# Pyrrolo[1,2-*b*]isoquinoline-5,10-diones and Indolizine-5,8-diones†

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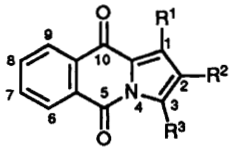
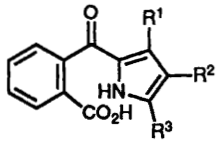
The synthesis of pyrroloisoquinolinediones from phthalic anhydride and pyrrolylmagnesium halides has been improved. A new synthesis, by cyclization of the novel 1-(2-carboxybenzoyl)pyrroles, was generally preferable. From pyrrolylmagnesium bromide and dimethylmaleic anhydride, followed by cyclization, 6,7-dimethylindolizine-5,8-dione was obtained. The process failed with maleic anhydride. Pyrrolo[1,2-*b*]isoquinoline-5,10-dione could be dinitrated in the pyrrolo ring (with some oxidation to isoquinoline-1,3,4-trione), reduced to 10-hydroxy-3,5-dihydropyrrolo[1,2-*b*]isoquinolin-5-one by zinc and acetic acid, and hydrogenated over palladium on carbon to 10-hydroxy-1,2,3,5-tetrahydropyrrolo[1,2-*b*]isoquinolin-5-one. The dihydro derivative reverted in air to the dione.



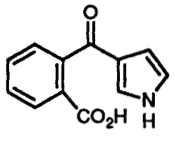
Thirty years ago Cornforth and Firth,[1] investigating a colour reaction of hexosamines, were led to examine the compounds, then called pyrrolene-phthalides, made by heating pyrroles with phthalic anhydride. The correct structure (**1**) was assigned to the parent compound, the two alternatives preferred by earlier workers being eliminated by analysis of the IR spectra. Little work has been published since that time on the ring-system (**1**), perhaps because hitherto there has been no convenient high-yielding synthesis. In the original synthesis[2] the pyrrole, phthalic anhydride and acetic acid are heated in a sealed tube; a simple but inefficient process ill-adapted to larger-scale work.



(1) $R^1-R^3 = H$
(8) $R^1, R^2 = H, R^3 = Me$
(9) $R^1 = Me, R^2, R^3 = H$
(10) $R^2 = Me, R^1, R^3 = H$
(11) $R^2, R^3 = Me, R^2 = H$



(2) $R^1, R^3 = Me, R^2 = H$
(3) $R^1-R^3 = H$
(4) $R^1, R^2 = H; R^3 = Me$
(5) $R^1 = Me, R^2, R^3 = H$
(6) $R^2 = Me, R^1, R^3 = H$



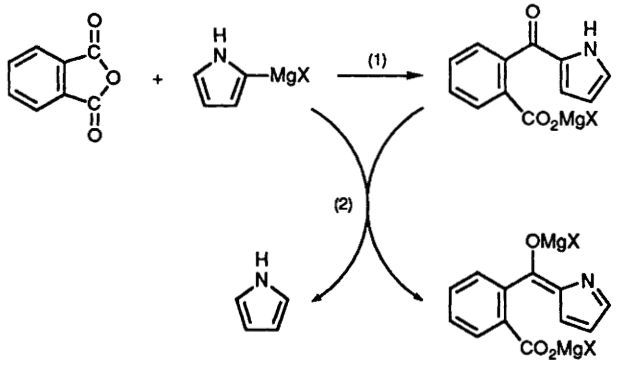
(7)

Oddo and his co-workers[3-5] obtained pyrrolene-phthalides in various ways from the products obtained from 3,3-dichlorophthalide ('phthalyl chloride') or phthalic anhydride with pyrrolylmagnesium bromides. No yields were reported and the interpretations were dubious. Later[1] it was shown in the case of 2,4-dimethylpyrrolylmagnesium bromide that the primary products from reaction of two equivalents of this reagent with one equivalent of phthalic anhydride, followed by treatment with ice and carbon dioxide, were one equivalent of 2,4-dimethylpyrrole and one equivalent of a magnesium salt of the keto acid (**2**). Acid of type (**2**), though not always correctly formulated, were already known by the earliest workers[2] to be formed from pyrrolene-phthalides by mild alkaline hydrolysis and to regenerate the phthalides in mild conditions (*e.g.*, heating with ammoniacal water). In the only other synthesis known,[6,7] base-catalysed condensation of 3-alkoxy- or 3-alkylthio-acrylonitriles with isoquinoline-1,4-diol gave a series of 3-aminopyrrolo[1,2-*b*]isoquinoline-5,10-diones. Though limited by substitution type and by availability of starting materials, this is a practical synthesis of the ring system.

