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Central Nervous System Active Compounds. VI* Reissert Compounds as Precursors of 1-(3-Phthalidyl)isoquinolines

Tran V. Hung, Brett A. Mooney, Rolf H. Prager and A. David Ward

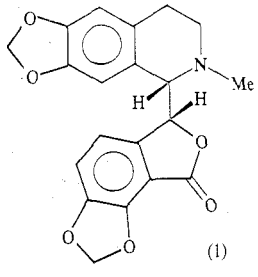
Organic Chemistry Department, University of Adelaide, P.O. Box 498, Adelaide, S.A. 5001.

Abstract

The reactions of isoquinoline and phthalazine Reissert compounds with phthalaldehydic acids and their derivatives have been investigated as a means of synthesizing 1-(3-phthalidyl)isoquinolines. Of a variety of conditions tried those involving phase transfer were found, in general, to be the most suitable. The products, which are analogues of the convulsant alkaloid bicuculline, showed weak central nervous system depressant activity.

Introduction

As part of a study[1] into the possibility of transforming the convulsant properties of bicuculline (1), a known antagonist of the neuro-transmitter GABA,[2] into GABA agonists,[3,4] we were interested in the synthesis and pharmacological properties of the isoquinoline analogues containing the general structure (2). It was expected that these compounds might exhibit altered central nervous system (CNS) activity since the altered stereochemistry and the additional electronic factors present in derivatives of



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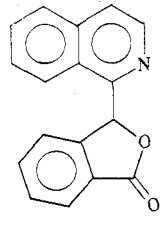

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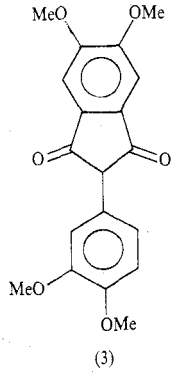

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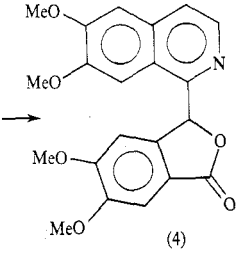


(4)

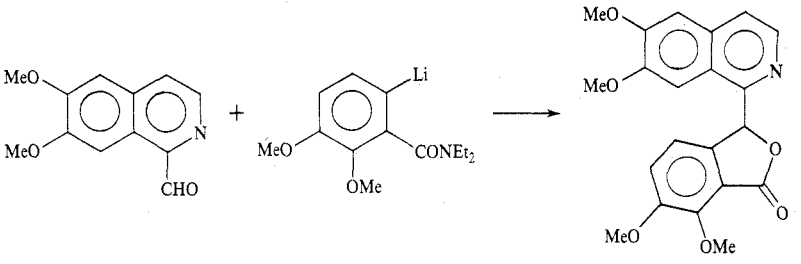
* Part V, *Aust. J. Chem.*, 1980, **33**, 2717.

[1] Hutchison, G. I., Marshall, P. A., Prager, R. H., Tippett, J. M., and Ward, A. D., *Aust. J. Chem.*, 1980, **33**, 2699.
[2] Curtis, D. R., Duggan, A. W., Felix, D., and Johnston, G. A. R., *Brain Res.*, 1971, **32**, 69.
[3] Curtis, D. R., Duggan, A. W., Felix, D., and Johnston, G. A. R., *Nature (London)*, 1970, **226**, 1222.
[4] Curtis, D. R., Duggan, A. W., Felix, D., and Johnston, G. A. R., *Nature (London)*, 1970, **228**, 676.

(2), compared to bicuculline, could significantly alter their interaction with relevant receptor sites.

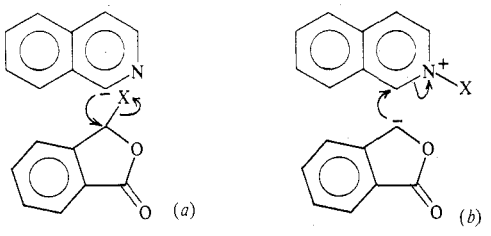
A number of isolated reports of the synthesis of molecules containing the general structure (2) have been reported. MacLean and coworkers[5] have used indanediones of type (3) as building blocks for this system but their procedure required the presence of alkoxyl substituents in the pendant phenyl ring.

Several groups of workers have converted other alkaloids into phthalide isoquinolines. For example, Shamma[6,7] has obtained (4) from papaverine and Iwai and Kondo[8] have also prepared (4) from norcoralyne, but the generality of these procedures has not been further investigated. Snieckus[9] has recently reported a single example of what may prove to be the most general route to compounds of type (2), using the procedure shown in Scheme 1. Finally the use of radical addition reactions with isoquinoline *N*-oxide[10] proceeds in very low yields and does not appear to be generally suitable.



Scheme 1

Initially it seemed to us that synthesis of the system (2) could be best achieved by forming the bond between the 1-position of isoquinoline and the 3-position of phthalide. Two types of reaction, (*a*) and (*b*), can be envisaged for this process.

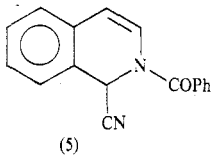


Discussion

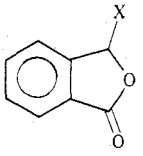
Reactions of type (*a*) are the subject of this paper and were investigated first, since isoquinolines are readily converted into nucleophiles at C1 via the Reissert com-

[5] Smula, V., Cundasawmy, N. E., Holland, H. L., and MacLean, D. B., *Can. J. Chem.*, 1973, **51**, 3287.
[6] Shamma, M., and Georgiev, V. St., *Tetrahedron Lett.*, 1974, 2339.
[7] Shamma, M., and Georgiev, V. St., *Tetrahedron*, 1976, **32**, 211.
[8] Iwai, J., and Kondo, Y., *Heterocycles*, 1977, **6**, 959.
[9] De Silva, S. O., Ahmad, I., and Snieckus, V., *Tetrahedron Lett.*, 1978, 5107.
[10] Natsume, M., and Tanabe, R., *Itsuu Kenkyusho Nempo*, 1968, 21 (*Chem. Abstr.*, 1969, **71**, 124746l).

