Studies Concerning Pyrrolo[2,1-*a*]phthalazines and Related Compounds

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A series of pyrrolo[2,1-*a*]phthalazine derivatives has been prepared including examples carrying a variety of *O*- and *N*-substituents at position-6. A number of the products and related tricyclic structures show mild anti-hypertensive activity including 6-allyloxy-1,2-dichloro-3-phenylpyrrolo[2,1-*a*]phthalazine.

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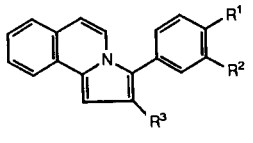
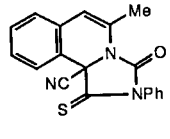
By use of cyclisation procedures involving carbanions of Reissert compounds [1], we have synthesised examples of a number of structurally similar tricyclic systems, including compounds of the pyrrolo[2,1-*a*]isoquinoline series, *e.g.* **1a,b** [2], of the imidazo[5,1-*a*]phthalazine and imidazo-[5,1-*a*]isoquinoline series, *e.g.* **2** [3,4], and of the pyrrolo[2,1-*a*]phthalazine series, *e.g.* **3** [5]. Some 3-substituted derivatives **4** of the isosteric *s*-triazolo[3,4-*a*]phthalazine system have recently been shown to possess hypotensive activity [6]. The peripheral vasodilator properties of the hydrazinophthalazine hydrallazine (**5**) are well known [7]. We now report the synthesis of a range of pyrrolo-[2,1-*a*]phthalazines, including examples substituted at position-6, for investigation as potential antiphypertensive agents, along with some examples of isosteric tricyclic systems.



	R^1	R^2	R^3
1a	OMe	H	$CONH_2$
1b	Me	H	$CONH_2$
1c	OMe	H	H
1d	OMe	OMe	$CONH_2$



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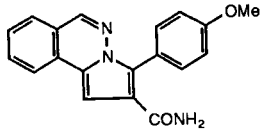

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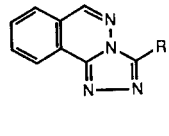

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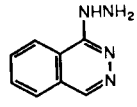

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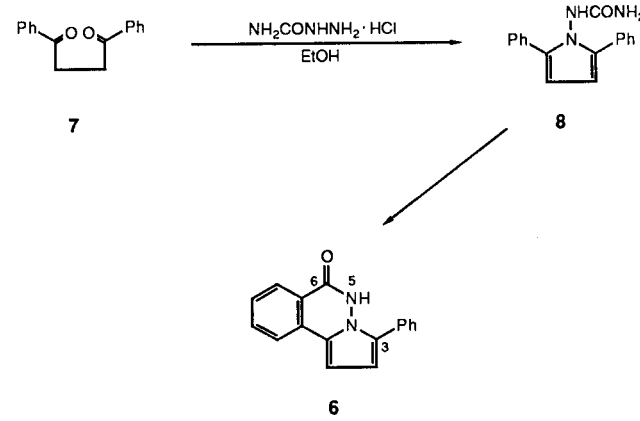
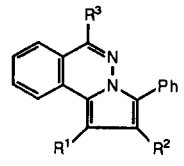
Sprio and co-workers [8] reported the preparation of examples of the pyrrolo[2,1-*a*]phthalazin-6(5*H*)-one system, *e.g.* **6**, which we considered would facilitate functional modification at the 6- and 5-positions. Compound **6** is available in two steps (Scheme 1) from 1,2-dibenzoylethane (**7**) [8]. This latter compound results from reduction of 1,2-dibenzoylethylene with stannous choride and hydrochloric acid in ethanol [9], but we found the reaction had to be worked-up immediately after mixing the hot reagents since heating the system under reflux converted the product **7** into 2,5-diphenylfuran.