In this paper we describe two effective procedures for obtaining the parent pyrroloisoquinolinedione (**1**) and several of its derivatives from pyrroles and phthalic anhydride. The second procedure constitutes a new synthesis.

## Results and Discussion

The reaction between phthalic anhydride and a pyrrolylmagnesium halide was depicted by Cornforth and Firth[1] as occurring in two stages (Scheme). The second step must be



**Scheme.**

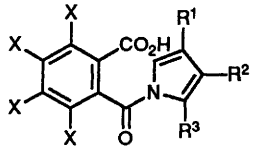
faster than the first since half of the pyrrole is recovered even when equimolar amounts of the reagents are taken. This is undesirable because the pyrrole is generally the more valuable component. But a pyrrolylmagnesium halide is generally prepared by mixing the pyrrole with an alkylmagnesium halide, an alkane being the other product. This reaction is very fast, and it was expected that a Grignard reagent added to a mixture of a pyrrole and phthalic anhydride would attack the pyrrole preferentially. If this were so, it could be predicted that addition of *two* equivalents of alkylmagnesium halide to one equivalent each of pyrrole and of phthalic anhydride could lead to total consumption of all reagents, and to the formation of one

† No reprints available.

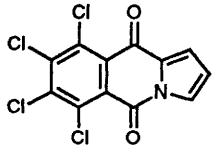
equivalent of the product *plus* two equivalents of alkane (provided that the alkylmagnesium halide was not added faster than pyrrole could be regenerated, by the second step of the Scheme, to react with it. In practice, we added one equivalent of ethylmagnesium bromide quite fast and the second equivalent more slowly to allow time for regeneration of pyrrole). In this way the keto acids (**2**), (**3**), (**4**), and a mixture of (**5**) and (**6**) were made in good yields from 2,4-dimethylpyrrole, pyrrole, 2-methylpyrrole, and 3-methylpyrrole respectively. We saw no sign of reaction between ethylmagnesium bromide and phthalic anhydride except in one experiment when a deficiency of the pyrrole was inadvertently taken and 3,3-diethylphthalide appeared among the products. The keto acids (**2**), (**3**), and (**4**) could be purified by recrystallization but it was easier to get pure specimens by hydrolysis[2] of the derived pyrroloisoquinolinediones. It has been reported[8] that pyrrolylmagnesium iodide with phthalic anhydride can yield a minor amount of the isomeric keto acid (**7**), though we have not confirmed this.

Cyclization of keto acids of type (**2**) to pyrroloisoquinolinediones can occur in a variety of ways (*e.g.*, by heat alone) but is seldom smooth. The original procedure of heating the ammonium salt in water is effective but slow. We obtained the best results by boiling a solution of the acid in aqueous sodium acetate. In this way sizeable specimens of (**1**), (**8**), (**9**), (**10**), and (**11**) were prepared from pyrrole, 2-methylpyrrole, 3-methylpyrrole and 2,4-dimethylpyrrole respectively in good overall yields. The isomers (**9**) and (**10**) were separated by chromatography.

Next, we examined an alternative mode of synthesis. The potassium or sodium salts of pyrroles, unlike the halogenomagnesium or lithium compounds, commonly add electrophiles to the nitrogen atom.[9] When potassio- or sodio-pyrrole was warmed with phthalic anhydride a new acid (**12**), isomeric with (**3**), was formed almost quantitatively. It was convenient to heat the pyrrole in toluene with sodium hydride and phthalic anhydride and, when no more hydrogen was evolved, to isolate the product acid by extraction with water followed by acidification. Cyclization to the pyrroloisoquinoline (**1**) could then be effected by boiling acetic anhydride, but it was better to use propionic anhydride or to distil acetic anhydride slowly out of a solution of the acid in 1,2-dichlorobenzene, and best of all to treat the acid with phosphoryl chloride in pyridine at room temperature when the product (**1**) was formed in 98% yield. The phthalamic acid (**13**) from 3-methylpyrrole cyclized somewhat more easily than (**12**), as might be expected since its pyrrole ring should have a higher electron density, and addition of acetic anhydride to the reaction mixture prepared from this pyrrole, phthalic anhydride, and sodium hydride in toluene gave, in a one-pot synthesis, a mixture of the diones (**9**) and (**10**) in 58% yield.



