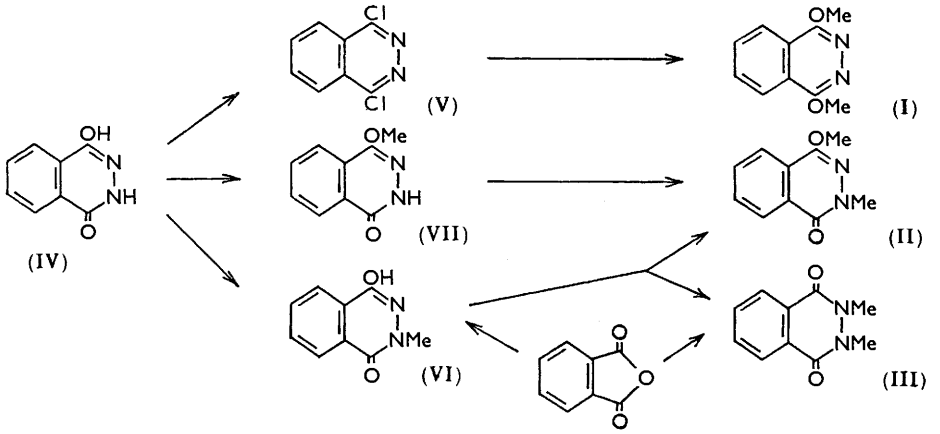
343. 1,4-*Dimethoxyphthalazine and the Other* O- *and* N-*Methyl Derivatives of Phthalhydrazide.*

By J. A. Elvidge and A. P. Redman.

1,4-Dimethoxyphthalazine (I) is now correctly described for the first time. Its structure has been verified through comparison with the other methyl derivatives of phthalhydrazide; *O*- and *N*-methyl groups have been determined, preparative evidence is summarised, and light absorptions are discussed. Where tautomerism is possible in this series, the 1,2-dihydrophthalazine form (IV) is preferred.

The di- and mono-*O*-methyl derivatives (I) and (VII) can methylate amines.

In order to prepare 1,4-dimethoxyphthalazine (I) we treated 1,4-dichlorophthalazine with methanolic sodium methoxide. This gave a product with the desired elementary composition. However, the melting point, 93°, was very different from the value, 121° (with sintering from 100°), claimed for 1,4-dimethoxyphthalazine by Drew and Garwood,[1] but was the same as that for the isomeric *ON*-dimethyl derivative (II) described by Rowe and Peters.[2] These dimethyl derivatives of phthalhydrazide had earlier been the subject of structural controversy, which seemed to have been resolved.[3] Nevertheless, there was now a need for a re-investigation.



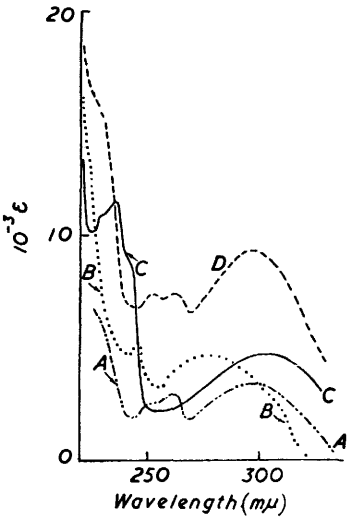
We conclude that our new product, m. p. 93°, is indeed 1,4-dimethoxyphthalazine (I). It happens to have the same melting point as the isomer (II) but the melting point of a mixture is strongly depressed. Drew and Garwood's product can hardly have been a pure compound.

The structure (I) for our product, indicated by the preparative route (IV) ⟶ (V) ⟶ (I), was supported by the infrared absorption, which shows no amide bands (see Table). Further support came from methyl-group analysis (by modified Zeisel and Friedrich methods [4]) which gave a correct value for two methoxyl groups and showed that *N*-methyl was absent; for comparison, the isomer (III)—of certain constitution because of its preparation [5] from phthalic anhydride and *NN'*-dimethylhydrazine—gave a correct value for two *N*-methyl groups with methoxyl absent.

The remaining isomer (II) was prepared as follows. Phthalhydrazide (IV) was first

[1] Drew and Garwood, *J.*, 1937, 1841.
[2] Rowe and Peters, *J.*, 1933, 1331.
[3] Vaughan, *Chem. Rev.*, 1948, **43**, 447.
[4] Clark, "Quantitative Methods of Organic Microanalysis," Butterworths, London, 1956.
[5] Drew, Hatt, and Hobart, *J.*, 1937, 33.

monomethylated with dimethyl sulphate and alkali to the *N*-methyl derivative (VI), also obtained [2] by unambiguous synthesis from phthalic anhydride and methylhydrazine. Further methylation of this derivative (VI) with dimethyl sulphate and alkali then gave



Light absorptions.

