

**196.** *Phthalocyanines and Related Compounds. Part XVIII. Intermediates for the Preparation of Tetrabenzporphins: The Thorpe Reaction with Phthalonitrile.*

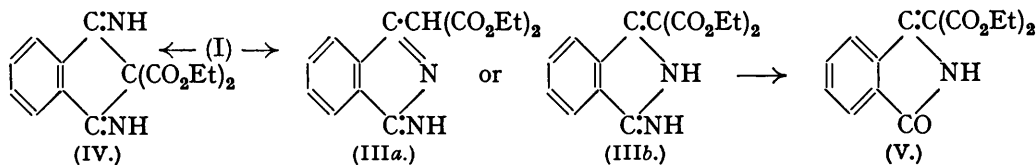
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Phthalonitrile condenses with various substances containing an active methylene group under the conditions of the Thorpe reaction to yield compounds containing the *isoindole* nucleus. The imino-compounds which are first formed can easily be hydrolysed to unsaturated derivatives of phthalimidine. The malonic ester condensation product has been hydrolysed to carboxymethylenephthalimidine and to an imino-malonic acid which is a useful intermediate for the preparation of tetrabenzporphin pigments.

IN Part XV (Barrett, Linstead, and Tuey, J., 1939, 1809) it was shown that the compounds formed from phthalonitrile by the Grignard reaction were valuable intermediates for the preparation of macrocyclic pigments containing methin links: tetrabenztriazaporphin could thus be formed in a reasonably good yield from readily accessible material. We now describe the application of the Thorpe reaction to phthalonitrile for the same purpose.

Atkinson, Ingham, and Thorpe (J., 1907, **91**, 578) showed that benzonitrile condensed with the sodio-derivatives of compounds containing an active methylene group to yield imino-compounds of the type  $\text{Ph}\cdot\text{C}(\text{NH})\cdot\text{CHX}_2$ . Phthalonitrile reacts exothermically in hot alcohol with the sodio-compounds of phenylacetonitrile, ethyl cyanoacetate, and ethyl

malonate. The products from the reaction with the malonic ester have been most fully studied, because of their interest as intermediates for macrocyclic pigments and in relation to the acids described in the preceding paper. The product was initially isolated as the *monohydrochloride* of an *imino-ester*,  $C_{15}H_{16}O_4N_2$ . The free base, m. p. 97°, was liberated by cold alkali, but dilute acid or even boiling aqueous alcohol yielded the corresponding "*keto-ester*,"  $C_{15}H_{15}O_5N$ , m. p. 108°. When the imine-hydrochloride was boiled for a few minutes with aqueous alkali, it yielded an *acid*, which approximated in composition to the corresponding imino-acid,  $C_{11}H_8O_4N_2$ . By simple analogy with the compounds studied by Thorpe, these esters would be given the formulæ  $CN \cdot C_6H_4 \cdot C(:NH) \cdot CH(CO_2Et)_2$  (I) and  $CN \cdot C_6H_4 \cdot CO \cdot CH(CO_2Et)_2$  (II). The "*keto-ester*," however, failed to show carbonyl reactivity, was insoluble in alkali, and gave no colour with ferric chloride. It was therefore clear that the first-formed compounds must have undergone isomeric change. The initial product would be the sodio-compound of (I) and this can cyclise by "transfer of the metal" to the *o*-cyano-group, just as do the lithium and magnesium compounds discussed in Part XV (Barrett, Linstead, and Tuey, *loc. cit.*). Such a reaction could lead to the formation of either an *isoindole* (III) or a diketohydrindene ring (IV).\*



The diketohydrindene structure is excluded by the fact that only one imino-group is removed on hydrolysis. The *isoindole* structure (V) for the "*keto-ester*," m. p. 108°, is proved by oxidation with permanganate in acetone, which gives a theoretical yield of phthalimide. Moreover, alkaline hydrolysis of the "*keto-ester*" gives 3-carboxymethylenephthalimidine, identical with that described in the preceding paper. The keto-ester is therefore undoubtedly 3-dicarbethoxymethylenephthalimidine (V): a direct comparison with the specimen prepared from iminophthalimidine (preceding paper) confirmed this; the ester prepared in the present work melted at 108°, that from iminophthalimidine at 104–105°, and mixtures at 106–107°. We have not yet been able to raise the lower melting point and have, in fact, obtained other samples from this source melting persistently lower (101–105°). The analytical figures for both preparations are satisfactory and the presence of an isomeric impurity in the lower-melting ester is indicated. From the ease of hydrolysis of the imino-ester to (V) it is almost certain that the imine also contains the *isoindole* ring, and of the two double-bond isomerides, form (IIIb) is the more probable.

