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Central Nervous System Active Compounds. IX* Cinnolinylisobenzofuranones [1-(3-Phthalidyl)cinnolin-4(1*H*)-ones]

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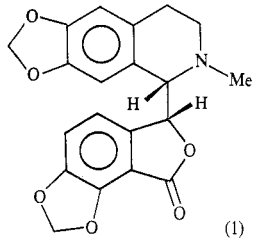
Abstract

The synthesis and central nervous system activity of a number of cinnolinylisobenzofuranones are described. The compounds are prepared in moderate yield by the reaction of the sodium salt of a cinnolin-4-one with the appropriate 3-bromophthalide. ^{1}H, ^{13}C n.m.r., and infrared spectral evidence for the structure of the compounds is presented. The compounds cause a loss of muscular control in mice.

Introduction

In recent papers in this series we have been concerned with reporting the synthesis of a variety of analogues of the convulsant alkaloid bicuculline[1] (1), in the hope of finding compounds that might be useful in the treatment of epilepsy. Thus we have described the synthesis of aminobenzylphthalides[2] (2), phthalidylisoquinolines[3] (3), and new syntheses of phthalide isoquinoline alkaloids.[1,2] Current work is directed towards the synthesis of nitrogen- and boron-containing analogues. In this paper we describe the synthesis of a number of phthalidylcinnolinones† (4), and a preliminary account of their central nervous system activity.



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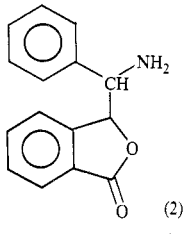

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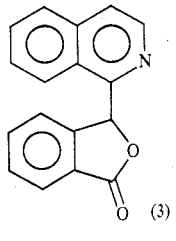

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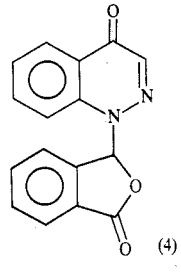

(4)

* Part VIII, *Aust. J. Chem.*, 1981, **34**, 1085.

† We refer to the compounds by this term in the Discussion to emphasize their relationship to the 'phthalide isoquinolines'. In the Experimental we refer to them correctly as dihydroisobenzofuranylcinnolinones.

[1] Prager, R. H., Tippett, J. M., and Ward, A. D., *Aust. J. Chem.*, 1981, **34**, 1085.
[2] Hutchison, G. I., Marshall, P. A., Prager, R. H., Tippett, J. M., and Ward, A. D., *Aust. J. Chem.*, 1980, **33**, 2699.
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It is felt that the most versatile method for constructing a number of molecules of type (4) would be the N1 alkylation of cinnolin-4(1*H*)-one (5) with a 3-bromophthalide (Scheme 1). The cinnolinones are readily prepared by the Borsche synthesis,[4] which involves diazotization of 2-aminoacetophenones, followed by thermal cyclization. The site of alkylation of cinnolin-4-ones depends on the alkylating agent, but Ames[5,6] has reported that methylation occurs mainly on N2, with lesser amounts at N1. In the course of the present work we have found that the use of methyl iodide in acetone in the presence of potassium carbonate leads to the 1-methyl derivative as the major product. *O*-Alkylation is relatively rare, but has been reported by Wagner and Heller[7] when the alkylating agent was 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in alkaline aqueous acetone. This alkylating agent, and the conditions used, most closely resemble the conditions used in the present work, in which we also suggest prior *O*-alkylation, followed by rearrangement to the *N*-alkyl product.

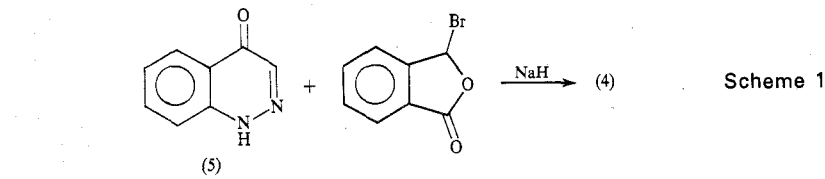
Discussion

Despite the successful condensation of amines with 2-formylbenzoic acid,[8] the reaction of cinnolin-4-ones with 2-formylbenzoic acid failed to give any condensation products. Reaction of 6,7-dimethoxycinnolin-4(1*H*)-one with sodium hydride, followed by addition of 3-bromophthalide, gave a compound with the desired molecular formula, but it was not immediately obvious whether the product was the N^1-, *O*- or N^2-alkylated material (6), (7) or (8).

