108. *The Condensation of Phthalaldehydic Acid and Related Compounds with Various Heterocyclic Systems.*

By C. W. Rees and C. R. Sabet.

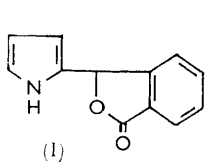
The previously described condensation of phthalaldehydic acid with indoles is extended to various other oxo-acids (mucochloric, *o*-acetylbenzoic, and naphthalaldehydic acid) and the analogous 3-hydroxy-2-methylphthalimidine, and to various other heterocyclic systems (pyrroles, carbazole, indazole, and benzotriazole). Further support is provided for the mechanism proposed earlier.

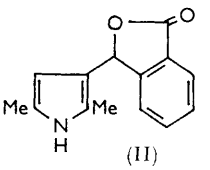
In view of the novel mechanism and the potential synthetical value of the reactions between phthalaldehydic acid and indoles, described in the preceding Paper,[1] it was interesting to see how far these reactions could be extended to other oxo-acids and heterocyclic systems. Phthalaldehydic acid reacted with pyrrole and with 2,5-dimethylpyrrole in boiling benzene to give high yields of the 2-phthalidyl (I) and the 3-phthalidyl derivative (II), respectively. These structures were assigned by analogy with the indole reactions coupled with the tendency for pyrroles to substitute in position 2 when possible, and on spectral properties. In particular, the N–H stretching absorption was present in both products, and the latter is not therefore a pyrrolenine. This parallels the absence of formation of indolenines from 3-substituted indoles. Furan, thiophen, thianaphthene and indazole did not react with phthalaldehydic acid in boiling benzene. However, indazole and benzotriazole did react on fusion at 180° with phthalaldehydic acid to give the *N*-phthalidyl derivatives (III) and (IV), respectively. Somewhat surprisingly, benziminazole,

[1] Rees and Sabet, preceding Paper.

which is closely related to indole, indazole, and benzotriazole, appeared not to undergo the reaction, and no crystalline product could be isolated. Isatin and carbazole, like 1,2,3,4-tetrahydrocarbazole, condensed with phthalaldehydic acid on fusion to give *N*-phthalidyl derivatives.

In an extension of these reactions to compounds related to phthalaldehydic acid, the condensation of some indoles with *o*-acetylbenzoic, naphthalaldehydic (8-formyl-1-naphthoic), and mucochloric acid (3,4-dichloro-2,5-dihydro-5-hydroxyfuran-2-one), and


(I)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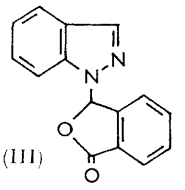
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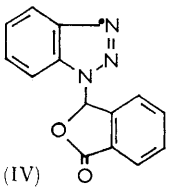
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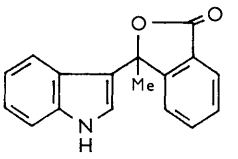
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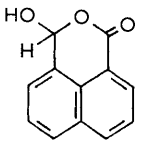

(VI)

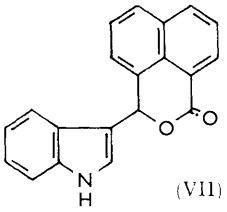
with 3-hydroxy-2-methylphthalimidine, were investigated. *o*-Acetylbenzoic acid is the simplest oxo-acid related to phthalaldehydic acid and can also exist in a cyclic, hydroxyphthalide form.[2] It did not react with indole in boiling benzene, but on fusion at 180° a small amount of the analogous product, 3-(3-indolyl)-3-methylphthalide (V) was obtained. *o*-Acetylbenzoic acid is thus much less reactive than phthalaldehydic acid, as is to be expected if the reaction proceeds by nucleophilic attack by indole on the carbonyl carbon atom.[1]