Scheme 1



7 **8** **6**

Attempts to introduce chlorine into the pyrrolo[2,1-*a*]-phthalazin-6(5*H*)-one **6** at position-6 with phosphoryl chloride did not yield a stable product. Immediate reaction of the product with hydrazine hydrate was also unsuccessful. These steps have been used to convert phthalazin-1(2*H*)-one to hydrallazine (**5**), the intermediate chloro compound being relatively unstable [10]. Reaction of **6** with phosphorus pentachloride [11] also yielded intractable material. However, use of a phosphoryl chloride-phosphorus pentachloride mixture [12] gave a crystalline product which proved to be 1,2,6-trichloro-3-phenylpyrrolo[2,1-*a*]-phthalazine (**9a**). In the ^{1}H-nmr spectrum the doublets at δ 6.5 and δ 6.7 for the protons of the pyrrole ring in **6** had gone, as had the carbonyl absorption (1660 cm^{-1}) from the infrared. Whilst there is no evidence for the order of chlorination it seems likely that substitution at positions-1 and -2 is electrophilic in character and nucleophilic at position-6. Electrophilic chlorination by phosphorus penta-



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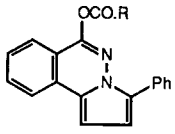
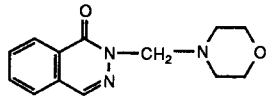
	R^1	R^2	R^3		R^1	R^2	R^3
9a	Cl	Cl	Cl	**9i**	Cl	Cl	EtO
9b	Cl	Cl	$(CH_2)_4$ N-	**9j**	Cl	Cl	*n*-PrO-
9c	H	H	$(CH_2)_4$ N-	**9k**	Cl	Cl	*i*-PrO-
9d	Cl	Cl	$(CH_2)_5$ N-	**9l**	Cl	Cl	furfuryloxy
9e	Cl	Cl	morpholino	**9m**	Cl	Cl	CH_2=$CHCH_2O$-
9f	Cl	Cl	3-methylpiperidino	**9n**	Cl	Cl	PhO
9g	Cl	Cl	$MeNNH_2$	**9o**	Cl	Cl	4-$MeOC_6H_4O$-
9h	Cl	Cl	MeO-	**9p**	Cl	Cl	2-naphthyloxy



R

10a	Me
10b	MeO
10c	EtO
10d	PhO



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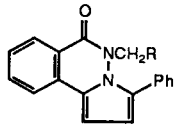


12

	R
12a	$(CH_2)_5N$-
12b	morpholino
12c	4-methylpiperidino
12d	4-methylpiperazino

chloride has been reported for a number of activated aromatic compounds, including mesitylene, aniline derivatives and polynuclear hydrocarbons such as anthracene [13].

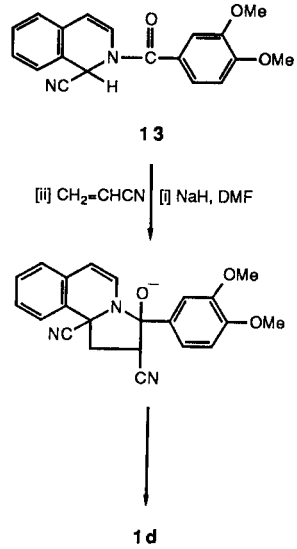
In keeping with the character of analogous phthalazines we anticipated that compound **9a** should readily undergo nucleophilic substitution of the C-6 chlorine. Heating **9a** under reflux as a solution in pyrrolidine gave the dichloro product **9b** in 76% yield. Removal of the chlorine atoms at the 1- and 2-positions was achieved reductively by use of hydrazine hydrate and 10% palladium-charcoal in ethanol, the dechlorinated product **9c** crystallising as yellow needles in 40% yield. A range of analogs of **9b**, *viz* compounds **9d-9p**, was then prepared using other amines, methylhydrazine and various oxygen nucleophiles. Use of hydrazine hydrate failed to give a stable product.

