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The Chemistry of Phthalide-3-carboxylic Acid. VII* Reaction with Isoquinoline Derivatives

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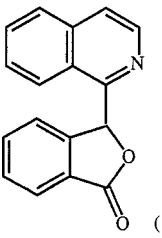
Abstract

Phthalide-3-carboxylic acid has been decarboxylated in the presence of isoquinoline, 1-chloroisoquinoline and isoquinoline *N*-oxides to give low yields of compounds resulting from alkylation of the isoquinoline heterocycle at C1 with a phthalidyl group. Attempted Barton decarboxylation–alkylation in the presence of isoquinolinium salts was unsuccessful.

Introduction

The phthalideisoquinoline alkaloids are widely used as pharmacological probes because of their specific antagonism of the depressant neurotransmitter GABA.[1] We have previously studied[2–4] the synthesis of a number of analogues of these compounds in the hope of finding GABA agonists, which could act as antiepileptic drugs, and various phthalides, substituted at C3 with heterocyclic aryl groups meet the requirements. In this paper, we report our attempts to make 3-(isoquinolin-1-yl)isobenzofuranones, e.g. (1), by the expedient of the decarboxylation–aklylation of phthalidecarboxylic acid in the presence of isoquinoline derivatives. Such compounds have been prepared before[2,5–8], but, in view of our success with the decarboxylation–alkylation of phthalidecarboxylates in the presence of imines[9–11] and their



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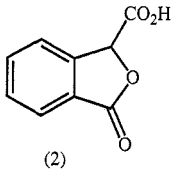
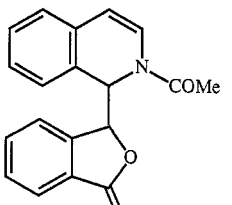
salts, we felt that isoquinolines, unsubstituted at C 1, or with a leaving group at C 1, might act as potential electrophiles.

Discussion

Reaction of phthalide-3-carboxylic acid (2) with isoquinoline alone resulted only in decarboxylation to phthalide, but in acetic anhydride at 135° for 30 min led to the isolation of the desired compound (3) in low yield (20%).



(2)



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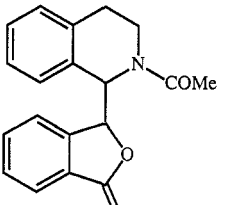
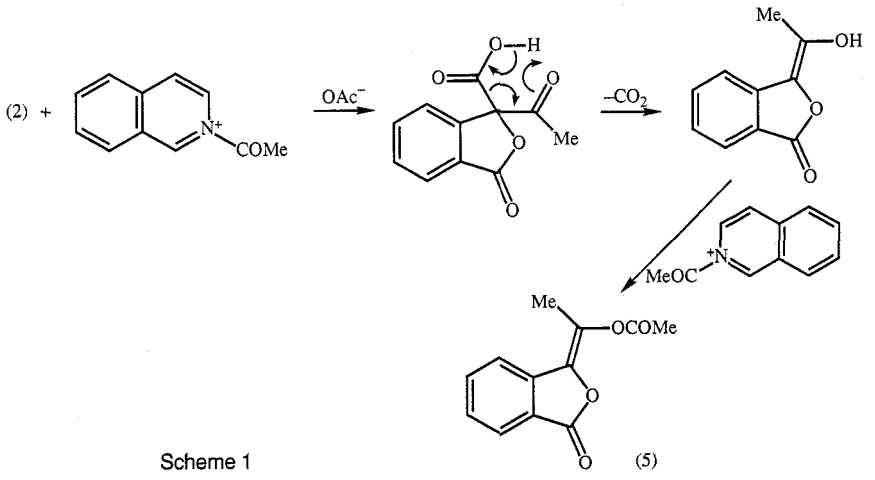


(4)