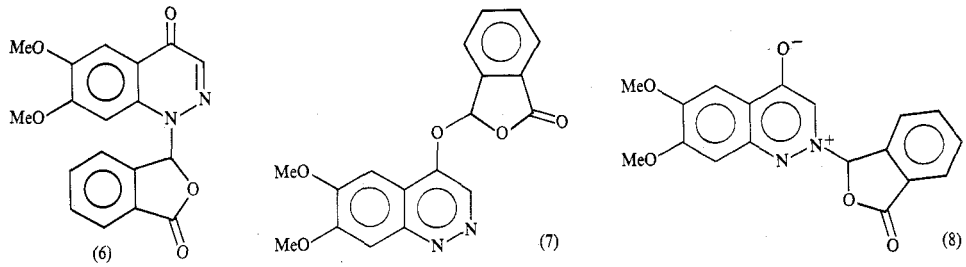
Examination of the literature revealed that the assignment of structure to alkylated cinnolinones was based mainly on the use of ultraviolet or ^{1}H n.m.r. spectroscopy (results are summarized by Singerman[9]). The *O*- and *N*-alkylated materials described below had essentially the same ultraviolet absorption spectra, hence we examined the n.m.r. spectra of the product and a series of model compounds. The compounds (9)–(16) were prepared by literature methods and their structures have been unambiguously assigned[6,10] by a variety of techniques, but mainly by using spectroscopic data. An examination of the n.m.r. data, collected in Table 1, shows that the *O*-alkylated structure (7) can be ruled out for our product since the model compound (12) clearly shows H8 to resonate at δ 7·29, whereas the product (6) has no aromatic resonances at higher field than 7·6. Similarly, the anhydro base structure (8) is ruled out, as the signal for H8 should be similar to that in (14), namely at 7·07. An examination of molecular models shows that H8 in the desired structure (6) would be considerably deshielded by the lactone group, and offers an explanation for its shift from 6·7 in the model compound (10) to 8·5 in (6). This type of deshielding is also noted in the N^1-acetyl derivatives (15) and (16).

By the same procedure, the phthalidylcinnolinones (4) and (17)–(27) were obtained and were generally isolated in around 50% yield after chromatography. Allowing for

[4] Borsche, W., and Herbert, A., *Justus Liebigs Ann. Chem.*, 1941, **546**, 293.
[5] Ames, D. E., *J. Chem. Soc.*, 1964, 1763.
[6] Ames, D. E., Ausari, H. R., France, A. D. G., Lovesy, A. C., Novitt, B., and Simpson, R., *J. Chem. Soc. C*, 1971, 3088.
[7] Wagner, G., and Heller, D., *Z. Chem.*, 1964, **4**, 386.
[8] Wheeler, D. D., Young, D. C., and Erley, D. C., *J. Org. Chem.*, 1957, **22**, 1547.
[9] Singerman, G. M., in 'Heterocyclic Compounds' (Ed. R. N. Castle) Vol. 27, p. 92 (Interscience: New York 1973).
[10] Bruce, J. M., Knowles, P., and Besford, L. S., *J. Chem. Soc.*, 1964, 4044.



Scheme 1



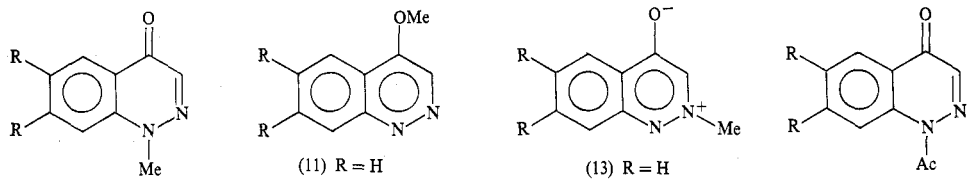


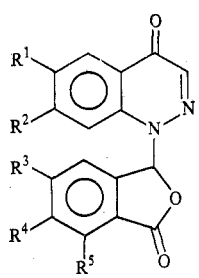
Table 1. ^{1}H n.m.r. and infrared spectral data for standard cinnoline derivatives

Compound	^{1}H chemical shifts H3	H5	H8	Infrared (cm^{-1})	Compound	^{1}H chemical shifts H3	H5	H8	Infrared (cm^{-1})
(9)	7·77	8·34	7·40	1625 1608	(14)[B]	7·84	7·61	7·07	[A]
(10)	7·77	7·61	6·70	1620 1585	(15)[C]	7·84	8·16	8·91	1660 1605
(11)	9·10	7·60	[A]	1575	(16)[C]	7·89	8·16	8·51	1670 1615
(12)	8·85	7·68	7·29	1555	(6)	7·65	7·58	8·50	1625 1610
(13)[B]	8·01	8·39	7·52	1610					

[A] Not determined.

[B] Ames, D. E., Ausari, H. R., France, A. D. G., Novitt, B., and Simpson, R., *J. Chem. Soc. C*, 1971, 3088.

[C] Bruce, J. M., Knowles, P., and Besford, L. S., *J. Chem. Soc.*, 1964, 4044.