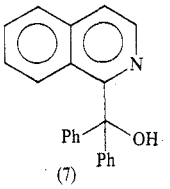
pounds[11,12] (5) and phthalides with suitable leaving groups at C 3 are readily available.[13] The anions of the Reissert compounds, generated by sodium hydride in xylene[14] or dimethylformamide,[15] phenyllithium in ether[16] or by sodium hydroxide under phase transfer conditions[17] react readily with aldehydes,[12,16] ketones[17] and alkyl halides.[18]



(5)



(6a) X = Br
(6b) X = OEt
(6c) X = OH



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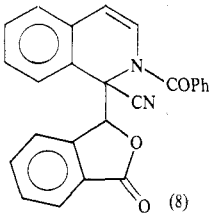

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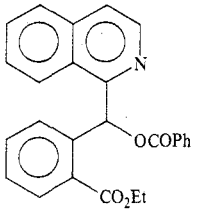


(9)

Our first attempt* in this area was to make the Reissert anion, generated by phenyllithium, react with 3-bromophthalide (6a) but the reaction was unsatisfactory as the anion partly rearranged† to 1-benzoylisoquinoline[20,21] under the reaction conditions, and this rearrangement product then reacted with phenyllithium to give the carbinol (7). A low yield of the alkylated material (8) was also obtained.

We were hopeful that the use of 3-ethoxyphthalide (6b) as the electrophile would have the additional advantage that the displaced ethoxide would complete the formation of (2) as shown in Scheme 2. Instead a mixture of products was obtained in all the reaction conditions tried and (2) was only formed in, at best, a moderate yield.

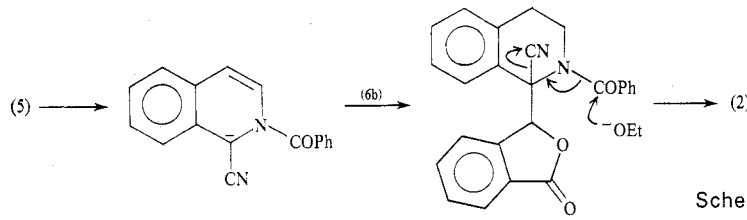
* The substance of this paper was presented at the Hobart Organic Division of the Royal Australian Chemical Institute, January 1979. Some time afterwards we became aware of the work of Kerekes,[19] who prepared compound (16) by essentially the same route as that described herein.

† The lithium salts of Reissert compounds do not generally rearrange so readily. It is possible that the substrate acts as a catalyst in some undetermined manner as has been noted with Grignard reagents.[20]

[11] McEwan, W. E., and Cobb, R. L., *Chem. Rev.*, 1955, **55**, 511.
[12] Popp, F. D., *Adv. Heterocycl. Chem.*, 1968, **9**, 1.
[13] Wheeler, D. D., Young, D. C., and Erley, D. S., *J. Org. Chem.*, 1957, **22**, 547.
[14] Wefer, J. M., *J. Org. Chem.*, 1965, **30**, 3075.
[15] Popp, F. D., and Wefer, J. M., *Chem. Commun.*, 1967, 207.
[16] Walters, L. R., Iyer, N. T., and McEwan, W. E., *J. Am. Chem. Soc.*, 1958, **80**, 1177.
[17] Jonczyk, A., *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, 1974, **22**, 849 (*Chem. Abstr.*, 1975, **82**, 139936w).
[18] Gibson, H. W., *J. Heterocycl. Chem.*, 1970, **7**, 1169.
[19] Kerekes, P., Horvath, G., Gaal, G., and Bognor, R., *Acta Chim. Acad. Sci. Hung.*, 1978, **97**, 353 (*Chem. Abstr.*, 1979, **90**, 39085q).
[20] Rose, N. C., and McEwan, W. E., *J. Org. Chem.*, 1958, **23**, 337.
[21] Spatz, D. M., and Popp, F. D., *J. Heterocycl. Chem.*, 1968, **5**, 497.

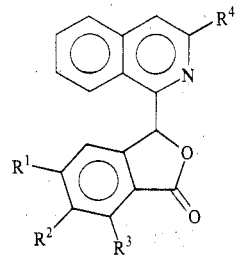
Other products included the benzoate (9), isocarbostyril, isoquinoline and the carbinol (7).

The successful alkylation of Reissert compounds under phase-transfer conditions[17] prompted us to investigate the reaction of (5) with phthalaldehydic acid (6c), in the expectation that both the anion of (5) and of (6c) would be transferred to the organic phase. Our first reaction, in which air was not rigorously excluded, gave a mixture of the desired compound (2) (49%), for which we suggest a pathway similar to that shown in Scheme 2, and isoquinoline-1-carbonitrile (27%). The latter is clearly a product of the base-catalysed autoxidation[22] of (5), for in the absence of oxygen it was not formed. The Reissert compound (5) gives a 95% yield of isoquinoline-1-carbonitrile in the absence of added electrophiles but in the presence of oxygen, a result which has recently been reported in the literature.[23]



Scheme 2

From a series of reactions designed to optimize the formation of (2) under phase-transfer conditions the best yield (72%) was obtained at room temperature with benzene/50% potassium hydroxide under nitrogen in the presence of benzyltriethylammonium chloride. Under these phase-transfer conditions the compounds (2) and (10)–(13) could be prepared.



	R^1	R^2	R^3	R^4
(10)	OMe	OMe	H	H
(11)	H	OMe	H	H
(12)	H	OMe	OMe	H
(13)	H	H	H	Me

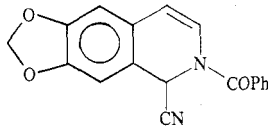
The Reissert compound (5) could not be made to react with 6,7-methylenedioxyphthalaldehydic acid but instead was converted into isoquinoline-1-carbonitrile. Similarly the Reissert compound from 3-methylisoquinoline failed to react with electron-rich phthalides. The decreased reactivity of this latter Reissert system has been previously reported[18] and has been ascribed to unfavourable electronic interactions.

