

### 107. Mechanism of the Reaction of Phthalaldehydic Acid with Indoles. Intramolecular Catalysis in Aldehyde Reactions.

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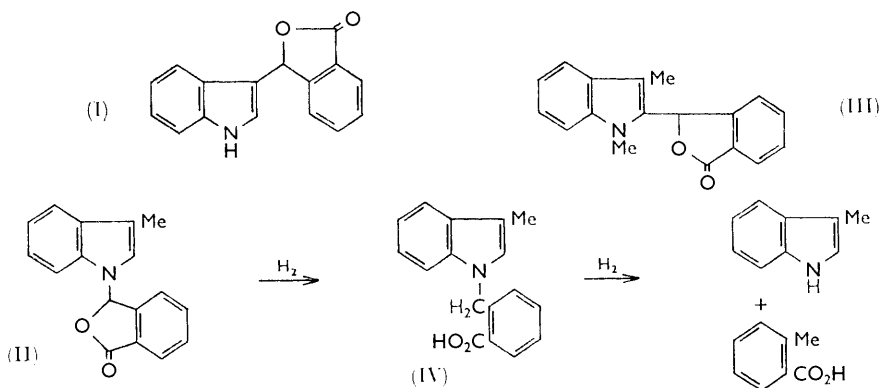
Indoles with a free 3-position react with phthalaldehydic acid in benzene, slowly in the cold and rapidly when heated, to give the 3-phthalidyl derivatives. With 3-substituted indoles the more vigorous conditions used earlier are necessary, giving the 1-phthalidyl and, with 1,3-disubstituted indoles, the 2-phthalidyl derivatives.

The reactions involve electrophilic substitution of the indole (in the orientation  $3 > 1 > 2$ ) by the aldehyde carbonyl of the open-ring form of phthalaldehydic acid. They are considered to owe their surprising rapidity in the non-polar solvent to intramolecular acid catalysis by the carboxyl group, followed by intramolecular base catalysis by the carboxylate group, (XII)  $\rightarrow$  (XIII)  $\rightarrow$  (XIV)  $\rightarrow$  (I).

Intramolecular acid catalysis in an aldehyde-group reaction thus appears to be demonstrated for the first time.

THE original work of Ludwig and Tache<sup>1</sup> on the condensations of phthalaldehydic and 5,6-dimethoxyphthalaldehydic acid with various simple indoles has recently been corrected and extended by Noland and Johnson.<sup>2</sup> When the reactants were fused together, at temperatures from 120 to  $>200^\circ$ , phthalidylindoles and water were formed. If the indole 3-position was free the 3-phthalidyl derivative, *e.g.*, (I) was formed. If the 3-position was blocked the 1-phthalidylindole, *e.g.*, (II) was formed, and if both the 1- and 3-positions were blocked the 2-phthalidylindole, *e.g.*, (III) was formed; thus the preferred orientation in the indole ring was  $3 > 1 > 2$ .

The mechanism of these condensations seemed particularly interesting to us because of the unusual nature of the reactions, the absence of external catalysts, and the possibility,



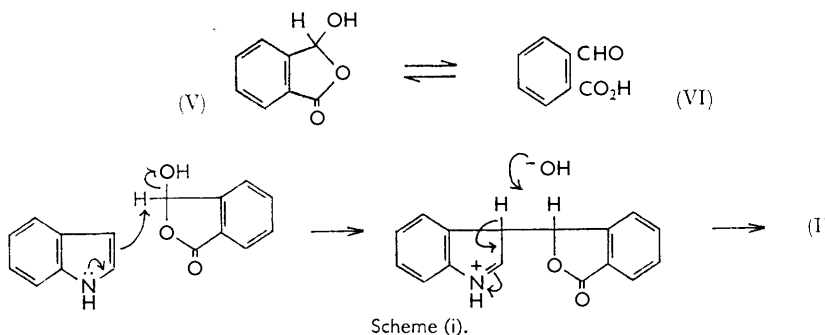
as yet unrecognized, of neighbouring-group participation by the carboxyl group in the aldehyde-group reactions of phthalaldehydic acid. Our preliminary results on the course of the reactions confirmed and extended those of Noland and Johnson.<sup>2</sup> When indole and phthalaldehydic acid were heated together, droplets of water appeared very quickly at about  $70^\circ$ , suggesting that the condensation might be effected under much milder conditions. Indeed, it proceeded cleanly, rapidly, and in better yield in dilute boiling benzene solution, and slowly in benzene at room temperature. The reactions of 2-methyl-, 7-methyl-, and 1,2-dimethyl-indole proceeded equally smoothly in hot benzene to give the same products

<sup>1</sup> Ludwig and Tache, *Bull. Chim. Soc. Române*, 1941—1942, **3A** [2], 3 (*Chem. Abs.*, 1944, **38**, 5499).