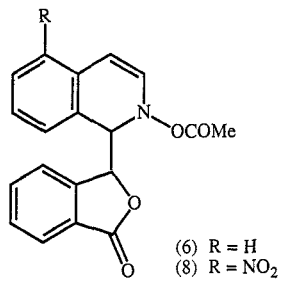
The identity of the product was confirmed by conversion into the mixture of *erythro* and *threo* isomers of (tetrahydroisoquinolin-1-yl)isobenzofuranone (4) by hydrogenation, and comparison with an authentic sample. Although (4) has not been described previously, it is readily made by the procedure we have previously pioneered.[10] The major product in this reaction was the enol acetate (5) of 3-acetylphthalide. The latter compound was not formed when (2) was decarboxylated in acetic anhydride alone, a result showing that it was probably formed by the pathway shown in Scheme 1.



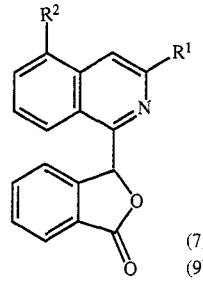
Scheme 1

The decarboxylation, as above, in the presence of the more electrophilic isoquinoline *N*-oxide was no more successful, the products consisting of the desired compound (1) (10%), (5) (25%) and the acetoxy compound (6) (20%), as a mixture of isomers. Even when 5-nitroisoquinoline *N*-oxide was used, only 15% of the nitro analogue (7) of (1) could be isolated, together with the stereoisomers of the acetoxy compound (8) (10%), which readily lost acetic acid on recrystallization.

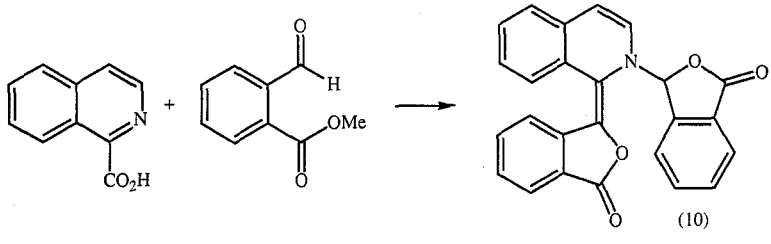
Heating a mixture of (2) and 1-chloroisoquinoline proved to be the most successful route to (1), but the yield was still only 20%. Similarly, (2) reacted with 1-chloro-3-methylisoquinoline to give (9) (34%). When synthesis of (1) was attempted in the reverse chemical sense to that above, viz. isoquinoline-1-carboxylic acid was heated in the presence of methyl 2-formylbenzoate (Scheme 2), the product (49%) was the 1 : 2 adduct (10), which yielded (1) on reaction with aqueous acid.



(6) R = H
(8) R = NO_2



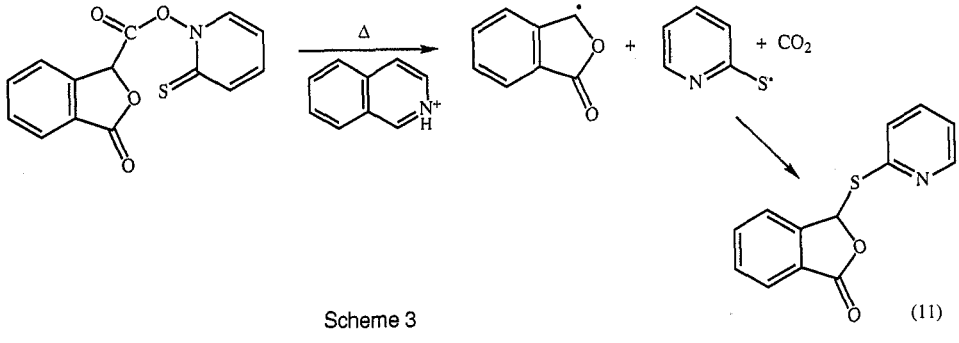
	R^1	R^2
(7)	H	NO_2
(9)	Me	H



(10)

Scheme 2

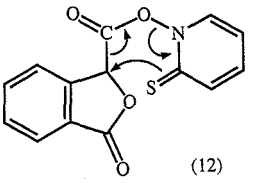
No alkylation products could be isolated when (2) or its potassium salt was heated in the presence of 2-methylisoquinolinium fluorosulfonate. Lastly, the Barton reaction[12] on (2) generated phthalidyl radicals which were insufficiently reactive to combine with isoquinolinium salts, and gave only the radical-coupling product (11) (Scheme 3), although such a product could also arise from a six-centred concerted reaction pathway (12).



