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Central Nervous System Active Compounds. IV* Synthesis of 3-Aminobenzylphthalides

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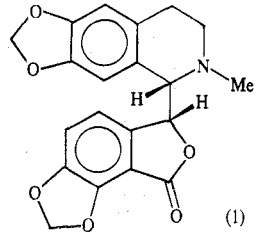
Abstract

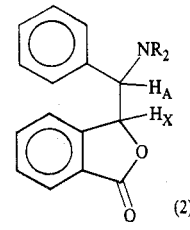
Several 3-aminobenzylphthalides have been prepared by reactions of 3-(2-oxo-1-phenylpropyl)-phthalides with hydrazoic acid or by the Beckmann rearrangement. The corresponding reactions with 3-(2-oxoindanyl)phthalides showed limited success but led to a new synthesis of phthalide-isoquinoline alkaloids. Preliminary biological testing of some of these derivatives indicates that they only have weak central nervous system activity.

Introduction

The convulsant alkaloid (+)-bicuculline[1–4] (1) is a competitive antagonist of γ-aminobutyric acid (GABA), an inhibitory transmitter in the mammalian central nervous system (CNS).[5–8] As part of an investigation into compounds that are analogues of the bicuculline structure we report on new procedures for the synthesis of 3-aminobenzylphthalides† (2) and our attempts to extend these methods to the synthesis of phthalideisoquinolines. In later papers in this series we intend to report other, more general, new approaches to this alkaloid system.



(1)



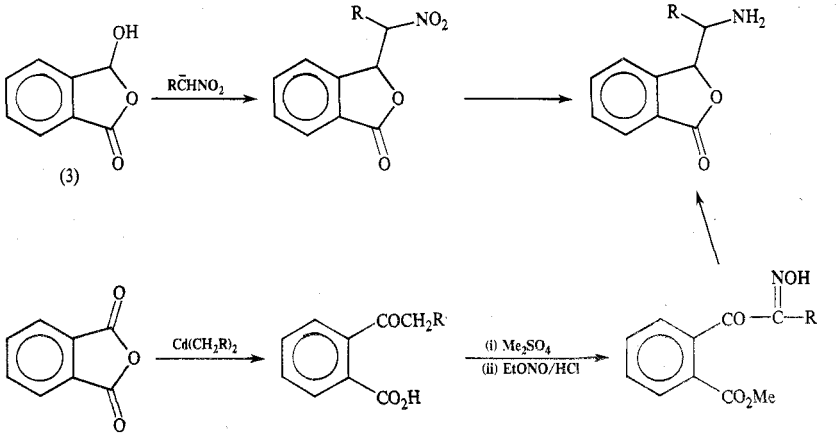
(2)

* Part III, *Aust. J. Chem.*, 1980, **33**, 2477.
† The trivial name 'phthalide' is retained throughout the Discussion section to emphasize the relationship to existing alkaloids.

[1] Manske, R. H. F., *Can. J. Res.*, 1932, **7**, 265.
[2] Manske, R. H. F., *Can. J. Res.*, 1933, **8**, 210, 407.
[3] Manske, R. H. F., *Can. J. Res.*, 1933, **8**, 436.
[4] Shamma, M., 'The Isoquinoline Alkaloids' p. 359 (Academic Press: New York 1972).
[5] Krnjevic, K., *Nature (London)*, 1970, **228**, 119.
[6] Curtis, D. R., Duggan, A. W., Felix, D., and Johnston, G. A. R., *Nature (London)*, 1970, **226**, 1222.
[7] Curtis, D. R., Duggan, A. W., Felix, D., and Johnston, G. A. R., *Nature (London)*, 1970, **228**, 676.
[8] Mitchell, J. F., and Srinivasan, V., *Nature (London)*, 1969, **224**, 663.

Only the *erythro* isomers of the phthalideisoquinolines show biological activity in the CNS.[4,9] Although a similar situation would be expected for compounds of type (2), the lack of the B ring should allow greater flexibility of the system and possibly reduce the steric requirements on molecules bound at the active site in the enzyme–inhibitor complex. The only aminoalkylphthalide so far screened for convulsant activity is 3-aminomethylphthalide and this was found to be inactive.[10] A number of aminoalkylphthalides have been tested for analgesic properties[11,12] but even those with oxygen substitution on the ring did not show convulsant properties.[13,14] Only one 3-aminobenzylphthalide system has been reported (2; R = H) but no biological activity was observed.[15]

Two general methods for the preparation of aminoalkylphthalides have been reported. The first[11,14–18] involves the formation of nitroalkylphthalides from the reaction of nitroalkanes and phthalaldehydic acid (3). However, the catalytic reduction of these products proceeds in poor yield. The second method[12,15] uses phthalic anhydride as starting material (Scheme 1) but the specificity of attack by the organometallic species on an unsymmetrical anhydride has not been ascertained.



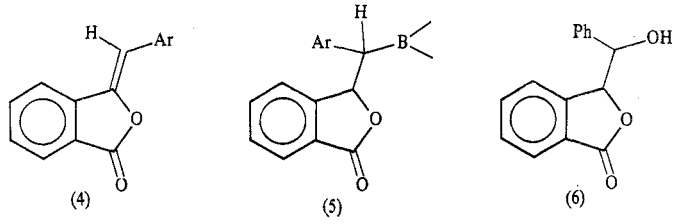
Scheme 1

Discussion

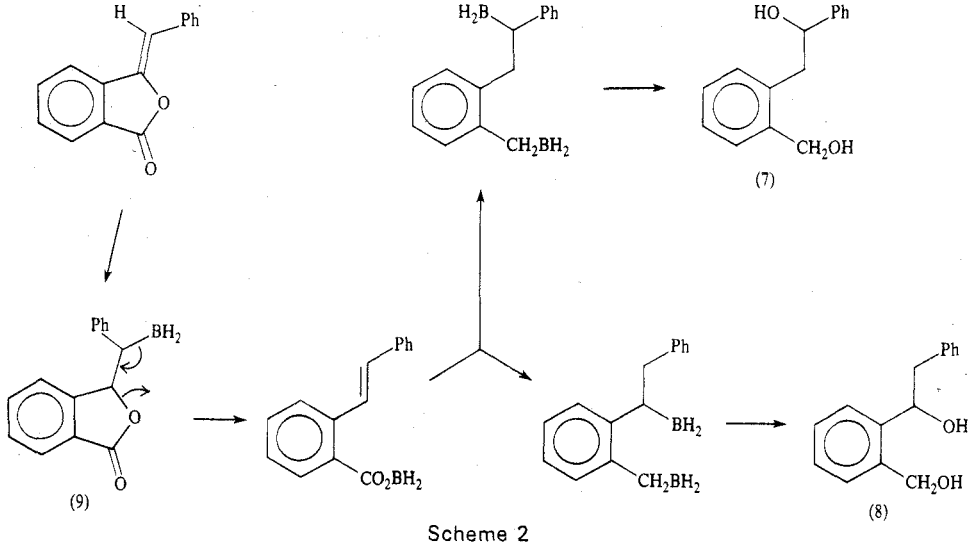
Since amines are readily available from organoboranes by reaction with hydroxylamine-*O*-sulfonic acid[19] it appeared that the 3-arylmethylenephthalides (4) might be capable of utilization in the synthesis of (2). It was hoped that both steric

[9] Tippett, J. M., Ph.D. Thesis, University of Adelaide, 1977.
[10] Beart, P., and Johnston, G. A. R., unpublished data.
[11] Ullyot, G. E., Stehle, J. J., Zirkle, C. L., Shriner, R. L., and Wolf, F. J., *J. Org. Chem.*, 1945, **10**, 429.
[12] Ullyot, G. E., Taylor, H. W., Jr, and Dawson, N., *J. Am. Chem. Soc.*, 1948, **70**, 542.
[13] Ivan, J., *Arzneim.-Forsch.*, 1962, **12**, 453 (*Chem. Abstr.*, 1962, **57**, 6549c).
[14] Beke, D., and Szantay, C., *Period. Polytech.*, 1958, **2**, 89 (*Chem. Abstr.*, 1959, **53**, 7090c).
[15] Wilson, J. W., Zirkle, C. L. Anderson, E. L., Stehle, J. J., and Ullyot, G. E., *J. Org. Chem.*, 1951, **16**, 792.
[16] Beke, D., and Szantay, C., *Arch. Pharm. (Weinheim, Ger.)*, 1958, **291**, 342.
[17] Szantay, C., and Szabo, E., *Period. Polytech.*, 1964, **8**, 15 (*Chem. Abstr.*, 1964, **61**, 9452h).
[18] Hashimoto, T., and Nagase, S., *Yakugaku Zasshi*, 1960, **80**, 1637 (*Chem. Abstr.*, 1961, **55**, 7415d).
[19] Rathke, M. W., Inoue, N., Varma, K. R., and Brown, H. C., *J. Am. Chem. Soc.*, 1966, **88**, 2870.

and electronic factors[20] would favour the addition of boron to yield (5) as the major product. Furthermore, because of the stereospecific nature of the borane addition the procedure should produce stereochemically pure amines from the (*E*)- and (*Z*)-isomers of (4), both of which are readily available.[21]