In view of the deleterious effects electron-donating groups on the phthalide system have on the product yields, the effect of a nitro group was investigated. The reaction

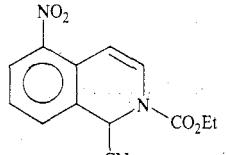
[22] Rozwadowska, M. D., and Brozda, D., *Tetrahedron Lett.*, 1978, 589.
[23] Rozwadowska, M. D., and Brozda, D., *Can. J. Chem.*, 1980, **58**, 1239.

of 6-nitrophthalaldehydic acid and (5) was notable for its extensive colour changes but the product, in essentially quantitative yield, was isoquinoline-1-carbonitrile. Popp[24] has noted decreased yields in the reaction of Reissert compounds with nitrobenzaldehydes. It is reasonable to propose that the colour changes indicate that 6-nitrophthalaldehydic acid is being oxidized, presumably by way of radical anions. However, addition of radical inhibitors to the reaction did not lead to any improvement.

The Reissert anion of (14), derived from 6,7-methylenedioxyisoquinoline, was clearly destabilized with respect to the anion of (5) and preferentially underwent intramolecular reactions. The Reissert compound from 5-nitroisoquinoline is obtainable only in very low yield,[25,26] and attempts to find alternative synthetic methods under phase-transfer conditions resulted in its decomposition to 1-benzoyl-5-nitroisoquinoline. Nitration of (5) was unsuccessful. Although it was possible to synthesize the *N*-ethoxycarbonyl Reissert compound (15) more efficiently it also rearranged too rapidly to be alkylated, even by aldehydes.



(14)



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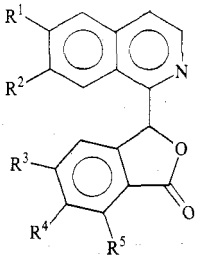
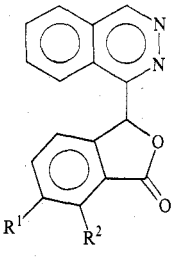


	R^1	R^2	R^3	R^4	R^5
(16)	H	H	H	$-OCH_2O-$	
(17)	$-OCH_2O-$		H	$-OCH_2O-$	
(18)	$-OCH_2O-$		H	OMe	H
(19)	$-OCH_2O-$		OMe	OMe	H
(20)	$-OCH_2O-$		H	H	H



	R^1	R^2
(21)	H	H
(22)	OMe	H
(23)	OMe	OMe
(24)	$-OCH_2O-$	

In order to increase the electrophilicity of the phthalide 3-position the alkylation reactions were repeated with the esters of the phthalaldehydic acids which have recently become readily available.[27] These alkylations proceeded more readily than

[24] Popp, F. D., and Gibson, H. W., *J. Heterocycl. Chem.*, 1964, **1**, 51.
[25] Popp, F. D., and Blount, N., *J. Org. Chem.*, 1962, **27**, 297.
[26] Uff, B. C., and Budhram, R. S., *Heterocycles*, 1977, **6**, 1789.
[27] Plauman, H. P., Keay, B. A., and Rodrigo, R., *Tetrahedron Lett.*, 1979, 4921.

those with the corresponding acids and the additional compounds (16)–(20) could be prepared by this procedure.

In view of our observation of marked central nervous system activity, of a depressant nature, in 1-phthalidylphthalazinones[28] and the successful alkylation of Reissert compounds of phthalazine[26] we used the above methods to synthesize compounds (21)–(24).

Biological Activity

None of the compounds reported herein showed strong activity in the CNS when subjected to a preliminary testing program.[29] The results are shown in Table 1.

Table 1. Central nervous system activity of phthalideisoquinolines and phthalidephthalazines

L, loss of muscle control; C, convulsions

Compound	Minimum dose (mg/kg)	Type of activity	Compound	Minimum dose (mg/kg)	Type of activity
(2)	70	L	(17)	50	L
(4)	75	L	(18)	55	C–L
(10)	100	L	(20)	75	L
(11)	60	C–L	(21)	65	L
(12)	55	L	(22)	70	C–L
(13)	>100	—	(23)	60	L
(16)	70	L	(24)	70	L

Experimental

General details have been given in Parts I and III.[29,30] Substituted phthalaldehydic acids have been described in Part IV.[1]

Reactions of 2-Benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (5) with 3-Ethoxyisobenzofuran-1(3H)-one (6b)

(i) *With phenyllithium.*—To a solution of the Reissert compound[31] (5) (260 mg, 1 mmol) in dry ether (4 ml) and dioxan (2 ml) at −40° under nitrogen, 0·6 M phenyllithium (2 ml, 1·2 mmol) was added slowly. A solution of the phthalide (6b)[13] (178 mg, 1 mmol) in dry ether (2 ml) was added, and the solution stirred at −10° for 1 h, then at 20° for 4 h. Water (10 ml) was added and the organic layer was separated, dried and solvent-evaporated to give a pale yellow oil (368 mg) which was separated by preparative t.l.c. with ether/light petroleum 1 : 1. The lower-R_F product was recrystallized from ethyl acetate/light petroleum to give *ethyl 2-(benzoyloxyisoquinol-1-ylmethyl)benzoate* (9) (109 mg, 30%), m.p. 127° (Found: C, 75·8; H, 5·2; N, 3·2; $M^{+\cdot}$, 411·1470. $C_{26}H_{21}NO_4$ requires C, 75·9; H, 5·1; N, 3·4%; $M^{+\cdot}$, 411·1470). ν_{max} ($CHCl_3$) 1720, 1200 cm^{-1}. N.m.r. δ 8·90, s, 1H, H9; 8·46, d, *J* 6 Hz, H3; 8·40–7·23, m, 14H; 4·15, q, *J* 7 Hz, OCH_2; 1·10, t, *J* 7 Hz, CH_3.