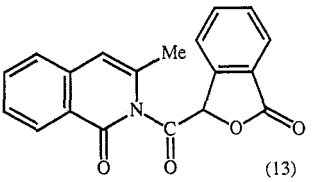
(11)

Scheme 3

[12] Barton, D. H. R., Garcia, B., Togo, H., and Zand, S. Z., *Tetrahedron Lett.*, 1986, **27**, 1327.



(12)



(13)

Experimental

^{1}H n.m.r. spectra were recorded on a Varian EM 360 spectrometer, operating at 60 MHz, or a Jeol FX 90, operating at 90 MHz, and were measured in $CDCl_3$ unless otherwise specified. Mass spectra were recorded on a Kratos MS 25RT spectrometer. Microanalyses were performed by the Australian Microanalytical Service, Melbourne, or the Canadian Microanalytical Service, New Westminster. Centrifugal chromatography was performed on silica gel $60PF_{254}$ by using a Chromatotron.

3-(2-Acetyl-1,2,3,4-tetrahydroisoquinolin-1-yl)isobenzofuran-1(3H)-one (4)

3-Oxo-1,3-dihydroisobenzofuran-1-carboxylic acid (2) (0·3 g, 1·68 mmol) was dissolved in acetic anhydride (5 ml), 3,4-dihydroisoquinoline (0·22 g, 1·68 mmol) was added, and the solution was refluxed for 1 h, after which time the solvent was evaporated. The resulting orange oil was taken up in ethyl acetate (50 ml), washed with saturated sodium carbonate solution (2×10 ml) and dilute hydrochloric acid (2×10 ml). The organic layer was dried and evaporated leaving an orange oil, which on trituration with a light petroleum/diethyl ether mixture yielded a white solid. The solid was shown to be a 3 : 2 mixture of the *threo* and *erythro* isomers of the *title compound* (0·23 g, 46%), m.p. 136–138° (Found: C, 74·6; H, 5·8. $C_{19}H_{17}NO_3$ requires C, 74·3; H, 5·6%). ν_{max} 1770, 1660, 1410, 1285, 1239, 1065, 1030, 970, 770 cm^{-1}. ^{1}H n.m.r. *threo* δ 2·30, s, 3H, CH_3; 2·65–4·10, m, 4H, CH_2CH_2; 6·00, s, 2H, CH–CH; 6·55–8·10, m, 8H, ArH; *erythro* δ 1·90, s, 3H, CH_3; 2·65–4·10, m, 4H, CH_2CH_2; 6·12, d, J 3 Hz 1H, CH; 6·44, d J 3 Hz, 1H; 6·55–8·10, m, 8H, ArH. The triturant yielded more of the *threo* isomer exclusively, as a white solid (100 mg).

Reaction of (2) with Isoquinoline in Acetic Anhydride

Acid (2) (0·5 g, 2·80 mmol) and isoquinoline (0·36 g, 2·80 mmol) were dissolved in acetic anhydride (5 ml), and the solution was refluxed for 1 h, after which time the solvent was evaporated. The resulting brown oil was taken up in ethyl acetate (50 ml), and washed with saturated sodium carbonate solution (2×30 ml) and then with 2 M hydrochloric acid solution (2×30 ml). The organic layer was dried and evaporated, leaving an orange-brown oil (0·56 g), which t.l.c. showed to be a mixture.