The reaction between cyanoacetic ester and phthalonitrile followed a similar course. In this case the imino-ester was not isolated, treatment of the product with acid giving the "*keto-ester*" direct. This was identified as 3-cyanocarbethoxymethylenephthalimidine (VII, X = CO<sub>2</sub>Et) by oxidation to phthalimide.



Under similar conditions phenylacetonitrile gave the *imino*-compound (VI, X = Ph) in good yield. This was readily hydrolysed to 3-cyanobenzylidenephthalimidine (VII, X = Ph). On the other hand, attempted condensation between phthalonitrile and acetonitrile, ethyl acetoacetate, or ethyl methylmalonate gave unfavourable indications. The bulk of the

\* The formation of a diketohydrindene derivative by a somewhat similar reaction has been recorded by Scheiber and Haun (*Ber.*, 1914, 47, 3326). We have, however, never encountered such a cyclisation when the formation of an *isoindole* ring is possible.

phthalonitrile was converted into phthalimide. This appears to be a general side reaction which intervenes if the Thorpe condensation does not occur rapidly.

These condensations are being further investigated. This preliminary report is given because of the value of iminophthalimidylmalonic acid as an intermediate in the preparation of macrocyclic pigments (following paper).

#### EXPERIMENTAL.

1. *Condensation with Phenylacetonitrile*.—46.8 G. of the nitrile were added to a solution of 9.2 g. of sodium in 100 c.c. of alcohol. 51.2 G. of phthalonitrile (equivalent amount) were then added and dissolved by warming. When the solution was heated to boiling under reflux, a vigorous reaction set in and the mixture turned dark red. The product was finally refluxed for 5 minutes and poured, while hot, into a mixture of 50 c.c. of concentrated hydrochloric acid and 100 c.c. of water. The buff precipitate was at once removed by filtration, washed with cold water, and dried by suction. Yield, 85 g. (87%); m. p. 290–300°. The hydrochloride of 1-imino-3-cyanobenzylidenephthalimidine (VI, X = Ph) formed long yellow needles from alcohol, m. p. 299° (Found: C, 68.3, 68.4; H, 4.0, 3.9; N, 15.1; Cl, 12.3.  $C_{16}H_{11}N_3 \cdot HCl$  requires C, 68.4; H, 4.2; N, 14.9; Cl, 12.6%). A solution of the hydrochloride (5 g) in the minimum quantity of hot alcohol was treated with an excess of ammonia and allowed to cool. 1-Imino-3-cyanobenzylidenephthalimidine separated in small needles (4 g.), m. p. 207–209° (Found: C, 78.4; H, 4.4; N, 17.0.  $C_{16}H_{11}N_3$  requires C, 78.4; H, 4.5; N, 17.1%). Treatment of the base with alcoholic hydrogen chloride regenerated the hydrochloride, m. p. 298°.

The hydrochloride was boiled with dilute aqueous-alcoholic hydrochloric acid for 6 hours. The cooled product deposited 3-cyanobenzylidenephthalimidine (VII, X = Ph) in fine yellow needles, m. p. 228–230°; yield, 90% (Found: C, 78.5; H, 4.1; N, 11.3.  $C_{16}H_{10}ON_2$  requires C, 78.0; H, 4.1; N, 11.4%). The same compound was formed by alkaline hydrolysis (aqueous-alcoholic alkali for 1 hour) but in worse yield (60%) and not so pure.

2. *Condensation with Ethyl Cyanoacetate*.—A cold solution of sodium (11.5 g.) in 250 c.c. of alcohol was treated successively with 56.5 g. of the cyanoacetic ester and 64 g. of finely powdered phthalonitrile (1 equiv. of each). The mixture was heated until, when it was nearly boiling, a vigorous reaction set in. When this had ceased, the dark brown product was cooled, poured on ice and an excess of hydrochloric acid, and kept overnight. The dark brown precipitate was collected, dried under reduced pressure, and crystallised from benzene, alumina being added to remove the colour. 3-Cyanocarbethoxymethylenephthalimidine (VII, X =  $CO_2Et$ ) was isolated in 70% yield in white needles, m. p. 170° (Found: C, 64.8, 64.9; H, 3.95, 4.2; N, 12.1, 11.8.  $C_{13}H_{10}O_3N_2$  requires C, 64.6; H, 4.1; N, 11.6%). Some higher-melting material (? imine hydrochloride) remained undissolved by the benzene.