<sup>2</sup> Noland and Johnson, *J. Amer. Chem. Soc.*, 1960, **82**, 5143.

as on fusion. 2-Phenylindole readily gave 2-benzyl-3-phthalidylindole under these conditions, whereas on fusion a dark brown polymer was formed and no crystalline product could be isolated.<sup>2</sup> However, 3-methyl-, 1,3-dimethyl-, and 2,3-dimethyl-indole did not react with phthalaldehydic acid in boiling benzene, the more vigorous fusion conditions being needed for rapid reaction.

Part of Noland and Johnson's evidence for the structure of the products was hydrogenolysis of the benzyl C-O bond of the phthalide ring, using Raney nickel and a few atmospheres pressure of hydrogen. Thus, 3-phthalidylindole (I) gave 3-(*o*-carboxybenzyl)indole and 3-methyl-1-phthalidylindole (II) gave 1-(*o*-carboxybenzyl)-3-methylindole (IV). We have repeated these hydrogenolyses, together with that of the closely related 3-phenylphthalide, more conveniently and rapidly with 10% palladium-charcoal at atmospheric pressure and have confirmed the structures of the 2- and 3-*o*-carboxybenzylindoles by their copper chromite decarboxylation to the known benzylindoles. In our hydrogenolysis of 3-methyl-1-phthalidylindole (II) 3-methylindole and *o*-toluic acid were also formed by further hydrogenolysis of the initial product (IV). The *o*-carboxybenzyl group must, therefore, have been attached to nitrogen since a *C*-benzyl group would not be removed under these conditions whilst hydrogenolysis of an *N*-benzyl group is entirely reasonable (cf. refs. 3 and 4).



The phthalide carbonyl absorptions in the products fell in the range 1761—1767  $\text{cm}^{-1}$  for the 1-phthalidyl derivatives and 1733—1745  $\text{cm}^{-1}$  for the 3-phthalidyl derivatives. 1,3-Diphthalidylindole was readily formed from indole in two stages and showed carbonyl absorption in both regions.

In addition to their possible synthetic value, these condensations may be of some analytical use: simple low-melting indoles are rapidly converted into high-melting, highly crystalline derivatives. Evidence for the presence of a free 3-position or a free 1- or 2-position is obtained from the conditions required for reaction, and the latter two possibilities are differentiated by the infrared spectrum. No acidic or basic catalyst is required and so the reaction is applicable to quite sensitive indole derivatives.

*The Reaction Mechanism.*—In view of the speed of, and orientation in, the formation of the phthalidylindoles, the reaction must be an electrophilic substitution of the indole, *i.e.*, nucleophilic attack by the indole on phthalaldehydic acid. In solution this acid exists largely in the cyclic form, 3-hydroxyphthalide (V), in rapid equilibrium with the open-ring form, *o*-formylbenzoic acid (VI).<sup>5,6</sup> Because of the much greater concentration of the cyclic form and the cyclic structure of the products the simplest mechanism would appear to be direct displacement of the hydroxyl group of 3-hydroxyphthalide (V) [Scheme (i)]. However, since the aldehydic carbon in phthalaldehydic acid (VI) is presumably much the

<sup>3</sup> Hartung and Simonoff, *Org. Reactions*, 1953, 7, 263.

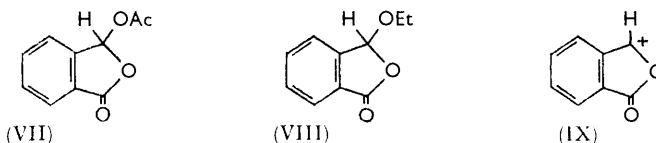
<sup>4</sup> Plieninger, *Chem. Ber.*, 1954, 87, 128.

<sup>5</sup> Buu-Hoi and Che-Kin Lin, *Compt. rend.*, 1939, 209, 221; Renson, *Bull. Soc. chim. Belges*, 1961, 70, 77.

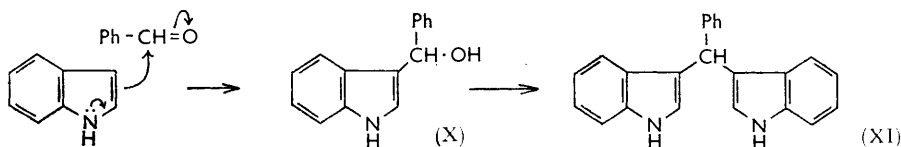
<sup>6</sup> Wheeler, Young, and Erley, *J. Org. Chem.*, 1957, 22, 547.

most strongly electrophilic centre in either species of the acid, nucleophilic attack on this carbon by indole [Scheme (ii)] may well be the favoured route.

