl* ester is a liquid, which is of interest in view of Mitchell and Thorpe's demonstration (J., 1910, **97**, 2271) that the supposed ethyl *o*-cyanophenylpropionate (a solid) of Gabriel and Hausmann (*Ber.*, 1889, **22**, 2017) was a derivative of hydrindone. The fact that the cyano-acid had not undergone conversion into a cyclic isomeride during reduction was proved by its hydrolysis to β-*o*-carboxyphenylpropionic acid.

The conversion of some of these intermediates into macrocyclic pigments is discussed in Part XIX.

Experimental.

(1) *Condensations of Iminophthalimidine.*—(a) *With ethyl acetoacetate.* Preliminary experiments showed that only very poor yields of condensation product were obtained above 140°. The following comparative experiments were performed by heating 3 g. of the imino-compound with the ester at this temperature. The last line gives the yield of unsaturated ester (VI, X = CO·CH_3).

Equivalents of ester	1	1	2	3	3	6
Time (mins.)	120	15	120	15	20	15
Yield, %	10	20	17	40	70	35

The reaction in all cases was exothermic and ammonia was evolved. The product was worked up as follows: Unchanged ester was recovered by distillation under reduced pressure. The residue was shaken with ether (100 c.c.). The insoluble residue was phthalimide, formed by a side reaction, no iminophthalimidine being recovered. The ethereal extract was freed from solvent, and the residue extracted with 500 c.c. of light petroleum (b. p. 90—120°) containing 5% of acetone. The extract was concentrated to about 100 c.c.; *ethyl phthalimidyl-3-acetoacetate* (VI, X = CO·CH_3) was deposited in pale yellow needles, m. p. 101° after recrystallisation from light petroleum (Found: C, 64·85, 64·7; H, 4·8, 4·9. $C_{14}H_{13}O_4N$ requires C, 64·8; H, 5·1%). The ester was soluble in cold aqueous alkali, but an alcoholic solution gave no colour with ferric chloride. Bromine in chloroform was slowly decolorised. The ester could not be catalytically hydrogenated under a variety of conditions.

The optimum yield of 70% could also be obtained in runs of 100 g. Poor or negligible yields were obtained in the presence of piperidine, acetic acid, sodium acetate or ammonium molybdate. When *o*-cyanobenzamide was used in place of iminophthalimidine, there was no reaction at 100° during short runs, and considerable tar-formation when either the time was prolonged or the temperature raised.

3·0 G. of phthalimidylacetoacetic ester, suspended in 50 c.c. of aqueous sodium bicarbonate, were treated with mechanical stirring with 100 c.c. of 3% potassium permanganate solution. The colour was discharged in an hour. The product was cleared with sulphur dioxide, and the phthalimide collected by filtration, more being recovered by constant extraction of the filtrate with ether. Yield 96%, m. p. 227°, mixed m. p. 231°.

(b) *With ethyl malonate.* Under the best conditions described above, the yield of condensation product from ethyl malonate was only about 10%, and in a number of experiments below the b. p. of the ester no yield above 16% was obtained. The best yield (39%) was obtained by the use of 3 equivs. of the malonic ester, the temperature being raised to the b. p. (199°) and held there during 20 minutes. In the evolution of heat and ammonia, and in the formation of phthalimide, the reaction resembled that with ethyl acetoacetate. The product from 100 g.

of iminophthalimidine was freed from the excess of malonic ester under reduced pressure, and the residue dissolved in 300 c.c. of warm acetone. The solution was cooled and diluted with 4 l. of ether, which precipitated phthalimide. The filtered solution was evaporated to a syrup. This was extracted thrice with a boiling mixture of 2 l. of petroleum (b. p. 90—120°) and acetone (150 c.c.), which left a tarry residue. The combined extracts on concentration yielded 3-*dicarbethoxymethylenephthalimidine* (VI, X = CO_2Et), which was finally crystallised from light petroleum. Yield 35%; m. p. 104—105°* (Found: C, 62·4; H, 5·0. $C_{12}H_{15}O_5N$ requires C, 62·3; H, 5·2%). The use of piperidine as a catalyst did not improve the yield. Chromatographic purification was without benefit.