Centrifugal chromatography, with dichloromethane as the eluent, yielded two fractions, the first of which was shown to be (Z) *3-(1-acetoxyethylidene)isobenzofuran-1-(3H)-one* (5) (0·22 g, 40%). Recrystallization from dichloromethane/hexane yielded white needles with m.p. 108–109° (Found: C, 65·9; H, 4·9. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6%). ν_{max} 1785, 1765, 1460, 1375, 1205, 1060 cm^{-1}. ^{1}H n.m.r. δ 2·32, s, 3H, $H_3CC{=}C$; 2·40, s, 3H, CH_3CO; 7·30–8·00, m, 4H, ArH. Mass spectrum *m/z* 218 (M), 176, 149, 133.

The second fraction (200 mg), which was a mixture, contained *3-(2-acetyl-1,2-dihydroisoquinolin-1-yl)isobenzofuran-1(3H)-one* (3) (20%). ^{1}H n.m.r. δ 2·10 and 2·35, s, 3H, $COCH_3$; 5·40–5·85, m, 2H, CH–CH; 5·90–6·40, m, 2H, isoquinolinyl H3 and H4; 7·10–8·25, m, 8H, ArH. Attempted purification of this compound was unsuccessful. Its identity was verified by catalytic reduction of the 3,4 double bond and subsequent comparison with the sample of (4) above.

Attempted Oxidation of (3)

The material containing the acetylated addition product (3) (100 mg) was recovered unchanged after 1 h reflux in methanol with iodine or bromine.

Reaction of (2) with Isoquinoline 2-Oxide in Acetic Anhydride

Acid (2) (0·3 g, 1·68 mmol) was dissolved in acetic anhydride (5 ml), and isoquinoline 2-oxide (0·25 g, 1·68 mmol) added. The solution was refluxed for 1 h, after which time the solvent was evaporated, leaving an orange-brown oil, which was taken up in ethyl acetate (50 ml), washed with saturated sodium carbonate solution (2×20 ml) and then with 2 M hydrochloric acid solution (2×20 ml). The carbonate washings contained only a trace of acidic material. The acid washings were basified with solid sodium carbonate, and extracted with dichloromethane (2×50 ml). The combined extracts were dried and evaporated leaving a yellow oil (0·12 g). Centrifugal chromatography (ethyl acetate/dichloromethane 1 : 4) separated this basic material into two products. The higher-R_F product was shown to be 3-(isoquinolin-1-yl)isobenzofuran-1(3*H*)-one (1) (40 mg, 10%) by direct comparison with an authentic sample of (1), m.p. 153–154° (lit.[2] 150–152°). ν_{max} 1770, 1600, 1300, 1290, 975, 745, 735 cm^{-1}. ^1H n.m.r. δ 7·27, s, 1H, H3; 7·35–8·70, m, 10H, ArH. The structure of the lower-R_F product (45 mg) could not be assigned. ν_{max} 1770, 1715, 1595 cm^{-1}.

The initial neutral ethyl acetate phase was dried and evaporated, leaving an orange oil (0·30 g). Centrifugal chromatography separated the mixture into four fractions. Elution with a 3 : 1 mixture of dichloromethane and hexane yielded the first two products. The higher-R_F product proved to be the alkylidene compound (5) (80 mg, 25%). The lower-R_F product (15 mg) was disregarded. Elution with CH_2Cl_2/ethyl acetate (1 : 1) yielded the two final products, the higher-R_F compound as an orange solid (80 mg) (20%), m.p. 86–89°, suggested to be a mixture of the *threo* and *erythro* isomer of *3-(2-acetoxy-1,2-dihydroisoquinolin-1-yl)isobenzofuran-1(3H)-one* (6), but it proved impossible to obtain a sufficiently pure sample for microanalysis. ν_{max} 1780, 1690 cm^{-1}. ^1H n.m.r. δ 2·25 and 2·35, s, 3H, $COCH_3$, isomers; 5·60–6·45, m, 2H, CH=CH; 6·50–8·00, m, 10H, ArH. After 1 h reflux with sodium acetate in acetic acid, (6) was converted into the known compound (1), identified by direct comparison. The lower-R_F fraction (30 mg) proved to be a complicated mixture, and consequently its composition was not investigated.

