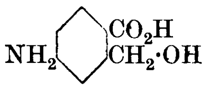
CXXIII.—4-*Aminophthalide and Some Derivatives.*

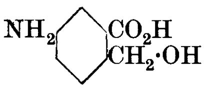
By Leopold Ferdinand Levy and Henry Stephen.

Reissert (*Ber.*, 1913, **46**, 1489) has shown that phthalimide can be reduced almost quantitatively to phthalide by zinc in an alkaline medium, and the method has now been successfully applied to the reduction of 4-aminophthalimide, which has recently been rendered accessible in quantity (Levy and Stephen, this vol., p. 79).

The reduction of 4-aminophthalimide should theoretically give two aminohydroxymethylbenzoic acids (I) and (II) and corresponding to these the two phthalides (III) and (IV). 5-Aminophthalide (IV), which is well known (Hoenig, *Ber.*, 1885, **18**, 3449; Teppema, *Rec. trav. chim.*, 1923, **42**, 30; Tasman, *ibid.*, 1927, **46**, 653), does not resemble the aminophthalide obtained by us in the above reduction, and a comparison of the derivatives of the two phthalides leaves no doubt that the latter is 4-*aminophthalide* (III).



(I.)



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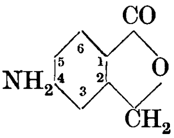
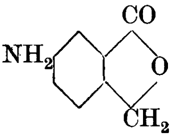


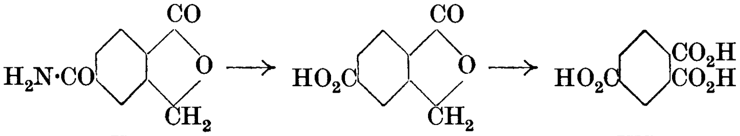
(III.)



(IV.)

The 4-*chloro*-, *bromo*-, *iodo*-, *cyano*-, and *hydroxy*-derivatives of phthalide were prepared from the 4-amino-derivative in good yields by the Sandmeyer reactions, and the first four differ from the corresponding 5-derivatives prepared by Tasman (*loc. cit.*); the 5-hydroxy-derivative has not been prepared. By reducing 4-hydroxyphthalimide with tin and hydrochloric acid, Rée (*Annalen*, 1886, **233**, 235) obtained a hydroxyphthalide (m. p. 222°) to which he did not assign a definite structure. The melting point agrees exactly with that found by us for 4-hydroxyphthalide, and there is little doubt that Rée's product is identical with it. 4-Chlorophthalide was also prepared, in theoretical yield, by reducing 4-chlorophthalimide (from 4-chlorophthalic anhydride) by Reissert's method, only one of the possible isomeric lactones being produced. 4-*Chloro*-2-*hydroxymethylbenzoic acid* derived from the phthalide is remarkable, since it sublimes unchanged at the melting point and loses a molecule of water by heating, only with difficulty. Treatment with acetic anhydride reproduced 4-chlorophthalide. An attempt to obtain 4-chlorophthalide by treatment with chlorine in alkaline solution according to the method used by Egerer and Meyer (*Monatsh.*, 1913, **34**, 81) for the preparation of 4-chlorophthalic acid did not succeed.

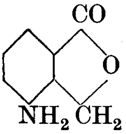
4-Cyanophthalide was converted by hydrolysis into *phthalide*-4-*carboxyamide* (V), which with alkali gave *phthalide*-4-*carboxylic acid* (VI), and on oxidation with potassium permanganate this gave 1 : 2 : 4-trimellitic acid (VII), which was also identified as its anhydride. These reactions leave no doubt as to the structure of the original 4-aminophthalide.

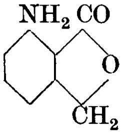


(V.) (VI.) (VII.)

The reduction of 3-aminophthalimide by Reissert's method gave rise to the two possible isomeric aminophthalides (VIII) and (IX), which were separated by fractional crystallisation. They must correspond to 3-amino- and 6-amino-phthalides, but their orientation has not been achieved. Both substances had all the properties of aminophthalides. One base, m. p. 120°, gave an acetyl derivative, m. p. 137°, and a chlorophthalide, m. p. 143°. The other base, m. p. 157°, gave an acetyl derivative, m. p. 182°, and a chlorophthalide, m. p. 86°.