The reaction of (4) with diborane was quite slow and more than one equivalent of hydride was required to effect a complete reaction. To check the direction of addition of diborane the intermediate organoborane was oxidized but the product was not the expected alcohol (6) but a 1 : 1 mixture of the diols (7) and (8). It appears that the initial product (9) undergoes a rapid elimination and rehydroboration as shown in Scheme 2. Unfortunately (4) was virtually inert towards disiamylborane, which would have been more likely to give a hydroboration product less prone to the above elimination.[22]

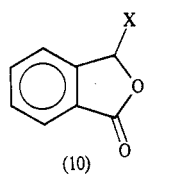


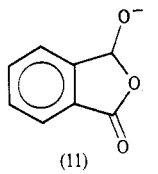
Scheme 2

In view of the above results it was decided to elaborate the required system (2) by utilizing the high electrophilicity of phthalaldehydic acid (3). This compound reacts[23] with weak nucleophiles (e.g. alcohols, thiols, amines and even amides) to form the corresponding derivatives (10; X = OR, SR etc). Stronger nucleophiles

[20] Hydroboration of isopropenyl acetate, quoted in ref. 16, Brown, H. C., and Sharp, R. L., *J. Am. Chem. Soc.*, 1968, **90**, 2915.
[21] Howe, R. K., *J. Org. Chem.*, 1973, **38**, 4164.
[22] Brown, H. C., and Cope, O. J., *J. Am. Chem. Soc.*, 1964, **86**, 1801.
[23] Wheeler, D. D., Young, D. C., and Erley, D. S., *J. Org. Chem.*, 1957, **22**, 547.

are sufficiently basic to form the anion (11) which, however, can still behave as an electrophile through the alternate form, (12), although this system is much less reactive than a normal aldehyde. We planned therefore to attach a 2-oxo-1-phenylpropyl substituent at the 3-position of the isobenzofuran system of (3) and to convert this product (13), by a Beckmann or a Schmidt rearrangement, into the acetylated derivative (14) of our required system (2).


(10)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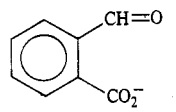
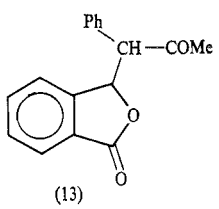

(12)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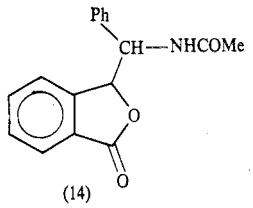
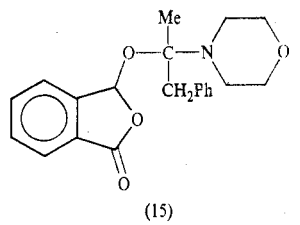
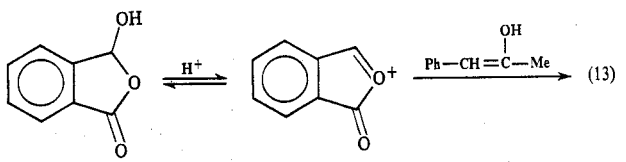

(14)


(15)

When the morpholine enamine of phenylpropan-2-one was treated with (3) the product obtained was not the expected enamine of (13) but instead (15) which presumably is formed after protonation of the enamine to an iminium salt. Alkylation of the enamine with 3-bromophthalide gave no recognizable products.

Alkylation of phenylpropan-2-one in basic conditions leads,[24] in some circumstances, to preferential reaction at the methyl group, a result which indicates that this system would not give the desired product (13) with (12). However, it has recently been shown[25] that phenylpropan-2-one undergoes an acid-catalysed alkylation with *p*-tolualdehyde to give the product of benzyl substitution. It was thus not surprising to find that phenylpropan-2-one and (3), in the presence of *p*-toluenesulfonic acid, gave a good yield of (13), which was obtained as a mixture of diastereoisomers. Although this reaction has proved to be a general one for the preparation of a range



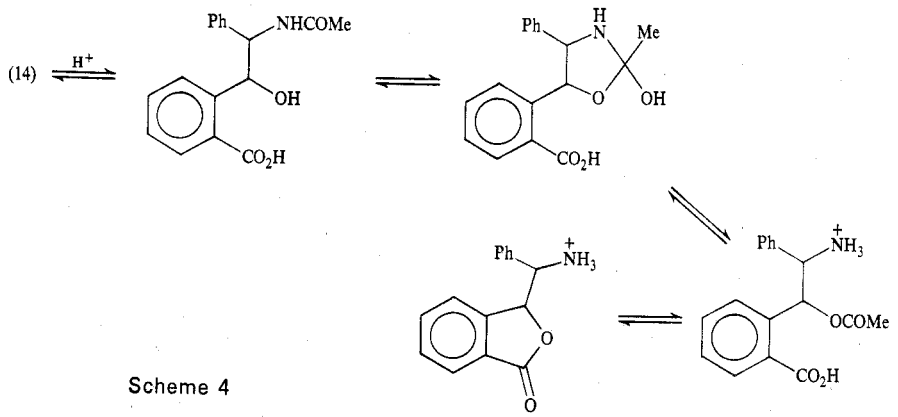
Scheme 3

[24] Fine, S. A., and Pulaski, P. D., *J. Org. Chem.*, 1973, **38**, 1747; but compare Suter, C. M., and Weston, A. W., *J. Am. Chem. Soc.*, 1942, **64**, 533.

[25] Onoda, R., Sasaki, K., and Kato, T., *Akita Daigaku Kyoiku Gakubu Kenkyu Kiyo, Shizen Kagaku*, 1973, 37 (*Chem. Abstr.*, 1973, **79**, 115262k).

of substituted arylpropan-2-ones, (13) and (17)–(20), it was unsuitable when phenylacetic acid, ethyl phenylacetate, phenylacetonitrile and the hydrazone (16) were subjected to similar conditions, for little or no reaction occurred with these compounds. Phenylacetaldehyde appeared to give some of the analogous product but this material could not be isolated because of its instability under the reaction conditions. We consider that the reactions with the arylpropan-2-ones proceed as shown in Scheme 3 since electron-donating substituents on the phthalide ring increased the rate of the reaction. This trend would not be the case if the open aldehyde form of the hydroxyphthalide (3) was the reactive species.

The Beckmann rearrangement of the oxime of (13) was not a very satisfactory reaction, being best achieved with *p*-toluenesulfonyl chloride in pyridine but the Schmidt rearrangement in polyphosphoric acid proceeded smoothly to give exclusively (14) which was readily hydrolysed to the desired amine (2; R = H) under acidic conditions. The ease of this hydrolysis suggests that it may be proceeding as shown in Scheme 4. The mixture of diastereoisomers of (2; R = H) was readily separated by chromatography. It is not possible at this stage to unambiguously assign the stereochemistry of these isomers as the possibility of hydrogen bonding between the lactone group and the amino group[26] complicates the interpretation of the coupling constant between H_A and H_X in (2). The required arylpropan-2-ones were conveniently prepared by rearrangement of the corresponding styryl epoxides with boron trifluoride.



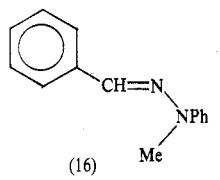
Scheme 4

Although the Schmidt reaction of (13) proceeded well, the analogous reaction of (17) and (18) did not yield any of the required amide. In ether, when the least fragmentation would be expected[27] the reaction did not proceed at all and in benzene and polyphosphoric acid fragmentation was the major pathway. As expected[27] the *meta*-substituted compound (19) afforded the required amide in high yield. The Beckmann rearrangement of the oxime tosylates of (17) and (18) gave only low yields of the required amides.

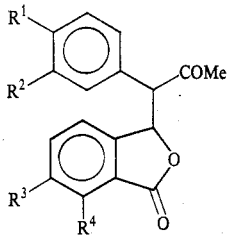
In principle, indan-2-one should also behave in a similar fashion to the arylpropan-2-ones. Indeed, the acid-catalysed condensation of indan-2-one and phthalaldehydic

[26] Shamma, M., and Georgiev, V. St., *Tetrahedron*, 1976, **32**, 211.
[27] Prager, R. H., Tippett, J. M., and Ward, A. D., *Aust. J. Chem.*, 1978, **31**, 1989.

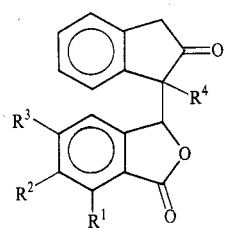
acid (3) proceeded smoothly to give the desired product (21), apparently as a single isomer, contaminated only by a small amount of the dialkylated product (27). In some analogous reactions with substituted phthalaldehydic acids, the presence of both isomers could be seen in the ^{1}H n.m.r. spectrum of the total product. 3-Bromophthalide did not react cleanly with either the enolate or an enamine of indan-2-one; complex reaction mixtures were also obtained with the analogous reactions of arylpropan-2-ones.