Reaction of (2) with 5-Nitroisoquinoline 2-Oxide in Acetic Anhydride

Acid (2) (0·3 g, 1·68 mmol) and 5-nitroisoquinoline 2-oxide[13] (0·32 g, 1·68 mmol) were dissolved in acetic anhydride (20 ml); the mixture was refluxed for 1 h, and the solvent was then evaporated. The resultant brown-red oil was taken up in ethyl acetate (50 ml), and washed with saturated sodium bicarbonate solution (2×30 ml) and then with dilute hydrochloric acid (2 M, 2×30 ml). The basic fraction yielded 5-nitroisoquinoline (90 mg, 30%), identified by comparison with an authentic sample. The initial neutral ethyl acetate phase was dried and evaporated leaving a red-brown solid. Centrifugal chromatography separated the mixture into three fractions, the first two of which were isolated by using dichloromethane as the eluent. The higher-R_F product was obtained as a red solid (80 mg, 15%) and identified as *3-(5-nitroisoquinolin-1-yl)isobenzofuran-1(3H)-one* (7), m.p. 203–205° (Found: C, 66·6; H, 3·2%; $M^{+\bullet}$, 306·0634. $C_{17}H_{10}N_2O_4$ requires C, 66·7; H, 3·3%; $M^{+\bullet}$, 306·0641). ^1H n.m.r. δ 7·68–9·20, m, 9H. ν_{max} 1780, 1680, 1530, 1345 cm^{-1}. The lower-R_F compound was isolated as an orange oil and spectral data suggested the structure to be a mixture of stereoisomers of *3-(2-acetoxy-5-nitro-1,2-dihydroisoquinolin-1-yl)isobenzofuran-1(3H)-one* (8) (70 mg, 10%). ν_{max} 1780, 1680, 1530, 1345 cm^{-1}. ^1H n.m.r. δ 2·25 and 2·40, s, 3H, $COCH_3$; 6·27–6·80, 2H, CH–CH; 6·87–7·20, m, 2H, isoquinolinyl H3, H4; 7·50–8·67, m, 7H, ArH. On attempted crystallization, this material aromatized to (7) and thus could not be further characterized. The final fraction (0·12 g), which was obtained as a brown oil by using ethyl acetate as the eluent, was found to be a complicated mixture, and thus was disregarded.

Reaction of (2) with 1-Chloroisoquinoline

Acid (2) (0·3 g, 1·68 mmol) and 1-chloroisoquinoline (0·28 g, 1·71 mmol) (prepared from the *N*-oxide with $POCl_3$[14]) were heated with stirring at 145° for 1 h. The resultant brown oil was taken up into dichloromethane (50 ml), and, on addition of hexane (25 ml), a pale brown

[13] Ochiai, E., and Ikehara, M., *J. Pharm. Soc. Jpn*, 1953, **73**, 666.
[14] Haworth, R. D., and Robinson, S., *J. Chem. Soc.*, 1948, 777.

solid precipitated. The solid was identified as the hydrochloride salt of (1) by treatment with saturated sodium carbonate solution (30 ml) followed by extraction with ethyl acetate (2×75 ml). Drying and evaporation of the extracts yielded 3-(isoquinolin-1-yl)isobenzofuran-1(3*H*)-one (1) as a pale yellow solid (90 mg, 20%), m.p. 152–153°, identical with the sample above. ν_{max} 1770, 1290, 1065, 975 cm^{-1}.