The middle R_F product was unchanged (5) (68 mg; 26%) and the highest R_F product was recrystallized from ethyl acetate/light petroleum as colourless needles of isoquinolin-1-yl(diphenyl)methanol (7) (45 mg, 16%), m.p. 136–137° (lit.[22] 143°) (Found: C, 84·8; H, 5·5; N, 4·6. Calc. for $C_{22}H_{17}NO$: C, 84·9; H, 5·5; N, 4·4%).

(ii) *With sodium hydride.*—Sodium hydride (79 mg, 50% in oil, 1·65 mmol) was washed with hexane at 0° under nitrogen, and then was covered with dry dimethylformamide (3 ml). A solution

[28] Marshall, P. A., Mooney, B. A., Prager, R. H., and Ward, A. D., unpublished data.
[29] Duong, T., Prager, R. H., Ward, A. D., and Kerr, D. I. B., *Aust. J. Chem.*, 1976, **29**, 2651.
[30] Hutchison, G. I., Prager, R. H., and Ward, A. D., *Aust. J. Chem.*, 1980, **33**, 2477.
[31] Popp, F. D., and Blount, W., *Chem. Ind. (London)*, 1961, 550.

of (5) (390 mg, 1·5 mmol) in dimethylformamide (2 ml) was introduced and the mixture stirred at −5° for 5 min. A solution of 3-ethoxyisobenzofuran-1(3*H*)-one (6b) (246 mg, 1·5 mmol) in dimethylformamide (2 ml) was added slowly and the mixture stirred at 20° for 18 h. Ethanol (2 ml) was added, and the mixture evaporated to dryness under high vacuum. The residue was extracted with ethyl acetate (3×20 ml) which yielded a solid (470 mg), the n.m.r. spectrum of which showed the presence of the benzoate (9), isocarbostyril and isoquinoline. The mixture was hydrolysed with sodium hydroxide in methanol at 70° for 2 h. The solvent was removed, then water (10 ml) was added, and the mixture extracted with dichloromethane (2×15 ml) which yielded a solid (79 mg) consisting of isocarbostyril (32%) and isoquinoline (8%), the structure of which was confirmed by n.m.r. and i.r. spectroscopy and by direct comparison. The aqueous phase was acidified with 10% HCl and boiled for 10 h, made alkaline with solid potassium carbonate and extracted with dichloromethane (3×15 ml). The combined extracts yielded 3-(isoquinolin-1-yl)isobenzofuran-1(3*H*)-one (2) (140 mg, 49%), m.p. 153–154° (lit.[10] 150–152°). Benzoic acid (74 mg) was isolated from the acid fraction.

(iii) *Under phase-transfer conditions.*—To a solution of (5) (520 mg, 2 mmol), (6b) (370 mg, 2 mmol), and benzyltriethylammonium chloride (30 mg) in dichloromethane (15 ml) at 20° under nitrogen, was added a 50% solution of potassium hydroxide (1 ml) dropwise. After 1 h of vigorous stirring, water (10 ml) was added and the organic phase and an extract of the aqueous phase were dried and solvent evaporated to yield a yellow oil (512 mg) which was separated by preparative t.l.c. (5% ether/dichloromethane). A major band yielded the benzoate (9) (154 mg, 24%). The aqueous phase was acidified to pH 3 and extracted with dichloromethane (3×15 ml), which yielded a yellow oil (292 mg). A major component was isolated by preparative t.l.c. and identified as the phthalideisoquinoline (2) (73 mg, 19%).

Reaction of 2-Benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (5) with 3-Bromoisobenzofuran-1(3H)-one (6a)

(i) When Reissert compound (5) was made to react with (6a) in the presence of phenyllithium as above, the product was the alcohol (7) (12%), and the alkylated product (8) (23%) [ν_{max} ($CHCl_3$) 2400, 1770, 1680 cm^{-1}; n.m.r. δ 8·30, d, *J* 8 Hz, H4; 8·16–6·56, m, 14H, ArH and CHO; 5·83, d, *J* 8 Hz, H3] which was hydrolysed with alkali to yield the phthalideisoquinoline (2). When sodium hydride in dimethylformamide was used, as above, the products were (8) (20%) and 1-benzoylisoquinoline, m.p. and mixed m.p. 74° (lit.[32] 75–76°) (54%).

(ii) Reaction of compounds (5) and (6a) in the presence of sodium hydride in dimethylformamide, as detailed above, gave isoquinoline (10%), 1-benzoylisoquinoline (10%), benzoic acid (72%) and the required 3-(isoquinolin-1-yl)isobenzofuran-1(3*H*)-one (2) (18%).

Reactions of 2-Benzoyl-1,2-dihydroisoquinoline-1-carbonitrile (5) with 3-Hydroxyisobenzofuran-1(3H)-one (Phthalaldehydic Acid) (6c)

(i) *With phenyllithium.*—The anion of (5) (3 mmol) was generated by phenyllithium at −40° as above. Then a solution of (6c) (0·45 g, 3 mmol) in ether (1 ml) and dioxan (6 ml), to which 0·4 M phenyllithium (8 ml, 3·2 mmol) had been added, was added slowly and the mixture stirred at 0° for 1 h and then at 20° for 4 h. Workup as above allowed the isolation of 1-benzoylisoquinoline (0·041 g, 6%), unchanged Reissert compound (0·345 g, 44%) and the alcohol (7) (0·189 g, 36%).

(ii) *Under phase-transfer conditions.*—The general procedure was that adopted above. Attempts to find the optimum conditions are summarized in Table 2.

(iii) *With sodium hydride.*—When the procedure detailed above with (6b) was used, the products isolated were isoquinoline (32%), 1-benzoylisoquinoline (61%), phthalaldehydic acid (82%) and benzoic acid (97%).