	R^1	R^2	R^3	R^4	R^5
(4)	H	H	H	H	H
(17)	H	H	H	OMe	H
(18)	H	H	H	OMe	OMe
(25)	H	H	OMe	OMe	H
(6)	OMe	OMe	H	H	H
(19)	OMe	OMe	H	OMe	H
(20)	OMe	OMe	H	OMe	OMe

	R^1	R^2	R^3	R^4	R^5
(27)	OMe	OMe	H	OCH_2O	
(21)	OCH_2O		H	H	H
(22)	OCH_2O		H	OMe	H
(23)	OCH_2O		H	OMe	OMe
(24)	OCH_2O		H	OCH_2O	
(26)	OCH_2O		OMe	OMe	H

starting material recovered, there was always about 30% material unaccounted for, and we suggest that this represents the yield of the anhydro base [structure as in (8)], which would be retained on the silica chromatography column used in this work.

The use of infrared spectroscopy appears, in hindsight, to be a satisfactory analytical tool, but at the outset of this study very little information was available for the cinnolines. The only relevant work was that of Mason[11] and Castle,[12] who had examined a few cinnolin-4-ones. We find that 1-alkylcinnolin-4(1*H*)-ones have absorptions around 1625 and 1610 cm^{-1}, whereas the *O*-alkyl derivatives absorb only around 1565 cm^{-1}. The anhydro bases, such as (13), have weaker absorptions in the region of 1610 cm^{-1}, but are generally pale yellow. With the series of compounds above in hand, it was found that, besides the ^1H n.m.r. and infrared spectra, the most diagnostic spectroscopic method, which further confirmed the validity of the previous assignments, was the ^{13}C n.m.r. spectrum. The chemical shifts of the products and reference compounds are listed in an Accessory Publication* and show that the single most diagnostic feature in the spectra of the phthalidylcinnolinones is the two resonances for carbonyl carbons, which is a feature unique to the N^1-alkylated structures. The suggested assignments of these chemical shifts are shown in Fig. 1, and are based on comparison with assigned spectra for pyridone, *N*-methylpyridone,[13,14] phthalide, dialkoxyphthalide,[15] and the reference compounds mentioned previously. Apart from the two carbonyl resonances already mentioned one other feature of the spectra served as a diagnostic tool. All the phthalidylcinnolinones had a signal between 87·4 and 88·2 ppm, ascribable to C 3′ (phthalide). This is the same as the corresponding signal of (28). The anhydro base structure would be expected[14] to have the corresponding signal at least 5 ppm further downfield. Similarly, the *O*-alkylated structures would result in C 3′ being about 10 ppm further downfield (the difference between an *N*-methyl and *O*-methyl resonance).[14]

When the reaction time for the preparation of these *N*-alkylated compounds (4), (6) and (17)–(27) was shortened considerably, a second product was often formed as indicated by t.l.c. Spectral data obtained on the reaction mixtures indicated that this second product had absorption at *c.* 1800 cm^{-1}, a low-field proton signal (*c.* δ 8·4), ^{13}C absorptions at *c.* 93 ppm, and only a single carbonyl absorption at *c.* 168 ppm. All these data are compatible with the *O*-alkylated structure, e.g. (7). Attempts to purify these *O*-alkylated materials were generally frustrated by their tendency to rearrange to the *N*-alkylated material; however, in one case (29) a pure sample was obtained. Such $O \rightarrow N$ alkyl migrations are rare in the cinnoline series.[7,16]

Two independent syntheses of the alkylated cinnolinones were attempted. The first (Scheme 2) failed when the nitroso compound (31) could not be induced to cyclize, and under the reaction conditions first hydrolysed and then cyclized to yield cinnolin-4-one. In view of the facile substitution by nucleophiles of halide in 4-chloro-

* Copies are available on application to the Editor-in-Chief, Editorial and Publications Service, CSIRO, 314 Albert Street, East Melbourne, Vic. 3002.

[11] Mason, S. F., *J. Chem. Soc.*, 1957, 4874.
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[14] Voegeli, U., and Von Philipsborn, W., *Org. Magn. Reson.*, 1973, **5**, 551.
[15] Hughes, D. W., Holland, H. L., and MacLean, D. B., *Can. J. Chem.*, 1976, **54**, 2252.
[16] Lowrie, H. S., *J. Med. Chem.*, 1966, **9**, 784.