The initially formed alcohol (XIV) would be expected to lactonise rapidly to the phthalide (I) isolated. The concentration of free aldehyde (VI) is probably very small under our conditions, but if this is preferentially removed by reaction with indole it will be rapidly replenished by the equilibrium,  $(V) \rightleftharpoons (VI)$ . This rapid equilibrium makes distinction between the two reaction schemes difficult for phthalaldehydic acid itself, so that attention was directed to simple derivatives of the acid which are necessarily fixed in one form. 3-Phthalidyl acetate (VII) cannot exist in the open-ring form and so would be inert if the free aldehyde form (VI) was involved, [Scheme (ii)] in the phthalaldehydic acid reaction. However, on the basis of Scheme (i) it should react faster than phthalaldehydic acid, since acetate is a better leaving group than hydroxyl. After boiling 3-phthalidyl acetate with indole in benzene for 2 hours, as for the acid, no 3-phthalidylindole (previously isolated many times from benzene) could be isolated and only very little, at most, could have been formed. Even after boiling for 16 hours no change in the composition of the initial mixture could be detected by infrared spectroscopy. Thus, the direct displacement mechanism of Scheme (i) may be ruled out. The reaction mixture from the acetate (VII) was shown by thin-layer chromatography to contain a very small amount of 3-phthalidylindole which may have arisen from slight hydrolysis of the acetate.



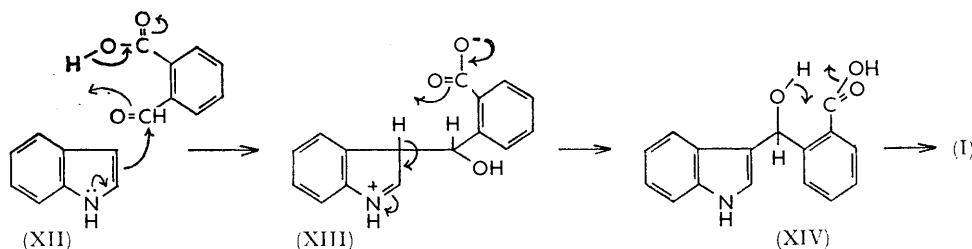
The reaction of 3-ethoxyphthalide (VIII), which again is not in equilibrium with a free aldehyde form, was investigated, since this pseudo-ester would presumably be less sensitive to hydrolysis by traces of water than the mixed anhydride, 3-phthalidyl acetate. As with the latter, no reaction with indole in boiling benzene could be detected by the isolation of 3-phthalidylindole, but the presence of a very small amount of this product was again indicated by thin-layer chromatography. The inertness of these phthalides compared with the parent acid, which must therefore react in the aldehyde form [Scheme (ii)], was not simply due to the absence of an acid, since the reaction of 3-phthalidyl acetate with indole was not catalysed by benzoic acid, which is comparable in acid strength to phthalaldehydic acid, nor indeed by toluene-*p*-sulphonic acid. The phthalaldehydic acid reaction is catalysed by the sulphonic acid, however (see below). Attempts to generate the potential intermediate ion of the direct displacement mechanism, the benzyl carbonium-oxonium



ion (IX), more efficiently from 3-bromophthalide and silver nitrate in methyl cyanide and to react it with indole failed; the product was a tar from which no 3-phthalidylindole could be isolated.

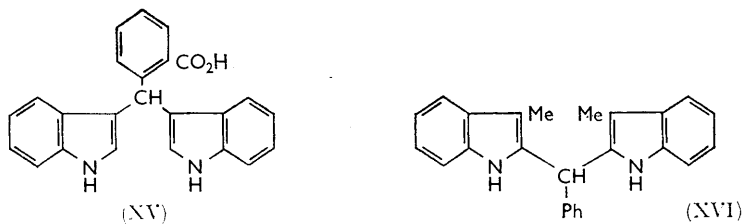
In view of the proposed mechanism it was interesting to compare the course and speed of the analogous reaction of indole with benzaldehyde. Under the standard conditions benzaldehyde reacted more slowly than phthalaldehydic acid to give recovered indole (64%), and the di-indolylmethane (XI) (20%) as the only isolable product. The latter was presumably formed by way of the carbinol (X); that this is reasonable was shown by the successful formation of the analogous 3-benzhydrylindole from diphenylmethanol, which