O-Acylation of the pyrrolo[2,1-*a*]phthalazin-6(5*H*)-one system was examined using **6** with acetic anhydride and with various chloroformate esters, providing derivatives **10a-10d** in yields of 56-69%. The infrared spectrum of the acetylated product **10a** showed the aryl ester carbonyl at 1760 cm^{-1} which compares with 1757 cm^{-1} for 1-acetoxy-4-isopropylphthalazine [14] prepared from 1-chloro-4-isopropylphthalazine and sodium acetate. The carbonate derivatives **10b-10d** showed the anticipated higher carbonyl stretching frequencies, *ca* 1775 cm^{-1}.

Substitution at position-5 of the pyrrolo[2,1-*a*]phthalazin-6(5*H*)-one system was effected through the Mannich reaction in a procedure analogous to that for bases such as **11** from phthalazinone [15]. Treatment of **6** with piperidine and aqueous formaldehyde in ethanol at 0° provided the 5-piperidinomethyl derivative **12a** in good yield and other derivatives **12b-12d** were similarly prepared. The amidic carbonyl in **12a** appeared at 1628 cm^{-1} in the infrared which compares with 1640 cm^{-1} reported for **11** [15]. In the ^1H nmr spectrum of **12a** the NCH_2N methylene appeared at δ 3.9, presumably experiencing some deshielding from the face of the 3-phenyl ring.

The pyrrolo[2,1-*a*]isoquinolines **1a,b** were prepared as previously recorded [2], as were related compounds **2** [4] and **3** [5]. Treatment of **1a** with phosphoric acid at 140-160° gave **1c** in 58% yield. 3-(3,4-Dimethoxyphenyl)-pyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**1d**) was prepared by cyclocondensation of the Reissert compound 2-(3,4-dimethoxybenzoyl)-1,2-dihydroisoquinoline-1-carbonitrile (**13**) with acrylonitrile at 0° (Scheme 2).

Scheme 2



Pharmacological examination for antihypertensive activity was carried out on selected compounds representative of the structural types prepared. The relevant data are shown in Table 1. It can be seen that relative to hydral-

lazine (**5**) all compounds were less active. The most active of the products was the 6-allyloxy derivative **9m**, which showed a 10% reduction in mean arterial blood pressure at 1 hour in normotensive rats [16] with a dose of 10 mg/kg (i.p.).

Table

Antihypertensive Activity [a]

Compound [b]	Activity	Compound [b]	Activity
1a [c]	+	**9g**	inactive
1b [d]	+	**9i**	+
2 [e]	+	**9l**	inactive
3 [f]	+	**9m**	+ +
5	+ + +	**10a**	+
6	inactive	**12b**	inactive
9f	inactive		

[a] + + + = 31% reduction in mean arterial blood pessure at 2 hours with dose of 5mg/kg (i.p.) in normotensive [16] rats; + + = 10% reduction in mean arterial blood pressure at 1 hour with dose of 10 mg/kg (i.p.) in normotensive rats; + = activity present but milder than + +. [b] Compounds showed negligible effect on heart rate except for **5** (18% rise at 3 hours); **9i** (51% rise at 2 hours, falling off at 3 hours); **10a** (32% rise at 1 hour, falling off at 3 hours). [c] mp 174-175° [2]. [d] mp 209-210° [2]. [e] mp 167-168° [3,4]. [f] mp 177-178° [5].

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian EM 360A spectrometer (60 MHz) and some on a Perkin Elmer R32 (90 MHz) instrument, with tetramethylsilane as internal reference. Infrared spectra were recorded on a Perkin Elmer 177 grating spectrometer and mass spectra on an AEI MS 12 machine. Microanalyses were determined by the Microanalytical Laboratory, University of Manchester, U.K.

1,2-Dibenzoylethane (**7**).

Trans-1,2-dibenzoylethylene was prepared [17] from fumaryl chloride [18] and benzene in the presence of aluminium chloride in 61% yield; ir (nujol): 1660 cm^{-1}.