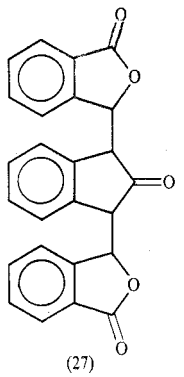
(16)



	R^1	R^2	R^3	R^4
(13)	H	H	H	H
(17)	OCH_2O		H	H
(18)	OMe	H	H	H
(19)	H	OMe	H	H
(20)	H	H	OMe	OMe



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

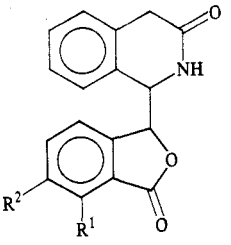


(27)

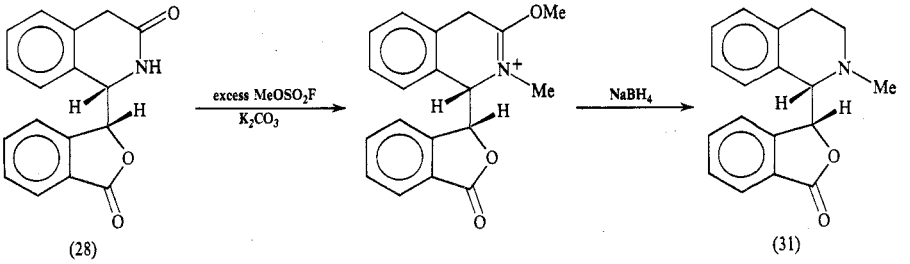
The conversion of (21) into (28) by the Schmidt reaction proved to be difficult to reproduce with commercial samples of polyphosphoric acid, and mixtures of phosphorus pentoxide in polyphosphoric acid were used to determine optimum conditions for each reaction leading to (28)–(30). The amide (28) was formed to the exclusion of the alternate rearrangement product, an expected result in view of the product composition noted with (13) and its analogues, and from the expectation that the more substituted bond should migrate.[28,29] Again the reaction proceeded without apparent epimerization at either of the chiral centres. From a comparison of the chemical shifts of the proton at C1, C9 and C2′ with the corresponding proton of some analogous synthetic phthalideisoquinolines,[26,30] the relative configuration of (28) is suggested to be *erythro*. This assignment was confirmed, as shown in Scheme 5, by the conversion of (28) into the *erythro* isomer of the phthalideisoquinoline (31), both isomers of which were available from other work.[9] It was not possible to isolate the intermediate imino ether from this sequence; hence the secondary amine

[28] Smith, P. A. S., *J. Am. Chem. Soc.*, 1950, **72**, 3718.
[29] Briggs, L. H., and Lyttleton, J. W., *J. Chem. Soc.*, 1943, 421.
[30] Shamma, M., and Georgiev, V. St., *Tetrahedron Lett.*, 1974, 2339.

corresponding to (31) could not be obtained in a pure state. Attempts to achieve the Beckmann rearrangement of the oxime of (21) proved unsatisfactory, and led mainly to tar formation.



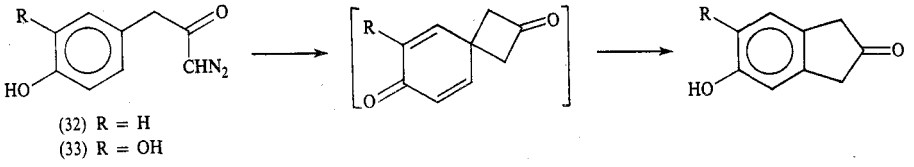
	R^1	R^2
(28)	H	H
(29)	OMe	OMe
(30)	OCH_2O	



(28) (31)

Scheme 5

Since the naturally occurring phthalideisoquinolines all have oxygenated functional groups at the C6 and C7 positions it was clearly desirable to achieve a condensation between a phthalaldehydic acid and, for example, 5,6-dimethoxyindan-2-one. However, oxygenated indan-2-ones of this type are relatively inaccessible and alternatives to the literature method, which proceeds via meconine,[31] were clearly desirable. Mander and coworkers[32] have demonstrated that the phenolic diazoketone (32) undergoes cyclization to afford the indan-2-one in the presence of trifluoracetic acid (Scheme 6).



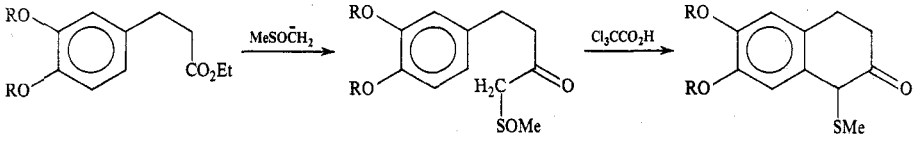
(32) R = H
(33) R = OH

Scheme 6

We have found that the phenolic diazoketone (33; R = OH) and the corresponding dimethyl ether give only trace amounts of the required indan-2-one and this result has recently been confirmed by Mander.[33] The hydroboration–oxidation of indene affords predominantly indan-2-ol[34] but 5,6-dimethoxyindene gave 84% of the 1-ol and only 16% of the 2-ol under these conditions. The successful synthesis of

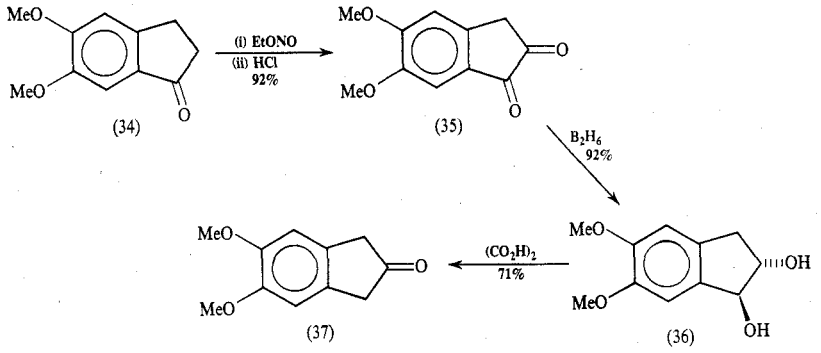
[31] Taylor, J. B., Lewis, J. W., and Jacklin, M., *J. Med. Chem.*, 1970, **13**, 1226.
[32] Beames, D. J., and Mander, L. N., *Aust. J. Chem.*, 1974, **27**, 1257.
[33] Mander, L. N., personal communication.
[34] Marshall, P. A., and Prager, R. H., *Aust. J. Chem.*, 1979, **32**, 1251.

β-tetralones[35] by the cyclization of β-keto sulfoxides (Scheme 7) suggested that this reaction might be applicable for our purpose. However, this possibility was frustrated when it was found that neither ethyl 3,4-dimethoxyphenylacetate nor the corresponding acid chloride underwent nucleophilic substitution by the dimsyl anion, presumably because the benzylic protons were too acidic and the resulting anion was inert to further attack. An efficient route to the required indan-2-ones was achieved by the method shown in Scheme 8, which appears to be general.



Scheme 7

Having achieved the synthesis of the required substituted indan-2-ones it was disappointing to find that they did not condense with phthalaldehydic acid, or its more reactive analogue opianic acid (5,6-dimethoxy-2-formylbenzoic acid), to form the desired condensation product. It appears that the substituted indan-2-ones are unstable under the mildly acidic conditions used and polymerize readily.



Scheme 8

Experimental

General experimental details have been given in Part I.[36]

Hydroboration of 3-Benzylideneisobenzofuran-1(3H)-one (4)

(i) *With diborane.*—Treatment of the (*Z*)-isomer[37] of 3-benzylideneisobenzofuran-1(3*H*)one[38] (4) with only one equivalent of borane resulted in an incomplete reaction as indicated by the ^{1}H n.m.r. spectrum of the reaction mixture (δ 6·4, s, CH=C).

Diborane (3 mmol of borane) in tetrahydrofuran (2 ml) was added dropwise to an ice-cold, stirred solution of (4) (0·444 g, 2 mmol) over a period of 5 min. The solution was allowed to warm to room temperature and stirring was continued for 6 h. Sodium hydroxide (2 ml, 30%) was added slowly followed by the dropwise addition of hydrogen peroxide (2 ml, 30%) and stirring was

[35] Oikawa, Y., and Yonemitsu, O., *Tetrahedron Lett.*, 1972, 3393; *Tetrahedron*, 1974, **30**, 2653.
[36] Duong, T., Prager, R. H., Ward, A. D., and Kerr, D. I. B., *Aust. J. Chem.*, 1976, **29**, 2651.
[37] Berti, G., *Gazz. Chim. Ital.*, 1956, **86**, 655.
[38] Weiss, R., *Org. Synth.*, 1933, **13**, 10.

continued at room temperature overnight. The layers were separated, the aqueous phase extracted with dichloromethane (2 × 10 ml), and the combined organic extracts dried and evaporated to give the crude product (0·43 g). Purification by preparative t.l.c. (50% ether/dichloromethane) gave *1-(2-hydroxymethylphenyl)-2-phenylethanol* (8) and 2-(2-hydroxymethylphenyl)-1-phenylethanol (7) (1 : 1 by n.m.r. analysis) as a light yellow oil (0·36 g, 79%). Crystallization of the mixture from ethanol/water and then chloroform/light petroleum gave (8) as a white solid, m.p. 102–105° (Found: C, 78·6; H, 7·1. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1%). ν_{max} 3280, 3370 cm^{-1}. N.m.r. δ 1·7, b, 2H, OH; 3·05, d, *J* 7 Hz, $ArCH_2$; 4·6, s, $ArCH_2OH$; 5·1, t, ArCHOH; 7·2–7·6, m, 9H, ArH. The triplet at δ 5·1 collapsed to a singlet on irradiating the signal at 3·05. The mass spectrum showed major fragmentations to *m/e* 137 and 91. The isomer (7) was identified by its n.m.r. spectrum: δ 3·5, b, 2H, OH; 3·05, d, *J* 7 Hz, $ArCH_2$; 4·6, s, $ArCH_2OH$; 4·8, t, *J* 7 Hz, ArCHOH; 7·2–7·6, m, 9H, ArH.