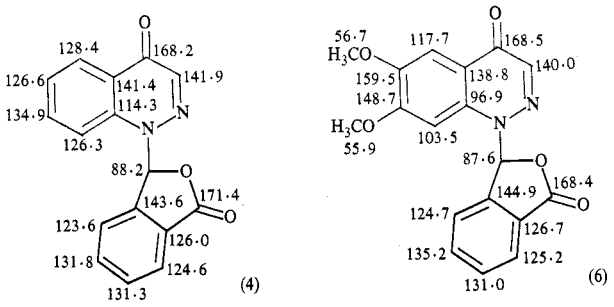
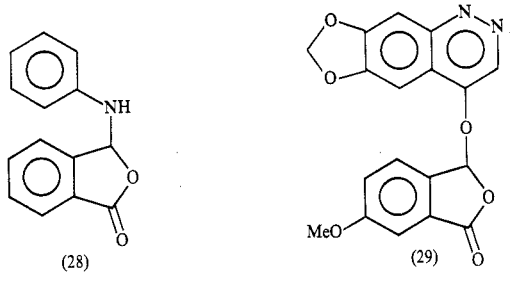
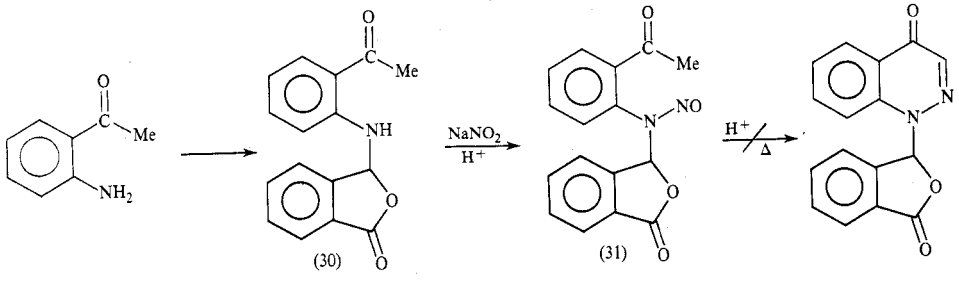
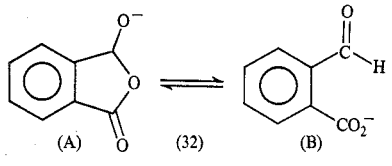


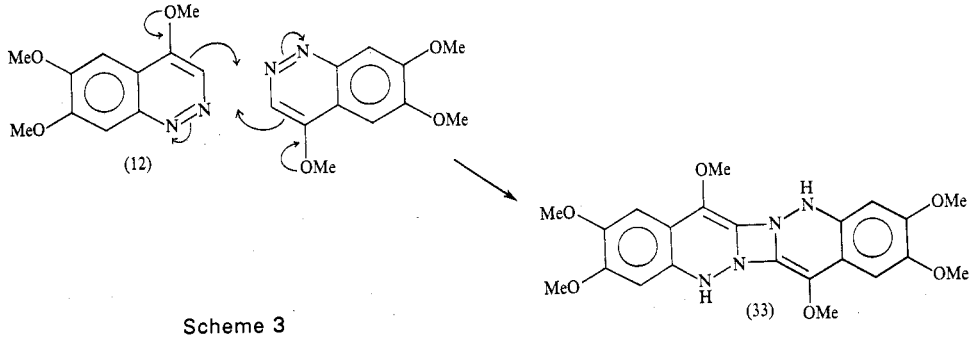
Fig. 1. Assignments of ^{13}C chemical shifts for compounds (4) and (6).





Scheme 2

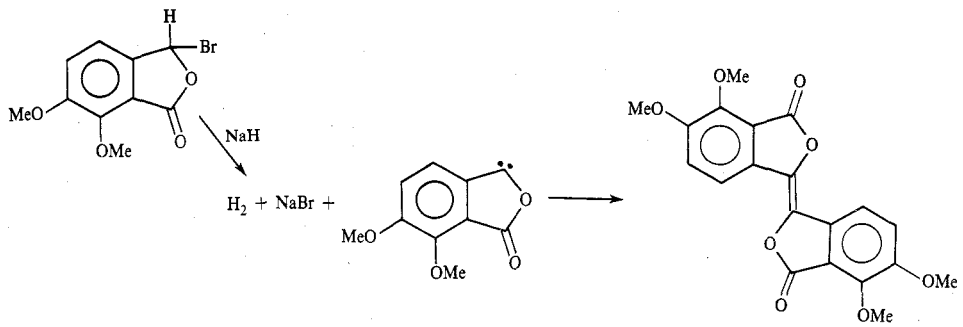




Scheme 3

cinnolines,[9,17,18] it was hoped that the anion (32) of 2-formylbenzoic acid might prove more nucleophilic in form (A) than form (B), and thus lead to the *O*-alkylated material (7), but no reaction could be induced to occur.

Two chemically interesting observations, not related to the main thrust of this communication, deserve mention. When the model compound (12) was initially prepared, its ^{1}H n.m.r. spectrum was identical with that reported in the literature.[10] After standing in diffuse light, the material was quantitatively altered to a less soluble product, the n.m.r. spectrum of which is consistent with it being the dimer (33) (Scheme 3). A sample of (11) was photolabile when irradiated by sunlight in chloroform solution, but inert in methanol. Demethylation, possibly caused by hydrogen chloride, was also observed.