Isoquinoline-1-carbonitrile

A mixture of the Reissert compound (5) (1·10 g, 4·3 mmol) and benzyltriethylammonium chloride (120 mg) in benzene (35 ml) and 50% potassium hydroxide (8 ml) was vigorously stirred in an open flask at 20° for 5 h. The phases were separated, the aqueous phase extracted with dichloromethane (3×30 ml), and the combined organic phases washed with water, dried (Na_2SO_4) and

[32] Popp, F. D., and Wefer, J. M., *J. Heterocycl. Chem.*, 1967, **41**, 183.

evaporated to dryness. The resultant solid was recrystallized from hexane to give isoquinoline-1-carbonitrile (0·56 g, 95%), m.p. 91° (lit.[14] 86–87°), with identical infrared and n.m.r. spectra to that of an authentic specimen.

Table 2. Reaction of the Reissert compound (5) with (6c) under phase-transfer conditions

Reactions under nitrogen unless specified otherwise

Mole ratio (6c)/(5)	Temp. (°C)	Phase-transfer catalyst	Solvent	Yield of (2) (%)
1	20	$PhCH_2(Et_3)NCl$	CH_2Cl_2	45
1·3	20	$PhCH_2(Et_3)NCl$	CH_2Cl_2	48
2	20	$PhCH_2(Et_3)NCl$	CH_2Cl_2	48
1·3	−70	$PhCH_2(Et_3)NCl$	CH_2Cl_2	32
1·3	−30	$PhCH_2(Et_3)NCl$	CH_2Cl_2	32
1·3	0	$PhCH_2(Et_3)NCl$	CH_2Cl_2	27
1·3	20	$PhCH_2(Et_3)NCl$	C_6H_6	72
1·3	20	$PhCH_2(Et_3)NCl$	nil	64
1·3	20	$PhCH_2(Et_3)NCl$	CH_2Cl_2[A]	49
1·3	20	Bu_4NHSO_4	C_6H_6	45[B]

[A] Nitrogen not rigorously excluded; product contains 27% isoquinoline-1-carbonitrile. [B] Reaction was only 60% complete.

3-(Isoquinolin-1-yl)-5,6-dimethoxyisobenzofuran-1(3H)-one (10)

Under the phase-transfer conditions, above, with benzene as solvent at 20°, the *phthalideisoquinoline* (10) was obtained from reaction of (5) with 5,6-dimethoxyphthalaldehydic acid as a colourless solid (56%), m.p. 174°, from dichloromethane/light petroleum (Found: C, 70·9; H, 5·0; N, 4·4. $C_{19}H_{15}NO_4$ requires C, 71·0; H, 4·7; N, 4·4%). ν_{max} ($CHCl_3$) 1760, 1600 cm^{-1}. N.m.r. δ: 8·41, d, *J* 6 Hz, H3; 8·23–6·96, m, 7H; 6·83, s, CHO; 3·96, 3·85, both s, OCH_3. Mass spectrum *m/e* 321 (M). The yield of (10) was only 20% when dichloromethane was used as solvent.

3-(Isoquinolin-1-yl)-6-methoxyisobenzofuran-1(3H)-one (11)

Reaction of (5) with 6-methoxyphthalaldehydic acid under phase-transfer conditions as above gave the *phthalideisoquinoline* (11) (48%), m.p. 167–168° from ethyl acetate/light petroleum (Found: C, 74·6; H, 4·5; N, 4·7; $M^{+\cdot}$, 291·0892. $C_{18}H_{13}NO_3$ requires C, 74·2; H, 4·5; N, 4·8%; $M^{+\cdot}$, 291·0895). ν_{max} ($CHCl_3$) 1760 cm^{-1}. N.m.r. δ 8·33, d, *J* 6 Hz, H3; 7·93–7·10, m, 8H; 7·06, s, CHO; 3·85, s, OCH_3. Mass spectrum *m/e* 291 (M).

3-(Isoquinolin-1-yl)-6,7-dimethoxyisobenzofuran-1(3H)-one (12)

Reaction of (5) with 6,7-dimethoxyphthaldehydic acid under phase-transfer conditions, as above, gave the *phthalideisoquinoline* (12) (59%) after continuous extraction with dichloromethane, m.p. 159° after recrystallization from ethyl acetate/light petroleum (Found: C, 70·8; H, 4·7; N, 4·1; $M^{+\cdot}$, 321·0997. $C_{19}H_{15}NO_4$ requires C, 71·0; H, 4·7; N, 4·4%; $M^{+\cdot}$, 321·1000). ν_{max} ($CHCl_3$) 1760 cm^{-1}. N.m.r. δ 8·56, d, *J* 6 Hz, H3; 8·40–6·90, m, 8H, ArH; 7·10, s, CH–O, 4·20, 3·91, both s, OCH_3.

Reaction of the Reissert Compound (5) with 6,7-Methylenedioxyphthalaldehydic Acid

Using the standard conditions described above the products isolated and characterized by direct comparison with authentic samples were isoquinoline-1-carbonitrile (66%), isoquinoline (31%) and benzoic acid (90%).

Reaction of the Reissert Compound (5) with 6-Nitrophthalaldehydic Acid[33]

When this reaction was carried out under the standard phase-transfer conditions isoquinoline-1-carbonitrile (71%) was isolated but no products derivable from the nitro compound could be

[33] Hoenig, M., *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 3447.

characterized. In the presence of the radical inhibitor hydroquinone the yield of the isoquinoline-1-carbonitrile was increased to 98%.

3-(3-Methylisoquinolin-1-yl)isobenzofuran-1(3H)-one (13)

The reaction of 2-benzoyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile[18] with phthalaldehydic acid, under phase-transfer conditions as above, gave the *phthalideisoquinoline* (13) (44%), m.p. 148–149° after recrystallization from dichloromethane/light petroleum (Found: C, 78·7; H, 4·8; N, 5·2. $C_{18}H_{13}NO_2$ requires C, 78·5; H, 4·8; N, 5·1%). ν_{max} ($CHCl_3$) 1760, 1585 cm^{-1}. N.m.r. δ 8·23–7·23, m, 9H; 7·16, s, CHO; 2·58, s, CH_3.