The ester formed pale yellow crystals insoluble in aqueous alkali and giving no ferric chloride reaction. The reaction with bromine in chloroform was very slow. The ester resisted catalytic hydrogenation. It was not reduced by sodium amalgam in aqueous alcohol at 0—20°, and in alcohol at 50—60° some hydrolysis to carboxymethylenephthalimidine occurred but no reduction was detected.

3 G. of 3-dicarbethoxymethylenephthalimidine were oxidised with 150 c.c. of 3% potassium permanganate solution in the manner described above for the acetoacetic ester. Yield of phthalimide 97%, m. p. 228°, mixed m. p. 231°.

3-Dicarbethoxymethylenephthalimidine (10·0 g.) was refluxed vigorously for 6½ hours with 27 g. of baryta in 400 c.c. of 50% alcohol. A yellow sludge was removed by filtration, and the solution acidified and extracted continuously with ether for 4 hours. The extract left a crude acid, which was crystallised from alcohol. Yield of 3-carboxymethylenephthalimidine 6·2 g. (95%), m. p. 220° (Found: C, 63·6; H, 3·7; N, 7·5; equiv., 183·0. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%; equiv., 189·0. When the acid was crystallised from water 3, 4 and 6 times, the analytical figures were respectively: C, 63·8; H, 3·6; C, 64·3; H, 3·6; and C, 64·5; H, 3·7%. This indicates a progressive slow decarboxylation).

Hydrolysis of the dicarbethoxymethylenephthalimidine with boiling aqueous baryta gave an acid, m. p. 162° (equiv., 142·0). Gentle refluxing with aqueous-alcoholic baryta gave a similar product, which clearly contained some dibasic acid. Hydrolysis with cold aqueous or aqueous-alcoholic alkali gave intractable gums. Boiling aqueous-alcoholic alkali gave the acid, m. p. 220°, but in worse yield than that obtained by the process described above.

3-Carboxymethylenephthalimidine (5·0 g.) was esterified with diazomethane in the usual manner. The *methyl* ester (4·4 g.) melted at 124—125° after crystallisation from alcohol (Found: C, 65·0; H, 4·4; N, 6·8. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·5; N, 6·9%). It was sparingly soluble in water and was readily oxidised by potassium permanganate. The acid (1 g.), dissolved in sodium bicarbonate solution, was oxidised with permanganate; phthalimide, m. p. 230°, was rapidly produced in quantitative yield.

(2) *The Action of Ammonia on Phthalylacetic Acid.*—(a) Finely ground phthalylacetic acid (40 g.) (Gabriel and Neumann, *Ber.*, 1893, **26**, 951) was added slowly to a stirred mixture of aqueous ammonia (40 c.c., *d* 0·880) and water (400 c.c.) at room temperature. Stirring was continued for ½ hour and the turbid liquid was then filtered and acidified with an excess of dilute hydrochloric acid (1 : 1) without cooling. The mixture was stirred for about an hour, and the yellow solid collected and dried at 40°; m. p. 216°, and 220° after careful crystallisation from hot water. Yield, 22 g. It was identified with the 3-carboxymethylenephthalimidine prepared above by mixed m. p. (220°), analysis (Found: C, 63·7; H, 3·8%; equiv., 187), and conversion into the methyl ester, m. p. and mixed m. p. 124—125° (Found: C, 65·0; H, 4·5%).

(b) Following Dent (*loc. cit.*), the amination and acidification were carried out at 0—5°. The monohydrate of o-*carbamylbenzoylacetic acid* (VII) so obtained (35 g. from 40 g. of phthalylacetic acid) was dried at 40°. It melted at 120° as reported by Dent, and began to melt at about 100° in admixture with 3-carboxymethylenephthalimidine. The acid, which could not be crystallised from hot water, was obtained as a pinkish powder.

A solution of 5 g. of the acid, m. p. 120°, in dilute sodium hydroxide solution (or in aqueous ammonia) was stirred at room temperature with an excess of hydrochloric acid (1 : 1) for 90 minutes. 3-Carboxymethylenephthalimidine was precipitated as a yellow powder (3·5 g.), m. p. 220° after crystallisation from hot water. Similar treatment of the 220° acid successively with alkali and acid at 0° failed to produce the 120° acid. Both acids readily yielded ammonia when warmed with caustic soda solution.