Scheme 4 (34)

Secondly, in several instances where excess of sodium hydride was used to generate the cinnolinone anion, and was therefore still present when the bromophthalide was added, a bright yellow solid could be isolated as a by-product. For instance, in the preparation of (18), the biphthalide (34)[19] could be characterized. This is presumably formed by dimerization of a carbene intermediate (Scheme 4). Such structures have been postulated as possible intermediates in the synthesis of biphthalide from phthalic anhydride and trimethyl phosphite.[20]

Table 2. Biological activity of phthalidylcinnolinones: approximate doses to cause loss of muscle control

Compound	(4)	(17)	(18)	(6)	(19)[A]	(20)	(21)[A]	(22)	(24)	(23)	(25)	(26)
ED (mg/kg)	90	200	100	90	40	80[B]	40	40	45	35	50[B]	60

[A] A short convulsion was initially observed. [B] Fatal dose 100 mg/kg.

Biological Activity

The phthalidylcinnolinones all caused muscular depression when injected intraperitoneally into mice. The structure–activity relationship (Table 2) is similar to that of the phthalide isoquinoline alkaloids, which are all, however, convulsants.[21] This suggests that the compounds may indeed be GABA agonists, and, in preliminary work,[22]

[17] Castle, R. N., and Onda, M., *J. Org. Chem.*, 1961, **26**, 2374.
[18] Albert, A., and Barlin, G. B., *J. Chem. Soc.*, 1962, 3129.
[19] Marshall, P., Mooney, B., Prager, R., and Ward, A. D., *Synthesis*, 1981, 197.
[20] Ramirez, F., Yamanaka, H., and Basedow, O. H., *J. Am. Chem. Soc.*, 1961, **83**, 173.
[21] Curtis, D. R., Duggan, A. W., Felix, D., and Johnston, G. A. R., *Brain Res.*, 1971, **32**, 69.
[22] Johnston, G. A. R., personal communication.

there is some evidence that the cinnolinones do indeed competitively inhibit the binding of GABA to its post-synaptic receptor site. The results, however, are erratic due to the very low water solubility of all products tested.

Experimental

Experimental details have been given in previous papers in this series. ^{13}C n.m.r. spectra were recorded on a Bruker WP80DS spectrometer in CD_3SOCD_3.

Cinnolin-4(1H)-one

To a stirred solution of 2-aminoacetophenone (2 g, 14·8 mmol) in concentrated hydrochloric acid (75 ml) and water (12 ml) was added sodium nitrite (1·2 g, 17·4 mmol) in water (3 ml) over a period of 45 min, the temperature being maintained between −5 and −10° during addition. The reaction mixture was stirred at 0° for 1 h, and then at 80° for 48 h. The mixture was concentrated to *c.* 20 ml, cooled, and the precipitate dissolved in 10% sodium hydroxide and reprecipitated with concentrated hydrochloric acid to yield cinnolin-4(1*H*)-one (0·75 g, 35%), m.p. 233–234° (lit.[23] 236–237°).

6,7-Methylenedioxycinnolin-4(1H)-one

4,5-Methylenedioxy-2-nitroacetophenone was prepared in 80% yield, by the general method of Simpson[24] from 3,4-methylenedioxyacetophenone,[25] as pale yellow needles from ethanol, m.p. 117–120° (Found: C, 51·7; H, 3·4; N, 6·5. $C_9H_7NO_5$ requires C, 51·7; H, 3·4; N, 6·7%). ν_{max} 1710 cm^{-1}. N.m.r. δ 7·33, s, 1H, ArH; 6·60, s, 1H, ArH; 6·07, s, 2H, OCH_2O; 2·40, s, 3H, $COCH_3$. This compound was reduced quantitatively by the method of Simpson,[24] to 2-amino-4,5-methylenedioxyacetophenone which was isolated as a colourless oil characterized only from its n.m.r. spectrum. δ 6·95, s, 1H, ArH; 6·03, s, 1H, ArH; 5·77, s, 2H, OCH_2O; 5·00, br, 2H, NH_2; 2·40, s, 3H, $COCH_3$. The acetophenone was converted by the general method of Castle and Kruse[26] into *6,7-methylenedioxycinnolin-4(1H)-one* in 95% yield, fawn needles from acetic acid, m.p. 320° (dec.) (Found: C, 56·9; H, 3·4; N, 14·7. $C_9H_6N_2O_3$ requires C, 56·9; H, 3·2; N, 14·7%). ν_{max} 3200, 1620, 1600, 1550 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 7·65, s, 1H, ArH; 7·39, s, 1H, ArH; 7·05, s, 1H, ArH; 6·25, s, 2H.