When dichloromethane was used as the solvent for this reaction the product was not (13) but 1-benzoyl-3-methylisoquinoline, m.p. 103° (lit.[18] 102°). ν_{max} 1660, 1590 cm^{-1}. N.m.r. δ 8·21–7·26, m, 10H; 2·71, s, CH_3.

Attempted Reactions of 2-Benzoyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile with Substituted Phthalaldehydic Acids

Reactions of the substituted dihydroisoquinoline with 5,6-dimethoxy- or 6-methoxy-phthalaldehydic acid under phase-transfer conditions as described above gave none of the desired phthalideisoquinolines. The major product in each case was 1-benzoyl-3-methylisoquinoline (40–92%).

Reaction of 2-Benzoyl-6,7-methylenedioxy-1,2-dihydroisoquinoline-1-carbonitrile (14) with Phthalaldehydic Acid

Reaction of the dihydroisoquinoline[34] with phthalaldehydic acid under the usual phase-transfer conditions led to the isolation of *6,7-methylenedioxyisoquinoline-1-carbonitrile* (60%), m.p. 230° after recrystallization from dichloromethane/light petroleum (Found: C, 66·3; H, 3·0; N, 14·0. $C_{11}H_6N_2O_2$ requires C, 66·6; H, 3·0; N, 14·1%). ν_{max} ($CHCl_3$) 2220 cm^{-1}. N.m.r. δ 8·48, d, *J* 6 Hz, H3; 7·70, d, *J* 6 Hz, H4; 7·58, s, 1H; 7·15, s, 1H; 6·20, s, OCH_2O. Mass spectrum *m/e* 198 (M).

Reaction of 3-Methyl-2-(4-nitrobenzoyl)-1,2-dihydroisoquinoline-1-carbonitrile with 6-Methoxyphthalaldehydic Acid

The *Reissert compound* was prepared by the general method of Popp[12] in 40% yield and had m.p. 148° after recrystallization from dichloromethane/light petroleum (Found: C, 67·5; H, 4·2; N, 13·2. $C_{18}H_{13}N_3O_3$ requires C, 67·7; H, 4·1; N, 13·2%). ν_{max} ($CHCl_3$) 1670, 1530 cm^{-1}. N.m.r. δ 8·26, d, *J* 8 Hz, 2H, ArH; 7·21, d, *J* 8 Hz, 2H, ArH; 7·51–7·20, m, 4H, ArH; 6·53, s, 1H; 6·33, s, 1H; 1·81, s, CH_3. Mass spectrum *m/e* 319 (M). The Reissert compound and 6-methoxyphthalaldehydic acid were made to react under phase-transfer conditions and worked up as described above to yield 3-methylisoquinoline-1-carbonitrile, m.p. and mixed[35] m.p. 98° (95%) and 4-nitrobenzoic acid (62%).

Preparation and Reactions of Reissert Compounds from 5-Nitroisoquinoline

(i) Attempts to prepare 2-benzoyl-5-nitro-1,2-dihydroisoquinoline-1-carbonitrile by the method of Popp[31] resulted in very low yields. By using solid potassium cyanide, in the absence of water, and with a phase-transfer catalyst, better, but still unacceptable, yields could be obtained.

(ii) *Reactions of ethyl 1-cyano-5-nitro-1,2-dihydroisoquinoline-2-carboxylate (15).*—To a solution of 5-nitroisoquinoline (0·552 g, 3 mmol) in dichloromethane (5 ml) under nitrogen at 20°, was added a solution of potassium cyanide (1·58 g, 14 mmol) in water (10 ml). To the vigorously stirred mixture was added slowly ethyl chloroformate (0·9 g, 9 mmol), and stirring was continued for 18 h. The organic phase and three washings of the aqueous phase were combined, washed with water, 3% hydrochloric acid, water, dried and evaporated to give the Reissert compound (15) as an unstable yellow oil (0·548 g, 64%), which was characterized only by its spectral properties. ν_{max} ($CHCl_3$) 1730, 1620, 1530, 1340 cm^{-1}. N.m.r. δ 8·76–6·59, m, 5H; 6·36, s, H1; 4·33, q, OCH_2CH_3; 1·38, t, OCH_2CH_3. Mass spectrum *m/e* 273 (M).

[34] Birch, A. J., Jackson, A. H., and Shannon, P. V. R., *J. Chem. Soc., Perkin Trans. 1*, 1974, 2185.
[35] Wefer, J. M., Catala, A., and Popp, F. D., *J. Org. Chem.*, 1965, **30**, 3075.

Reaction of this Reissert compound with methyl 2-formylbenzoate under phase-transfer conditions in the presence of potassium carbonate led only to the recovery of unchanged Reissert compound (84%). When these two reactants were treated under the usual phase-transfer conditions, the reaction turned red-black, and the majority of the product was water-soluble and could not be isolated by continuous dichloromethane extraction at pH 4, 7 or 9. The only isolated product was a yellow oil (15%), the spectral characteristics of which were consistent with it containing mainly ethyl 5-nitroisoquinoline-1-carboxylate. ν_{max} 1730, 1630, 1530 cm^{-1}. N.m.r. δ 8·76–6·59, m, 5H; 4·33, q, OCH_2; 1·36, t, CH_3. Mass spectrum *m/e* 247 (M+1).

When (15) was treated with 1 equiv. of methyl 2-formyl-4,5-dimethoxybenzoate under the standard conditions in dimethylformamide in the presence of sodium hydride, a 5% yield of the desired product, *ethyl* [*(4,5-dimethoxy-2-methoxycarbonylphenyl)(5-nitroisoquinolin-1-yl)]methyl carbonate*, was obtained as a colourless oil by t.l.c. (Found: accurate mass 470·1325. $C_{23}H_{22}N_2O_9$ requires 470·1312). ν_{max} (film) 1745, 1720, 1600, 1520, 1350 cm^{-1}. N.m.r. δ 8·61, s, 1H; 8·5–6·3, m, 7H; 4·10–3·73, m, 11H, 3×OCH_3, OCH_2; 1·23, t, CH_3.