Naphthalaldehydic acid also exists as a stable hydroxy-lactone (VI),[3] in this case a δ-lactone. It too was much less reactive than phthalaldehydic acid and did not condense with the indole in boiling benzene, but did react on fusion with indole and 3-methylindole to give high yields of products with the expected analysis. The product from indole had an infrared spectrum in agreement with the 3-naphthalidyl structure (VII) assigned by analogy with the phthalaldehydic acid product; the N–H absorption was retained and the lactone carbonyl absorption (1684 cm.$^{-1}$) was very close to that for the starting acid itself (1681 cm.$^{-1}$). The infrared spectrum of the product from 3-methylindole showed the same strong carbonyl absorption (1692 cm.$^{-1}$) but was anomalous in having absorption (3257 cm.$^{-1}$) in the N–H region similar to that of other indolic N–H groups; though relatively weak, this absorption was retained after sublimation and crystallisation of the product. Thus 3-methyl-1-naphthalidylindole cannot have been formed, in contrast with the phthalaldehydic acid reactions. In the latter, 2-phthalidylindoles are formed if the 1-position is blocked, and it is possible that here the 2-naphthalidyl somer (VIII) is formed preferentially, for steric reasons.

The acidic reactants in the condensations so far described have been aromatic compounds. Since the present reaction provides a simple method of introducing 3-substituents into indole in high yields under mild conditions, it would be of value to extend it to aliphatic acids. A new route would then be provided to the very important indole-3-alkanoic acids. β-Formylacrylic acid is the closest aliphatic analogue of phthalaldehydic acid, and, like it,

[2] Wheeler, *Canad. J. Chem.*, 1961, **39**, 2605.
[3] Rodionov and Fedorova, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1950, 247.

exists in a hydroxy-γ-lactone form (IX; R = H).[4] If β-formylacrylic acid condensed with indole in the same way as phthalaldehydic acid 2,5-dihydro-5-(3-indolyl)furan-2-one (X; R = H) would be formed, in which a straight chain of four carbon atoms, each associated with functionality, had been introduced into the indole 3-position. This acid reacted very rapidly with indole to give a gum which quickly became a dark infusible, apparently polymeric solid, which could not be purified. When the reactants were stirred together in anhydrous ether at 0° under nitrogen, in the presence of anhydrous magnesium sulphate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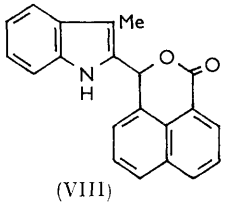
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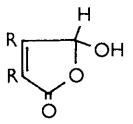
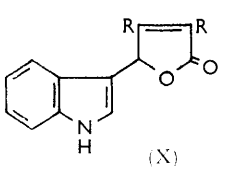

(IX)

to absorb the water produced, and very carefully and rapidly worked-up, the initial product was a pink solid, but this quickly deteriorated on all attempts at purification. However, the more stable mucochloric acid (IX; R = Cl) condensed smoothly with indole and with 2-methylindole in boiling benzene to give 3,4-dichloro-2,5-dihydro-5-(3-indolyl)furan-2-one (X; R = Cl) and the 2′-methyl derivative, respectively. The chemistry of these products was not investigated further but they could obviously give rise to many interesting 3-substituted indoles. Mucochloric acid did not react with 3-methylindole in boiling benzene and, on fusion together, much decomposition occurred and no crystalline product could be isolated.