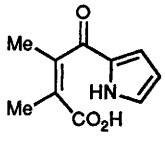
(**12**) $R^1 - R^3 = X = H$
(**13**) $R^1 = Me$, $R^2$, $R^3 = X = H$
(**14**) $R^1 - R^3 = H$, $X = Cl$



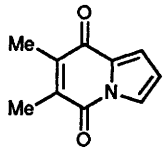
(**15**)

The earlier paper[1] could not assign a structure to each of these two isomers but proton magnetic resonance spectra now resolved this problem without effort, the two pyrrolic hydrogens being more strongly coupled in (**9**) than in (**10**). The different chemical shifts of the methyl signals also made easy the analysis of mixtures of the two isomers as obtained by the new synthesis and by the Grignard method (above). In this way it was shown that cyclization of (**13**) gave a marked preponderance of the 1-methyl isomer (**9**) (6.7:1), but that cyclization of the mixed acids [(**5**) and (**6**)] from phthalic anhydride and 3-methylpyrrolylmagnesium bromide gave a ratio for (**9**):(**10**) of only 1.9:1. Though this quantitative analysis was not available in the earlier work,[1] where the mixture was prepared by the old method of heating 3-methylpyrrole and phthalic anhydride in acetic acid under pressure, the relative amounts obtained by crystallization indicated a definite but not large preponderance of (**9**). This suggests that in the old synthesis the first step is *C*-acylation, not *N*-acylation, of the pyrrole.

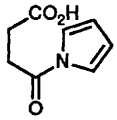
The new synthesis was applied to prepare a pyrroloisoquinolinedione (**15**) from tetrachlorophthalic anhydride and pyrrole by way of the acid (**14**); the Grignard method failed in this case and it is generally inferior to the new method in respect of yield and convenience.



(**16**)



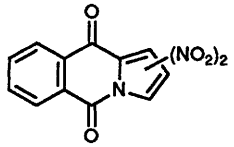
(**17**)



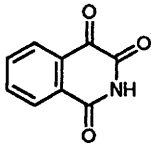
(**18**)

It was of interest to test whether maleic anhydride could be substituted for phthalic anhydride in these syntheses, although the one precedent[10] was not encouraging: maleic acid adds to pyrrole by way of its double bond. In the event, we were unable to obtain acids corresponding to (**3**) or (**12**) by combination of maleic anhydride with either pyrrolylmagnesium bromide or sodiopyrrole. With dimethylmaleic anhydride, where the double bond is less electrophilic and more hindered, the Grignard method gave easily the acid (**16**) which cyclized in boiling aqueous sodium acetate to the yellow, steam-volatile indolizinedione (**17**). This appears to be the first member of the class of indolizine-5,8-diones. Reaction of sodio pyrrole with succinic anhydride gave the expected product (**18**), but it was not found to be possible to cyclize this to indolizine-5,8-diol or to a tautomer thereof.

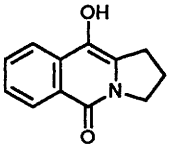
Until now, the easy ring-opening by aqueous alkali to form acids of type (**3**) was the only recorded reaction of pyrroloisoquinolinediones. The coupling with diazonium salts reported by Italian workers[3–5] was always preceded by this alkaline hydrolysis and has no relevance to the parent ring system, which we found not to react with diazotized 4-nitroaniline. In agreement with an earlier observation[2] we found no reaction of (**1**) with hydroxylamine under any of the conditions tried. The Vilsmeier–Haack reaction (phosphoryl chloride–dimethylformamide) also failed with (**1**), another indication of lack of nucleophilic reactivity in the pyrrole ring.



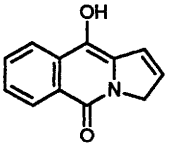
(**19**)



(**20**)

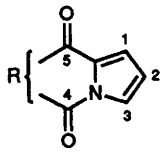


(**21**)



(**22**)

**Table.** $^1H$ and $^{13}C$ NMR [a] assignments for structures of the heterocyclic compounds.



| Position No. | (1) R = $C_6H_4$ — | (9) R = $C_6H_4$ 1-Me | (10) R = $C_6H_4$ 2-Me | (8) R = $C_6H_4$ 3-Me | (11) R = $C_6H_4$ 1,3-$Me_2$ | (17) R = $Me_2C_2$ — |
|---|---|---|---|---|---|---|
| 1 | 7.36 | — | 7.12 | 7.36 | — | 7.00 |
| | *120.80* | *137.45* | *121.21* | *120.30* | *137.02* | *119.87* |
| 2 | 6.55 | 6.34 | — | 6.28 | 6.08 | 6.38 |
| | *114.97* | *117.73* | *129.57* | *115.05* | *118.28* | 113.85 |
| 3 | 7.80 | 7.66 | 7.48 | — | — | 7.45 |
| | *123.46* | *122.43* | *122.37* | *139.89* | *138.85* | *122.94* |
| 4 | — | — | — | — | — | — |
| | *158.30* | *151.90* | *157.83* | *159.91* | *159.91* | *159.04* |
| 5 | — | — | — | — | — | — |
| | *173.33* | *170.00* | *173.15* | *172.60* | *173.46* | *174.83* |

[a] Solvent: $CDCl_3$. All chemical shifts are in ppm downfield from tetramethylsilane. $^{13}C$ shifts in *italics*.