would be less reactive than the carbinol (X), and indole. With phthalaldehydic acid the first addition to the carbonyl group would presumably proceed similarly but faster, partly because of activation of the aldehyde group by the *o*-carboxylic acid group, and partly because of the possibility for intramolecular acid catalysis by this group as shown [arrows in (XII)]. As far as we are aware this provides the first demonstration of intramolecular acid catalysis by the carboxyl group in a simple aldehyde reaction. Proton removal, which can be intramolecularly base-catalysed [arrows in (XIII)], will then give the hydroxy-acid (XIV) which is the equivalent of the intermediate (X) in the benzaldehyde reaction. The latter was seen to react intermolecularly with a second mole of indole, but before the former can do this it undergoes a more highly favoured intramolecular reaction [arrows in (XIV)]. Even in the presence of three moles of the most reactive indole studied, 2-methylindole, phthalaldehydic acid reacted exclusively to give 2-methyl-3-phthalidyndole, and no di-indolylmethane. The intramolecular acid and base catalysis involved in the above sequence of reactions (XII)  $\rightarrow$  (XIII)  $\rightarrow$  (XIV)  $\rightarrow$  (I) is considered necessary to explain the rapidity of the polar reaction, which is fairly fast even at room temperature, in the non-polar solvent benzene; at no stage are dissociated ionic species postulated.



Scheme (ii).

These reactions of indoles with phthalaldehydic acid thus provide an example of intramolecular trapping of the tetrahedral intermediate normally postulated in aldehyde reactions; this trapping technique could probably be usefully extended to other aldehyde condensation reactions. If this trapping had not occurred the di-indolylmethane (XV), analogous to compound (XI) in the benzaldehyde reaction, would have been formed. Compound (XV) was prepared by opening the lactone ring of 3-phthalidyndole (I) with alkali and treating the resulting salt with indole; if the *o*-carboxylic acid group is neutralised lactonisation cannot occur. This product (XV) is completely stable under the vigorous conditions of its formation and therefore the fact that it is not isolated in the phthalaldehydic acid reaction is not due to its instability.



The above proposal of intramolecular acid catalysis suggested that these condensations may also be subject to catalysis by external acid. This was clearly demonstrated for reactions of indole and 3-methylindole (see Experimental section). The latter, for example, does not react significantly with phthalaldehydic acid in boiling benzene, but in the presence of 0.1 mole of toluene-*p*-sulphonic acid 37% of 3-methyl-1-phthalidyndole (II) was isolated after 30 minutes.

The mechanism proposed in Scheme (ii) for the reaction of phthalaldehydic acid with

indole is considered to apply equally to the substituted indoles: if the 3-position is substituted, the nitrogen becomes the nucleophilic centre, and if this is substituted, C-2 is the nucleophilic centre.

Finally, it is considered that the mechanism detailed above for the reaction of phthalaldehydic acid with indoles applies equally well to its reactions with a wide variety of other nucleophiles such as amines, alcohols, thiols, and amides,<sup>6</sup> and goes some way towards explaining the great reactivity of this acid, which is comparable to that of an acid anhydride.

In view of the slow reaction of indole with benzaldehyde and the very much slower reaction of 3-methylindole than of indole with phthalaldehydic acid, described above, we would expect 3-methylindole to react with benzaldehyde extremely slowly at low temperatures. It was therefore surprising to learn that Kamal and Ali Qureshi<sup>7</sup> obtained a 77% yield of phenyldi-(3-methyl-2-indolyl)methane (XVI) from 3-methylindole and benzaldehyde in dilute aqueous acetic acid at room temperature. We were unable to confirm their findings; in a repeat experiment we could isolate none of this product, and we recovered 85% of 3-methylindole. In a similar experiment phthalaldehydic acid did react with 3-methylindole to give a small yield of 3-methyl-1-phthalidyndole; this again illustrates the greater reactivity of this acid over benzaldehyde.

#### EXPERIMENTAL

Infrared spectra were determined for Nujol mulls with a Grubb-Parsons double-beam spectrophotometer. Ultraviolet spectra were determined for ethanol solutions with a Unicam S.P. 500 spectrophotometer. Column chromatography was on type H alumina (P. Spence Ltd.) or on silica gel (B.D.H.) and thin-layer chromatography on silica gel G (E. Merck A.G.). Organic extracts were dried with anhydrous magnesium sulphate and solvents were removed in a rotary evaporator under reduced pressure. Products were identified, where applicable, by mixed m. p. determination and comparison of infrared spectra.