3. *Condensation with Ethyl Malonate*.—The procedure was as in (2), the reactants being a solution of 9.2 g. of sodium in 200 c.c. of alcohol, 64 g. of the malonic ester, and 51.2 g. of phthalonitrile. The dark brown solution obtained on decomposition with hydrochloric acid and ice was extracted once with benzene (100 c.c.), which removed considerable low-melting material. The aqueous layer deposited overnight 70 g. (60%) of yellow crystals, which were either recrystallised from aqueous alcohol, or converted into the oily base by means of alkali and regenerated with concentrated hydrochloric acid. The hydrochloride of 1-imino-3-dicarbethoxymethylenephthalimidine formed colourless plates, m. p. 210° (Found: C, 55.5; H, 5.3; N, 8.55; Cl, 10.8.  $C_{15}H_{16}O_4N_2 \cdot HCl$  requires C, 55.5; H, 5.25; N, 8.6; Cl, 10.9%). The free imino-ester (IIIb) was isolated by treatment of an aqueous solution of the hydrochloride with alkali, and extraction with ether. The oily base soon solidified in ice, and crystallised from light petroleum in colourless needles, m. p. 97° (Found: N, 9.7.  $C_{15}H_{16}O_4N_2$  requires N, 9.7%).

*Hydrolyses.* (a) *To the imino-acid*. 50 G. of the imino-ester hydrochloride were dissolved in 100 c.c. of rectified spirit and treated with a solution of 19 g. of caustic soda in 50 c.c. of water. After 8 minutes' refluxing, the alcohol was removed as fast as possible by means of steam. The residue was cooled and made barely acid with hydrochloric acid. The precipitated acid was coagulated by heating it just to the boiling point and then cooling rapidly. The dull purple solid was collected, washed with water, and dried under reduced pressure. The yield of imino-acid was about 90%. This substance is a useful intermediate for the preparation of macrocyclic pigments (see Part XIX). Unfortunately, its sparingly soluble and intractable nature have prevented its being obtained analytically pure. It tends to separate from solution in the usual solvents as an amorphous jelly. It melts between 280° and 300° with decomposition

(Found : C, 59.6; H, 4.35; N, 11.2, 11.3.  $C_{11}H_8O_4N_2$  requires C, 57.0; H, 3.5; N, 12.1%). The nitrogen figure shows that little hydrolysis of the imino-group has occurred. The high carbon figure indicates a partial decarboxylation.

(b) To 3-dicarbethoxymethylenephthalimidine (with G. A. ROWE). The imino-ester hydrochloride (10 g.) was refluxed with 20 c.c. of concentrated hydrochloric acid and 50 c.c. of water. The keto-ester soon separated as a red oil; after 30 minutes the product was cooled and the solid cake was dried and crystallised from alcohol (charcoal). 3-Dicarbethoxymethylenephthalimidine (V) formed colourless needles (8 g.), m. p. 108° (Found : C, 62.2; H, 5.1; N, 4.75. Calc. for  $C_{15}H_{15}O_5N$  : C, 62.3; H, 5.2; N, 4.85%).

(c) To 3-carboxymethylenephthalimidine. 3-Dicarbethoxymethylenephthalimidine (10 g.) was refluxed for 30 minutes with 5 g. of sodium hydroxide in 100 c.c. of aqueous alcohol (1 : 1). The alcohol was removed in steam. Acidification of the cold product yielded a crude acid, which on crystallisation from water gave 3-carboxymethylenephthalimidine (1.5 g.), m. p. 220°, alone or in admixture with the acid prepared by the methods of Part XVII (Found : C, 63.6; H, 3.55; equiv., 186. Calc. for  $C_{10}H_7O_3N$  : C, 63.5; H, 3.7%; equiv., 189). Another similar hydrolysis gave a better yield of an impure lower-melting acid (m. p. 185° decomp.) which probably contained some dicarboxylic acid.

*Oxidations* (with J. J. LEAVITT).—1.0 G. of 3-cyanocarbethoxymethylenephthalimidine was dissolved in 90 c.c. of acetone and 25 c.c. of water, 3 g. of potassium permanganate added to the mechanically stirred mixture, and stirring continued for 80 minutes. The excess of permanganate was removed by means of sulphur dioxide, and the acetone on the steam-bath. The resulting solution deposited phthalimide in long white needles, which were collected and dried at 100° (yield, 90%). A similar oxidation of 3-dicarbethoxymethylenephthalimidine, m. p. 108°, gave a theoretical yield of phthalimide. The imide was identified by m. p. and mixed m. p.

Oxidations with alkaline permanganate in aqueous solution were unsatisfactory.

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