The dione (**1**) dissolved without alteration in concentrated sulphuric acid, and addition of potassium nitrate in sulphuric acid to the cold solution gave a mixture from which two products were isolated. The first was a dinitro derivative of (**1**); we cannot with certainty assign the positions of the nitro groups but the NMR spectrum showed that both of them are in the pyrrole ring [as (**19**)]. The other product was identified as Gabriel and Colman's[11] 'phthalonimid' (**20**), isoquinoline-1,3,4-trione, from oxidative destruction of the pyrrole ring.

When heated with sodium borohydride in 1,4-dioxane the dione (**1**) was not reduced but hydrolysed to the acid (**3**), which also resisted reduction. Catalytic hydrogenation of the dione over palladium led to the smooth reduction of the pyrrole ring, the stable tetrahydro derivative (**21**) being formed. The dione (**1**) was also reduced by zinc in cold acetic acid. The product, the 3,5-dihydro compound (**22**) as identified by its spectra, was unstable in air, reverting in a few days to the dione (**1**).

The $^1H$ and $^{13}C$ NMR spectra of the diones (**1**) and (**17**) were interpreted, with respect to positions on and near the pyrrole ring, by reference to the corresponding spectra of the methyl derivatives [(**8**), (**9**), and (**10**)]. The relevant data are collected in the Table.

## Experimental

For general experimental directions see the preceding paper.[12]

*General Preparation of* 2-(*Pyrrol-2-ylcarbonyl*)*benzoic Acids*.—Powdered phthalic anhydride was stirred in dry ether (10 ml $g^{-1}$). The pyrrole (1 molar equiv.) was added, followed by ethereal ethylmagnesium bromide (2 molar equiv.; *ca.* 1.2M). The first half of the reagent was added during 15 min and the second half during 25 min; finally, the stirred mixture was heated under reflux for a further 30 min. The solid was collected and its solution in ice–water was filtered, washed twice with ether, acidified with dilute sulphuric acid, and extracted four times with ether. Evaporation of the dried ($MgSO_4$) ether left the crude acids as solids. These were used directly to prepare the diones (see below). They could be recrystallized wastefully to purity, but it was better to boil the pure diones with aqueous potassium hydroxide (*ca.* 1.5M, 40 ml $g^{-1}$, 3 h) and acidify the cooled solutions, when the white precipitates could be recrystallized easily.

2-(*Pyrrol-2-ylcarbonyl*)*benzoic Acid* (**3**).—From pyrrole (0.67 g, 10 mmol) the crude acid (1.4 g) was obtained as above. The pure acid, from the dione, crystallized from acetone–hexanes; m.p. 183–186 °C (decomp.) [lit.,[2] m.p. 174–184 °C (decomp.)] (Found: C, 66.7; H, 4.2; N, 6.5. Calc. for $C_{12}H_9NO_3$: C, 67.0; H, 4.2; N, 6.5%); $\delta_H$(90 MHz, [$^2H_6$]acetone) 7.4–8.0 (4 H, m), 7.20 (1 H, m, pyrrole 5-H), 6.38 (1 H, m, pyrrole 3-H), and 6.28 (1 H, m, pyrrole 4-H).

2-(3,5-*Dimethylpyrrol*-2-*ylcarbonyl*)*benzoic Acid*.—From 2,4-dimethylpyrrole (2.4 g, 25 mmol), as in the general procedure, the crude acid (4.3 g) was obtained. The pure acid (**2**), from the dione, crystallized from acetone–hexanes and had m.p. 190–192 °C (decomp.) [lit.,[1] m.p. 195–196.5 °C (decomp.)] (Found: C, 68.9; H, 5.5; N, 5.7. Calc. for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.4; N, 5.8%); $\delta_H$(90 MHz, [$^2H_6$]acetone) 7.38–8.0 (4 H, m), and 5.78 (1 H, s, pyrrole 4-H).

2-(5-*Methylpyrrol*-2-*ylcarbonyl*)*benzoic Acid* (**4**).—From 2-methylpyrrole (1.2 g, 16 mmol) as above the crude acid (2.4 g) was obtained. The pure *acid* (**4**), from the dione, crystallized from acetone–hexanes; m.p. 185–188 °C (decomp.) (Found: C, 68.0; H, 4.8; N, 6.0. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%); $\delta_H$(90 MHz, [$^2H_6$]acetone) 7.4–8.0 (4 H, m), 6.24 (1 H, d, *J* 3.6 Hz, pyrrole 3-H), and 5.90 (1 H, d, *J* 3.6 Hz, pyrrole 4-H).