Photolysis of 4-Methoxycinnoline

(i) 4-Methoxycinnoline[18] (10 mg) was dissolved in deuterochloroform (0·5 ml) and exposed to sunlight through Pyrex for 5 days, the progress of the photolysis being monitored by n.m.r. spectroscopy. The reaction was a complex one, being accompanied by demethylation, only 18% of the OMe resonance remaining after this period. The absence of any absorption around δ 9·1 showed that C3 had been substituted. N.m.r. δ 7·92–6·78, m.

(ii) Under the same conditions as above, but in methanol, there was no change after 5 days of irradiation.

Photolysis of 4,6,7-Trimethoxycinnoline

A solid sample of 4,6,7-trimethoxycinnoline,[27] m.p. 206–209° (lit.[27] 210°) (n.m.r. δ 8·85, s, 1H, H3; 7·68, s, H5; 7·29, s, H8; 4·10, 4·06, 2×s, 9H, OCH_3), was kept in diffuse, laboratory light for 2 weeks. The product was now considerably less soluble in chloroform, and had m.p. 143–145° (Found: C, 60·4; H, 5·3. $C_{22}H_{24}N_4O_6$ requires C, 60·0; H, 5·5%). ν_{max} 3300, 1590 cm^{-1}. N.m.r. δ 9·21, br, exch., 2H, NH; 7·81, s, 2H, ArH; 7·35, s, 2H, ArH; 4·20, 4·15, 4·10, 3×s, 6×OMe. The mass spectrum failed to show a peak for the molecular ion.

[23] Barber, H. J., Washbourn, K., Wragg, W. R., and Lunt, E., *J. Chem. Soc.*, 1961, 2828.
[24] Simpson, J. C. E., *J. Chem. Soc.*, 1946, 94.
[25] Mathur, K. B. L., Sharma, J. N., Venkataraman, K., Krishnamnoty, H. G., *J. Am. Chem. Soc.*, 1957, **79**, 3582.
[26] Castle, R. N., and Kruse, F. H., *J. Org. Chem.*, 1952, **17**, 1571.
[27] Ellis, A. W., and Lovesey, A. C., *J. Chem. Soc. B*, 1967, 1285.

1-Methylcinnolin-4(1H)-ones

(i) 6,7-Dimethoxycinnolin-4(1*H*)-one[26] (100 mg, 0·49 mmol), potassium carbonate (1·5 g), methyl iodide (0·5 ml) and acetone (30 ml) were stirred at 20° for 10 h. The mixture was poured into dichloromethane (50 ml), filtered and evaporated. The resulting oil (120 mg) was separated into its components by preparative t.l.c. (ethyl acetate) to yield 6,7-dimethoxy-1-methylcinnolin-4(1*H*)-one as colourless crystals (54 mg, 50%), m.p. 205–206° (lit.[6] 209–210°). The n.m.r. spectrum was identical with that published.[27] The n.m.r. spectrum of the crude product showed that methylation had occurred at N1 (66%) and at N2 (34%).

(ii) In the same way 1-methylcinnolin-4(1*H*)-one, m.p. 113–115° (lit.[28] 114–116°), was prepared in 38% yield.

Attempted Condensation of Cinnolin-4-ones with 2-Formylbenzoic Acid

No products other than starting materials could be isolated when 6,7-dimethoxycinnolin-4(1*H*)-one or 6-methyl-4-oxo-1,4-dihydrocinnoline-3-carboxylic acid[29] was refluxed with 2-formylbenzoic acid or its trifluoroacetate in the presence of *p*-toluenesulfonic acid or Triton B.

Preparation of 1-(3'-Oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-ones

A typical reaction procedure is described. Some of the compounds below were non-crystalline white powders and retained solvent tenaciously during attempted purifications. Accurate mass data only are provided in cases where analysis or n.m.r. data indicated strong retention of solvent.

(i) A mixture of 6,7-dimethoxycinnolin-4(1*H*)-one (300 mg, 1·45 mmol), sodium hydride (85 mg, 1·7 mmol) and dry tetrahydrofuran (160 ml) was stirred at 20° under nitrogen for 12 h. 3-Bromo-6-methoxyisobenzofuran-1(3*H*)-one (350 mg, 1·45 mmol) in dry tetrahydrofuran (30 ml) was added dropwise, and the reaction mixture stirred at 20° for 24 h, and then at reflux temperature for 24 h. The reaction mixture was filtered and the filtrate absorbed directly onto chromatographic silica. The material was chromatographed on silica. Elution with dichloromethane/ethyl acetate (1 : 1) gave *6,7-dimethoxy-1-(5'-methoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (19) (250 mg, 53%) after recrystallization from acetic acid, m.p. 283–283·5° (Found: C, 62·0; H, 4·4; N, 7·6. $C_{19}H_{16}N_2O_6$ requires C, 62·0; H, 4·5; N, 7·5%). ν_{max} 1785, 1640, 1610 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·30, s, H8; 7·75–7·45, m, 6H, ArH, H1'; 4·05, s, OMe; 3·97, s, 6H, 2 × OMe.

