CENTRAL NERVOUS SYSTEM ACTIVE COMPOUNDS XI. 1-(3-PHTHALIDYL)-PHTHALAZIN-4-ONES.[a]

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Abstract - Phthalidylphthalazinones can be readily prepared by the reaction of hydrazines with the corresponding biphthalide. The reaction with unsymmetrical biphthalides appears to be controlled mainly by electronic factors. Phthalidylphthalazinone undergoes the Mannich reaction leading to a 3-substituted product. 1-Chlorophthalazine reacts with butyllithium by addition at C-4; the resulting anion is alkylated at C-3 with methyl 2-formylbenzoate. The compounds cause loss of muscular control in mice, but their insolubility hinders further pharmacological investigation.

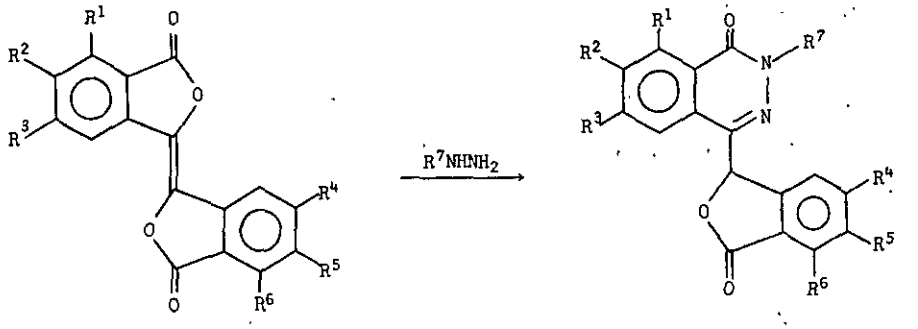
INTRODUCTION

The convulsant alkaloid bicuculline (1) has provided a model compound for our synthetic endeavours, aimed at the synthesis of phthalide isoquinolines[1-3] as well as their aromatic[4] and aza analogues.[4] These compounds are potential agonists of 4-aminobutyric acid (GABA)[5] and as such could find use in the treatment of epilepsy and other diseases of the central nervous system (CNS).[6] This paper, describing the synthesis of a number of phthalidylphthalazinones (2) and providing a preliminary account of their CNS activity, is a further part of this overall project.

DISCUSSION

Phthalazin-4-ones are readily available from the reaction of phthaldehydic acids[7] or benzylidene phthalides[8] with hydrazines. The substrates required to achieve our purposes were thus the biphthalides which should react with hydrazines as shown in Scheme 1. We have recently published a general procedure for the synthesis of substituted biphthalides[9] and accordingly we investigated their reactions with hydrazine and substituted hydrazines. Unsymmetrical biphthalides could, in principle, form two products on treatment with hydrazine but it was expected that

electronic effects should be paramount in determining the site of initial attack by the hydrazine and this has been born out by experience. The biphthalides (3)-(10) were converted to the phthalidylphthalazinones (11)-(27) by the procedure outlined in Scheme 1.

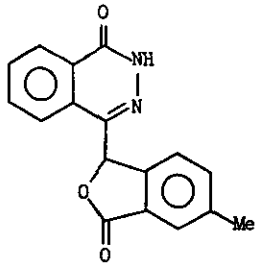


Scheme 1

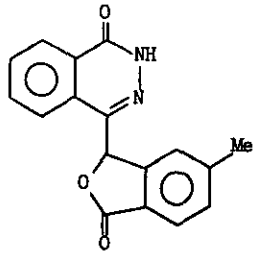
	R^1	R^2	R^3	R^4	R^5	R^6	R^7	
(3)	H	H	H	H	H	H	H	(11)
	H	H	H	H	H	H	Me	(12)
	H	H	H	H	H	H	Et	(13)
(4)	H	OMe	OMe	OMe	OMe	H	H	(14)
	H	OMe	OMe	OMe	OMe	H	Me	(15)
	H	OMe	OMe	OMe	OMe	H	Et	(16)
(5)	H	H	H	OMe	OMe	H	H	(17)
	H	H	H	OMe	OMe	H	Me	(18)
(6)	H	—Me—		H	H	H	H	(19)
	H	—Me—		H	H	H	Me	(20)
(7)	H	NO_2	H	H	H	H	Me	(21)
(8)	$-OCH_2O-$		H	OMe	OMe	H	H	(22)
	$-OCH_2O-$		H	OMe	OMe	H	Me	(23)
	H	OMe	OMe	H	$-OCH_2O-$		H	(24)
(9)	H	H	H	H	$-OCH_2O-$		H	(25)
	$-OCH_2O-$		H	H	H	H	H	(26)
(10)	H	H	H	—Cl—		H	H	(27)

The reaction of 3-methylphthalic anhydride with triphenyl-3-phthalidylphosphonium bromide and

triethylamine gave an inseparable mixture of two isomeric biphthalides[9] (6) which under normal conditions of addition of hydrazine or methylhydrazine gave an inseparable mixture of four isomers, but when the hydrazine was added very slowly only the isomers (19a) and (19b) were formed.