The final extension of this reaction in the present work was to 3-hydroxy-2-methylphthalimidine (XI) which, though not an acid, is the nitrogen-heterocyclic analogue of phthalaldehydic acid; the nitrogen is methylated to avoid reaction at this site. Unlike phthalaldehydic acid this compound does not exist in equilibrium with the open-ring isomer *o*-formyl-*N*-methylbenzamide, as shown for example by its failure to give a positive 2,4-dinitrophenylhydrazine test. It should, therefore, be inert towards indole on the basis of our reaction mechanism.[1] It did not react at all with indole in boiling benzene, and is thus very much less reactive than phthalaldehydic acid, but it did react on fusion at 180° to give 3-(3-indolyl)-2-methylphthalimidine (XII). This structure was assigned on the basis of the analysis and infrared spectrum and by analogy with the earlier work, and was proved by its synthesis from 3-phthalidylindole and methylamine. The much greater reactivity of phthalaldehydic acid over the phthalimidine (XI) provides additonal support for the mechanism proposed; the phthalimidine may react in the cyclic form, by direct displacement of the hydroxyl group by indole or, like phthalaldehydic acid, by way of the open-ring isomer which is possibly formed at the elevated reaction temperature. The relative reactivities of the oxo-acids described above are readily explained on the basis of the phthalaldehydic acid reaction mechanism.[1]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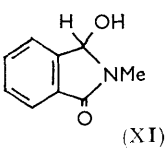
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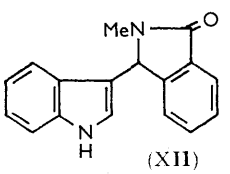
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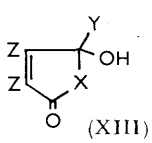
(XIII)

From these results it appears that the condensation described in this and the preceding paper is of fairly wide generality. It would be expected to occur, on heating but in the

[1] Franzen and Fikentscher, *Annalen*, 1959, **623**, 68.

absence of any external catalyst, between electron-rich heteroaromatic compounds of the pyrrole type and compounds with the structural features shown in formula (XIII). In the present work X = O or NMe, Y = H or Me, Z = Cl, Z–Z completes a benzene ring, and Z–Z–Y completes the bicyclic naphthalene system.

Experimental

For general directions, and for some preparations, see before.[1] Except where noted materials were commercial specimens, or prepared by standard procedures, and were purified to give the literature m. p.s or b. p.s. Naphthalaldehydic acid, prepared [5] from acenaphthenequinone, had m. p. 164—166° (lit.,[5] 169—171°). 3-Hydroxy-2-methylphthalimidine, prepared [6] by reduction of *N*-methylphthalimide, had m. p. 128—129° (lit.,[6] 126—127°).

Reactions with Phthalaldehydic Acid.—These reactions were conducted as described earlier,[1] either in boiling benzene for 2 hr. or on fusion of the reactants at *ca.* 180° for 30 min.

In boiling benzene. Pyrrole (0·45 g.) and phthalaldehydic acid (1·0 g.) gave needles of 2-*phthalidylpyrrole* (0·6 g., 75%), m. p. 116—117° (Found: C, 72·3; H, 4·8; N, 6·8. $C_{12}H_9NO_2$ requires C, 72·35; H, 4·6; N, 7·0%), $\nu_{max.}$ 3279 (NH) and 1748 cm.$^{-1}$ (γ-lactone C=O). The compound, $C_{12}H_9NO_2$, m. p. 118°, formed by reduction [7] of the condensation product of pyrrole with phthalic anhydride is presumably the same. 2,5-Dimethylpyrrole (0·65 g.) and phthalaldehydic acid (1·0 g.) gave prisms of 2,5-*dimethyl*-3-*phthalidylpyrrole* (1·2 g., 80%), m. p. 186—187° (Found: C, 73·8; H, 6·0; N, 6·2. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·8; N, 6·2%), $\nu_{max.}$ 3390 (NH) and 1733 cm.$^{-1}$ (γ-lactone C=O). With furan, thiophen, thianaphthene, and indazole no reaction occurred under these conditions, phthalaldehydic acid being recovered almost quantitatively.