(ii) *1-(3'-Oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (4) was prepared as above (48%), m.p. 235–236° (Found: M$^{+\cdot}$ 278·0682. $C_{16}H_{10}N_2O_3$ requires M$^{+\cdot}$ 278·0691). ν_{max} 1780, 1625, 1610 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·39, dd, *J* 9 Hz, H8; 8·10–7·32, m, ArH, H1'.

(iii) *1-(5'-Methoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (17) was prepared as above (65%), and had m.p. 207–209° after recrystallization from ethanol (Found: C, 65·6; H, 4·4; N, 8·8; M$^{+\cdot}$ 308·0794. $C_{17}H_{12}N_2O_4$ requires C, 66·2; H, 3·9; N, 9·1%; M$^{+\cdot}$ 308·0797). ν_{max} 1780, 1645, 1610 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·39, d, *J* 8 Hz, H8; 8·00–7·30, m, 8H, ArH, H1'; 3·98, s, OMe.

(iv) *1-(4',5'-Dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (18) was obtained in 64% yield, and had m.p. 235–237° after recrystallization from ethanol (Found: C, 63·7; H, 4·3; N, 8·0. $C_{18}H_{14}N_2O_5$ requires C, 63·9; H, 4·2; N, 8·3%). ν_{max} 1760, 1620, 1600 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·25, dd, *J* 7, 1 Hz, H8; 7·80–7·30, m, 5H, ArH; 7·17, d, 7 Hz, 1H, H6'; 7·03, s, *J* 7 Hz, 1H, H7'; 4·17, s, OMe; 3·93, s, OMe. Elution with dichloromethane/ethyl acetate (2 : 1) gave 6,6',7,7'-tetramethoxy-$\Delta^{3,3'}$-biphthalide (34) (6%), m.p. 308–311° (lit.[27] 305°).

(v) *6,7-Dimethoxy-1-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (6) was obtained in 47% yield, and was purified by precipitation from acetic acid, m.p. 265–267° (Found: M$^{+\cdot}$ 338·0908. $C_{18}H_{14}N_2O_5$ requires M$^{+\cdot}$ 338·0903). ν_{max} 1780, 1625, 1615 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·45, s, H8; 8·31–7·59, m, 7H, ArH, H1'; 4·07, s, OMe; 3·98, s, OMe.

(vi) *1-(4',5'-Dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)-6,7-dimethoxycinnolin-4(1H)-one* (20) was obtained in 31% yield and recrystallized from ethanol, m.p. 249–251° (Found: C, 60·1; H, 4·9; N, 7·0. $C_{20}H_{18}N_2O_7$ requires C, 60·3; H, 4·6; N, 7·0%). ν_{max} 1780, 1625, 1600 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 7·56, s, H8; 7·53, s, ArH; 7·43, s, ArH; 7·2, d, *J* 8 Hz, H6'; 7·06, d, *J* 8 Hz, H7'; 6·9, s, H1'; 4·10–3·96, 4 × s, 12H, OMe.

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(vii) *6,7-Methylenedioxy-1-(3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (21) was obtained in 39% yield and recrystallized from acetic acid, m.p. 284–285° (Found: C, 63·5; H, 3·3; N, 8·4. $C_{17}H_{10}N_2O_5$ requires C, 63·4; H, 3·1; N, 8·7%). ν_{max} 1780, 1640, 1630, 1600 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·32, s, H8; 8·17–7·70, m, 4H, ArH; 7·9, s, 1H, ArH; 7·65, s, 1H, ArH; 7·50, s, 1H, H1'; 6·35, s, OCH_2O.

(viii) *1-(5'-Methoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)-6,7-methylenedioxycinnolin-4(1H)-one* (22) was obtained in 25% yield and recrystallized from acetic acid, m.p. 270–272° (Found: C, 61·1; H, 3·8; N, 7·8. $C_{18}H_{12}N_2O_6$ requires C, 61·4; H, 3·4; N, 7·6%). ν_{max} 1785, 1625, 1600 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·25, s, H8; 7·87, s, 1H, ArH; 7·76–7·40, m, 5H, ArH, H1'; 6·35, s, OCH_2O; 3·95, s, OMe.