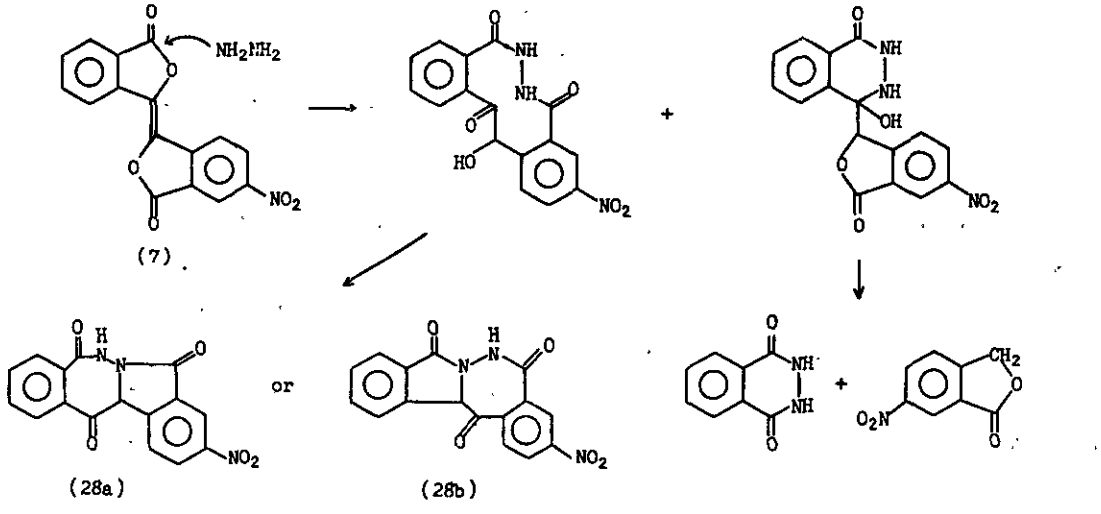


(19a)



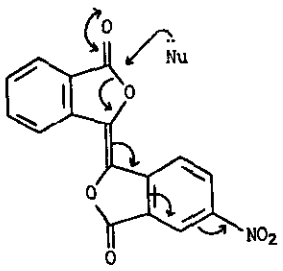
(19b)

The reaction of hydrazine with the nitrobiphthalide (7) resulted in the formation of 6-nitrophthalide, 1,4-phthalazinedione and a compound suggested to be the ketodiamide (28a) or (28b) (Scheme 2). Although the infrared spectrum (ν_{max} 1720, 1690, 1670 cm^{-1}) is consistent with the



Scheme 2

presence of a five and a seven-membered lactam rather than the alternative two six-membered lactams, it does not permit the differentiation of (28a) and (28b). Initially it appeared anomalous to us that hydrazine had reacted first at the carbonyl group in the unsubstituted ring but we now believe it is likely that the electronic effect of the nitro group is relayed from one ring to the other (cf. 29).



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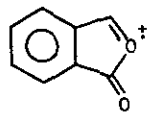
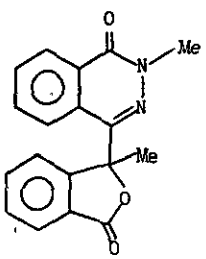


(30)

The reaction of the nitrobiphthalide (7) with methylhydrazine gave, besides 6-nitrophthalide and 2-methyl-1,4-phthalazinedione, the required phthalidylphthalazinone (21). The structure of (21) was confirmed by its mass spectral fragmentation, which showed a base peak at m/e 133, corresponding to (30). The structure of compounds (11)-(27) was confirmed by spectral means; in particular they showed the characteristic n.m.r. signal due to the phthalidyl proton at ca δ 7.0 and the typical infrared absorptions (1750 cm^{-1}, phthalide; 3300, 1690 cm^{-1} amide). The mass spectra of these compounds typically showed a major peak due to the phthalide ring, analogous to (30). The position of attack of the hydrazine on the biphthalides is that expected on the basis of electronic effects. Only in the case of (8) could steric effects be expected to be significant but again the products from the reactions with both hydrazine and methylhydrazine reflect the preference (ca. 2:1) for attack at the carbonyl group adjacent to the methylenedioxy group, consistent with its lower electron-donating properties compared to two methoxyl groups.