The initial dichloromethane/hexane mixture was washed with 2 M hydrochloric acid (2×30 ml), and then with saturated sodium carbonate solution (2×30 ml). The acid extract was basified with solid sodium carbonate, and extraction with ethyl acetate (2×50 ml) yielded a further 25 mg (5%) of compound (1). On acidification with dilute hydrochloric acid, the carbonate extract yielded only starting acid (2) (10%) when extracted with ethyl acetate (2×50 ml). The neutral dichloroethane/hexane phase was dried and evaporated leaving an orange oil. Centrifugal chromatography separated the mixture into two components, the first of which was isolated by using dichloromethane as the eluent and shown to be isobenzofuranone (15 mg, 5%). The major fraction was eluted by using ethyl acetate and found to be isocarbostyril (0·13 g, 55%), m.p. 211–212° (lit.[15] 209–210°). ν_{max} 1660 cm^{-1}. ^1H n.m.r. [$(CD_3)_2SO$] δ 6·55, d, *J* 7 Hz, 1H, H4; 7·20, d, *J* 7 Hz, 1H, H3; 7·30–7·80, m, 3H, ArH; 8·30, d, *J* 7 Hz, 1H, H8.

Reaction of 3-Oxo-1,3-dihydroisobenzofuran-1-carboxylic Acid with 1-Chloro-3-methylisoquinoline

A mixture of the acid (2) (178 mg, 1 mmol) and 1-chloro-3-methylisoquinoline[16] (177 mg, 1 mmol) was heated at 140° (oil bath), the evolution of carbon dioxide being complete within 5–10 min. The mixture was dissolved in ethyl acetate (15 ml), washed with 10% hydrochloric acid (2×5 ml), then with water (2×5 ml). The organic layer was dried, and solvent removed to give a solid which was separated by preparative t.l.c. (ethyl acetate/light petroleum 9 : 1) to give two major products. The higher-R_F product was identified as 3-methylisocarbostyril (97 mg, 60%) which had m.p. 208° (lit.[16] 210–212°) and identical spectra to those of an authentic sample. The lower-R_F product was identified as *3-methyl-2-[(3-oxo-1,3-dihydroisobenzofuran-1-yl)carbonyl]isoquinolin-1(2H)-one* (13) (23 mg, 7%), m.p. 146° (Found: C, 71·2; H, 4·0. $C_{19}H_{13}NO_4$ requires C, 71·5; H, 4·1%). ν_{max} ($CHCl_3$) 1760, 1740, 1660 cm^{-1}. ^1H n.m.r. δ 2·70, s, 3H, CH_3; 7·30, s, 1H, isobenzofuranyl H3; 7·30–10·2, m, 9H, ArH.

The aqueous layer was made alkaline with solid potassium carbonate and extracted with ethyl acetate (2×10 ml); the extract was dried and solvent removed. The product was separated by preparative t.l.c. (ethyl acetate/light petroleum 9:1) to give 3-(3-methylisoquinolin-1-yl)isobenzofuran-1(3*H*)-one (9) (94 mg, 34%), m.p. 148–149° (lit.[2] 148–149°).

Reaction of Isoquinoline-1-carboxylic Acid with Methyl 2-Formylbenzoate

Methyl 2-formylbenzoate (654 mg, 4 mmol) and isoquinoline-1-carboxylic acid (346 mg, 2 mmol) were heated at 140° (oil bath). After 5 min, carbon dioxide evolution commenced, and the colour changed from yellow to brown. After 90 min, the reaction mixture was cooled, a solution of 10% hydrochloric acid (20 ml) was added, and the mixture extracted with dichloromethane (3×10 ml). The organic layer was separated, dried and evaporated, and the residue was recrystallized from light petroleum/ethyl acetate to give a light yellow solid, m.p. 192°, identified as *3-[1-(3-oxo-1,3-dihydroisobenzofuran-1-ylidene)-1,2-dihydroisoquinolin-2-yl)]isobenzofuran-1(3H)-one* (10) (385 mg, 49%) (Found: C, 76·3; H, 3·8; N, 3·4. $C_{25}H_{15}NO_4$ requires C, 76·1; H, 4·0; N, 3·5%). ν_{max} ($CHCl_3$) 1780, 1765, 1290 cm^{-1}. ^1H n.m.r. δ 6·81, s, 1H, H3; 8·91–9·12, m, 14H, ArH. The mother liquor was washed with 10% hydrochloric acid, dried, and solvent removed to give a yellow oil (300 mg) which was identified as unreacted methyl 2-formylbenzoate by its n.m.r. and i.r. spectra. The aqueous layer was made alkaline with solid potassium carbonate, and extracted with dichloromethane, which was dried and solvent removed to give isoquinoline (100 mg, 41%), identified by its n.m.r. and i.r. spectra.