On fusion. 2,5-Dimethylpyrrole (0·65 g.) and phthalaldehydic acid (1·0 g.), heated under nitrogen, gave a solid mass which crystallised to give 2,5-dimethyl-3-phthalidylpyrrole (0·35 g., 23%), m. p. and mixed m. p. with the previous specimen, 186—187°. Isatin (1·0 g.) and phthalaldehydic acid (1·0 g.), heated at 200—210°, gave orange needles of N-*phthalidylisatin* (0·5 g., 26%), m. p. 240—241° (Found: C, 68·5; H, 3·5; N, 5·1. $C_{16}H_9NO_4$ requires C, 68·8; H, 3·3; N, 5·0%). The infrared spectrum showed no NH peak and an extra C=O peak at 1802 cm.$^{-1}$. Indazole (0·2 g.) and phthalaldehydic acid (0·25 g.) gave needles of 1-*phthalidylindazole* (0·23 g., 56%), m. p. 146—147° (Found: C, 72·0; H, 4·1; N, 11·0. $C_{15}H_{10}N_2O_2$ requires C, 72·0; H, 4·0; N, 11·2%), $\nu_{max.}$ 1754 cm.$^{-1}$ (γ-lactone C=O), no NH peak. Benzotriazole (1·0 g.) and phthalaldehydic acid (1·3 g.) gave needles of 1-*phthalidylbenzotriazole* (0·9 g., 43%), m. p. 159° (Found: C, 66·7; H, 3·6. $C_{14}H_9N_3O_2$ requires C, 66·9; H, 3·6%), $\nu_{max.}$ 1783 cm.$^{-1}$ (γ-lactone C=O), no NH peak. Carbazole (1·1 g.) and phthalaldehydic acid (1·0 g.) heated at 220° gave prisms of N-*phthalidylcarbazole* (1·0 g., 50%), m. p. 155—157° (Found: C, 80·0; H, 4·4; N, 4·4. $C_{20}H_{13}NO_2$ requires C, 80·25; H, 4·4; N, 4·7%), $\nu_{max.}$ 1767 cm.$^{-1}$ (γ-lactone C=O), no NH peak.

Reactions of Indoles with Other Oxo-acids.—Indole with o-acetylbenzoic acid. When these compounds were boiled in benzene for 2 hr. and for 16 hr. no reaction was detected and 93 and 90%, respectively, of *o*-acetylbenzoic acid was recovered. *o*-Acetylbenzoic acid (1·4 g.) and indole (1·0 g.) were heated at 180° for 30 min. The product was dissolved in benzene and adsorbed on silica gel; elution with light petroleum (b. p. 80—100°) gave indole and with benzene gave a solid which crystallised from benzene–light petroleum (b. p. 80—100°) as 3-(3-*indolyl*)-3-*methylphthalide*, m. p. 159—160° (Found: C, 77·8; H, 5·2; N, 5·3. $C_{17}H_{13}NO_2$ requires C, 77·6; H, 5·0; N, 5·3%), $\nu_{max.}$ 3333 (NH) and 1724 cm.$^{-1}$ (γ-lactone C=O); the infrared spectrum was similar to that of 3-phthalidylindole.

Indole with naphthalaldehydic acid. When boiled with indole in benzene for 2 hr. naphthalaldehydic acid was recovered quantitatively. Indole (0·6 g.) and naphthalaldehydic acid (1·0 g.) were heated at 180° for 30 min. The product was crystallised from ethanol–light petroleum (b. p. 60—80°) to give 3-*naphthalidylindole* (1·2 g., 80%), m. p. 184—185° (Found: C, 79·7; H, 4·4; N, 4·6. $C_{20}H_{13}NO_2$ requires C, 80·2; H, 4·4; N, 4·7%), $\nu_{max.}$ 3289 (NH) and 1684 cm.$^{-1}$ (δ-lactone C=O), cf. 1681 cm.$^{-1}$ for the carbonyl absorption of naphthalaldehydic acid.

[5] Cason and Wordie, *J. Org. Chem.*, 1950, **15**, 612.
[6] Brewster, Fusco, Carosino, and Corman, *J. Org. Chem.*, 1963, **28**, 500.
[7] Dennstedt and Zimmermann, *Ber.*, 1888, **21**, 1554.

3-*Methylindole with naphthalaldehydic acid.* 3-Methylindole (0·7 g.) and naphthalaldehydic acid (1·0 g.) were heated at 180° for 30 min. Crystallisation from ethanol gave 3-*methyl*-2-*naphthalidylindole* (?) (1·3 g., 81%), m. p. 253—255° (Found: C, 80·1; H, 4·8; N, 4·5. $C_{21}H_{15}NO_2$ requires C, 80·5; H, 4·8; N, 4·5%), $\nu_{max.}$ 3257w (NH) and 1692 cm.$^{-1}$ (δ-lactone C=O).