Reaction of Reissert Compounds with Methyl 2-Formylbenzoates

(i) *Reaction of 2-benzoyl-6,7-methylenedioxyisoquinoline-1-carbonitrile (14) with methyl 4,5-dimethoxy-2-formylbenzoate.*—A solution of (14) (244 mg, 0·8 mmol) in dry dimethylformamide (5 ml) was added slowly to sodium hydride (48 mg) in dimethylformamide at −10° under nitrogen. After 5 min a solution of methyl 4,5-dimethoxy-2-formylbenzoate (179 mg, 0·8 mmol) in dimethylformamide (4 ml) was added slowly over 10 min and stirring was continued for 2 h at 0° and 18 h at 20°. Water was then added and the mixture was extracted with dichloromethane to yield a yellow oil (360 mg) which contained the desired benzoate. The oil was refluxed for 1 h with sodium hydroxide in methanol and worked up to give an acidic and a non-acidic fraction. The latter (88 mg) was separated by preparative t.l.c. into 6,7-methylenedioxyisoquinoline (30 mg, 24%) and 1-benzoyl-6,7-methylenedioxyisoquinoline, m.p. 142° (lit.[36] 144°) (58 mg, 30%).

The acidic fraction was boiled briefly with dilute hydrochloric acid, basified to pH 9 and then extracted with dichloromethane to give *5,6-dimethoxy-3-(6,7-methylenedioxyisoquinolin-1-yl)isobenzofuran-1(3H)-one* (19) (110 mg, 43%), m.p. 204° after recrystallization from ethyl acetate (Found: $M^{+\cdot}$, 365·0891. $C_{20}H_{15}NO_2$ requires $M^{+\cdot}$, 365·0899). ν_{max} ($CHCl_3$) 1765, 1470 cm^{-1}. N.m.r. δ 8·46–6·46, m, 6H; 7·05, s, CH–O; 6·06, s, OCH_2O; 3·96, s, 2×OCH_3.

(ii) *Reaction of (5) with methyl 2-formyl-3,4-methylenedioxybenzoate.*—By the procedure described in (i) above *3-(isoquinolin-1-yl)-6,7-methylenedioxyisobenzofuran-1(3H)-one* (16) was obtained in 19% yield, m.p. 192°, after recrystallization from ethyl acetate (Found: C, 71·1; H, 3·4; N, 4·8. $C_{18}H_{11}NO_4$ requires C, 70·8; H, 3·6; N, 4·6%). ν_{max} ($CHCl_3$) 1765 cm^{-1}. N.m.r. δ 8·50, d, *J* 6 Hz, H3; 8·33–6·80, m, 8H, ArH and CH–O; 6·23, s, OCH_2O.

(iii) *Reaction of (14) with methyl 2-formylbenzoate.*—The Reissert compound (14) (304 mg, 1 mmol) and methyl 2-formylbenzoate[37] (164 mg, 1 mmol) were allowed to react under the usual phase-transfer conditions. The basic material (159 mg) was separated into two fractions by preparative t.l.c. (ethyl acetate). The upper fraction (110 mg) was identified as a mixture of 6,7-methylenedioxyisoquinoline-1-carbonitrile, which was identified by its n.m.r. spectrum, and [*(2-methoxycarbonylphenyl)(6,7-methylenedioxyisoquinolin-1-yl)]methyl benzoate* (Found: $M^{+\cdot}$, 441·1217. $C_{26}H_{19}NO_6$ requires $M^{+\cdot}$, 441·1211). ν_{max} ($CHCl_3$) 1720 cm^{-1}. N.m.r. δ 8·59, s, H9; 8·14, d, *J* 6 Hz, H3; 8·16–7·10, m, 12H; 6·03, s, OCH_2O; 3·66, s, OCH_3. The third fraction was 6,7-methylenedioxyisoquinoline (27 mg, 18%).

The mixture containing the benzoate was hydrolysed with aqueous sodium hydroxide, extracted with dichloromethane, acidified to pH 2 with dilute hydrochloric acid and, after 5 min, made alkaline with solid sodium carbonate. Extraction with dichloromethane gave *3-(6,7-methylenedioxyisoquinolin-1-yl)isobenzofuran-1(3H)-one* (20) (7 mg), m.p. 168–169° after recrystallization from dichloromethane/light petroleum (Found: $M^{+\cdot}$, 305·0689. $C_{18}H_{11}NO_4$ requires $M^{+\cdot}$, 305·0688). ν_{max} ($CHCl_3$) 1765, 1480 cm^{-1}. N.m.r. δ 8·45, d, *J* 6 Hz, H3; 8·30–7·20, m, 7H; 7·10, s, CH–O; 6·20, s, OCH_2O.

[36] Weisbach, J. A., Kirkpatrick, J. L., Macko, E., and Douglas, B., *J. Med. Chem.*, 1968, **11**, 760.
[37] Brown, C., and Sargent, M. V., *J. Chem. Soc. C*, 1969, 1818.

(iv) *Reaction of (14) with methyl 2-formyl-3,4-methylenedioxybenzoate.*—By the procedure described in (i) above *6,7-methylenedioxy-3-(6,7-methylenedioxyisoquinolin-1-yl)isobenzofuran-1(3H)-one* (17) was obtained in 45% yield, m.p. 212–214° after recrystallization from ethyl acetate (Found: C, 65·6; H, 3·4; N, 3·9. $C_{19}H_{11}NO_6$ requires C, 65·3; H, 3·2; N, 4·0%). ν_{max} ($CHCl_3$) 1765, 1470 cm^{-1}. N.m.r. δ 9·00, d, J 6 Hz, H 3; 8·50–6·93, m, 6H; 6·10, s, 2 × OCH_2O.