*Mixture of* 2-(3-*Methylpyrrol*-2-*ylcarbonyl*)*benzoic Acid* (**5**) *and* 2-(4-*Methylpyrrol*-2-*ylcarbonyl*)*benzoic Acid* (**6**).—From 3-methylpyrrole[12] (2.13 g, 26.2 mmol) the crude mixed acids (3.51 g) were obtained as usual.

*Pyrroloisoquinolinediones from* 2-(*Pyrrol*-2-*ylcarbonyl*)-*benzoic Acids*.—The crude keto acids obtained above were dissolved in aqueous sodium acetate (10–20 ml $g^{-1}$, 5–15%) and the solutions were heated under reflux for 1–2 h. The crystalline solids were collected after cooling and recrystallized.

From the crude acid [(**3**); 1.4 g], pyrrolo[1,2-*b*]isoquinoline-5,10-dione [(**1**); 0.75 g] was obtained and was recrystallized from chloroform–methanol; m.p. 240–242 °C (lit.,[2] m.p. 240–241 °C) (Found: C, 72.8; H, 3.8; N, 6.9. Calc. for $C_{12}H_7NO_2$: C, 73.1; H, 3.6; N, 7.1%); $\delta_H$(90 MHz, $CDCl_3$) 8.36 (2 H, m, 6-, 9-H), 7.88 (2 H, m, 7-, 8-H), 7.80 (1 H, m, 3-H), 7.36 (1 H, m, 1-H), and 6.55 (1 H, t, *J* 3.6 Hz, 2-H). 1,3-Dimethylpyrrolo-[1,2-*b*]isoquinoline-5,10-dione [(**11**); 60 mg] was obtained from

the crude acid [(**2**); 0.1 g] and was recrystallized from ethanol; m.p. 186–188 °C (lit.,[1] m.p. 181–183 °C); $\delta_H$(90 MHz, $CDCl_3$) 8.26 (2 H, m, 6-, 9-H), 7.76 (2 H, m, 7-, 8-H), 6.08 (1 H s, 2-H), 2.72 (3 H, s, 3-$CH_3$), and 2.55 (3 H, s, 1-$CH_3$). The crude acid (**4**) gave 3-methylpyrrolo[1,2-*b*]isoquinoline-5,10-dione (**8**) which was recrystallized from hexanes; m.p. 172–174 °C (lit.,[1] m.p. 173–174 °C) (Found: C, 74.1; H, 4.4; N, 6.4. Calc. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3; N, 6.6%); $\delta_H$(90 MHz, $CDCl_3$) 8.36 (2 H, m, 6-, 9-H), 7.84 (2 H, m, 7-, 8-H), 7.36 (1 H, d, 1-H), 6.28 (1 H, d, 2-H), and 2.76 (3 H, s, 3-$CH_3$).

The crude mixture of acids [(**5**) and (**6**); 3.51 g] gave a crystalline mixture (2.36 g) which was separated by chromatography on neutral alumina (hexanes–ethyl acetate 9:1, or toluene). Separation was not total but enriched fractions could be crystallized to purity. From the first eluates, 1-methylpyrrolo[1,2-*b*]isoquinoline-5,10-dione (**9**) separated as needles from methanol; m.p. 176.5–178 °C (lit.,[1] m.p. 169–170 °C) Found: C, 73.7; H, 4.5; N, 6.3. Calc. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3; N, 6.6%); $\delta_H$(90 MHz, $CDCl_3$) 8.30 (2 H, m, 6-, 9-H), 7.76 (2 H, m, 7-, 8-H), 7.66 (1 H, d, *J* 3.6 Hz, 3-H), 6.34 (1 H, d, *J* 3.6 Hz, 2-H), and 2.59 (3 H, s, 1-$CH_3$). Later fractions on recrystallization from ethanol gave 2-methylpyrrolo[1,2-*b*]isoquinoline-5,10-dione (**10**); m.p. 233–234 °C (lit.,[1] m.p. 223 °C) (Found: C, 73.9; H, 4.3; N, 6.6. Calc. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3; N, 6.6%); $\delta_H$(90 MHz, $CDCl_3$) 8.24 (2 H, m, 6-, 9-H), 7.72 (2 H, m, 7-, 8-H), 7.48 (1 H, d, *J* 1.8 Hz, 3-H), 7.12 (1 H, d, *J* 1.8 Hz, 1-H), and 2.19 (3 H, s, 2-$CH_3$).