A solution of 5 g. of the keto-acid (VII) in aqueous sodium bicarbonate was treated slowly with 3% permanganate solution, first at 20° and subsequently on the steam-bath. There was

* There is reason to believe that this material may contain some isomeric impurity (see following paper).

no appreciable reaction. After 2 hours, when about 10 c.c. of the reagent had been added, the mixture was cooled, decolorised with sulphur dioxide, and acidified at 20° with hydrochloric acid. 3·0 G. of 3-carboxymethylenephthalimidine were obtained, m. p. and mixed m. p. 220°; a mixture with phthalimide melted at 204°.

Esterification of the keto-acid (5·0 g.) with diazomethane at 0° yielded the *methyl* ester (4·8 g.), m. p. 116—117° (Found : C, 60·1; H, 5·3; N, 6·65. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%). A mixture with 3-carbomethoxymethylenephthalimidine (m. p. 124—125°) melted at 105—107°. The ester was freely soluble in cold water and the solution was stable to permanganate. It gave a weak brown colour with ferric chloride in alcohol It was unchanged by 3 hours' heating at 110° (toluene bath). When its aqueous solution was acidified with cold concentrated hydrochloric acid, 3-carbomethoxymethylenephthalimidine was rapidly precipitated, m. p. and mixed m. p. 124—125°. Attempted preparations of ketonic derivatives led to the same change. Both methyl esters evolved ammonia readily when boiled with caustic soda solution, but not with sodium carbonate.

The keto-acid, when heated at 80° under reduced pressure, lost weight as follows : 11·5% in ½ hour, 16·7% in ¾ hour, 20·7% in 1 hour (theo. loss for $2H_2O$, 16·0%); the appearance of the residue also showed that secondary decomposition was occurring. A sample of the acid was heated at 80° until it had lost 16% by weight; when the residue was esterified with diazomethane, a rather low yield of the keto-ester was obtained, m. p. and mixed m. p. 116—117°.

(3) *Sodium Amalgam Reductions.*—(a) *Of 3-carboxymethylenephthalimidine.* A solution of 4·7 g. of the acid in 20 c.c. of 5% aqueous sodium hydroxide was mechanically stirred at 0° while 50 g. of 3% sodium amalgam were added during 2 hours. After a further 2 hours' stirring, the liquid was decanted, acidified, and kept at 0° overnight. 3-Carboxymethylphthalimidine (IV) separated in crystalline tufts, m. p. 180°. High yields (85—97%) were obtained both on this small scale and from 50 g. batches, provided that the temperature during the reduction and during the acidification was not allowed to exceed 5°. The highest yields were obtained when the mother-liquors were concentrated to yield a second crop (Found : C, 62·85; H, 5·0; N, 7·5; equiv., 184. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·8; N, 7·3%; equiv. 191). The acid was stable to alkaline permanganate, and did not liberate ammonia when boiled with aqueous alkali. Esterification with diazomethane gave the *methyl* ester, m. p. 139—140°, needles from alcohol, in 93% yield (Found : C, 64·6; H, 5·5; MeO,14·7. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; MeO, 15·1%).

(b) *Of the keto-acid, m. p.* 120° (With F. G. RUNDALL). A solution of 7·0 g. of the acid in 30 c.c. of 5% aqueous caustic soda was mechanically stirred at room temperature while 70 g. of 3% sodium amalgam were added. After 4 hours' stirring, the product was worked up as described above, 5·8 g. of 3-carboxymethylphthalimidine, m. p. 180°, being obtained. This was identical with the material already described (Found : C, 62·8; H, 4·7; N, 7·3%), mixed m. p. 180°. It gave the same methyl ester, m. p. and mixed m. p. 139—140°. A sample of *iso*-indolinone-3-acetic acid prepared by the method of Rowe, Haigh, and Peters * (*loc. cit.*) melted at 182°, showed no depression in m. p. in admixture with our acid, and yielded the same methyl ester (m. p. and mixed m. p. 139—140°).