(ii) *With disiamylborane.*—2-Methylbut-2-ene (2·8 g, 40 mmol) was added dropwise with stirring, to a solution of diborane (20 mmol of borane) in tetrahydrofuran (12 ml), over a period of 30 min. After stirring for an additional 1 h at 0°, 3-benzylideneisobenzofuran-1(3*H*)-one (0·888 g, 4 mmol) in tetrahydrofuran (3 ml) was added and the solution allowed to warm to room temperature. The reaction was monitored by ^1H n.m.r. spectroscopy. After 1 week the majority of the olefin still remained.

Reaction of 2-(N-morpholino)-1-phenylprop-1-ene with Phthalaldehydic Acid

A solution of phenylpropan-2-one (8 g), morpholine (6·2 g) and *p*-toluenesulfonic acid (50 mg) in toluene (15 ml) was refluxed until separation of water was complete (*c.* 4 h). The toluene was removed at reduced pressure and the residue distilled to produce 2-(*N*-morpholino)-1-phenylpropene, b.p. 98°/0·15 mm. N.m.r.: δ 1·9, s, CH_3; 2·8–3·1, m, 4H, CH_2N; 3·6–3·9, m, 4H, CH_2O; 5·5, s, CH=C; 7·2, s, ArH.

A mixture of phthalaldehydic acid (0·3 g) and the enamine (0·406 g) was heated at 100° for 1 h. Examination of the ^1H n.m.r. spectrum of the product indicated that no enamine remained and from this spectrum the structure (15) was assigned to the product. N.m.r.: δ 2·2, s, CH_3; 2·6–2·9, m, 4H, CH_2N; 3·6–3·9, m, 4H, CH_2O; 3·7, s, CH_2Ar; 6·2, s, CHO; 7·2–8·1, m, 9H, ArH. Mass spectrum *m/e* 352 (M − 1). Crystallization of this product from ethyl acetate, however, resulted in its conversion into 3-morpholinoisobenzofuran-1(3*H*)-one, m.p. and mixed m.p.[23] 127–129° (Found: C, 65·8; H, 6·0; N, 6·4. Calc. for $C_{12}H_{13}NO_3$: C, 65·7; H, 6·0; N, 6·4%). Mass spectrum *m/e* 219 (M).

3-(2-Oxo-1-phenylpropyl)isobenzofuran-1(3H)-one (13) and Substituted Analogues

(i) A mixture of phenylpropan-2-one (0·54 g, 4 mmol), phthalaldehydic acid (0·6 g, 4 mmol), and a crystal of *p*-toluenesulfonic acid was heated at 130° until the ^1H n.m.r. spectrum of an aliquot indicated that the singlet at δ 3·65, corresponding to the methylene protons of the starting ketone, had disappeared. The mixture was cooled, chloroform (10 ml) was added and the resulting solution washed with sodium carbonate solution (10 ml, 10%). Drying and evaporation of the organic phase gave the crude product which was recrystallized from chloroform/light petroleum to give (13) (0·8 g, 75%). ν_{max} 1720, 1750 cm^{-1}. N.m.r.: δ 2·1, 2·2, 2s, 3H, CH_3; 3·8–4·1, two overlapping doublets, 1H, CHCO; 6·2, d, *J* 8 Hz, 1H, CHO; 7·1–8·0, m, 9H, ArH. Mass spectrum *m/e* 266 (M). Recrystallization concentrated the minor isomer, being less soluble, but did not lead to a pure product. A portion of this mixture of diastereoisomers was purified by preparative t.l.c. (75% ether/light petroleum) and the faster running isomer of *3-(2-oxo-1-phenylpropyl)isobenzofuran-1(3H)-one* was recrystallized from chloroform/light petroleum to give a white solid, m.p. 146–149° (Found: C, 76·6; H, 5·3. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%). This was the major isomer from the reaction. The slower running isomer could not be obtained pure.

(ii) Condensation of phthalaldehydic acid with 1-(3,4-methylenedioxyphenyl)propan-2-one[27] gave *3-[1-(3,4-methylenedioxyphenyl)-2-oxopropyl]isobenzofuran-1(3H)-one* (17) as a mixture of diastereoisomers in 75% yield, purified by column chromatography on silica, and having m.p. *c.* 125–140° (Found: C, 69·3; H, 4·6. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·6%). Mass spectrum *m/e* 310 (M).

(iii) Condensation of phthalaldehydic acid with 1-(4-methoxyphenyl)propan-2-one gave *3-[1-(4-methoxyphenyl)-2-oxopropyl]isobenzofuran-1(3H)-one* (18) in 60% yield, m.p. 145–150° (Found: C, 73·1; H, 5·5. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). Mass spectrum *m/e* 296 (M).

(iv) Condensation of phthalaldehydic acid with 1-(3-methoxyphenyl)propan-2-one[27] gave a 75% yield of *3-[1-(3-methoxyphenyl)-2-oxopropyl]isobenzofuran-1(3H)-one* (19), m.p. *c.* 100–130° (Found: C, 72·7; H, 5·4. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). Mass spectrum *m/e* 296 (M).

(v) Condensation of 6,7-dimethoxyphthalaldehydic acid[39,40] with phenylpropan-2-one gave a 71% yield of *6,7-dimethoxy-3-(2-oxo-1-phenylpropyl)isobenzofuran-1(3H)-one* (20), m.p. *c.* 144–165° (Found: C, 69·9; H, 5·6. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%).

The ^{1}H n.m.r. spectra of all the keto phthalides prepared above were compatible with the assigned structures. In particular the protons attached to the asymmetric carbons appeared as an AX quartet. The multiplicity of signals in the ^{1}H n.m.r. spectra and the wide melting range of the compounds indicated that a mixture of diastereoisomers was produced in each case.

Reaction of Phthalaldehydic Acid with Other α-Substituted Toluenes

(i) Treatment of phthalaldehydic acid with equimolar amounts of phenylacetic acid or ethyl phenylacetate under the conditions above did not produce any product, starting materials remaining even after several hours of heating.

(ii) A mixture of phenylacetaldehyde (0·052 g, 0·43 mmol), phthalaldehydic acid (0·065 g, 0·43 mmol) and a crystal of *p*-toluenesulfonic acid was heated at 130°. After a reaction time of 5 min an aliquot was removed and its ^{1}H n.m.r. spectrum recorded. The doublet at δ 3·6 (J 2 Hz) (ascribable to the benzyl protons of the starting aldehyde) had disappeared and doublets were observed at 4·1 and 6·2 (J 7 Hz) suggesting that the aldophthalide had formed. Integration of these resonances relative to the aromatic resonances indicated, however, that the desired product was present in only a low yield. No improvement of yield was noted, when benzene was used as solvent in a Dean–Stark apparatus. Apparently the product was decomposing at a rate comparable to its formation.

(iii) Heating equimolar amounts of phenylacetonitrile and phthalaldehydic acid at 130° with a catalytic amount of *p*-toluenesulfonic acid for 3 h resulted in a partial solidification of the reaction mixture. The solid product was only sparingly soluble in organic solvents and was recrystallized from acetone to yield 3,3′-oxydiphthalide, m.p. 220–235° (Found: C, 68·1; H, 3·6. $C_{16}H_{10}O_6$ requires C, 68·1; H, 3·6%). Further fractional crystallization from acetone gave the two isomers in a pure state. The least soluble had m.p. 241–244°, and was characterized by a sharp singlet at δ 7·10 (CD_3SOCD_3) in its ^{1}H n.m.r. spectrum. The more soluble isomer, m.p. 196–200°, had a sharp singlet at δ 7·00 (CD_3SOCD_3). An isomer of 3,3′-oxydiphthalide is reported[41] to have m.p. 234–236°, and is formed from phthalaldehydic acid above 240°.[42]

N-[*(3-Oxo-1,3-dihydroisobenzofuran-1-yl)(phenyl)methyl*]*acetamide* (*14*)

(i) *From the Schmidt reaction of 3-(2-oxo-1-phenylpropyl)isobenzofuran-1(3H)-one* (*13*).—Sodium azide (0·49 g, 7·5 mmol) was added to an ice-cold stirred solution of (13) (1 g, 3·8 mmol) in polyphosphoric acid (30 g). Stirring was continued for 1·5 h at 0° and then for 1·5 h at room temperature. The reaction temperature was raised to 60° over a period of 30 min and after an additional 2 h of heating the reaction was cooled and ice-water (100 ml) added. The resulting solution was extracted with dichloromethane (3 × 100 ml); the combined organic extracts were dried and evaporated to yield the crude amide (1·0 g, 95%) which was shown by t.l.c. to be essentially pure. The product was further purified by preparative t.l.c. (ether) and then crystallization (dichloromethane/light petroleum) to give (14), m.p. *c.* 164–192° (Found: C, 72·4; H, 5·5; N, 4·9. $C_{17}H_{15}O_3N$ requires C, 72·6; H, 5·4; N, 5·0%). ν_{max} 1660, 1750 cm^{-1}. N.m.r.: δ 1·8, 2·2, 2s, 3H, CH_3CO; 5·7–6·0, m, 2H, CHN, CHO; 7·0–8·0, m, 9H, ArH. Mass spectrum *m/e* 281 (M).