Since phthalazinones can be readily N-methylated using base and methyl iodide,[10-12] this procedure appeared to offer an alternative method for the preparation of the 2-methylated phthalidylphthalazinones. When (11) was treated with methyl iodide and potassium carbonate in acetone, without the rigorous exclusion of air and moisture, two products were isolated and identified as (31) and (32). The latter was subsequently shown to arise by aerial oxidation of the hydroxy ester (33), which appears to form very readily in the presence of any moisture. Under anhydrous



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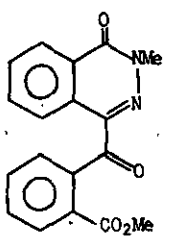

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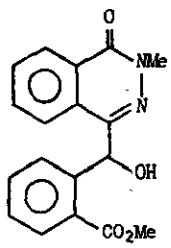
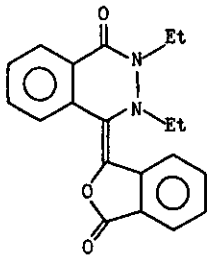


(33)

anaerobic conditions the alkylation products are (12) and (31), the former being capable of C-alkylation to give (31). The structure of (32) was confirmed by reduction with sodium borohydride, followed by alkaline hydrolysis, to yield (12). Alkylation of (11) with ethyl iodide gave (13) at room temperature and a mixture containing the dialkylated materials (34) and (35) under more vigorous conditions. In contrast ethylation of the tetramethoxy derivative (14) gave only N-ethylated material (16).



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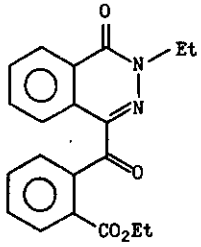

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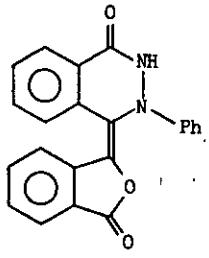
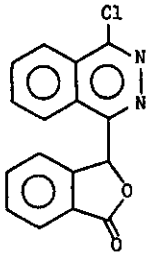


(36)

Whereas alkylhydrazines react as nucleophiles initially though the secondary nitrogen, aryl hydrazines react through the primary nitrogen.[13,14] Phenylhydrazine reacted with biphthalide to give a mixture of stereoisomers of (36) which, like biphthalide, is yellow. No attempt was made to separate the isomers since their physiological activity was only slight.

The phthalidylphthalazinones, particularly those containing alkoxyl groups, were only sparingly soluble in a range of solvents, so methods were sought to convert them into more water-soluble derivatives. Attempts to convert them into phthalazine derivatives were frustrated by our inability to prepare the 4-chloro derivative (37) under standard conditions.



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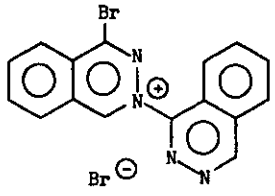

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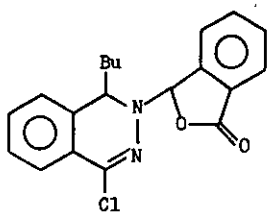
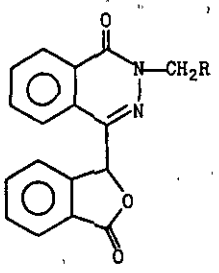


(39)

Attempts to alkylate 1-phthalidyl lithium failed when the reaction of freshly prepared 1-bromophthalazine[b] with butyllithium, followed by addition of methyl 2-formylbenzoate, afforded mainly polymeric material. Although there do not appear to be many examples of trans-metallation of aryl chlorides, an attempt was made to lithiate 1-chlorophthalazine. Addition of butyl lithium at -80° gave a red solution, the colour of which was immediately discharged on addition of the aldehyde to produce a compound which is assigned the structure (39), on the basis of its ^{1}H and ^{13}C n.m.r. spectra and its stability towards attempted dehydrochlorination reactions. It is interesting to note that the alkyllithium reagent has cleanly added to C-4 and not C-1, which is the case with other nucleophiles.[16-18]

The Mannich reaction has been successfully carried out on 1-alkylphthalazin-4-ones[19] and by this means the derivatives (41) and (42) were prepared, together with intermediate hydroxymethyl compound (40). As expected these compounds showed a considerably higher solubility in propylene glycol, the solvent used in the biological testing. The n.m.r. spectra of the compounds (40)-(42) were interesting in that the methylene protons were diasterotopic inspite of their distance from the chiral centre.



(40) R = OH

(41) R = 

(42) R = 

The results obtained from a preliminary investigation of the biological activity of these compounds, obtained by intraperitoneal injection into mice, are recorded in Table 1.