2-(*Pyrrol*-1-*ylcarbonyl*)*benzoic Acid* (**12**).—(i) Potassium (1 g) was stirred and heated under reflux in toluene (25 ml) during addition of a mixture of pyrrole (1.9 g) and ethanol (0.3 ml). When the metal had dissolved, the ethanol was distilled out and phthalic anhydride (3.7 g) was added to the cooled stirred suspension, which was then heated at reflux for 2 h. The solid potassium salt was collected, dried (5.2 g), and added to ice-cold hydrochloric acid (16 ml of 2M). The crystalline *acid* (**12**) was collected (4.7 g) and recrystallized from ethyl acetate–hexanes (35:65); m.p. 165–166 °C (Found: C, 66.7; H, 4.5; N, 6.4. $C_{12}H_9NO_3$ requires C, 67.0; H, 4.2; N, 6.5%); $\delta_H$(90 MHz, [$^2H_6$]acetone) 7.5–7.8 (2 H, m, benzene 3-, 6-H), 7.12 (2 H, m, benzene 4-, 5-H), 7.04 (2 H, m, pyrrole 2-, 5-H, and 6.28 (2 H, m, pyrrole 3-, 4-H).

(ii) A mixture of sodium hydride (60% in mineral oil; 2.1 g), pyrrole (3.35 g), and phthalic anhydride (7.45 g) in toluene (120 ml) was stirred and heated at reflux under nitrogen until evolution of hydrogen ceased (2.5 h), after which it was cooled, poured on ice–water, and shaken. The toluene layer was washed well with more water and the aqueous extracts promptly cooled and acidified to pH <3 (2M HCl). The crystalline acid (**12**) was collected (9.13 g, 84%). It was suitable for cyclization (see below).

*Cyclizations of the Acid* (**12**).—(i) The acid (0.5 g), acetic anhydride (2.5 ml), 1,2-dichlorobenzene (3 ml), and pyridine (2 drops) were heated at reflux under nitrogen for 10 min. Acetic acid and anhydride were then distilled out and the remainder was heated at reflux for 45 min. The yellow crystalline solid was collected after cooling and washed with methanol. The yield of the dione (**1**) was 0.39 g (85%). (ii) The acid (0.5 g), propionic anhydride (6 ml), and pyridine (3 drops) was heated under nitrogen at reflux for 2 h, and then distilled. The residue was collected by means of methanol and consisted of the dione (**1**) (0.39 g). (iii) To the acid (0.16 g) in pyridine (2 ml), phosphoryl chloride (0.2 ml) was added. The mixture was stirred for 2 h. Water was added and the mixture was worked up to isolate neutral ether-soluble material. Evaporation of the ether left the dione (**1**) as yellow needles (0.14 g, 98%).

1-*Methyl- and* 2-*Methyl-pyrrolo*[1,2-b]*isoquinoline*-5,10-*diones*.—A mixture of sodium hydride (60% in mineral oil; 0.42 g), 3-methylpyrrole (0.81 g), phthalic anhydride (1.48 g), and toluene (5 ml) was stirred and heated under nitrogen at 85–95 °C for 45 min and then at reflux for 2 h. Acetic anhydride (3 ml) was added and heating at reflux was continued for 3 h. Acetic anhydride was destroyed by addition of water and the toluene layer, after being washed with water and aqueous sodium hydrogen carbonate, was concentrated and put through a short column of alumina. Elution with toluene gave a crystalline mixture (1.22 g, 58%) of the diones (**9**) (6.7 parts) and (**10**) (1 part). These were separated as described above.

*Tetrachloro*-2-(*pyrrol*-1-*ylcarbonyl*)*benzoic Acid*.—A mixture of sodium hydride (0.42 g of 60% in mineral oil), pyrrole (0.67 g), toluene (10 ml), and tetrachlorophthalic anhydride (2.76 g) was stirred at 80 °C under nitrogen for 1.5 h. The solid was collected and washed with hexanes. The salt (3.52 g) was added to hydrochloric acid (21 ml of 2M) and the crude *acid* [(**14**); 3.1 g] was collected and recrystallized from dichloromethane; m.p. 165–168 °C (Found: C, 40.5; H, 1.7; N, 3.7. $C_{12}H_5Cl_4NO_3$ requires C, 40.8; H, 1.4; N, 4.0%); $\nu_{max}$ 3 439 and 1 699 $cm^{-1}$; $\delta_H$(60 MHz; $CDCl_3$ + $(CD_3)_2SO$) 7.35 (2 H, m, pyrrole 2-, 5-H) and 6.43 (2 H, m, pyrrole 3-, 4-H).