5 G. of the acid of m. p. 120° were reduced in the same way, but the temperature was kept at 0°, first with a freezing mixture and subsequently in ice. All subsequent operations were carried out at 0°. 3·0 G. of β-*hydroxy*-β-o-*carbamylphenylpropionic acid* (X) were obtained, m. p. 180° (Found : C, 58·0; H, 5·1; N, 7·0; equiv., 208. $C_{10}H_{11}O_4N$ requires C, 57·4; H, 5·3; N, 6·7%; equiv., 209), sparingly soluble in ether and hydrocarbons, easily soluble in hot alcohols and hot water. It slowly decolorised permanganate and was stable to boiling alkali.

The same compound was obtained when the acid of m. p. 120° (40 g.), dissolved in 600 c.c. of methanol, was reduced with 600 g. of sodium amalgam at 50°. The resulting solution was evaporated under reduced pressure until the sodium salt separated as a thick paste. This was collected and dissolved in a little water, and the solution filtered from mercury. The acid was then liberated below 5°, and crystallised from boiling water. Yield 23 g., m. p. 178° (Found : C, 57·7; H, 5·5%; equiv., 208).

When heated under reduced pressure at 105°, the hydroxy-acid lost 8·7% of water in 1 hour (calc. for $1H_2O$, 8·6%) and there was no further loss in weight at this temperature. The product was 3-carboxymethylphthalimidine (Found : C, 62·9; H, 4·9; N, 7·1%; equiv., 190) and gave the methyl ester, m. p. 139—140° (Found : C, 64·4; H, 5·6%). The same cyclisation was brought about by boiling the hydroxy-acid with dilute hydrochloric acid for an hour; the cyclic

* We are indebted to Mr. G. A. P. Tuey of the Imperial College for this material.

acid crystallised, on cooling, in quantitative yield, m. p. and mixed m. p. 180° (equiv., 186, 185). We were unable to obtain the hydroxy-acid by any treatment of the cyclic acid with water, or by dissolving it in alkali and precipitating it at 0°.

An intimate mixture of the hydroxy-acid (which for the purpose of this experiment is equivalent to the cyclic acid) and copper bronze was heated under reduced pressure in a stream of nitrogen until carbon dioxide was evolved. 3-Methylphthalimidine slowly distilled (b. p. 160°/2 mm.). It was crystallised from ethyl acetate, and then melted at 114°, alone or in admixture with material made by the method of Gabriel and Neumann (*Ber.*, 1893, **26**, 705).

The hydroxy-acid on treatment with diazomethane yielded 3-carbomethoxymethylphthalimidine in quantitative yield, m. p. and mixed m. p. 139—140° (Found : C, 64·3; H, 5·3; N, 6·9. Calc. for $C_{11}H_{11}O_3N$: C, 64·4; H, 5·4; N, 6·8%). The same result was obtained when the reaction was performed in moist ether, although in this case esterification was much slower.

β-o-*Cyanophenylpropionic Acid* (With G. A. P. Tuey).—10 G. of *o*-cyanocinnamic acid (Edwards, *loc. cit.*; David and Poole, J., 1927, 2661), m. p. 255°, were dissolved in 300 c.c. of methanol and 10 c.c. of water. 120 G. of sodium amalgam were added to the mechanically stirred solution during an hour and the mixture was then warmed at 50° for a further hour. The product was decanted from mercury, neutralised, and freed from methanol. Acidification of the residual sodium salts yielded 7 g. of β-*o*-cyanophenylpropionic acid, colourless needles from alcohol, m. p. 128° (Edwards gives 127°) (Found : C, 68·7; H, 5·1; N, 8·1. Calc. : C, 68·6; H, 5·4; N, 8·0%). The *methyl* ester, prepared by means of diazomethane, had b. p. 290—295° and failed to solidify (Found : C, 69·8; H, 5·6. $C_{11}H_{11}O_2N$ requires C, 69·8; H, 5·8%).

β-*o*-Cyanophenylpropionic acid dissolved in hot concentrated hydrochloric acid and separated unchanged when the solution was cooled. 1 G. of the acid was boiled for 2 hours with 10 c.c. of 50% (vol.) sulphuric acid. After recrystallisation from water, the product yielded 0·6 g. of β-*o*-carboxyphenylpropionic acid in needles, m. p. 167° (Gabriel and Michael, *Ber.*, 1877, **10**, 2204, give 166°) (Found : C, 61·8; H, 5·2. Calc. : C, 61·9; H, 5·2%).

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