To a hot suspension of 8 g of stannous chloride in 12 ml of 8*N* hydrochloric acid and 4 ml of ethanol was added dropwise with stirring a hot solution of 8 g of *trans*-1,2-dibenzoylethylene in 40 ml of ethanol. The mixture was diluted immediately with water, cooled and filtered. The product **7** crystallized from ethanol to afford 5.67 g (70%) as pale yellow needles, mp 144-147° (reported [9] 145-147°); ir (nujol): 1680 cm^{-1}; pmr (deuteriochloroform): δ 3.4 (CH_2).

If, after mixing the reagents, the above reaction was heated under reflux for 30 minutes, dilution with water precipitated 3.7 g (49%) of 2,5-diphenylfuran which crystallized from ethanol as colourless plates, mp 89-90° (reported [19] 89.5-90°).

3-Phenylpyrrolo[2,1-*a*]phthalazin-6(5*H*)-one (**6**).

This was prepared by the method of Sprio *et al.* [8] from 1,2-dibenzoylethane (**7**) *via* 2,5-diphenylureidopyrrole (**8**) [20]. The product **6** had mp 185-186° (reported [8] 185-186°); ir (potassium bromide): 1660 cm^{-1}; pmr (deuteriochloroform): δ 6.5 (d, 1H, H-1 or H-2, J = 3.0 Hz), 6.7 (d, 1H, H-1 or H-2, J = 3.0 Hz), 7.0-8.2 (m, 9H, aromatic), 12.0 (br, 1H, NH); uv (ethanol): λ max 250 (log ϵ 3.11), 293 (3.61), 333 nm (3.53).

1,2,6-Trichloro-3-phenylpyrrolo[2,1-*a*]phthalazine (**9a**).

A mixture of 2 g of **6**, 19 g of phosphoryl chloride and 6 g of phosphorus pentachloride was heated at 70° for 90 minutes. After pouring on to ice the mixture was basified to *p*H 8 with ammonium hydroxide. The product **9a** was filtered off and recrystallized from carbon tetrachloride to give 1.7 g (63%) as yellow needles, mp 206-208°; ir (potassium bromide): 1615 cm^{-1}; pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 50:50): δ 7.2-8.9 (m, aromatic); uv (ethanol): λ max 253 (log ϵ 2.55), 285 (2.92), 316 (2.44); ms: 352/350/348/346 (M^+ 100).

Anal. Calcd. for $C_{17}H_9Cl_3N_2$: C, 58.7; H, 2.6; N, 8.1. Found: C, 59.1; H, 2.5; N, 8.0.

Preparation of 6-Amino-1,2-dichloro-3-phenylpyrrolo[2,1-*a*]-phthalazines.

A mixture of 3 mmoles of **9a** and 0.1 mole of the appropriate amine was heated under reflux for 19 hours. If **9a** was not soluble in the amine 25 ml of dry toluene was added as solvent. Concentration under reduced pressure was followed by recrystallization of the residue.

Using this procedure compounds **9b-9f** were prepared.

1,2-Dichloro-3-phenyl-6-pyrrolidinopyrrolo[2,1-*a*]phthalazine (**9b**).

This compound crystallized from cyclohexane as pale yellow needles, mp 169-171°, in 76% yield; pmr (deuteriochloroform): δ 1.86 (m, 4H), 3.50 (m, 4H).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3$: C, 66.0: H, 4.5; N, 11.0. Found: C, 65.6; H, 4.5; N, 10.8.

1,2-Dichloro-3-phenyl-6-piperidinopyrrolo[2,1-*a*]phthalazine (**9d**).

The compound crystallized from cyclohexane as pale yellow needles, mp 151-153° in 45% yield; pmr (deuteriochloroform): δ 1.7 (m, 6H), 3.2 (m, 4H), 7.1-8.8 (m, 9H); ms: 399/397/395 (M^+ 100).

Anal. Calcd. for $C_{22}H_{19}Cl_2N_3$: C, 66.6; H, 4.8; N, 10.6. Found: C, 66.4; H, 4.8; N, 10.9.

1,2-Dichloro-6-morpholino-3-phenylpyrrolo[2,1-*a*]phthalazine (**9e**).