*Materials.*—Most of the heterocyclic bases were recrystallised commercial specimens with m. p.s in agreement with the literature values. 7-Methylindole was prepared from *N*-formyl-2,6-dimethylaniline by Galat and Friedman's method<sup>8</sup> and 3-benzylindole from benzyl toluene-*p*-sulphonate<sup>9</sup> by Plieninger's method;<sup>4</sup> 1,3- and 2,3-dimethylindole have been described earlier.<sup>10</sup> Phthalaldehydic acid, either a commercial specimen or prepared from phthalide by bromination<sup>11</sup> and hydrolysis,<sup>12</sup> was crystallised from water to m. p. 97—98° (lit.,<sup>12</sup> 95—96°). Phthalidyl acetate, m. p. 66—67°, and 3-ethoxyphthalide, m. p. 63—64°, were prepared as described by Wheeler, Young, and Erley<sup>6</sup> who record m. p.s 62—63° and 64—65°, respectively.

*Condensation of Phthalaldehydic Acid with Indoles in Boiling Benzene.*—The indole (*ca.* 1 g.) and phthalaldehydic acid (1 mol.) were boiled under reflux in benzene (30 ml.) for 2 hr. The product separated from solution on cooling, after concentration when necessary, and was recrystallised from ethanol unless stated otherwise. Indole (1.1 g.) gave 3-phthalidyndole (1.8 g., 84%), m. p. 177° (lit.,<sup>2</sup> 176°). This product was also obtained (44%) by allowing the reactants to stand in benzene at room temperature for 10 days. 2-Methylindole (1.0 g.) gave needles of 2-methyl-3-phthalidyndole (2.0 g., 100%), m. p. 199—200° (lit.,<sup>2</sup> 196°). This product was also obtained (97%) when a three-molar excess of the indole was used. 7-Methylindole (1.0 g.) gave 7-methyl-3-phthalidyndole (1.0 g., 50%) as needles, m. p. 156—157° [from benzene-light petroleum (b. p. 60—80°)] (Found: C, 77.3; H, 5.1; N, 5.3. C<sub>17</sub>H<sub>13</sub>NO<sub>2</sub> requires C, 77.55; H, 5.0; N, 5.3%).  $\nu_{\max}$  3425 (NH), 1739 cm.<sup>-1</sup> ( $\gamma$ -lactone C=O). Ludwig and Tache<sup>1</sup> recorded m. p. 153° for this compound, the correct structure of which was suggested by Noland and Johnson.<sup>2</sup> 1,2-Dimethylindole (1.0 g.) gave 1,2-dimethyl-3-phthalidyndole (1.2 g., 63%), m. p. 205° [from benzene-light petroleum (b. p. 60—80°)] (lit.,<sup>2</sup> 204—206°). 2-Phenylindole (1.0 g.) gave a product (1.2 g.) which crystallised as needles of 2-phenyl-3-phthalidyndole (0.5 g., 29%), m. p. 247° (Found: C, 81.0; H, 4.7; N, 4.4. C<sub>22</sub>H<sub>15</sub>NO<sub>2</sub> requires C, 81.2; H, 4.7; N,

<sup>7</sup> Kamal and Ali Qureshi, *Tetrahedron*, 1963, **19**, 513.

<sup>8</sup> Galat and Friedman, *J. Amer. Chem. Soc.*, 1948, **70**, 1280.

<sup>9</sup> Hahn and Walter, *Ber.*, 1921, **54**, 1540.

<sup>10</sup> Rees and Smithen, *J.*, 1964, 928, 938.

<sup>11</sup> *Org. Synth.*, 1962, **42**, 26.

<sup>12</sup> *Org. Synth.*, 1955, Coll. Vol. III, 737.

4.3%),  $\nu_{\max}$  3289 (NH), 1733  $\text{cm}^{-1}$  ( $\gamma$ -lactone C=O). 3-Methylindole and phthalaldehydic acid did not react significantly under these conditions; the acid was recovered almost quantitatively.