6,7,8,9-*Tetrachloropyrrolo*[1,2-b]*isoquinoline*-5,10-*dione*.—(i) The crude acid (**14**) (0.5 g) and acetic anhydride (2 ml) were heated at reflux under nitrogen for 20 min. Water was added to destroy the excess of anhydride and the product (0.1 g) was collected when cold. The *dione* (**15**) crystallized from cyclohexane; m.p. 162.5–164 °C (Found: C, 42.8; H, 1.1; N, 4.0. $C_{12}H_3Cl_4NO_2$ requires C, 43.0; H, 0.9; N, 4.2%); $\delta_H$(80 MHz) 7.72 (1 H, m, 3-H), 7.26 (1 H, m, 1-H), and 6.54 (t, *J* 3.6 Hz, 2-H); $\lambda_{max}$($CHCl_3$) 256, 282, and 359 nm. (ii) A mixture of the crude acid (**14**) (0.5 g), pyridine (5 ml), and phosphoryl chloride (0.5 ml) was stirred for 8 h and kept for 3 days. The crude ether-soluble neutral product was put on silica and eluted with ether to yield the dione (**15**) (0.15 g).

6,7-*Dimethylindolizine*-5,8-*dione*.—A solution of pyrrole (1.34 g, 20 mmol) in ether (8 ml) was added to ethylmagnesium bromide [from magnesium and ethyl bromide (20 mmol each) in ether (14 ml)] and heated at reflux for 0.5 h. Dimethylmaleic anhydride (1.26 g, 10 mmol) was added and after the exothermic reaction the mixture was heated at reflux for 0.5 h. The solid was collected (5 g). The ether filtrate and washings yielded pyrrole (0.5 g) on evaporation. Part of the solid (1.5 g) was dissolved in cold water, acidified to pH 1 and extracted with ether (4 × 10 ml) to yield 0.62 g which was boiled under reflux with aqueous sodium acetate (0.6 g in 10 ml) for 15 min. Steam-distillation then gave a yellow distillate (*ca.* 100 ml) which was extracted with ether (4 × 20 ml). The dried ($MgSO_4$) extract yielded yellow crystals (0.39 g) of the *indolizinedione* (**17**); m.p. 96–98 °C after recrystallization from hexanes (Found: C, 68.6; H, 5.2; N, 8.0. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.2; N, 8.0%); $\lambda_{max}$(MeOH) 269, 315, and 385 nm (ε: 12 850, 3 500, and 1 680); $\delta_H$(60 MHz, $CDCl_3$) 7.45 (1 H, m, 3-H), 7.00 (1 H, m, 1-H), 6.38 (1 H, m, 2-H), 2.13 (3 H, s,), and 2.08 (3 H, s); *m/z* (CI) 176 (*M* + H).

4-*Oxo*-4-*pyrrol*-1-*ylbutanoic Acid*.—To a stirred suspension of potassium (0.78 g) in hot toluene (20 ml) under nitrogen, pyrrole (1.34 g) and ethanol (0.1 ml) were added. After 2 h at reflux the ethanol was distilled out and the white suspension was cooled in water during addition of succinic anhydride (2 g) in tetrahydrofuran (20 ml) over 10 min; the mixture was then stirred for 0.5 h and finally warmed at 96 °C for 3 h. The solid (3.73 g) collected by filtration and washed with hexanes was dissolved in ice-water and acidified (4M $H_2SO_4$) to pH 1. The

crystalline precipitate, together with a little more obtained by ether extraction of the filtrate and water washings, amounted to 2.72 g (81%). Recrystallization from dichloromethane gave the pure *acid* (**18**), m.p. 145–147.5 °C (Found: C, 57.3; H, 5.5; N, 8.4. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4%); $\delta_H$[60 MHz; $CDCl_3$ + $(CD_3)_2SO$] 7.35 (2 H, m, pyrrole 2-, 5-H), 6.30 (2 H, m, pyrrole 3-, 4-H), 3.13 (2 H, q, *J* 7.2 Hz, 3-$H_2$), and 2.78 (2 H, q, *J* 7.2 Hz, 2-$H_2$); *m/z* (CI) 168 ($M$ + H).