Ultraviolet (in ethanol, except as indicated)

	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$
A, Phthalhydrazide (IV) *	263	2·93
	298	3·6
B, 1,4-Dimethoxyphthalazine (I)	245	5·32
	280	4·75
C, *NN'*-Dimethyl derivative (III)	214	57·0
	230 †	11·0
	236	11·5
	242 †	8·85
	302	4·84
D, *ON*-Dimethyl derivative (II)	227 †	16·55
	234 †	12·8
	252	7·4
	263	7·4
	298	9·3
Monomethoxy-derivative (VII)	227	11·1
	252	3·7
	262	4·2
	295	5·1
Mono-*N*-methyl derivative (VI)	228	11·1
	255	3·2
	264	3·5
	304	6·0
1,4-Diphenoxyphthalazine (VIII)	213	58·3
	260 †	5·55
	318	6·11

* In propylene carbonate. † Inflexion.

Infrared (KBr disc, except as indicated)

	N–H	Ar–H C–H	C=O	C=N C=C	Other vibrations (max., $cm.^{-1}$)
(IV)	3130m	2990s	1655s	1599m	1372m, 1343m, 1323m, 1299m, 1258m, 1215w,
		2865s		1552m	1076m, 1017w, 825m, 790m, 780w, 683m
				1487s	
				1451w	
				1437w	
(I)		3072w		1600w	1370s, 1291w, 1268w, 1211w, 1194m, 1171m,
		2967m		1557s	1142w, 1100s, 1080w, 1068m, 1024m, 997m,
		2945m		1508w	976s, 794m, 779m, 752s, 718m
		2895w		1458s	
		2865w		1434m	
(III)		3017w	1626s	1604w	1415m, 1360s, 1285s, 1182m, 1129m, 1025w,
		2915w		1576w	995m, 795m, 706s, 689w
				1487m	
(II)		3067w	1642s	1616w	1404w, 1377w, 1344s, 1311w, 1274w, 1257m,
		2963w		1582s	1199m, 1186w, 1159w, 1135m, 1099s, 1052w,
		2911w		1564m	1026w, 983m, 955m, 829w, 796s, 786s, 732s, 691s
				1488m	
				1456w	
				1444m	
(VII)	3120m	2994m	1650s	1618w	1372m, 1348s, 1333m, 1221s, 1155w, 1098s,
		2874m		1596s	1024w, 983m, 813w, 775s, 763s, 713w, 682m
				1560w	
				1493s	
				1439m	
(VI)		3030m	1629m	1585w	1405w, 1364m, 1325m, 1252s, 1170w, 1142m,
		(broad)		1565s	1099s, 958m, 833w, 789s, 737s, 689s
				1489m	
(IX) *		3012m		1595m	1336w, 1203w, 1196s, 1163m, 1147w, 1074m,
				1582w	1019m, 1006w, 916m, 853s, 793m, 782s, 737m,
				1555m	718s, 691s, 666m
				1486m	

* Nujol mull.

nearly equal amounts of the *NN'*-dimethyl compound (III) and an isomer. The latter necessarily had the structure (II), and in agreement analysis showed one methoxyl and one *N*-methyl group. An alternative synthesis was also achieved. Methylation of the silver derivative of phthalhydrazide gave the monomethoxy-compound (VII), as described by Rowe and Peters,[2] which is isomeric with (VI); and further methylation, with dimethyl sulphate and alkali, then gave the *ON*-dimethyl compound (II) as sole product.

Attempts at further methylation of the monomethyl ether (VII) *via* its silver derivative by Drew and Garwood's method [1] and modifications thereof resulted only in recovery of starting material. We did not detect any product of m. p. 121° (with sintering from 100°) which they had claimed was 1,4-dimethoxyphthalazine. The failure of the silver derivative–methyl iodide method with (VII) was paralleled by failure with the isomer (VI), both being in contrast to the successful methylations with dimethyl sulphate and alkali.

Light Absorptions and Structures.—The dimethyl derivatives (I), (II), and (III) represent (as fixed structures) the three tautomeric forms possible for the parent phthalhydrazide. Their ultraviolet absorption curves are shown in the Figure. In this series, fine structure cannot be correlated merely with the position of the band of longest wavelength, as is possible for imidines,[6] because that for the cyclic diamide (III) (a tetrahydrodioxophthalazine) is at the same position, *ca.* 300 mμ, as that for the monoamide (II) (a dihydro-oxophthalazine: spectral envelopes must be compared. Curve *A* for phthalhydrazide and the curves for its potentially tautomeric monomethyl derivatives (data in Table) have a shape very similar only to that for the (fixed) *ON*-dimethyl compound (II). This is good evidence that phthalhydrazide exists (in solution) in the dihydro-oxophthalazine form (IV) and that the monomethyl derivatives are best represented by the analogous structures (VI) and (VII). This resolves an earlier investigation.[2] We disagree with the idea [2] that in neutral solution phthalhydrazide exists as 1,4-dihydroxyphthalazine. The latter name and phthalaz-1,4-dione, both currently used,[7] are strictly incorrect. Neither are we convinced that there is any change of tautomeric form just before the melting point.[7b,8]

The same conclusion that phthalhydrazide is best represented by structure (IV) was reached from the infrared absorption.[9] We have measured the infrared spectra of solid phthalhydrazide and of the solid methyl derivatives (I), (II), (III), (VI), and (VII), but consider that conclusions about the fine structures of the potentially tautomeric compounds can hardly be drawn unambiguously (see Table), as is possible from the ultraviolet results. Nevertheless, the tentative assignments (Table) lend support to our structures.