(ii) *From the Beckmann rearrangement of 3-(2-hydroxyimino-1-phenylpropyl)isobenzofuran-1(3H)-one.*—A solution of (13) (0·5 g) and hydroxylamine hydrochloride (0·5 g) in pyridine (0·5 ml) and ethanol (5 ml) was refluxed for 1·5 h. Water was slowly added to the hot solution and the resulting precipitate was collected and dried, m.p. 202–204°. Analysis of this compound by ^{1}H n.m.r. spectroscopy suggested that it consisted of a single diastereoisomer, due to the presence of only one methyl resonance (δ 1·8) and doublets at δ 3·8 and 6·2 corresponding to CHN and CHO respectively.

[39] Edwards, G. A., Perkin, W. H., Jr, and Stoyle, F. W., *J. Chem. Soc.*, 1925, **127**, 195.
[40] Koten, I. A., and Sauer, R. J., *Org. Synth.*, 1962, **42**, 26.
[41] Hawthorne, J. O., and Wilt, M. H., *J. Org. Chem.*, 1960, **25**, 2215.
[42] Graebe, C., and Trump, F., *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 369

On allowing the mother liquor to stand a further crop of crystals was obtained, the ^1H n.m.r. spectrum of which showed two doublets around δ 3·8, suggesting that this compound was a mixture of diastereoisomers.

The oxime, m.p. 202–204°, was treated with phosphorus pentachloride[43] and boron trifluoride.[44] In neither case was an appreciable amount of amide product formed. Treatment of this oxime (0·5 g, 1·8 mmol) in pyridine (1·5 ml) with *p*-toluenesulfonyl chloride (0·6 g, 3·2 mmol) at 0° followed by stirring at room temperature for 20 h and then at 75° for 2 h resulted in the formation of a dark reaction mixture which was shown by infrared spectroscopy to contain some amide product. The reaction was cooled, poured onto ice-water (20 ml) and acidified with 10% hydrochloric acid. The solution was extracted with dichloromethane (2×20 ml) and the combined organic extracts dried and evaporated to yield the crude product which was purified by preparative t.l.c. (ether). The resulting product (15%) was identified as one isomer of *N*-[(3-oxo-1,3-dihydroisobenzofuran-1-yl)(phenyl)methyl]acetamide (14) by t.l.c. and ^1H n.m.r. comparison with the sample obtained above. No other amide containing products were isolated.

3-[Amino(phenyl)methyl]isobenzofuran-1(3H)-one (2; R = H)

The crude *N*-[(3-oxo-1,3-dihydroisobenzofuran-1-yl)(phenyl)methyl]acetamide (1·0 g) prepared above was refluxed with concentrated hydrochloric acid (15 ml) for 4 h. The solution was cooled, neutralized with solid sodium carbonate and extracted with dichloromethane (3×20 ml). The combined organic extracts were dried and evaporated to yield the crude amine (0·85 g, 95% from ketone (13)) which was shown by t.l.c. and ^1H n.m.r. analysis to be a mixture of both stereoisomers of (2; R = H). No appreciable amount of any other product could be detected. The hydrochloride of the mixture of amines was prepared and recrystallized from methanol/ether, m.p. 210–220° (with sublimation). Repeated microanalysis of this compound indicated that methanol (0·25 mol) remained in its crystal structure even after prolonged drying (48 h, 60°/0·1 mm) (Found: C, 64·5; H, 5·0; Cl, 12·9; N, 4·7. Calc. for $C_{15}H_{14}ClNO_2$,0·25CH_3OH: C, 64·5; H, 5·3; Cl, 12·5; N, 4·9%). This compound has been previously reported[15] but the only microanalytical data given were for chlorine and nitrogen, both values being too low to be significantly affected by the inclusion of a small amount of solvent. The presence of solvent was confirmed by the n.m.r. spectrum of the analytical sample. Separation of the diastereoisomers was effected by preparative t.l.c. (5% methanol/ether). The high R_F isomer (500 mg) was an oil with the following spectral data: ν_{max} 1770 cm^{-1}. N.m.r.: δ 1·9, b, NH_2; 4·1, d, *J* 7 Hz, CHN; 5·5, d, *J* 7 Hz, CHO; 6·8–8·1, m, 9H, ArH. The hydrochloride was recrystallized from ethanol/light petroleum as a white solid, m.p. 210–213° (Found: C, 65·0; H, 5·1; N, 5·0. $C_{15}H_{14}ClNO_2$,0·25C_2H_5OH requires C, 64·8; H, 5·4; N, 4·9%). The lower R_F isomer had ν_{max} 1770 cm^{-1}. N.m.r.: δ 1·7, b, NH_2; 4·6, d, *J* 4 Hz, CHN; 5·7, d, *J* 4 Hz, CHO; 7·6–8·1, m, 9H, ArH. The hydrochloride was recrystallized from ethanol/light petroleum, and had m.p. 238–242° (Found: C, 65·2; H, 5·3; N, 5·2. $C_{15}H_{14}ClNO_2$,0·25C_2H_5OH requires C, 64·8; H, 5·4; N, 4·9%).

N-*[3-Methoxyphenyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl]acetamide*

Sodium azide (0·225 g, 3·45 mmol) was added to an ice cold, stirred solution of 1-(3-methoxyphenyl)-1-(3-oxo-1,3-dihydroisobenzofuran-1-yl)propan-2-one (19) (0·5 g, 1·7 mmol) in polyphosphoric acid (20 g). Stirring was continued at 0° for 1·5 h and then at room temperature for 24 h. Water (50 ml) was added and the solution extracted with dichloromethane (2×50 ml). The combined organic extracts were dried and evaporated and the residue crystallized from dichloromethane/light petroleum to give the amide as a white solid (0·3 g, 57%), m.p. *c.* 130–169° (Found: C, 69·2; H, 5·6; N, 4·7. $C_{18}H_{17}NO_4$ requires C, 69·4; H, 5·5; N, 4·5%). The mother liquor from the crystallization was chromatographed (preparative t.l.c.) to yield an additional 0·13 g (25%) of product. ν_{max} ($CHCl_3$) 1675, 1760 cm^{-1}. N.m.r.: δ 1·8, 2·1, 2s, 3H, CH_3; 3·6, 3·8, 2s, 3H, CH_3O; 5·6–5·9, m, 2H, CHO, CHN; 7·5–7·9, m, 8H, ArH. Mass spectrum *m/e* 311 (M).

3-[Amino(3-methoxyphenyl)methyl]isobenzofuran-1(3H)-one

A solution of the amide prepared above (0·1 g) in concentrated hydrochloric acid was heated under reflux for 1·25 h. The reaction was worked up as above to give the amine as a yellow oil

[43] Drake, N. L., Kline, G. M., and Rose, W. G., *J. Am. Chem. Soc.*, 1934, **56**, 2076.
[44] Hauser, C. R., and Hoffenberg, D. S., *J. Org. Chem.*, 1955, **20**, 1482.

(0·075 g, 86%). ν_{max} ($CHCl_3$) 1760 cm^{-1}. N.m.r.: δ 2·6, b, 2H, NH_2; 3·8–4·1, m, 4H, CH_3O, CHN; 5·6, d, *J* 8 Hz; 5·8, d, *J* 4 Hz, total 1H, CHO; 7·6–8·0, m, 8H, ArH. This compound formed a crystalline hydrochloride which sublimed at 225–235° (Found: C, 62·7; H, 5·3; N, 4·9. $C_{16}H_{16}ClNO_3$ requires C, 62·8; H, 5·3; N, 4·6%).

N-[*(4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)(phenyl)methyl]acetamide*

Treatment of 6,7-dimethoxy-3-(2-oxo-1-phenylpropyl)isobenzofuran-1(3*H*)-one (20) with hydrazoic acid in polyphosphoric acid under the conditions described above and separation of the crude product by preparative t.l.c. (5% methanol/ether) gave a 70% yield of the above acetamide as a viscous oil. Crystallization from ethyl acetate/light petroleum gave a white solid, m.p. 205–207° (Found: C, 66·5; H, 5·9; N, 3·9. $C_{19}H_{19}NO_5$ requires C, 66·8; H, 5·6; N, 4·1%). ν_{max} ($CHCl_3$) 1675, 1760 cm^{-1}. N.m.r.: δ 1·8, 2·1, 2s, 3H, CH_3; 3·8, 3·9, 4·1, 3s, 6H, CH_3O; 5·6–5·9, m, 2H, CHO, CHN; 7·0–7·6, m, 7H, ArH. Mass spectrum *m/e* 341 (M).

3-[Amino(phenyl)methyl]-6,7-dimethoxyisobenzofuran-1(3H)-one

A solution of *N*-[(4,5-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)(phenyl)methyl]acetamide (0·1 g) in concentrated hydrochloric acid (4 ml) was heated under reflux for 2·5 h. Water (5 ml) was added and the solution neutralized with solid sodium carbonate. Extraction with dichloromethane (4×10 ml) followed by drying and evaporation of the combined organic extracts gave the crude product (0·07 g). ν_{max} ($CHCl_3$) 1755 cm^{-1}. N.m.r.: δ 2·4, b, 2H, NH_2; 3·7–4·1, m, 7H, CH_3O, CHN; 5·2–5·6, m, impurity; 6·0–6·6, m, 1H, CHO; 6·8–7·4, m, 7H, ArH. This compound could not be obtained in a sufficiently pure state for microanalysis.