*Nitration of Pyrrolo*[1,2-b]*isoquinoline*-5,10-*dione*.—The yellow solution of the dione (**1**) (1.8 g) in sulphuric acid (*d* 1.84; 6 ml) was cooled in ice and stirred during dropwise addition of a cold solution of potassium nitrate (2.7 g) in sulphuric acid (*d* 1.84; 6 ml). After a further 20 min, the mixture was poured on ice (*ca.* 70 g) and stirred. Nitrous fumes were noticed. The yellow solid (0.95 g) was collected and washed well with water. Recrystallizations from chloroform gave the pure *dinitro compound* (**19**), m.p. 217–220 °C (vac. capillary) (Found: C, 50.1; H, 1.7; N, 14.7. $C_{12}H_5N_3O_6$ requires C, 50.2; H, 1.8; N, 14.6%); $\delta_H$[360 MHz, $(CD_3)_2SO$] 8.354 [1 H, dd, *J* 7.9, 1.2 Hz, (6?) 9-H], 8.277 [1 H, dd, *J* 7.8, 1.3 Hz, (9?) 6-H], 8.087 [1 H, ddd, *J* 7.9, 7.5, 1.3 Hz, (7?) 8-H], 8.061 [1 H, ddd, *J* 7.8, 7.5, 1.2 Hz, (8?) 7-H] and, 7.83 (1 H, s, pyrrole H); *m/z* (EI) 287 ($M^+$).

The aqueous filtrate and washings were extracted with ether which was washed with a little aqueous sodium hydrogen carbonate and evaporated. The residue (0.16 g) was recrystallized from water to yield pale yellow pointed prisms, m.p. 225–227 °C (decomp.) [lit.,[11] m.p. 225 °C (decomp.)], of isoquinoline-1,3,4-trione (**20**); $\delta_H$[90 MHz, $(CD_3)_2SO$] 8.15 (2 H, m), and 7.90 (2 H, m); *m/z* (EI) 175 (11%, $M^+$), 147 (55, $M^+$ −CO), 132 (11, $M^+$ − HNCO), 104 (100, $M^+$ − CO–HNCO), and 76 (90, $M^+$ − 2CO–HNCO); $\nu_{max}$(paraffin) 1 746, 1 709, and 1 680 $cm^{-1}$.

10-*Hydroxy*-1,2,3,5-*tetrahydropyrrolo*[1,2-b]*isoquinolin*-5-*one* (**21**).—The dione (**1**) (0.2 g) in ethanol (50 ml) was stirred under hydrogen with palladium on carbon (10%; 100 mg). Absorption ceased after 30 min and the filtered solution was evaporated. The residue crystallized from water as colourless prisms of the *tetrahydro compound*, m.p. 178–181 °C (Found: C, 71.3; H, 5.3; N, 6.8. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); $\delta_H$[360 MHz, $(CD_3)_2SO$] 8.48 (1 H, s, 10-OH), 8.17 (1 H, d, 6-H), 7.85 (1 H, d, 9-H), 7.70 (1 H, dd, 8-H), 7.42 (1 H, dd, 7-H), 4.00 (2 H, t, 3-H), 3.10 (2 H, t, 1-H), and 2.17 (2 H, dt, 2-H); *m/z* (EI) 201 ($M^+$), 186, 172, 144, 133, 117, 105, and 76; $\nu_{max}$(KBr) 3 390 and 1 725 $cm^{-1}$. The substance dissolved on addition of sodium hydroxide to an aqueous methanolic suspension, and was reprecipitated by acid.

10-*Hydroxy*-3,5-*dihydropyrrolo*[1,2-b]*isoquinolin*-5-*one* (**22**).—The dione (**1**) (1 g) in dichloromethane (20 ml) was added during 10 min to a stirred, ice-cooled mixture of zinc powder (1 g) and acetic acid (5 ml of 90%) under nitrogen. After 2.5 h aqueous sodium hydrogen carbonate was added to neutralize acetic acid and the mixture was filtered. The filter cake was quickly washed with acetone (200 ml) which was then dried ($MgSO_4$) and evaporated at 30–40 °C. Extraction of the filtrate with dichloromethane gave a little more product. Recrystallization from toluene–ethanol under nitrogen gave cream-coloured needles of the *dihydro compound*, m.p. 182.5–185.5 °C (Found: C, 72.3; H, 4.6; N, 7.1. $C_{12}H_9NO_2$ requires C, 72.3; H, 4.6; N, 7.0%); $\delta_H$[360 MHz, $(CD_3)_2SO$] 9.14 (br s, 10-OH), 8.25 (1 H, d, 6-H), 7.95 (1 H, d, 9-H), 7.75 (1 H, dd, 7-H), 7.50 (1 H, dd, 8-H), 7.05 (1 H, dt, 1-H), 6.59 (1 H, dt, *J* 2.11, 1.97 Hz, 2-H), and 4.67 (2 H, app t, *J* 2.2 Hz, 3-H). A sample of the compound (100 mg) kept for 3 days in air turned yellow; recrystallization from chloroform then gave the dione (**1**) (60 mg), m.p. 240–244 °C, the IR spectrum being identical with that of (**1**).

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