This compound crystallized from toluene as yellow needles, mp 145-148° in 38% yield; pmr (deuteriochloroform): δ 2.95 (m, 4H), 3.55 (m, 4H), 6.95-8.8 (m, 9H); ms: 401/399/397 (M^+ 100).

Anal. Calcd. for $C_{21}H_{17}Cl_2N_3O$: C, 63.3, H, 4.3; N, 10.5. Found: C, 63.0; H, 4.3; N, 10.55.

1,2-Dichloro-6-(3-methylpiperidino)-3-phenylpyrrolo[2,1-*a*]phthalazine (**9f**).

This compound crystallized from toluene as pale yellow needles, mp 129-131° in 40% yield.

Anal. Calcd. for $C_{23}H_{21}Cl_2N_3$: C, 67.3; H, 5.2; N, 10.2. Found: C, 67.5; H, 5.25; N, 10.1.

3-Phenyl-6-pyrrolidinopyrrolo[2,1-*a*]phthalazine (**9c**).

To a solution of 0.1 g of **9b** in 10 ml of ethanol was added 0.1 g of palladium charcoal (10%) and 8 g (0.16 mole) of 100% hydrazine hydrate. The mixture was heated under reflux for 90 minutes. The catalyst was filtered off and the filtrate evaporated under reduced pressure. The residue was washed with water,

filtered, dried and crystallized from cyclohexane to give 30 mg (40%) of **9c** as light yellow needles, mp 110-112°.

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.5; H, 6.1; N, 13.4. Found: C, 80.3; H, 6.0; N, 13.2.

1,2-Dichloro-6-(α-methylhydrazino)-3-phenylpyrrolo[2,1-*a*]-phthalazine (**9g**).

A solution of 0.8 g of **9a** and 10 ml of methylhydrazine in 10 ml of toluene was heated under reflux for 6 days and the mixture concentrated under reduced pressure. The residual oil was triturated and crystallized from toluene to afford 0.3 g (36%) of **9g** as pale yellow needles, mp 169-171°; ir (potassium bromide): 3320 cm^{-1} (br); pmr (deuteriochloroform): δ 3.0 (s, 3H, NMe), 5.2 (br, 2H, NH_2), 7.0-8.8 (m, 9H).

Anal. Calcd. for $C_{18}H_{14}Cl_2N_4$: C, 60.5; H, 3.95; N, 15.7. Found: C, 60.5; H, 3.9; N, 15.4.

Preparation of 6-Alkoxy-1,2-dichloro-3-phenylpyrrolo[2,1-*a*]-phthalazines.

To the sodium alkoxide, prepared from 0.02 mole of sodium and 20 ml of the appropriate dry alcohol, was added a solution of 4 mmoles of **9a** in 10 ml of the same solvent. The mixture was heated under reflux for 72 hours and the solvent removed under reduced pressure. The residue was suspended in water and extracted with three 40 ml portions of chloroform. The combined extracts were dried and concentrated under reduced pressure to give the product.

By use of this procedure compounds **9h-9m** were prepared.

1,2-Dichloro-6-methoxy-3-phenylpyrrolo[2,1-*a*]phthalazine (**9h**).

This compound crystallized from carbon tetrachloride as pale yellow needles, mp 116-118°, in 81% yield.

Anal. Calcd. for $C_{18}H_{12}Cl_2N_2O$: C, 63.0; H, 3.5; N, 8.2. Found: C, 62.8; H, 3.4; N, 7.9.

1,2-Dichloro-6-ethoxy-3-phenylpyrrolo[2,1-*a*]phthalazine (**9i**).

This compound crystallized from cyclohexane as pale yellow needles, mp 125-127°, in 37% yield; pmr (deuteriochloroform): δ 1.4 (t, 3H), 4.3 (q, 2H), 7.1-8.8 (m, 9H).

Anal. Calcd. for $C_{19}H_{14}Cl_2N_2O$: C, 63.9; H, 3.95; N, 7.8. Found: C, 63.55; H, 3.8; N, 7.5.