TABLE 1.[A] Approximate ED doses to cause loss of muscle control.

Compound	ED mg/Kg	Compound	ED mg/Kg
(11)	30[B]	(23)	90
(12)	60	(25)	>150
(13)	>100	(26)	100[C]
(14)	90	(27)	80
(15)	100	(31)	90[C]
(16)	>100	(32)	80[C]
(17)	85	(36)	70
(18)	85	(39)	90
(19)	80[C]	(40)	65
(20)	45[C]	(41)	75
(21)	100	(42)	75
(22)	95		

[A] Details of the testing procedure are given in Part III (Aust. J. Chem., 1980, 33, 2477).

[B] Convulsions at 125 mg/Kg

[C] Fatal dose 120 mg/Kg.

EXPERIMENTAL

Reaction of Biphthalides with Hydrazine

A typical preparation of a "phthalidylphthalazinone" is detailed below.

(i) Hydrazine hydrate (0.095 g, 1.9 mmol) in ethanol (20 ml) was added dropwise over 30 min to a stirred refluxing suspension of biphthalide (3)[9] (0.5 g, 1.9 mmol) in ethanol (60 ml). The reaction mixture was then refluxed for a further 14 h and the solvent removed. The product was recrystallised from ethyl acetate; 4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (11), (0.34 g, 65%) was isolated as colourless needles, m.p. 230-231°. (Found: C, 68.9; H, 3.5; N, 10.1. $C_{16}H_{10}N_2O_3$ requires C, 69.1; H, 3.6; N, 10.1%). ν_{max} 3140, 1780, 1675 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 10.2, br, NH; 8.41-7.63, m, ArH; 7.33, s, ArCH.

The same procedure was used to prepare the following:

(ii) 4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (17) was obtained in 73% yield, m.p. 291-293° from acetic acid. (Found: $M^{+\cdot}$ 338.0899. $C_{18}H_{14}N_2O_5$ requires $M^{+\cdot}$ 338.0903). ν_{max} 3250, 1750, 1670 cm^{-1}. N.m.r. (CD_3SOCD_3/CF_3CO_2D, 1:1) δ 8.33-7.51, m, 7H, ArH; 7.20, s, ArCH; 4.15, s, OMe; 4.05, s, OMe.

(iii) 4-(5- or 6-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (19) was obtained in 95% yield, m.p. 195-204° and 214-215° from ethanol. (Found: C, 69.9; H, 4.1; N, 9.6. $C_{17}H_{12}N_2O_3$ requires C, 69.7; H, 4.4; N, 9.2%). ν_{max} 3450-3200, 1775, 1750, 1660 cm^{-1}. N.m.r. δ 8.41-7.16, m, ArH; 6.65, 6.62, 2 x s, 1H, ArCH; 2.49, 2.45, 2 x s, $ArCH_3$. Mass spectrum m/e 306 (M), 147 ($C_9H_7O_2$). More rapid addition gave a product with four C-CH_3 resonances in its n.m.r. spectrum, and fragment ions at 147 ($C_9H_7O_2$) and 133 ($C_8H_5O_2$) in the ratio 4:3.

(iv) 6,7-dimethoxy-4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (14) was obtained in 98% yield, m.p. 287-289° from acetic acid, when 10 equivalents of hydrazine were used. (Found: $M^{+\cdot}$ 398.1120. $C_{20}H_{18}N_2O_7$ requires $M^{+\cdot}$ 398.1114). ν_{max} 3250, 1740, 1670, 1610 cm^{-1}. N.m.r. (CF_3CO_2D) δ 8.00, s, ArH; 7.63, s, ArH; 7.55, s, ArH; 7.20, s, ArH; 7.05, s, ArCH; 4.20, 4.18, 4.05, 4.02, 4 x s, OMe.

(v) reaction of 6-nitrobiphthalide (7) with hydrazine. Hydrazine hydrate (0.085 g, 1.7 mmol) in ethanol (20 ml) was added dropwise over 1 h to a stirred refluxing suspension of (7) (0.5 g, 1.6 mmol) in ethanol (50 ml). Refluxing was continued for 24 h, and the mixture then concentrated. The precipitated solid 3-nitro-8H-[1,2-b]-isoindolo-2,3-benzodiazepin-5(6H),8,13(12bH)-trione (28) (0.13 g, 27%) could not be adequately purified by chromatography or recrystallisation, and had m.p. 203°. (Found: $M^{+\cdot}$ 339.0496, $C_{16}H_9N_3O_6$ requires 339.0491). ν_{max} 1720, 1690, 1680 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 11.2, br, NH; 8.45, br s, ArH; 8.21-7.60, m, 6H, ArH; 4.81, s, ArCH.