*Condensation of Phthalaldehydic Acid with Indoles on Fusion.*—An intimate mixture of the indole (1.0 g.) and phthalaldehydic acid (1 mol.) was heated in an oil-bath at 180° for 30 min. The product was crystallised from ethanol. Indole gave 3-phthalidylindole (56%), m. p. and mixed m. p. 177°. 3-Methylindole gave 3-methyl-1-phthalidylindole (50%), m. p. 156° (Ludwig and Tache<sup>1</sup> record m. p. 140—141° and Noland and Johnson<sup>2</sup> record m. p.s 140—141° and 155—156° for dimorphic forms). 1,3-Dimethylindole gave 1,3-dimethyl-2-phthalidylindole (38%), m. p. 177—178° (lit.,<sup>2</sup> 177—179°). 2,3-Dimethylindole gave 2,3-dimethyl-1-phthalidylindole (34%), m. p. 141—142° (lit.,<sup>2</sup> 154.5—155.5°) (Found: C, 77.6; H, 5.5; N, 5.1. Calc. for  $\text{C}_{18}\text{H}_{15}\text{NO}_2$ : C, 78.0; H, 5.5; N, 5.05%). Tetrahydrocarbazole gave 1,2,3,4-tetrahydro-9-phthalidylcarbazole (23%), m. p. 179—180° (Found: C, 78.8; H, 5.3; N, 4.9.  $\text{C}_{20}\text{H}_{17}\text{NO}_2$  requires C, 79.2; H, 5.6; N, 4.6%)  $\nu_{\max}$  1764  $\text{cm}^{-1}$  ( $\gamma$ -lactone C=O). 3-Phthalidylindole gave 1,3-diphthalidylindole (28%), m. p. 183—185° (Found: C, 76.3; H, 4.2; N, 3.9.  $\text{C}_{24}\text{H}_{15}\text{NO}_4$  requires C, 75.6; H, 4.0; N, 3.7%),  $\nu_{\max}$  1745 and 1767  $\text{cm}^{-1}$  ( $\gamma$ -lactone C=O's).

*Acid-catalysed Condensations of Phthalaldehydic Acid.*—*With indole.* (a) A mixture of indole (0.6 g.), phthalaldehydic acid (0.76 g.), and toluene-*p*-sulphonic acid (0.1 g.) dissolved in anhydrous benzene (100 ml.) was set aside at room temperature for 24 hr. A solid (0.6 g.), m. p. 148—153°, separated. The filtrate was allowed to evaporate to yield more solid (0.7 g.), m. p. 140—146°. Crystallisation of the combined solids gave 3-phthalidylindole (0.4 g., 32%), m. p. 175—177°.

(b) From a similar mixture, set aside for 3 days, 3-phthalidylindole (0.7 g., 56%), m. p. 177°, was obtained.

*With 3-methylindole.* 3-Methylindole (0.5 g.), phthalaldehydic acid (0.55 g.), and toluene-*p*-sulphonic acid (0.1 g.) were boiled under reflux in benzene (30 ml.) for 30 min. The benzene was removed under reduced pressure and the residue crystallised from ethanol to give 3-methyl-1-phthalidylindole (0.4 g., 37%), m. p. 155°. Longer reflux times gave lower yields of this acid-sensitive product.

*Reactions of Indole with Phthalaldehydic Acid Derivatives.*—*Phthalidyl acetate.* (a) A mixture of indole (0.5 g.) and phthalidyl acetate (0.8 g.) was boiled under reflux in anhydrous benzene (30 ml.). Portions of the solution were withdrawn immediately after mixing, after 2 hr., and after 16 hr. The solvent was removed and the infrared spectra of the residues measured. The three spectra were very similar and in good agreement with that expected for a mixture of the reactants, indicating that no reaction had occurred. After 2 hr. reflux, a portion of the solution was subjected to thin-layer chromatography, with benzene as eluant and iodine as developer. The two main spots were those of the reactants but a third, faint spot was due to 3-phthalidylindole, indicating that a very little reaction had occurred. No 3-phthalidylindole could be isolated.

(b) A solution of indole (0.6 g.), phthalidyl acetate (0.95 g.), and toluene-*p*-sulphonic acid (0.1 g.) in anhydrous benzene (100 ml.) was set aside for 24 hr. A sample was subjected to thin-layer chromatography as above, using two different eluants, benzene and 2% methanol in benzene. In each case the two main spots of the reactants together with a third faint spot for 3-phthalidylindole were observed; thus, a small amount of this product had been formed but, again, none could be isolated.

(c) Indole (0.5 g.), phthalidyl acetate (0.8 g.), and benzoic acid (0.05 g.) were boiled under reflux in benzene (30 ml.) for 2 hr. The solution was concentrated, but no product separated. Indole (0.42 g., 84%) was recovered by chromatography on alumina.

*3-Ethoxyphthalide.* From a similar reaction of indole (1.0 g.) and 3-ethoxyphthalide (1.2 g.) in boiling anhydrous benzene (25 ml.) for 2 hr., 3-phthalidylindole was again carefully sought. None could be isolated but a faint spot due to it was observed in thin-layer chromatography.

*Hydrolysis of Phthalidylindoles.*—A known weight of the phthalidylindole (*ca.* 0.2 g.) was heated under reflux in an excess of ethanolic potassium hydroxide (0.656N; *ca.* 3 ml.) for 1 hr. The remaining potassium hydroxide was titrated with hydrochloric acid (0.20N) using phenolphthalein as indicator. 3-Phenylphthalide was treated identically, as a control, and blank determinations were run simultaneously. In each case  $1.0 \pm 0.05$  moles of potassium hydroxide were consumed.