1,2-Dichloro-3-phenyl-6-propoxypyrrolo[2,1-*a*]phthalazine (**9j**).

This compound crystallized from cyclohexane as pale yellow needles, mp 128-130°, in 49% yield; pmr (deuteriochloroform): δ 1.21 (t, 3H), 1.93 (m, 2H), 4.22 (t, 2H), 7.0-8.8 (m, 9H).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O$: C, 64.7; H, 4.3; N, 7.55. Found: C, 64.9; H, 4.2; N, 7.4.

1,2-Dichloro-6-isopropoxy-3-phenylpyrrolo[2,1-*a*]phthalazine (**9k**).

This compound crystallized from 2-propanol as pale yellow needles, mp 124-126°, in 56% yield, pmr (deuteriochloroform): δ 1.3 (d, 6H), 3.95 (m, 1H), 6.7-8.8 (m, 9H).

Anal. Calcd. for $C_{20}H_{16}Cl_2N_2O$: C, 64.7; H, 4.3; N, 7.55. Found: C, 64.9; H, 4.0; N, 7.5.

1,2-Dichloro-6-furfuryloxy-3-phenylpyrrolo[2,1-*a*]phthalazine (**9l**).

This compound crystallized from cyclohexane as pale yellow needles, mp 126-128°, in 60% yield; pmr (deuteriochloroform): δ 4.2 (s, 2H), 6.9-8.8 (m, 12H).

Anal. Calcd. for $C_{22}H_{14}Cl_2N_2O$: C, 64.6; H, 3.4; N, 6.8. Found: C, 64.3; H, 3.8; N, 6.7.

6-Allyloxy-1,2-dichloro-3-phenylpyrrolo[2,1-*a*]phthalazine (**9m**).

This compound crystallized from ethanol as pale yellow needles, mp 129-131°, in 57% yield; pmr (deuteriochloroform): δ 4.75 (br d, 2H, $OCH_2CH=CH_2$), 5.41 (m, 2H, $OCH_2CH=CH_2$), 6.1 (m, 1H, $OCH_2CH=CH_2$), 7.1-8.9 (m, 9H, aromatic).

Anal. Calcd. for $C_{20}H_{14}Cl_2N_2O$: C, 65.05; H, 3.8; N, 7.6. Found: C, 65.0; H, 3.9; N, 7.4.

Preparation of 6-Aryloxy-1,2-dichloro-3-phenylpyrrolo[2,1-*a*]-phthalazines.

A mixture of 3 mmoles of **9a** and 40 mmoles of the appropriate phenol was heated with 14 mmoles of anhydrous potassium carbonate at 190° for 19 hours. The product mixture was partitioned between 40% aqueous sodium hydroxide and chloroform. Concentration of the dried chloroform extract provided the product.

By use of this procedure compound **9n-9p** were prepared.

1,2-Dichloro-6-phenoxy-3-phenylpyrrolo[2,1-*a*]phthalazine (**9n**).

This compound crystallized from cyclohexane as pale yellow needles, mp 148-150°, 69% yield; pmr (deuteriochloroform): δ 6.8-8.9 (m).

Anal. Calcd. for $C_{23}H_{14}Cl_2N_2O$: C, 68.2; H, 3.5; N, 6.9. Found: C, 68.2; H, 3.4; N, 6.8.

1,2-Dichloro-6-(4-methoxyphenoxy)-3-phenylpyrrolo[2,1-*a*]-phthalazine (**9o**).

This compound crystallized from cyclohexane as buff coloured plates, mp 162-164°, in 40% yield; pmr (deuteriochloroform): δ 3.78 (s, 3H), 6.5-8.9 (m, 13H).

Anal. Calcd. for $C_{24}H_{16}Cl_2N_2O_2$: C, 66.2; H, 3.7; N, 6.4. Found: C, 66.6; H, 3.9; N, 6.3.

1,2-Dichloro-6-(2-naphthyloxy)-3-phenylpyrrolo[2,1-*a*]phthalazine (**9p**).