When the starting acetamide was treated with concentrated hydrochloric acid at room temperature or 70° virtually no hydrolysis of the amide occurred. Similarly, no hydrolysis occurred with sodium peroxide[45] in water.

N-[*3,4-Methylenedioxyphenyl(3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl]acetamide*

A solution of 3-[1-(3,4-methylenedioxyphenyl)-2-oxopropyl]isobenzofuran-1(3*H*)-one (17) (0·6 g) and hydroxylamine hydrochloride (0·6 g) in ethanol (6 ml) and pyridine (0·6 ml) was refluxed for 2 h. Water (30 ml) was added, the solution acidified with dilute hydrochloric acid and the reaction mixture extracted with dichloromethane (2×30 ml). The combined organic extracts were dried and evaporated to give the crude oxime, which was dissolved in pyridine (4 ml). The solution was cooled in an ice–salt bath and *p*-toluenesulfonyl chloride (1·47 g, 4 equiv.) was added with stirring. The solution was allowed to warm to room temperature and stirring was continued for 22 h. The infrared spectrum of an aliquot showed that no amide was present. The mixture was stirred at 40° for 24 h. At this stage the infrared spectrum indicated that some amide product was present. Stirring for an additional 24 h at 55° did not appear to markedly increase the amide content. The solution was cooled, acidified with dilute hydrochloric acid and extracted with dichloromethane (2×10 ml). The combined organic extracts were dried and evaporated to yield the crude product which was purified by preparative t.l.c. (ether). Both isomers of the acetamide were isolated; the low R_F isomer (0·06 g), and the high R_F isomer (0·04 g) (total yield 15% from ketone). The high R_F isomer could not be obtained crystalline, but had the following spectral data: ν_{max} ($CHCl_3$) 1680, 1765 cm^{-1}. N.m.r.: δ 1·8, s, CH_3; 5·6–6·1, m, 4H, CH_2O, CHO, CHN; 6·5–8·0, m, 7H, ArH. The low R_F isomer was crystallized from ethyl acetate/light petroleum to give a white solid, m.p. 185–188° (Found: C, 66·2; H, 4·8; N, 4·2. $C_{18}H_{15}NO_5$ requires C, 66·4; H, 4·7; N, 4·3%). ν_{max} ($CHCl_3$) 1670, 1755 cm^{-1}. N.m.r.: δ 2·1, s, CH_3; 5·6–6·1, m, 4H, CH_2O, CHO, CHN; 6·6–7·9, m, 7H, ArH.

Attempted Rearrangement of 3-[1-(3,4-Methylenedioxyphenyl)-2-oxopropyl]isobenzofuran-1(3H)-one (17) and 3-[1-(4-Methoxyphenyl)-2-oxopropyl]isobenzofuran-1(3H)-one (18) with Hydrazoic Acid

Treatment of either of these compounds with hydrazoic acid in polyphosphoric acid by the method described above gave only a low recovery of organic material, the infrared spectrum of which indicated that only small quantities of amide product were present. The course of the reaction could be followed by t.l.c. or infrared spectroscopy and the starting material was shown to slowly disappear. Treatment

[45] Vaughn, H. L., and Robbins, M. D., *J. Org. Chem.*, 1975, **40**, 1187.

of the ketones with polyphosphoric acid in the absence of sodium azide did not result in disappearance of starting material.

Similarly, the ketoxime *p*-toluenesulfonates, on refluxing in dioxan/water, gave less than 10% of amide product, the major reaction pathway being fragmentation.

*Attempted Condensation of Indan-2-one with 3-Bromoisobenzofuran-1(3*H*)-one*

To a solution of triphenylmethyllithium[46] (2·0 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise, under nitrogen, indan-2-one (264 mg; 2·0 mmol) in tetrahydrofuran (3 ml). The resultant mixture was cooled to 0° whereupon a solution of 3-bromoisobenzofuran-1(3*H*)-one[47] (424 mg; 2·0 mmol) in tetrahydrofuran (5 ml) was added. The mixture was then stirred at 0° for 2 h and hydrolysed by the careful addition of water (1 ml) followed by 10% hydrochloric acid (5 ml). After stirring at room temperature for 15 min, the mixture was extracted with ether (3 × 25 ml) and the combined organic layers were washed with water (2 × 20 ml), dried and evaporated to give a dark yellow oil, trituration of which with light petroleum gave a yellow solid (974 mg). Preparative t.l.c. of *c.* 300 mg of this solid (with 20% ether/light petroleum as a developing solvent) afforded four major components. Fractions 1 and 3 were complex mixtures, the spectra of which did not indicate the presence of any of the desired compound. Fraction 2, R_F 0·2 was an off-white solid (47 mg) and was identified as 3-bromoisobenzofuran-1(3*H*)-one, m.p. 78–80° (lit.[48] 78–80°). Fraction 4, R_F 0·9 (148 mg), was triphenylmethane.

Attempted Alkylation of the Enamine of Indan-2-one

The method of Blomquist and Moriconi[48] was used to prepare 2-(pyrrolidin-1-yl)-1*H*-indene which was used immediately without further purification. To an ice-cooled solution of the enamine (1 mmol) thus prepared in benzene (10 ml) was added a solution of 3-bromoisobenzofuran-1(3*H*)-one (212 mg; 1 mmol) in benzene (2 ml) and the resultant mixture was stirred at room temperature (*c.* 30°) for 2 h, then quenched by the addition of 10% hydrochloric acid (5 ml). After stirring at room temperature for 30 min, the mixture was extracted with ether (2 × 30 ml) and the combined organic extracts were washed with successive portions of 10% hydrochloric acid (2 × 10 ml) and water (2 × 10 ml), dried and evaporated to give a dark yellow oil (181 mg). Analytical t.l.c. (25% dichloromethane/light petroleum) of this oil indicated the presence of at least six components one of which (R_F 0·3) was identified as 3-bromoisobenzofuran-1(3*H*)-one (*c.* 30% of product after preparative t.l.c.). The ^{1}H n.m.r. spectrum of the residue obtained above showed a complex mixture which did not appear to contain the desired compound, and this reaction was not investigated further.

Condensation of Indan-2-ones with 2-Formylbenzoic Acids

General procedure.—A solution of the indan-2-one (10 mmol) and the phthalaldehydic acid (10 mmol) in dry benzene (50 ml) containing a crystal of *p*-toluenesulfonic acid was stirred under reflux and the water formed during the reaction was removed by means of a Dean–Stark water separator. When analysis of the reaction mixture by t.l.c. no longer showed the presence of starting material (3–5 h), the mixture was cooled, stripped of solvent to give a viscous red oil which was triturated with ether to afford the desired product as a yellow powder which could not be induced to crystallize. Attempted sublimation led to decomposition and it was found that chromatography of these compounds on silica or alumina was of little value. Attempted formation of derivatives (oximes, 2,4-dinitrophenylhydrazones and semicarbazones) generally led to cleavage even under mild conditions; derivatization was hampered by the extreme insolubility of the 3-(2-oxo-2,3-dihydro-inden-1-yl)isobenzofuran-1(3*H*)-one in common solvents. The ^{1}H n.m.r. spectra were thus often obtained as dilute solutions in $CDCl_3$ and in some cases were poorly resolved. The following compounds were prepared by this general method.

(i) *3-(2-Oxo-2,3-dihydroinden-1-yl)isobenzofuran-1(3*H*)-one* (*21*).—The benzene was initially filtered to remove a precipitated solid (140 mg) and the filtrate was treated as described above to afford an off-white solid (2·2 g; 72%) which had m.p. 146–148°. ν_{max} 1765, 1760, 1755 cm^{-1}. N.m.r.: δ 7·60, complex, 7H, ArH; 6·20, overlapping doublets, 2H, ArH and ArCHO; 4·12,

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[47] Koten, I. A., and Sauer, R. J., *Org. Synth.*, 1973, Coll. Vol. V, 145.
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d, *J* 3 Hz, ArCHCO; 3·60, s, $ArCH_2CO$. N.m.r.: (C_6D_6/CF_3CO_2D): δ 7·52, m, ArH (H7); 7·0, m, 6H, ArH; 5·83, d, *J* 8 Hz, ArH; 5·58, d, *J* 3 Hz, ArCHO; 3·55, d, *J* 3 Hz, ArCHCO; 3·10, s, $ArCH_2CO$. Irradiation at: δ 7·0 caused the collapse of the doublet at 5·83 to a singlet; 5·58 caused the collapse of the doublet at 3·55 to a singlet; 3·55 caused the collapse of the doublet at 5·58 to a singlet. Mass spectrum *m/e* 264 (M), 133 ($M-C_9H_7O$). This compound was characterized as the *oxime*, prepared according to the general method of Ruzicka *et al.*,[49] which was recrystallized from acetone/light petroleum as colourless needles, m.p. 193–195° (dec.) (Found: C, 73·4; H, 4·8; N, 4·6. $C_{17}H_{13}NO_3$ requires C, 73·1; H, 4·7; N, 5·0%). ν_{max} 3350, 1745, 1610, 740 cm^{-1}. The insoluble material, for which structure (27) is proposed, was recrystallized from dioxan, m.p. 235–238° (dec.) (Found: C, 75·3; H, 4·2. Calc. for $C_{25}H_{16}O_5$: C, 75·7; H, 4·1%). ν_{max} 1770, 1762 cm^{-1}. Mass spectrum *m/e* 396 (M).