(VIII.)





(IX.)

EXPERIMENTAL.

4-*Aminophthalide* (III).—4-Aminophthalimide (20 g.) was well powdered and added with stirring during ½ hour to a suspension of pure zinc dust (40 g.) in a solution of sodium hydroxide (12 g.) in water (48 c.c.) cooled in ice. Stirring was continued for 30 minutes, water (60 c.c.) added, and the mixture warmed at 60° until the evolution of ammonia ceased. The filtered solution was acidified with concentrated hydrochloric acid, boiled for 10 minutes, and neutralised with powdered sodium carbonate. 4-*Aminophthalide*, precipitated as a brown powder, crystallised from hot water in flat needles, m. p. 194°, moderately easily soluble in hot water and slightly in cold, very soluble in ethyl alcohol, methyl alcohol, acetone and chloroform, and insoluble in hot benzene, toluene, ether, and light petroleum (Found: C, 64·2; H, 4·75. $C_8H_7O_2N$ requires C, 64·4; H, 4·7%). The base gives a well-defined platinum salt, decomposing above 200°.

The base (3·8 g.) was heated in a sealed tube with fuming hydriodic acid (11·3 g.) and red phosphorus (0·6 g.) at 150° for 4 hours. *m*-Toluidine was identified in the product: its presence affords good evidence of the relative positions of the NH_2 and CH_2 groups in the base and establishes the constitution of the latter.

4-*Amino-2-hydroxymethylbenzoic Acid* (I).—When a solution of the base in aqueous ammonia was carefully neutralised with hydrochloric acid, the *acid* (I) was precipitated as a pale brown powder, m. p. 182° (efferv.; re-melting at 193°) (Found: loss at 110°, 11·4; equiv., by titration with *N*/40-NaOH, 165·4, 166·2. $C_8H_9O_3N$ requires loss of H_2O, 10·8%; equiv., 167).

4-*Acetamidophthalide*, obtained by treatment of the base with acetic anhydride, crystallised from dilute alcohol in colourless needles, m. p. 205°, readily soluble in the usual solvents except ether, benzene, and toluene (Found: C, 63·05; H, 5·0. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·7%).

4-*Benzamidophthalide*, prepared from the base by the pyridine–benzoyl chloride method, crystallised from dilute acetic acid in colourless needles, m. p. 191° (Found: C, 71·1; H, 4·0. $C_{15}H_{11}O_3N$ requires C, 71·15; H, 4·35%).

5-*Benzamidophthalide*, prepared in a similar manner from the corresponding base, crystallised in colourless needles, m. p. 225° (Found: C, 71·8; H, 4·1%).

4-*Chlorophthalide*, prepared by diazotising the base in the usual manner and treating the solution with cuprous chloride, separated as a white precipitate, which crystallised from alcohol in long silky needles, m. p. 153·5° (Found: Cl, 20·95. $C_8H_5O_2Cl$ requires Cl, 21·1%). By treatment with sodium hydroxide solution, and subsequent acidification in the cold with concentrated hydrochloric acid, it gave 4-*chloro*-2-*hydroxymethylbenzoic acid* (Found : equiv., 189·7. $C_8H_7O_3Cl$ requires equiv., 186·5). The acid sublimed in an open dish in long silvery needles, m. p. 135—136°, but when heated in a capillary tube above the melting point it effervesced, re-forming 4-chlorophthalide.

4-*Bromophthalide*, prepared by warming a solution of the diazotised base with cuprous bromide, crystallised from dilute alcohol in colourless needles, m. p. 161° (Found : Br, 36·9. $C_8H_5O_2Br$ requires Br, 37·55%). 4-*Bromo*-2-*hydroxymethylbenzoic acid*, precipitated from a solution of 4-bromophthalide in aqueous ammonia by addition of hydrochloric acid, crystallised in pale yellow needles, m. p. 155° (efferv., re-forming 4-bromophthalide), fairly readily soluble in hot water (Found : equiv., 233·4. $C_8H_7O_3Br$ requires equiv., 231).