This compound crystallized from cyclohexane as pale yellow needles, mp 161-163°, in 70% yield; pmr (deuteriochloroform): δ 6.7-8.9 (m).

Anal. Calcd. for $C_{27}H_{16}Cl_2N_2O$: C, 71.2; H, 3.5; N, 6.15. Found: C, 71.4; H, 3.9; N, 5.7.

6-Acetoxy-3-phenylpyrrolo[2,1-*a*]phthalazine (**10a**).

A mixture of 0.5 g of **6** and 10 g of acetic anhydride were heated at 80° with stirring for 10 hours. After cooling to room temperature the mixture was poured on to ice and the precipitated product filtered off, washed with water and dried to give 0.4 g (69%) of **10a** which crystallized as yellow needles from methanol, mp 122-124°; ir (nujol): 1760 cm^{-1}; pmr (deuteriochloroform): δ 2.55 (s, 3H), 6.9-8.1 (m, 11H).

Anal. Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.7; H, 4.7; N, 9.3. Found: C, 75.2; H, 4.7; N, 9.3.

Methyl 3-Phenylpyrrolo[2,1-*a*]phthalazin-6-ylcarbonate (**10b**).

A mixture of 0.5 g of **6** and 10 ml of methyl chloroformate was heated at 75° with stirring for 2 days. On cooling the solution was poured on to ice and the precipitate filtered, washed with water and dried. Crystallization from methanol gave 0.4 g (67%) of **10b** as greenish yellow needles, mp 136-137°; ir (nujol): 1770 cm^{-1}; pmr (deuteriochloroform): δ 3.90 (s, 3H), 6.88-8.1 (m, 11H).

Anal. Calcd. for $C_{19}H_{14}N_2O_3$: C, 71.7; H, 4.4; N, 8.8. Found: C, 71.7; H, 4.3; N, 8.9.

Use of ethyl chloroformate under the same conditions gave ethyl 3-phenylpyrrolo[2,1-*a*]phthalazin-6-ylcarbonate (**10c**) in 60% yield as yellow needles from ethanol, mp 138-140°; ir (potassium bromide): 1775 cm^{-1}; pmr (deuteriochloroform): δ 1.5 (t, 3H), 4.5 (q, 2H), 6.88-8.2 (m, 11H).

Anal. Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.3; H, 4.9; N, 8.4. Found: C, 72.3; H, 4.9; N, 8.2.

Use of phenyl chloroformate under the same conditions gave phenyl 3-phenylpyrrolo[2,1-*a*]phthalazin-6-ylcarbonate (**10d**) in 56% yield as greenish-yellow needles from ethanol, mp 141-143°; ir (nujol): 1780 cm^{-1}; pmr (deuteriochloroform): δ 6.9-8.2 (m).

Anal. Calcd. for $C_{24}H_{16}N_2O_3$: C, 75.8; H, 4.2; N, 7.4. Found: C, 75.7; H, 4.1; N, 7.5.

Preparation of 5-Alkylaminomethyl-3-phenylpyrrolo[2,1-*a*]phthalazin-6(5*H*)-ones.

A mixture of 3 mmoles of **6** and 4 mmoles of the appropriate amine in ethanol was stirred at 0° with 0.2 ml of formaldehyde (40% w/v aqueous solution) for 24 hours. After removal of the volatile material under reduced pressure the residue was passed down a column of Hyflosupercel, being eluted with chloroform. Evaporation of the eluate and trituration with ether gave the product.

The procedure was used to prepare **12a-12d**.

3-Phenyl-5-piperidinomethylpyrrolo[2,1-*a*]phthalazin-6(5*H*)-one (**12a**).

This compound crystallized as pale yellow needles from methanol, mp 203-205°, in 60% yield; ir (potassium bromide): 1628 cm^{-1}; pmr (deuteriochlorform): δ 1.5 (m, 6H), 2.57 (m, 4H), 3.9 (s, 2H), 6.3-8.2 (m, 11H).