(ii) *6,7-Dimethoxy-3-(2-oxo-2,3-dihydroinden-2-yl)isobenzofuran-1(3H)-one (22).*—The ketone (22) was obtained from indan-2-one (1·32 g; 10 mmol) and 6,7-dimethoxyphthalaldehydic acid (2·2 g; 10 mmol), as an off-white powder (695 mg; 23%), m.p. 114–120°, and was characterized as the *2,4-dinitrophenylhydrazone*, m.p. 226–230° (dec.) (Found: C, 59·6; H, 4·2; N, 11·2. $C_{25}H_{20}N_4O_8$ requires C, 59·5; H, 4·0; N, 11·1%). The ketone had the following spectral properties: ν_{max} 1750, 1740, 1015, 765, 750 cm^{-1}. N.m.r.: δ 7·30, m, 5H, ArH; 6·20, d, *J* 8 Hz, ArH; 6·00, d, *J* 3 Hz, ArCHO; 4·10–4·00, 2 singlets overlapping with a doublet, 7H, $2\times CH_3O$ and ArCHCO; 3·60, s, $ArCH_2CO$. Mass spectrum *m/e* 324 (M), 193 ($M-C_9H_7O$).

(iii) *6,7-Methylenedioxy-3-(2-oxo-2,3-dihydroinden-1-yl)isobenzofuran-1(3H)-one (23).*—The *ketone* (23) (3·06 g, 99%) was obtained from indan-2-one (1·32 g; 10 mmol) and 6,7-methylenedioxyphthalaldehydic acid[50] (2·04 g; 10 mmol), as a yellow insoluble powder (m.p. 107–113°) (Found: $M^{+\cdot}$, 308·0684. $C_{18}H_{12}O_5$ requires $M^{+\cdot}$, 308·0685). All derivatization attempts led to decomposition. ν_{max} 1765, 1760, 1740, 740, 710, 695 cm^{-1}. N.m.r.: δ 7·42–6·85, m, 5H, ArH; 6·23, singlet overlapping with 2 doublets, 4H, OCH_2O, ArH and ArCHO; 4·00, br d, ArCHCO; 3·21, s, $ArCH_2CO$. The crude product, before recrystallization, contained varying amounts (up to 40%) of a second isomer, indicated by a doublet at δ 4·35. Mass spectrum *m/e* 308 (M), 177 ($M-C_9H_7O$).

(iv) *5,6-Dimethoxy-3-(2-oxo-2,3-dihydroinden-1-yl)isobenzofuran-1(3H)-one (24).*—The ketone (24) was obtained from indan-2-one (132 mg; 1·0 mmol) and 4,5-dimethoxy-2-formylbenzoic acid[51] (220 mg; 1·0 mmol), as a pale yellow powder (300 mg, 92%), m.p. 132–138° (Found: $M^{+\cdot}$, 324·1001. $C_{18}H_{14}O_4$ requires $M^{+\cdot}$, 324·0998). All derivatization attempts led to decomposition. ν_{max} 1760, 1752, 1710, 740, 720 cm^{-1}. N.m.r.: δ 7·27, m, 5H, ArH; 6·40, d, *J* 8 Hz, ArH; 5·93, d, *J* 3 Hz, ArCHO; 3·93, two singlets overlapping with doublet, 7H, $2\times OCH_3$ and ArCHCO; 3·53, s, $ArCH_2CO$. Mass spectrum *m/e* 324 (M), 193 ($M-C_9H_7O$).

(v) *6-Methoxy-3-(2-oxo-2,3-dihydroinden-1-yl)isobenzofuran-1(3H)-one (25).*—The *ketone* (25) was obtained from indan-2-one (132 mg; 1·0 mmol) and 2-formyl-5-methoxybenzoic acid[50] (180 mg; 1·0 mmol), as a yellow gum (270 mg; 89%) (Found: $M^{+\cdot}$, 294·0884. $C_{18}H_{14}O_4$ requires $M^{+\cdot}$, 294·0892). ν_{max} 1760, 1750, 1740, 720, 680 cm^{-1}. N.m.r.: δ 7·27, m, 7H, ArH; 5·20, br d, 1H, ArCHO; 3·91, m, 3H, $ArCH_2CO$ and ArCHCO; 3·50, s, CH_3O. Mass spectrum *m/e* 294 (M), 163 ($M-C_9H_7O$).

(vi) *Attempted condensation of 5,6-dimethoxyindan-2-one with phthalaldehydic acid.*—When 5,6-dimethoxyindan-2-one (37) (47 mg; 0·26 mmol) was treated with phthalaldehydic acid (40 mg; 0·26 mmol) in benzene (5 ml) containing a catalytic amount of *p*-toluenesulfonic acid, either at room temperature or at 80°, there was no evidence (by i.r. or ^1H n.m.r. spectroscopy) for the formation of any condensation product but only of involatile polymeric material.

(vii) *Attempted condensation of 5,6-dimethoxyindan-2-one with 5,6-dimethoxyphthalaldehydic acid.*—Treatment of 5,6-dimethoxyindan-2-one (37) (94 mg; 0·5 mmol) with 5,6-dimethoxyphthalaldehydic acid (80 mg; 0·5 mmol) in benzene (8 ml) under the usual conditions afforded only starting compounds (by ^1H n.m.r. spectroscopy) with some polymeric material.

(viii) *3-(1-Methyl-2-oxo-2,3-dihydroinden-1-yl)isobenzofuran-(3H)-one (26).*—1-Methylindan-2-one[34] (1·46 g; 10 mmol) and phthalaldehydic acid (1·4 g; 10 mmol) afforded (26), as a mixture of diastereoisomers (2·1 g, 76%), which had the following spectral properties: ν_{max} 1760, 1740, 740, 715, 695 cm^{-1}. N.m.r.: δ 8·0–7·20, m, 8H, ArH; 5·85, 5·73, 2s, 1H, ArCHO; 3·60, 3·58, 2s,

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2H, $ArCH_2CO$; 1·75, 1·63, 2s, CH_3. The spectrum indicated that the material was a 1 : 1 mixture of diastereoisomers. Mass spectrum *m/e* 278 (M), 133 ($M-C_{10}H_9O$).

Preparation of (RS,SR)-*1-(3-oxo-1,3-dihydroisobenzofuran-1-yl)-1,4-dihydroisoquinolin-3*(2H)-*ones* (*28*)–(*30*).—The phthalides (21)–(23) (1·25 mmol) were dissolved or suspended in a homogeneous mixture of phosphorus pentoxide (7 g) and phosphoric acid (85%, 12 g) by swirling for 10 min. Sodium azide (4·6 mmol) was added all at once and thoroughly mixed by manual stirring. The solution began to bubble after 10 min, and was allowed to stand at room temperature until bubbling ceased (1·5–2 days). Water (50 ml) was added with stirring and cooling, and the mixture was extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with saturated sodium bicarbonate solution (30 ml), dried and the solvent was removed to give the crude amide which was recrystallized from methanol. In this manner the following compounds were obtained.

(RS,SR)-*1-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-1,4-dihydroisoquinolin-3*(2H)-*one* (28) (80%), m.p. 263–265° (Found: C, 72·7; H, 4·9; N, 4·6. $C_{17}H_{13}NO_3$ requires C, 73·1; H, 4·7; N, 5·0%). ν_{max} 1760, 1660 cm^{-1}. N.m.r.: δ 8·2–7·2, 8H, ArH, NH; 7·0–6·7, m, 1H, ArH; 5·8, d, *J* 4 Hz, CHO; 5·2, m, (simplifies on treatment with D_2O) CHN; 3·40, br s, CH_2. Mass spectrum *m/e* 279 (M).

(RS,SR)-*1-(4,5-Dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-1,4-dihydroisoquinolin-3*(2H)-*one* (29) (81%), m.p. 212–220° (dec.) (Found: C, 67·1; H, 5·0; N, 4·4. $C_{19}H_{17}NO_5$ requires C, 67·2; H, 5·0; N, 4·1%). ν_{max} ($CHCl_3$) 1760, 1670 cm^{-1}. N.m.r.: δ 7·75, br, NH; 7·3–6·9, m, 5H, ArH; 6·42, d, *J* 8 Hz, 1H, ArH; 5·55, d, *J* 3 Hz, CHO; 5·1, m, CHN; 3·90 and 3·85, 2s, 6H, OCH_3; 3·35, br s, CH_2. Mass spectrum *m/e* 339 (M).