When the reaction time was shortened to 4 h reflux, t.l.c. showed clearly the presence of two products. Fractional crystallization of the dichloromethane-soluble material gave 6-methoxy-3-(6',7'-methylenedioxycinnolin-4'-yloxy)isobenzofuran-1(3*H*)-one (29) as yellow *needles*, m.p. 208–210° (Found: $M^{+\cdot}$ 352·0692. $C_{18}H_{12}N_2O_6$ requires $M^{+\cdot}$ 352·0695). ν_{max} 1820, 1610, 1590 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·42, s, H3' (cinnoline); 7·72, s, H5' (cinnoline); 7·71–7·21, m, 3H, ArH; 7·38, s, H3; 7·14, s, H8'; 6·25, s, OCH_2O; 3·87, s, OMe. When a small sample was refluxed in tetrahydrofuran the infrared spectrum showed absorbances, characteristic of (22), at 1785 and 1625 cm^{-1}.

(ix) *1-(4',5'-Dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)-6,7-methylenedioxycinnolin-4(1H)-one* (23) was obtained in 44% yield and recrystallized from acetic acid, m.p. 288·5–290° (Found: C, 59·4; H, 4·0; N, 7·2. $C_{19}H_{14}N_2O_7$ requires C, 59·7; H, 3·7; N, 7·3%). ν_{max} 1780, 1625 cm^{-1}. N.m.r. (CF_3CO_2D) δ 8·51, s, H8; 7·99, s, 1H, ArH; 7·67, s, 2H, ArH, H1'; 7·43, d, *J* 10 Hz, H6'; 7·30, d, *J* 10 Hz, H7'; 6·33, s, OCH_2O; 4·23, s, OMe; 4·03, s, OMe.

(x) *6,7-Methylenedioxy-1-(4',5'-methylenedioxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (24) was obtained in 30% yield and was purified by precipitation from acetic acid, m.p. 280–281·5° (Found: $M^{+\cdot}$ 366·0488. $C_{18}H_{10}N_2O_7$ requires $M^{+\cdot}$ 366·0488). ν_{max} 1780, 1630 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 7·87, s, H8; 7·67, s, 1H, ArH; 7·53, s, 1H, ArH; 7·43, s, 2H, ArH, H1'; 7·08, d, *J* 10 Hz, H6'; 6·93, d, *J* 10 Hz, H7'; 6·27, s, OCH_2O; 6·17, s, OCH_2O.

(xi) *1-(5',6'-Dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (25) was obtained in 45% yield after crystallization from ethanol, m.p. 287–291° (Found: $M^{+\cdot}$ 338·0899. $C_{18}H_{14}N_2O_5$ requires $M^{+\cdot}$ 338·0903). ν_{max} 1765, 1640, 1605 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·8–7·8, ArH; 7·50, s, H4'; 7·00, s, H1'; 4·00, s, OMe; 3·88, s, OMe.

(xii) *1-(5',6'-Dimethoxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)-6,7-methylenedioxycinnolin-4(1H)-one* (26) was obtained in 50% yield after crystallization from acetic acid, m.p. 295–297° (Found: $M^{+\cdot}$ 382·0809. $C_{19}H_{14}N_2O_7$ requires $M^{+\cdot}$ 382·0802). ν_{max} 1790, 1650 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·50, s, 1H, ArH; 7·75, s, 2H, ArH; 7·50, s, H4'; 7·05, s, ArCH; 6·35, s, OCH_2O; 4·10, s, OMe; 3·95, s, OMe.

(xiii) *6,7-Dimethoxy-1-(4',5'-methylenedioxy-3'-oxo-1',3'-dihydroisobenzofuran-1'-yl)cinnolin-4(1H)-one* (27) was obtained in 47% yield after crystallization from acetic acid, m.p. 298–299° (Found: $M^{+\cdot}$ 382·0794. $C_{19}H_{14}N_2O_7$ requires $M^{+\cdot}$ 382·0802). ν_{max} 1775, 1640 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8·00, s, ArH; 7·6, br, 4H, ArH; 7·00, s, ArCH; 6·35, s, OCH_2O; 4·00, s, OMe, 3·85, s, OMe.

3-(2-Acetylphenylamino)isobenzofuran-1(3H)-one (30)

A solution of 2-aminoacetophenone (1·0 g, 7·4 mmol), 2-formylbenzoic acid (1·1 g, 7·4 mmol) and *p*-toluenesulfonic acid (2 mg) in acetone (40 ml) was refluxed for 3 h. The colourless solid obtained on evaporation was recrystallized from ethanol as colourless *needles* (1·6 g, 80%), m.p. 126–128° (Found: C, 71·8; H, 4·9; N, 5·3. $C_{14}H_{13}NO_3$ requires C, 71·9; H, 4·9; N, 5·2%). ν_{max} 1760, 1640 cm^{-1}. N.m.r. δ 7·90–7·31, m, 6H, ArH; 7·19, s, H3; 7·07–6·78, m, 3H, ArH, NH; 2·60, s, $COCH_3$.

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