Anal. Calcd. for $C_{23}H_{23}N_3O$: C, 77.3; H, 6.5; N, 11.6. Found: C, 77.1; H, 6.5; N, 11.4.

5-Morpholinomethyl-3-phenylpyrrolo[2,1-*a*]phthalazin-6(5*H*)-one (**12b**).

This compound crystallized as pale yellow needles from methanol, mp 207-209°, in 55% yield; ir (potassium bromide): 1628 cm^{-1}; pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 50:50): δ 2.72 (4H), 3.61 (4H), 3.9 (s, 2H), 6.6-8.3 (11H).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.5; H, 5.9; N, 11.7. Found: C, 73.4; H, 5.9; N, 11.5.

5-(4-Methylpiperidinomethyl)-3-phenylpyrrolo[2,1-*a*]phthalazin-6(5*H*)-one (**12c**).

This compound crystallized as pale yellow needles from ethanol, mp 190-192°, in 15% yield; ir (potassium bromide): 1628 cm^{-1}; pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 50:50): δ 0.78 (3H), 1.3 (5H),2.6 (4H), 3.85 (s, 2H).

Anal. Calcd. for $C_{24}H_{25}N_3O$: C, 77.6; H, 6.8; N, 11.3. Found: C, 77.3; H, 6.5; N, 10.9.

5-(4-Methylpiperazinomethyl)-3-phenylpyrrolo[2,1-*a*]phthalazin-6(5*H*)-one (**12d**).

This compound crystallized as pale yellow needles from methanol, mp 231-233°, in 55% yield; ir (potassium bromide): 1628 cm^{-1}; pmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide, 50:50): δ 2.1 (3H), 2.6 (8H), 6.3-8.2 (11H).

Anal. Calcd. for $C_{23}H_{24}N_4O$: C, 74.2; H, 6.5; N, 15.0. Found: C, 73.8; H, 6.5; N, 14.9.

3-(4-Methoxyphenyl)pyrrolo[2,1-*a*]phthalazine (**1c**).

A mixture of 1 g of **1a** and 20 ml of 88-93% phosphoric acid was heated at 140-160° for 30 minutes by which time evolution of gas had ceased. The mixture was cooled and poured on to 20 g of ice. The precipitate which formed was removed by filtration and the solid crystallised from ethanol to give 0.5 g (58%) of **1c** as greenish-yellow rhombs, mp 122-125°; uv (ethanol): λ max 250 sh, 276 (log ε 4.86), 330 nm (4.32); pmr (deuteriochloroform): δ 3.9 (s, 3H, OMe).

Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.5; H, 5.5; N, 5.1. Found: C, 83.6; H, 5.9; N, 5.0.

3-(3,4-Dimethoxyphenyl)pyrrolo[2,1-*a*]isoquinoline-2-carboxamide (**1d**).

To a suspension of 3.48 g (0.072 mole) of sodium hydride (50% dispersion in oil) in 100 ml of dimethylformamide at 0° under nitrogen was added 13.24 g (0.041 mole) of **13** [21] in 60 ml of dimethylformamide over 30 minutes. After stirring for a further 30 minutes, 3.82 g (0.072 mole) of acrylonitrile in 40 ml of dimethylformamide was added and the reaction maintained at 0° for 3 hours. The mixture was concentrated to small volume under reduced pressure, and added to 100 ml of water, and the *p*H adjusted to neutral with dilute hydrochloric acid. Extraction with chloroform, washing the extract with dilute hydrochloric acid and water, drying over potassium carbonate and removal of solvent gave a dark red oil. The oil was purified by column chromatography on neutral alumina, using toluene:ethyl acetate (4:1) as eluant, to give a solid which on crystallisation from benzene-light petroleum (bp 60-80°) provided 1.31 g of **1d** as yellow rhombs mp 167-168°; ir (potassium bromide): 1645 cm^{-1}; pmr (deuteriochloroform): δ 3.9.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.8; H, 5.2; N, 8.1. Found: C, 72.5; H, 5.5; N, 7.9.

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