(RS,SR)-*1-(4,5-Methylenedioxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-1,4-dihydroisoquinolin-3*(2H)-*one* (30) (59%), m.p. 280–285° (dec.) (Found: C, 66·5; H, 4·1; N, 4·2. $C_{18}H_{13}NO_5$ requires C, 66·9; H, 4·1; N, 4·3%). ν_{max} ($CHCl_3$) 1760, 1675 cm^{-1}. N.m.r.: δ 7·6–7·1, 5H, ArH and NH; 7·0, d, *J* 8 Hz, 1H, ArH; 6·2, s, OCH_2O; 6·1, dd, *J* 8 Hz, 1H, ArH; 6·75, d, *J* 4 Hz, CHO; 5·2, m, CHN; 3·4, s, CCH_2CO. Mass spectrum *m/e* 323 (M). Recrystallization of (30) from chloroform/light petroleum resulted in the formation of a chloroform solvate, m.p. 280–285° (dec.); (change at 151°) (Found: C, 50·8; H, 3·1; Cl, 23·1; N, 3·2. $C_{18}H_{13}NO_5,CHCl_3$ requires C, 51·5; H, 3·2; Cl, 24·0; N, 3·2%).

Reduction of 1,4-dihydroisoquinolin-3(2H)-*one*

(i) 1,2-Dihydroisoquinolin-3(2*H*)-one (300 mg; 2 mmol) was dissolved in dichloromethane (10 ml) at 0°, and methyl fluorosulfonate (0·17 ml; 2 mmol) added slowly. After 1 h the solvent was removed and replaced by ethanol (5 ml). Sodium borohydride (0·2 g) was added, and the mixture stirred at 20° for 2 h. Water (20 ml) was added, and the mixture was extracted with dichloromethane and worked up in the usual way to yield a colourless oil (240 mg), which had i.r. and n.m.r. spectra identical with those of 1,2,3,4-tetrahydroisoquinoline.

(ii) When the above procedure was repeated with three equivalents of methyl fluorosulfonate in the presence of potassium carbonate, the product was a 40 : 60 mixture of tetrahydroisoquinoline and its *N*-methyl derivative.

(RS,SR)-*3-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-1-yl)isobenzofuran-1*(3H)-*one* (*31*)

The phthalide amide (28) (300 mg; 1·08 mmol) was dissolved in dry dichloromethane (20 ml) and anhydrous potassium carbonate (6 g) added. Methyl fluorosulfonate (0·5 ml; 6 mmol) was added with stirring, and stirring was continued for 4 h under nitrogen. The mixture was filtered, the dichloromethane removed, ethanol (20 ml) and sodium borohydride (0·3 g) were added and the mixture was stirred overnight. Water was added, and the mixture brought to pH 6, and after 1 h, extracted, and the extract worked up in the usual way to yield a brown glass (400 mg). Preparative t.l.c. on silica (ether/light petroleum) gave 133 mg (47%) of the amine (31), m.p. 100–102° from methanol (lit.[9] 100–102°), which had identical i.r. and ^1H n.m.r. spectra with those of an authentic sample of the *erythro* isomer.

Reaction of 3,4-Dimethoxybenzyl Diazomethyl Ketone with Trifluoroacetic Acid

A solution of the diazoketone, prepared[35] in 94% yield from 3,4-dimethoxyphenylacetic acid, (1·0 g; 4·5 mmol) in dichloromethane (50 ml) was added dropwise to cold (−20°), stirred trifluoroacetic acid. After the addition, the mixture was stirred at −20° for 10 min and at 0° for

15 min. The mixture was then diluted with dichloromethane (100 ml), washed with water (2 × 100 ml) dried and evaporated to give a reddish oil (0·8 g), whose spectral properties suggested that it was a 2 : 1 mixture of 3-(3,4-dimethoxyphenyl)-2-oxopropyl trifluoroacetate and 5,6-dimethoxyindan-2-one (37). ν_{max} (film): 1795, 1740, 1240, 1160, 700 cm^{-1}. N.m.r. (CCl_4): δ 6·85, 2s, ArH; 4·92, s, $ArCH_2COCH_2OCOCF_3$; 3·85, s, OCH_3; 3·67, s, $ArCH_2COCH_2OCOCF_3$; 3·52, s, $ArCH_2CO$.

5,6-Dimethoxyindene

A solution of 5,6-dimethoxyindan-1-ol (10·2 g) in dimethyl sulfoxide (100 ml) was heated at 180° under an atmosphere of nitrogen for 6 h. Upon cooling, the mixture was poured onto ice (*c.* 250 g) and extracted with ether (4 × 150 ml). The combined ether extracts were washed with water (6 × 50 ml), dried and evaporated to give a red oil (8·45 g) which was chromatographed on silica (*c.* 200 g). Elution with dichloromethane gave the olefin as a white solid, m.p. 69–70° (lit.[51] 71°). N.m.r. (CCl_4): δ 6·90, s, H4; 6·83, s, H7; 6·75, m, ArCH=CH; 6·35, dt, ArCH=CH; 3·75, s, 2 × OCH_3; 3·20, s, $ArCH_2$.

Hydroboration of 5,6-Dimethoxyindene

A solution of diborane in tetrahydrofuran (2 ml of 1·5 M; 3 mmol) was added, under nitrogen, to an ice-cooled, stirred solution of 5,6-dimethoxyindene (200 mg; 1·14 mmol) in tetrahydrofuran (5 ml). When the mixture had been stirred at 0° for 15 min and at 20° for 45 min, water (3 ml) was cautiously added to the recooled (0°) mixture to destroy excess diborane. The mixture was diluted with ether (10 ml) and the reaction was oxidized with aqueous sodium dichromate according to the general method of Brown.[52] The mixture was then extracted with ether (2 × 20 ml) and the combined extracts were washed with water (10 ml), saturated sodium bicarbonate solution (2 × 10 ml) and with more water (20 ml), dried and evaporated to afford a yellow solid (184 mg, 96%) which on recrystallization from light petroleum afforded 5,6-dimethoxyindan-1-one (34), m.p. 117–119° (lit.[53] 117–119°), as colourless needles. Analysis of the crude product by ^1H n.m.r. spectroscopy indicated the presence of 5,6-dimethoxyindan-2-one (37). The ratio of (37) : (34) was *c.* 16 : 84 by integration.

Reduction of Indene-1,2(3H)-dione with Diborane

A solution of indene-1,2(3*H*)-dione[54] (200 mg; 1·4 mmol) in anhydrous tetrahydrofuran (10 ml) was added slowly under nitrogen to an ice-cooled, stirred solution of diborane in tetrahydrofuran (1 ml of 2·0 M solution; 2 mmol). After addition, stirring was continued at room temperature until the yellow solution became colourless (2–3 h). After cooling the solution to 0°, water (5 ml) was added cautiously followed by concentrated sulfuric acid (*c.* 2–3 drops) and stirring was maintained for a further 30 min to ensure hydrolysis. The layers were separated with the aid of saturated brine and the aqueous layer was extracted further with ether (3 × 10 ml). The combined organic layers were washed with saturated brine (10 ml), dried and evaporated under reduced pressure to give 202 mg (99%) of *trans*-indane-1,2-diol, m.p. 161–163° (lit.[55] 160–163°), which had an identical ^1H n.m.r. spectrum with that of an authentic sample.

Reduction of 5,6-Dimethoxyindene-1,2(3H)-dione (35)

A solution of the diketone[56,57] (35) (2·04 g; 10 mmol) in dry tetrahydrofuran (50 ml) was added, under nitrogen, to an ice-cooled, stirred solution of diborane (10 ml of 2 M solution; 20 mmol). After addition, the yellow solution was stirred at room temperature until the solution became colourless (*c.* 18 h). An analogous workup procedure to that described above afforded 1·91 g (92%) of *trans*-5,6-dimethoxyindane-1,2-diol (36) as an off-white solid (m.p. 186–188°) which discoloured on standing. ν_{max} 3350, 1605, 770 cm^{-1}. N.m.r.: δ 6·93, 6·80, 2s, ArH; 5·03, d, *J* 5 Hz,

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ArCHO; 4·46, ddd, $ArCH_2CHO$; 3·90, 2s, OCH_3; 3·20, dd, $ArCH_2$; 2·67, br s, D_2O exch., 2 OH. Mass spectrum *m/e* 192 ($M-H_2O$).

Rearrangement of Diol (36) to 5,6-Dimethoxyindan-2-one (37)

A solution of the diol (36) (50 mg) in 10% aqueous oxalic acid was stirred at 60° for 1 h, the reaction being monitored by analytical t.l.c. (4% ethyl acetate/dichloromethane). The reaction mixture was extracted with dichloromethane (2 × 10 ml). The combined extracts were then dried, solvent was removed and the product purified by t.l.c. on silica, using 12% ethyl acetate in chloroform. The ketone (37) was obtained as colourless needles (36 mg; 71%), m.p. 136–137° (lit.[31] 137–139°). ν_{max} 1740, 1605, 760 cm^{-1}. N.m.r.: δ 6·80, s, ArH; 3·83, s, OCH_3; 3·47, s, $ArCH_2$. Mass spectrum *m/e* 192 (M).

Biological Results

All aminobenzylphthalides described in this paper have been subjected to preliminary biological testing for CNS activity, as previously described.[58] The compounds showed very low activity around 200 mg/kg, causing drowsiness, except for one of the isomers* of 3-[amino(3-methoxyphenyl)methyl]isobenzofuran-1(3*H*)-one and (2), both of which caused lack of muscular coordination at 70–90 mg/kg.

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* The separation and assignment of configuration to the isomers will be published separately. The active isomers in this series are believed to be, once again, the *erythro* ones.

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