*Hydrogenolyses.*—*3-Phenylphthalide.* 3-Phenylphthalide (0.5 g., 0.0024 mole) in absolute ethanol (120 ml.) was shaken with hydrogen in the presence of 10% palladised charcoal (0.05 g.).

Uptake of hydrogen (60 ml., 0.0027 mole) was complete in 30 min. The solution was filtered (Celite) and ethanol removed to yield *o*-benzylbenzoic acid (0.37 g.), m. p. 116—117° [from benzene—light petroleum (b. p. 60—80°)] (lit.,<sup>13</sup> 118°),  $\nu_{\max}$ . 2618w, 935 (acid OH), and 1684 cm.<sup>-1</sup> (acid C=O); a mixed m. p. 91—97° was obtained on admixture with 3-phenylphthalide (m. p. 116—117°).

**3-Phthalidyndole.** 3-Phthalidyndole (1.5 g., 0.006 mole), 10% palladised charcoal (0.15 g.), and absolute ethanol (120 ml.) were treated as above. Uptake of hydrogen (0.0066 mole) was complete in 1 hr. The solution was filtered (Celite), concentrated, treated with charcoal, and filtered, yielding needles of 3-(*o*-carboxybenzyl)indole (1.0 g., 67%), m. p. 214—215° (lit.,<sup>2</sup> 210—212°) (Found: C, 76.2; H, 5.4. Calc. for C<sub>16</sub>H<sub>13</sub>NO<sub>2</sub>: C, 76.5; H, 5.2%),  $\nu_{\max}$ . 3472 (NH), 2667w, 926 (acid OH), and 1695 cm.<sup>-1</sup> (acid C=O). The acid was soluble in aqueous sodium hydrogen carbonate and precipitated on addition of acid. The acid (0.3 g.) was boiled in quinoline (5 ml.) and copper chromite (0.05 g.) was added in small portions. After 1 hr. the mixture was filtered (Celite) into 5*N*-hydrochloric acid (50 ml.), and extracted with chloroform. The chloroform solution was washed with 5*N*-hydrochloric acid, dried, and evaporated, to give 3-benzylindole (0.1 g., 40%), m. p. 92—98°, after chromatography on alumina.

**3-Methyl-1-phthalidyndole.** 3-Methyl-1-phthalidyndole (1.5 g., 0.0057 mole), 10% palladised charcoal (0.15 g.), and absolute ethanol (120 ml.) were treated as above; hydrogen (0.017 mole) was absorbed. The solution was filtered (Celite) and evaporated, and the resulting gum was partitioned between ether and 10% aqueous sodium hydroxide. The ether solution was dried and evaporated to yield a gum which was passed through a small column of alumina to give 3-methylindole (0.1 g.). The aqueous alkaline solution was acidified and a white solid (0.8 g.) was precipitated which, on crystallisation from benzene—light petroleum (b. p. 60—80°), gave 1-(*o*-carboxybenzyl)-3-methylindole, m. p. 166—167° (lit.,<sup>2</sup> 168—169°) (Found: N, 5.3. Calc. for C<sub>17</sub>H<sub>15</sub>NO<sub>2</sub>: N, 5.3%),  $\nu_{\max}$ . 2688w, 926 (acid OH), and 1701 cm.<sup>-1</sup> (acid C=O), and no peak in the NH region; the compound was soluble in aqueous hydrogen carbonate and precipitated on addition of acid. The acid filtrate, from which the above white solid was removed, was extracted with ether; the ether was dried and removed to give *o*-toluic acid (0.1 g.).

**1,3-Dimethyl-2-phthalidyndole.** 1,3-Dimethyl-2-phthalidyndole (0.32 g., 0.0011 mole), 10% palladised charcoal (0.05 g.), and absolute ethanol (50 ml.) were treated as above; hydrogen (0.0014 mole) was absorbed. The solution was filtered (Celite) and the solvent removed to give needles of 2-(*o*-carboxybenzyl)-1,3-dimethylindole (0.3 g.), m. p. 234—236° (lit.,<sup>2</sup> 237—245°) (Found: C, 77.0; H, 6.0; N, 5.0. Calc. for C<sub>18</sub>H<sub>17</sub>NO<sub>2</sub>: C, 77.4; H, 6.1; N, 5.0%),  $\nu_{\max}$ . 2639w, 929 (acid OH), and 1689 (acid C=O); the compound was soluble in aqueous sodium hydrogen carbonate and precipitated on addition of acid. This acid (0.2 g.) was boiled in quinoline (4 ml.), and copper chromite (0.05 g.) was added in small portions. After 1 hr. the mixture was treated as in the decarboxylation above to give crystalline 2-benzyl-1,3-dimethylindole, m. p. 92—94° (lit.,<sup>14</sup> 92—93°) (Found: C, 86.7; H, 7.2; N, 6.1. Calc. for C<sub>17</sub>H<sub>17</sub>N: C, 86.8; H, 7.3; N, 6.0%), picrate, m. p. 112—112.5° (lit.,<sup>14</sup> 111.5—112.5°).