The filtrate was concentrated and separated into its components by preparative t.l.c., which allowed the isolation of 6-nitrophthalide (0.1 g), m.p. 140-142° (lit.[20] 145°), and phthalazine-2,4-dione (0.24 g), m.p. 349-350° (lit.[21] 344°).

(vi) 4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-7,8-methylenedioxyphthalazin-1(2H)-one (22) (50%) and 6,7-dimethoxy-4-(4,5-methylenedioxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (24) (25%) were separated by fractional crystallisation from methanol-ethanol. Compound (22), m.p. 322-325° (dec.) was less soluble and was obtained pure after a further recrystallisation from methanol/dichloromethane. (Found: C, 59.4; H, 3.8; N, 6.9; $M^{+\cdot}$ 382.0805. $C_{19}H_{14}N_2O_7$ requires C, 59.7; H, 3.7; N, 7.3%; $M^{+\cdot}$ 382.0801). Mass spectrum m/e 382 (M), 193

(M - $C_9H_5N_2O_3$), no peak at 177. ν_{max} 3300, 1750, 1680 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8.05, d, J 8Hz, H-5; 7.53, d, J 8Hz, H-6; 7.38, s, H-4'; 7.25, s, H-7'; 7.06, s, ArCH; 6.40, s, OCH_2O; 3.86, 3.80, 2 x s, OMe.

Compound (24), m.p. 293-295° was obtained from the mother liquors, and was not absolutely free of (22). (Found: $M^{+\cdot}$ 382.0795. $C_{19}H_{14}N_2O_7$ requires $M^{+\cdot}$ 382.0801). Mass spectrum m/e 382 (M), 177 ($C_9H_5O_4$), no peak at 193. ν_{max} 3300, 1740, 1680 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 7.69, s, H-8; 7.60, d, J 8Hz, H-7'; 7.55, s, H-5; 7.35, s, Ar-CH; 7.15, d, J 8Hz, H-6'; 6.21, s, OCH_2O; 3.97, s, 2 x OMe.

(vii) 4-(4,5-methylenedioxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (25) and 7,8-methylenedioxy-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (26) were obtained as a 2:1 mixture after the reaction of (9) with hydrazine. The mixture was separated by preparative t.l.c. (ethyl acetate). The major product (25), had R_F 0.6, and was recrystallised as colourless needles, m.p. 296° (dec.) from aqueous ethanol. (Found: C, 59.6; H, 3.55; N, 8.0. $C_{17}H_{10}N_2O_5$. H_2O requires C, 60.0; H, 3.5; N, 8.2%). ν_{max} 3300, 3250, 1770, 1695 cm^{-1}. N.m.r. δ 8.4-7.9, m, ArH; 7.60, d, J 9Hz, H-7'; 7.35, s, ArCH; 7.28, d, J 9Hz, H-6'; 6.25, s, OCH_2O. Mass spectrum m/e 322 (M), 177 ($C_9H_5O_4$), no peak at 133.

The minor isomer (26), ν_{max} 1775 cm^{-1}, δ 6.18 (OCH_2O), R_F 0.4, could not be obtained completely free of (25), but its structure was confirmed by its mass spectral fragmentation pattern, particularly the strong peak at m/e 133 ($C_8H_5O_2$), absent in (25).

(viii) 4-(5- or 6-chloro-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (27) was obtained in 60% yield, and had m.p. 239-242° after crystallisation from aqueous ethanol. The infrared spectrum showed the presence of two products, ν_{max} 1785, 1760 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8.4-7.6, m, 8H ArH, NH; 7.22, s, ArCH. The product clung to water of crystallisation tenaciously. (Found: C, 59.2; H, 2.75; N, 8.8; $M^{+\cdot}$ 312.0296. $C_{16}H_9ClN_2O_3$ requires C, 59.7; H, 3.1; N, 8.7%; $M^{+\cdot}$ 312.0302). Mass spectrum m/e 314, 312 (M); 167, 169 ($C_8H_4ClO_2$), 133 ($C_8H_5O_2$) ca. 1:1.

Reaction of Biphthalides with Methylhydrazine

The general procedure was as in (i) above. The residue, after evaporation, recrystallised from ethanol to yield 2-methyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (12) (0.43 g, 86%), m.p. 187-189°. (Found: C, 69.6; H, 4.4; N, 9.5. $C_{17}H_{12}N_2O_3$ requires C, 69.9; H, 4.1; N, 9.6%). ν_{max} 1775, 1670, 1650 cm^{-1}. N.m.r. δ 8.52, m, H-8; 8.21-7.45, m, 7H, ArH; 6.83, s, ArCH; 3.83, s, NMe.