4-*Iodophthalide*.—Potassium iodide was added to a diazonium solution of the base cooled to −5°, and after remaining overnight the *iodo*-compound was filtered off, washed with a solution of sodium thiosulphate, and crystallised from dilute alcohol (charcoal). It was obtained as light brown needles, m. p. 193·5°, sparingly soluble in hot water, moderately easily in hot alcohol, and easily in methyl alcohol, acetone, chloroform, and acetic acid (Found : I, 48·7. $C_8H_5O_2I$ requires I, 48·8%).

4-*Hydroxyphthalide*.—When a diazonium solution of the base was warmed, a reddish-brown deposit separated, which was filtered off and boiled with water (charcoal). The filtered cooled solution deposited 4-*hydroxyphthalide* in small colourless needles, which were purified by sublimation; m. p. 222° after softening at 210°. The compound is moderately easily soluble in hot water, sparingly soluble in cold, easily in alcohol, acetone, chloroform and acetic acid, and insoluble in benzene, toluene, and ether (Found : C, 64·7 ; H, 4·4. $C_8H_6O_3$ requires C, 64·0 ; H, 4·0%). The *acetyl* derivative, formed by means of acetic anhydride, crystallised from hot water in silvery leaflets, m. p. 126·5° (Found : C, 62·4 ; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5 ; H, 4·2%).

4-*Cyanophthalide*.—A diazonium solution of the base was treated with cuprous cyanide and the *cyano*-compound produced was separated from cuprous cyanide by extraction with absolute alcohol, washed with dilute sodium hydroxide solution, and crystallised from dilute alcohol, forming long yellow needles, m. p. 200°, which sublimed as flat silvery needles, moderately easily soluble in hot water and only slightly in cold (Found : C, 67·75 ; H, 2·9. $C_9H_5O_2N$ requires C, 67·9 ; H, 3·2%). Hydrolysis of the nitrile with 75% sulphuric acid at 80° proceeded smoothly, and when the cold solution was poured on ice, *phthalide*-4-*carboxyamide* was deposited ; this crystallised from acetone in colourless needles, m. p. 245—248°, sparingly soluble in all the usual solvents, but moderately easily soluble in nitrobenzene (Found : volatile NH_3, 8·1. $C_9H_7O_3N$ requires NH_3, 7·9%). *Phthalide-4-carboxylic acid* (VI) was obtained by boiling the amide with fairly concentrated aqueous sodium hydroxide and acidifying the solution; m. p. 293—294° (corr.) (Found : equiv., 175·7. $C_9H_6O_4$ requires equiv., 178). The *silver* salt prepared from it in the usual way was found to be that of 2-hydroxymethylterephthalic acid resulting from the fission of the lactone ring in phthalide-4-carboxylic acid (Found: Ag, 52·4. $C_9H_6O_5Ag_2$ requires Ag, 52·7%).

Phthalide-4-carboxylyl chloride was deposited as colourless needles, m. p. 128°, when the acid was dissolved in thionyl chloride. When the acid chloride was dissolved in methyl alcohol, *methyl phthalide-4-carboxylate* separated immediately as colourless needles, m. p. 164·5° (Found : M, 191·2. $C_{10}H_8O_4$ requires M, 192·0). *Ethyl phthalide-4-carboxylate* was prepared similarly and separated as colourless needles, m. p. 148° (Found : M, 204·6. $C_{11}H_{10}O_4$ requires M, 206·0).

To a boiling solution of phthalide-4-carboxylic acid (1 g.) in 100 c.c. of N-sodium hydroxide, potassium permanganate (1 g.), dissolved in 20 c.c. of water, was gradually added during 1 hour. The hot solution was then filtered, acidified with concentrated hydrochloric acid, and evaporated to dryness. 1 : 2 : 4-Trimellitic acid, extracted from the dry mass with ether and crystallised from this solvent, melted with vigorous effervescence at 216° (Baeyer, *Annalen*, *Suppl.* **7**, 41, and Schultz, *Ber.*, 1909, **42**, 3604, both give 218°). Phthalic anhydride was formed in the upper part of the capillary tube and identified by the melting point and the usual fluorescein reaction. When the acid was warmed with acetic anhydride, 1 : 2 : 4-trimellitic anhydride was obtained, m. p. 156° (Baeyer, *Annalen*, 1873, **166**, 340, gives 157—158°).

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