(v) *Reaction of (14) with methyl 2-formyl-4-methoxybenzoate.*—By the procedure described in (i) above *6-methoxy-3-(6,7-methylenedioxyisoquinolin-1-yl)isobenzofuran-1(3H)-one* (18) was obtained in 31% yield, m.p. 187–188°, after recrystallization from ethyl acetate/light petroleum (Found: C, 67·8; H, 4·2; N, 3·9. $C_{19}H_{13}NO_5$ requires C, 68·1; H, 3·9; N, 4·2%). ν_{max} ($CHCl_3$) 1765 cm^{-1}. N.m.r. δ 8·20, d, J 6 Hz, H 3; 7·46–6·83, m, 7H; 6·05, s, OCH_2O; 3·86, s, OCH_3. Mass spectrum *m/e* 335 (M).

(vi) By the procedure described in (i) above, compound (11), identical with that prepared previously, was obtained in 37% yield.

(vii) Under the conditions described in (i) above, 2-benzoyl-3-methyl-1,2-dihydroisoquinoline-1-carbonitrile and methyl 2-formyl-3,4-methylenedioxybenzoate failed to give the desired phthalideisoquinoline; the product, isolated in 95% yield, was 1-benzoyl-3-methylisoquinoline.

Methyl 2-Formyl-5-methoxybenzoate

Potassium carbonate (10 g) was added to a solution of 6-methoxyphthalaldehydic acid[38] (3 g) and methyl iodide (5 ml) in acetone, and the mixture refluxed for 12 h. The mixture was cooled, diluted with dichloromethane (100 ml), filtered, and the solvent removed from the filtrate to yield a pale yellow solid (2·9 g, 91%) which was sufficiently pure for further reaction. A small sample was distilled for analysis, b.p. 175–180°/15 mm (block) (Found: C, 62·1; H, 5·4. $C_{10}H_{10}O_4$ requires C, 61·9; H, 5·2%). ν_{max} (film) 1715, 1680 cm^{-1}. N.m.r. δ 10·23, s, CHO; 7·8, d, J 8 Hz, H 6; 7·25, d, J 3 Hz, H 3; 7·0, dd, J 8, 3 Hz, H 5; 3·9, s, OCH_3, CO_2CH_3.

Methyl 2-Formyl-5,6-methylenedioxybenzoate

This *compound* was prepared in an analogous manner to that above (74%), and had b.p. 123–126°/0·5 mm (block) (Found: C, 58·2; H, 4·2. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%). ν_{max} (film) 1710, 1680, 1615 cm^{-1}. N.m.r. δ 10·0, s, CHO; 7·45, d, J 8 Hz, H 6; 6·9, d, J 8 Hz, H 5; 6·1, s, OCH_2O; 4·0, s, CO_2CH_3.

6,7-Dimethoxy-3-(phthalazin-1-yl)isobenzofuran-1(3H)-one (23)

This *compound* was obtained in 20% yield under the standard phase-transfer conditions from 2-benzoyl-1,2-dihydrophthalazine-1-carbonitrile[39] and 6,7-dimethoxyphthalaldehydic acid, and had m.p. 181–182°, from ethanol (Found: C, 67·1; H, 4·4; N, 8·7. $C_{18}H_{14}N_2O_4$ requires C, 66·9; H, 4·5; N, 8·6%). ν_{max} 1770 cm^{-1}. N.m.r. δ 9·3, s, H 4; 8·0–7·6, m, 4H; 7·1, s, 2H; 6·9, s, CH–O; 4·1, 3·9, both s, OCH_3.

The major by-products were phthalazine and 1-benzoylphthalazine.

3-(Phthalazin-1-yl)isobenzofuran-1(3H)-one (21)

This *compound* was prepared under the standard phase-transfer conditions from 2-benzoyl-1,2-dihydrophthalazine-1-carbonitrile and methyl 2-formylbenzoate in 40% yield, m.p. 186–188° (dec.) (Found: C, 72·9; H, 4·2; N, 10·6. $C_{16}H_{10}N_2O_2$ requires C, 73·3; H, 3·8; N, 10·7%). ν_{max} 1760 cm^{-1}. N.m.r. δ 9·4, s, H 4; 9·1–7·45, m, 8H; 7·2, s, CHO.

6-Methoxy-3-(phthalazin-1-yl)isobenzofuran-1(3H)-one (22)

This *compound* was prepared, as above, from methyl 2-formyl-5-methoxybenzoate in 22% yield, m.p. 169–171° from ethanol (Found: C, 67·0; H, 4·5, N, 9·6. $C_{17}H_{12}N_2O_3$ requires C, 69·9; H, 4·2; N, 10·0%). ν_{max} 1760 cm^{-1}. N.m.r. δ 9·3, s, H 3; 8·0–7·2, m, 7H; 7·0, s, CH–O; 3·9, s, OCH_3.

[38] Blair, J., Brown, J. J., and Newbold, G. T., *J. Chem. Soc.*, 1955, 708.
[39] Popp, F. D., and Wefer, J. M., *Chem. Commun.*, 1967, 59.

6,7-Methylenedioxy-3-(phthalazin-1-yl)isobenzofuran-1(3H)-one (*24*)

This *compound* was prepared, as above, from methyl 2-formyl-5,6-methylenedioxybenzoate in 23% yield, m.p. 193–195° from ethanol (Found: $M^{+\cdot}$, 306·0536. $C_{17}H_{10}N_2O_4$ requires $M^{+\cdot}$, 306·0541). ν_{max} 1760 cm^{-1}. N.m.r. δ 9·37, s, H4; 7·9–7·6, m, 4H; 6·8, d, *J* 8 Hz, ArH; 7·0, d, *J* 8 Hz, ArH; 7·03, s, CH–O; 6·13, s, OCH_2O.

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