Using the same procedure, the following compounds were prepared.

(ii) 6,7-dimethoxy-4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2-methylphthalazin-1(2H)-one (15) (92%), m.p. 277-279° from acetic acid when 10 equivalents of methylhydrazine were used. (Found: $M^{+\cdot}$ 412.1278. $C_{21}H_{20}N_2O_7$ requires $M^{+\cdot}$ 412.1270). ν_{max} 1760, 1665, 1610 cm^{-1}. N.m.r. (CF_3CO_2D) δ 8.05, s, ArH; 7.65, s, ArH; 7.60, s, ArH; 7.25, s, ArH; 7.05, s, ArCH; 4.31-4.01, 5 x s, 4 x OMe, NMe.

(iii) 4-(5,6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2-methylphthalazin-1(2H)-one (18), (86%), m.p. 259-261° from ethanol. (Found: C, 64.9; H, 4.6; N, 8.0. $C_{19}H_{16}N_2O_5$ requires C, 64.8; N, 4.6; N, 8.0%). ν_{max} 1780, 1670 cm^{-1}. N.m.r. δ 8.41, m, H-8; 7.85-7.50, m, 3H, ArH; 7.31, s, H-4; 6.85, s, H-7; 6.56, s, ArCH; 4.00, s, OMe; 3.94, s, OMe; 3,75, s, NMe.

(iv) 2-methyl-4-(5- *or* 6-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (20), (96%), m.p. 163-173° and 180-189° from ethanol-water. (Found: C, 70.5; H, 4.8; N, 9.1. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%). ν_{max} 1770, 1650 cm^{-1}. N.m.r. δ 8.35, m, 1H, ArH; 8.06-7.11, m, 6H, ArH; 6.71, m, ArCH; 3.68, m, NMe; 2.42, m, ArMe. More rapid addition of the hydrazine gave a product with essentially equal amounts of mass spectral fragmentation at m/e 133 and 147.

(v) *reaction of* (7) with methylhydrazine. Reaction of (7) with methylhydrazine as above gave three products, analysed by t.l.c. Fractional crystallisation afforded 2-methyl-7-nitro-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (21), m.p. 256-258° (26%) after recrystallisation from ethanol. (Found: C, 60.6; H, 3.4; N, 12.2. $C_{17}H_{11}N_3O_5$ requires C, 60.5; H, 3.3; N, 12.5%). Mass spectrum m/e 337, M^+; 133, 100% ($C_8H_5O_2$). ν_{max} 1780, 1650 cm^{-1}. N.m.r. (CD_3SOCD_3) δ 8.98, d, J 1Hz, H-8; 8.85-8.43, m, 2H, ArH; 8.20-7.61, m, ArH; 7.50, s, ArCH; 3.71, s, NMe.

Further fractional crystallisation yielded 2-methylphthalazine-2,4-dione (0.06 g), m.p. 238-240° (lit.[22] 239-240°). *Analysis of the mother* liquor residues by n.m.r. spectroscopy and t.l.c. indicated the presence of 6-nitrophthalide.

(vi) 3-(1,2-dihydro-2-methyl-7,8-methylenedioxy-1-oxophthalazin-4-yl)5,6-dimethoxyisobenzofuran-1(3H)-one (23), 85%, was obtained after separation from its isomer by preparative t.l.c. (ethyl acetate). It had m.p. 264-267°, from ethanol. (Found: C, 60.6; H, 4.4; N, 6.8. $C_{20}H_{16}N_2O_7$ requires C, 60.6; H, 4.1; N, 7.1%). ν_{max} 1782, 1660 cm^{-1}. N.m.r. δ 7.95, s, ArH; 7.60, s, ArH; 7.55, s, ArH; 7.25, s, ArH; 7.10, s, ArCH; 6.10, s, OCH_2O; 4.15, 4.03, 2 x s, OMe.

Methylation of (11)

(i) A mixture of (11) (0.16 g, 0.61 mmol), potassium carbonate (1.6 g) and methyl iodide (1 ml) in acetone (25 ml) was stirred under nitrogen and refluxed for 48 h. The mixture was cooled, diluted with dichloromethane (50 ml), filtered, and the filtrate evaporated to dryness. The product (0.24 g) was purified by preparative t.l.c. (dichloromethane). The major compound was 2-methyl-4-(1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (31) (0.06 g, 34%), m.p. 184-5°. (Found: C, 70.4; H, 4.6; N, 8.9. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%) ν_{max} 1760, 1650 cm^{-1}. N.m.r. δ 8.57-8.18, m, 2H; ArH; 8.05-7.45, m, 6H, ArH; 3.78, s, NMe; 2.10, s, C-Me.