[15] 'Dictionary of Organic Compounds' 5th Edn, Vol. 3 (Chapman & Hall: New York 1982).
[16] Robinson, M. M., and Robinson, B. L., *J. Org. Chem.*, 1957, **21**, 1337.

Reactions of 3-Oxo-1,3-dihydroisobenzofuran-1-carbonyl Chloride with Isoquinolinium Salts

To a solution of isoquinolinium trifluoroacetate (0·5 g, 21 mmol) in dry dichloromethane (15 ml), under an N_2 atmosphere, was added the sodium salt of 1-hydroxypyridine-2-(1*H*)-thione (0·37 g, 2·47 mmol) and dimethylaminopyridine (10 mg). To this suspension was added the acid chloride of (2) (0·4 g, 2·1 mmol) over a period of 20 min, with stirring. The refluxing reaction mixture was exposed to the light of a 300-W tungsten lamp for 1 h, after which time further dichloromethane (10 ml) was added, and the mixture washed with saturated sodium carbonate solution. The organic phase was dried and evaporated leaving a brown oil (0·55 g). Centrifugal chromatography separated the oil into four fractions, the first two of which were collected by using dichloromethane as the eluent. The higher-R_F compound was a colourless solid, identified as 3-(2-pyridylthio)isobenzofuran-1(3*H*)-one by direct comparison with the sample synthesized below, and the lower-R_F compound was identified as 2,2′-dipyridyl disulfide (80 mg, 15%) by comparison with an authentic sample. The next fraction collected (25 mg) could not be identified. The final fraction was collected by using ethyl acetate as the eluent, and found to be isoquinoline (0·24 g, 90%). The initial carbonate extract was acidified to pH 1 with 2 M hydrochloric acid to yield the acid (2) (190 mg, 50%). The use of higher temperatures and other solvents led to no more successful a conclusion.

*3-(2-Pyridylthio)isobenzofuran-1(3*H*)-one (11)*

To a solution of 3-bromoisobenzofuran-1(3*H*)-one (790 mg, 3·70 mmol) in carbon tetrachloride (25 ml) was added 2-mercaptopyridine (0·41 g, 3·70 mmol) and triethylamine (0·4 g, 4·0 mmol), and the mixture was refluxed for 2·5 h under nitrogen, after which time solid triethylamine hydrobromide was removed by filtration, and the solvent evaporated, leaving a brown oil. Trituration with hexane yielded pale brown crystals (0·70 g, 77%). Recrystallization from ethyl acetate/hexane yielded colourless *crystals* of the title compound with m.p. 92–93° (Found: C, 64·3; H, 3·6%; $M^{+\bullet}$, 243·0374. $C_{13}H_9NO_2S$ requires C, 64·2; H, 3·7%; $M^{+\bullet}$, 243·0354). ν_{max} 1760, 1580, 1455, 1415, 1265, 1115, 1050, 960 cm^{-1}. ^1H n.m.r. δ 7·10–8·13, s, 1H, H3, and m, 7H, ArH; 8·60, d, *J* 5 Hz, 1H, ArH. Mass spectrum *m/z* 243 (M).

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