*Miscellaneous Reactions of Indole.—With benzaldehyde.* Indole (1.1 g.) and benzaldehyde (1.0 g.) were refluxed in benzene (30 ml.) for 2 hr. Most of the solvent was removed and the solution was adsorbed on alumina. Elution with light petroleum (b. p. 60—80°) gave indole (0.7 g.) and with benzene gave a solid (0.3 g.) which, on crystallisation from benzene—light petroleum (b. p. 60—80°), gave phenyl-3,3'-di-indolylmethane (0.25 g.), m. p. 124—125° (lit.,<sup>7</sup> 125°) (Found: C, 86.0; H, 5.8. Calc. for C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>: C, 85.7; H, 5.6%).

*With diphenylmethanol.* An intimate mixture of indole (1.0 g.) and diphenylmethanol (1.6 g.) was heated at 180° for 30 min. The product was dissolved in benzene, adsorbed on alumina, and eluted as follows. Light petroleum (b. p. 80—100°; 750 ml.) gave indole (0.5 g.). Benzene—light petroleum (b. p. 80—100°) (2:1; 500 ml.) gave a white solid (0.18 g.), m. p. 85—90°, which on crystallisation from the same solvent gave 3-benzhydryndole, m. p. 126—127.5° (lit.,<sup>15</sup> 127—128°). Benzene (750 ml.) gave diphenylmethanol (0.9 g.).

*With 3-phthalidyndole in basic solution.* 3-Phthalidyndole (1 g.) was boiled under reflux in an alcoholic solution of potassium hydroxide (20 ml.; 0.6*N*) for 30 min. Indole (1.9 g.) was added and the mixture was boiled for 1 hr. Most of the unreacted indole was precipitated as the insoluble picrate. The filtrate was acidified and the product precipitated with water. The

<sup>13</sup> Barnett, Cook, and Nixon, *J.*, 1927, 508.

<sup>14</sup> Janetzky and Verkade, *Rec. Trav. chim.*, 1945, **64**, 136.

<sup>15</sup> Pratt and Botimer, *J. Amer. Chem. Soc.*, 1957, **79**, 5248.

precipitate was extracted with ether, and the ether was dried and evaporated. The solid (0.8 g.) obtained by trituration of the residue was crystallised from benzene-ethanol to give  $\alpha, \alpha$ -di-3-indolyl-o-toluic acid benzene solvate, m. p. 156—157° (Found: C, 80.7; H, 5.55; N, 6.5.  $C_{30}H_{24}N_2O_2$  requires C, 81.0; H, 5.4; N, 6.3%). This solvate was dried under high vacuum at 90° for 4 hr. to give the *unsolvated acid*, m. p. 164—165° (Found: C, 79.15; H, 5.2.  $C_{24}H_{18}N_2O_2$  requires C, 78.7; H, 5.0%),  $\nu_{max}$  3407 (NH), 2632w (acid OH), and 1678  $cm^{-1}$  (acid C=O). The acid dissolved in aqueous sodium hydrogen carbonate and was reprecipitated on acidification.

*Condensations of 3-Methylindole in Acetic Acid.*—The reaction conditions of Kamal and Ali Qureshi<sup>7</sup> were followed precisely.

*With benzaldehyde.* To 3-methylindole (2.6 g.), suspended in water (50 ml.) containing acetic acid (0.6 g.), benzaldehyde (1.06 g.) was added. The mixture was stored for 10 days with occasional shaking. An oil was formed; the mixture was extracted with ether, the ether was dried and evaporated. The residue, on crystallisation from benzene-light petroleum (b. p. 40—60°), yielded 3-methylindole (2.2 g., 85%). No crystalline material separated from the aqueous solution, as claimed by Kamal and Ali Qureshi,<sup>7</sup> and no other crystalline solid could be isolated.

*With phthalaldehydic acid.* 3-Methylindole (2.6 g.) and phthalaldehydic acid (1.5 g.) were suspended in water (50 ml.) containing acetic acid (0.6 g.) and treated exactly as above, for the same time. The mixture was filtered and the solid, after two crystallisations from ethanol-light petroleum (b. p. 60—80°), gave 3-methyl-1-phthalidyndole (0.1 g.).

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