(ii) When the above reaction was repeated without the rigorous exclusion of oxygen, separation of the crude product by preparative t.l.c. (ethyl acetate/dichloromethane, 3:7) gave two compounds. The higher R_F product was methyl 2-(3,4-dihydro-3-methyl-4-oxophthalazine-1-carbonyl)benzoate (32) (0.04 g, 22%), which was purified by sublimation at 100°/2 mm, and had m.p. 136-8°. (Found: C, 67.2; H, 4.6; N, 8.4. $C_{18}H_{14}N_2O_4$ requires C, 67.1; H, 4.4; N, 8.7%). ν_{max} 1715, 1695, 1660 cm^{-1}. N.m.r. δ 9.10, m, 1H, ArH; 8.51, m, 1H, ArH; 8.14-7.51, m, 6H, ArH; 3.72, s, OMe; 3.66, s, NMe.

The lower R_F product was (31) (0.06 g, 34%).

Conversion of (32) to (12)

Reaction of (32) with ethanolic sodium borohydride at 0-5° for 2 h, followed by stirring with 10% sodium hydroxide at 20° for 6 h and acidification, gave a quantitative yield of (12), identical with the sample prepared above from biphthalide and methylhydrazine. [Methylation of (12) as in (i) above gave only a 20% yield of (31), the remainder being starting material.]

Methylation of (17)

Methylation of (17) as in (i) above gave a 69% yield of (18), isolated by preparative t.l.c. (ethyl acetate/dichloromethane, 1:1). It had m.p. 259-261°, and was identical with the sample prepared above directly from biphthalide (5).

Ethylation of (11)

When (11) was treated with ethyl iodide for 6 h at 20°, as above, preparative t.l.c. allowed the isolation of 2-ethyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (13) (54%). It was purified by sublimation at 180°/0.2 mm, and had m.p. 128-130°. (Found: C, 70.7; H, 5.0;

N, 8.8. $C_{18}H_{14}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.1%). ν_{max} 1770, 1660 cm^{-1}. N.m.r. δ 8.51, m, H-8; 8.16-7.41, m, ArH; 6.78, s, ArCH; 4.17, q, J 6Hz, NCH_2; 1.30, t, J 6Hz, CH_2CH_3.

Ethylation of (14)

When (14) was treated with ethyl iodide at 60° for 48 h, as above, 6,7-dimethoxy-4-(5;6-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-1-yl)-2-ethylphthalazin-1(2H)-one (16) (71%) was isolated by crystallisation from ethyl acetate, m.p. 266-269°. (Found: $M^{+\cdot}$ 426.1432. $C_{22}H_{22}N_2O_7$ requires $M^{+\cdot}$ 426.1427). ν_{max} 1770, 1660, 1610 cm^{-1}. N.m.r. δ 7.69, s, ArH; 7.32, s, ArH; 6.90, s, ArH; 6.82, s, ArH; 6.53, s, ArCH; 4.24, d, J 6Hz, NCH_2; 4.00, 3.97, 3.88, 3.81, 4 x s, OMe; 1.32, t, J 6Hz, CH_2CH_3.

4-(3-Oxo-1,3-dihydroisobenzofuran-1-ylidene)-3-phenylphthalazin-1(2H)-one (36)

Phenylhydrazine (0.11 g, 0.1 mmol) in xylene (5 ml) was added to a refluxing solution of biphthalide (0.25 g, 0.1 mmol) in xylene (20 ml), and the reaction mixture refluxed under nitrogen for 72 h. On cooling, the precipitated solid was recrystallised twice from xylene to give (36) (0.14 g, 40%) as pale yellow needles, m.p. 279-284°, 290-295°. (Found: C, 74.1; H, 3.8; $M^{+\cdot}$ 354.1009. $C_{22}H_{14}N_2O_2$ requires C, 74.5; H, 4.0%, $M^{+\cdot}$ 354.1004). ν_{max} 3200, 1780, 1660 cm^{-1}. N.m.r. (CF_3CO_2D) δ 8.89-6.91, m, ArH.