Indole with mucochloric acid. Indole (1·0 g.) and mucochloric acid (1·4 g.) were refluxed in benzene (75 ml.) overnight. (After 2 hr. the starting materials were largely recovered.) After concentration, crystalline 3,4-*dichloro*-2,5-*dihydro*-5-(3-*indolyl*)*furan*-2-*one* (1·6 g., 70%) separated; this compound did not melt but decomposed at about 170° (Found: C, 53·8; H, 2·7; N, 4·7. $C_{12}H_7Cl_2NO_2$ requires C, 53·7; H, 2·6; N, 5·2%), $\nu_{max.}$ 3333 (NH), 1745 (γ-lactone C=O), and 1629 cm.$^{-1}$ (conjugated C=C); it decolourised potassium permanganate.

2-*Methylindole with mucochloric acid.* 2-Methylindole (1·0 g.) and mucochloric acid (1·3 g.) were refluxed in benzene overnight. Needles of 3,4-*dichloro*-2,5-*dihydro*-5-(2-*methyl*-3-*indolyl*)-*furan*-2-*one* (1·5 g., 68%) separated; this compound did not melt but decomposed at about 170° (Found: C, 55·2; H, 3·1; N, 5·3. $C_{13}H_9Cl_2NO_2$ requires C, 55·3; H, 3·2; N, 5·0%), $\nu_{max.}$ 3300 (NH), 1742 (γ-lactone C=O), and 1621 cm.$^{-1}$ (conjugated C=C); it decolourised potassium permanganate.

3-(3-*Indolyl*)-2-*methylphthalimidine.*—(*a*) When indole and 3-hydroxy-2-methylphthalimidine were refluxed in benzene for 2 hr. no reaction occurred and the phthalimidine (90%) was recovered. Indole (0·3 g) and 3-hydroxy-2-methylphthalimidine (0·5 g.) were heated at 180° for 30 min. Crystallisation from ethanol gave 3-(3-*indolyl*)-2-*methylphthalimidine* (0·5 g., 58%), m. p. 225° (Found: C, 78·1; H, 5·5; N, 11·0. $C_{17}H_{14}N_2O$ requires C, 77·8; H, 5·4; N, 10·7%), $\nu_{max.}$ 3205 (NH) and 1675 cm.$^{-1}$ (γ-lactone C=O).

(*b*) 3-Phthalidylindole (0·5 g.) in methylamine (33%) in ethanol (5 ml.) was heated in a sealed tube at 100° for 24 hr. The solution was concentrated and set aside; needles (0·4 g.) separated and were recrystallised from benzene–light petroleum (b. p. 60—80°) to give the same phthalimidine, m. p. and mixed m. p. 225°. The infrared spectra of the products from (*a*) and (*b*) were very similar but not identical.

Reaction of Indoles with N-*Benzylideneaniline.*—The following reactions were carried out as described by Passerini and Bonciani.[8]

2-*Methylindole.* *N*-Benzylideneaniline (1·6 g.) in benzene (10 ml.) was added to 2-methylindole (1·2 g.) in benzene (10 ml.) and set aside for 4 days. A solid separated which was recrystallised from benzene to give 3-(α-anilinobenzyl)-2-methylindole (1·5 g., 54%), m. p. 154° (lit.,[8] 154°).

3-*Methylindole.* When 3-methylindole was treated identically, no solid separated, even after concentration of the solution, indicating that no reaction had occurred. Passerini and Bonciani [8] reported that in this case they obtained a similar product, 2-(α-anilinobenzyl)-3-methylindole, m. p. 155—156°.

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Strand, London W.C.2. [*Received, May 25th*, 1964.]

[8] Passerini and Bonciani, *Gazzetta*, 1933, **63**, 138.