3-(1-Butyl-4-Chloro-1,2-dihydrophthalazin-2-yl)isobenzofuran-1(3H)-one (39)

Butyllithium (6.1 mmol) in hexane (3.2 ml) was added to a solution of 1-chlorophthalazine[23] (1.0 g, 6.1 mmol) in dry tetrahydrofuran (30 ml) under an atmosphere of nitrogen at -80°. After 2 min, methyl 2-formylbenzoate[24] (0.92 g, 6.1 mmol) in dry tetrahydrofuran (15 ml) was added to the blood red solution, and the reaction mixture allowed to warm to room temperature overnight. The reaction mixture was quenched with 10% hydrochloric acid and extracted with dichloromethane to yield a red oil (2.2 g) which was chromatographed on silica. Elution with ethyl acetate/light petroleum, 1:1, gave the title compound (1.1 g, 51%) as a single diastereoisomer, m.p. 160.5-163°, from ethanol. (Found: C, 67.5; H, 5.6; N, 7.6. $C_{20}H_{19}ClN_2O$ requires C, 67.7; H, 5.4; N, 7.9%). ν_{max} 1780 cm^{-1}. N.m.r. δ 7.90-7.07, m, 8H, ArH; 6.70, s, ArCH; 4.47, t, J 6Hz, ArCHN; 2.03-0.68, m, C_4H_9. ^{13}C N.m.r. δ 170.6; 145.5; 138.2; 135.2; 134.8; 134.5; 131.9; 131.1; 130.3; 128.9; 126.2; 125.6; 124.6; 124.4; 124.0; 96.3; 61.6; 33.4; 27.2; 22.7.

When (39) was treated with sodium hydride, potassium t-butoxide, or sodium methoxide, intractable mixtures of products resulted.

2-Hydroxymethyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1(2H)-one (40)

The method of Billman[25] gave a 60% yield of (40), but the method of Mustafa[19] proved superior. The cinnolinone (11) (0.278 g, 1 mmol) was refluxed for 3 h in a mixture of 35% formalin (3.5 ml) and methanol (12 ml). On cooling (40) (0.05 g) crystallised out, and a further 0.2 g was obtained after concentration. This product was recrystallised from aqueous methanol as a white solid, m.p. 229-231°. (Found: C, 66.5; H, 4.0; N, 8.9. $C_{17}H_{12}N_2O_4$ requires C, 66.2; H, 3.9; N, 9.1%). ν_{max} 3300 br, 1785, 1655 cm^{-1}. N.m.r. δ 7.39-7.00, m, ArH; 6.65, s, ArCH; 6.12, s, OH; 4.98, d, J 3Hz, N-CH-O; 4.89, d, J 3Hz, N-CH-O.

4-(3-Oxo-1,3-dihydroisobenzofuran-1-yl)-2-(1-piperidinomethyl)phthalazin-1-(2H)-one (41)

The cinnolinone (11) (0.278 g, 1 mmol) was refluxed with a mixture of 35% formalin (0.200 g), piperidine (0.170 g, 2 mmol) and methanol (10 ml) until solution was achieved, and then stirred at 20° overnight. Half the solvent was removed and the precipitated product (0.21 g) collected. It was recrystallised from ethanol as colourless needles, m.p. 156-157°. (Found: C, 70.0; H, 5.9; N, 11.1. $C_{22}H_{21}N_3O_3$ requires C, 70.4; H, 5.6; N, 11.2%). ν_{max} 1768, 1662 cm^{-1}. N.m.r. δ 7.8-7.3, ArH; 6.70, s, ArCH; 4.98, d, J 6Hz, N-CH-N; 4.80, d, J 6Hz, N-CH-N; 2.55, br, CH_2N; 1.4, br, CH_2.

2-Morpholinomethyl-4-(3-oxo-1,3-dihydroisobenzofuran-1-yl)phthalazin-1-(2H)-one (42)

When (11) was treated with morpholine as above, only starting material was recovered. The addition of triethylamine proved beneficial. Phthalazinone (11) (1 g), morpholine (0.8 ml), formalin (0.8 ml), triethylamine (5 drops) and methanol (30 ml) were refluxed for 18 h, and concentrated to half volume. Water (10 ml) was added and the precipitate (0.67 g) collected. A second crop (0.23 g) was obtained from the mother liquors. It was recrystallised from ethanol as colourless needles, m.p. 175-176°. (Found: C, 66.7; H, 5.1; N, 11.0. $C_{21}H_{19}N_3O_4$ requires C, 66.8; H, 5.1; N, 11.1%). ν_{max} 1768, 1660 cm^{-1}. N.m.r. δ 8.3-7.7, m, ArH; 7.25, s, ArCH; 5.58, d, J 13 Hz, N-CH-N; 5.34, d, J 13Hz, N-CH-N; 4.08, tr, J 4.5Hz, CH_2-O; 3.14, tr, J 4.5Hz, CH_2N.

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REFERENCES AND NOTES

a The name phthalidylphthalazinone is used in the *Discussion* section to emphasise the relationship to the "phthalide-isoquinolines" but the systematic name, 4-(3-oxodihydroisobenzofuran-1-yl)phthalazinone, is used in the Experimental section.

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