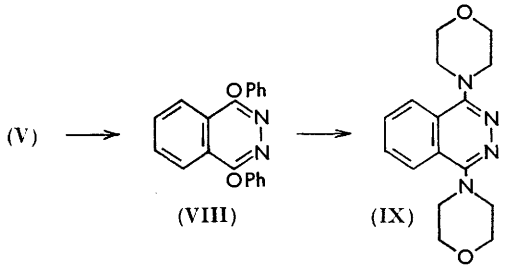
That the monolactim forms (IV), (VI), and (VII) are preferred is perhaps not surprising: these structures permit resonance stabilisation in the way that Arndt [10] has indicated for the related maleic hydrazide, assumption of the dilactim form being unnecessary for the attainment of aromaticity.

Methylation of Amines by Compounds (I) *and* (VII).—In an attempt to obtain additional support for the structure (I) for our dimethyl derivative, the compound was heated with morpholine. Instead of 1,4-dimorpholinophthalazine, however, phthalhydrazide was isolated in high yield, an unexpected result which nevertheless does support the structure (I). Repetition of the reaction with exclusion of moisture gave the same result, indicating that hydrolysis of the ether (I) by water in the morpholine [11] was not responsible. It was then shown by gas–liquid chromatography that *N*-methylmorpholine was the second product. The dimethoxyphthalazine (I) had therefore methylated the amine, itself being transformed into phthalhydrazide. An implication was that the monomethoxy-derivative

[6] Clark, Elvidge, and Golden, *J.*, 1956, 4135.
[7] *E.g.*, (*a*) Albert, " Heterocyclic Chemistry," The Athlone Press, London, 1959, p. 120; (*b*) Rodd, " Chemistry of Carbon Compounds," Elsevier, Amsterdam, 1959, Vol. IVB, p. 1248.
[8] Drew and Hatt, *J.*, 1937, 16.
[9] Sheĭnker, Gortinskaya, and Sycheva, *Zhur. fiz. Khim.*, 1957, **31**, 599.
[10] Arndt, *Angew. Chem.*, 1949, **61**, 397.
[11] Cf. Clark, Elvidge, and Linstead, *J.*, 1953, 3593.

(VII) was capable of methylating amines, and indeed this was demonstrated. After the monomethoxy-compound (VII) had been heated with an excess of aniline, phthalhydrazide was isolated in 72% yield and *N*-methylaniline (as the tosyl derivative) in 87% yield. (Comparable recovery of the excess of aniline was made as the alkali-soluble toluene-*p*-sulphonate.)

Methylation of amines by the methoxyphthalazines (I) and (VII) resembles, for example, alkylation by toluene-*p*-sulphonic esters.[12] Presumably the reaction is an S_N2 attack on methyl, facilitated by the second electron-withdrawing grouping of the ring, *viz.*, $-N{=}\overset{|}{C}{-}OMe$ or $-NH{-}\overset{|}{C}O$ respectively. Additional activation is absent in simple imidic esters R·C(OEt):NH and these are substituted by amines to yield amidines.[13]



1,4-Diphenoxyphthalazine (VIII), prepared from 1,4-dichlorophthalazine (V) and sodium phenoxide, reacted smoothly with morpholine at 200°, to yield 1,4-dimorpholinophthalazine (IX). This is an expected nucleophilic displacement for which there are numerous analogies.[14]

Experimental

Phthalhydrazide [8] (IV) crystallised from dimethylformamide as thin prisms, m. p. 333—334° (cf. refs. 8 and 15) (Found: N, 17·6. Calc. for $C_8H_6O_2N_2$: N, 17·3%).

1,4-*Dimethoxyphthalazine* (I).—Conversion [8] of phthalhydrazide into 1,4-dichlorophthalazine was modified in that a benzene extract of the reaction mixture was evaporated under reduced pressure and the residue sublimed at 120—130°/10^{-5} mm. The dichlorophthalazine was thus obtained as needles, m. p. 164—165° (Found: Cl, 34·8. Calc. for $C_8H_4N_2Cl_2$: Cl, 35·7%). To dry methanol (35 c.c.) containing sodium methoxide (from 750 mg. of sodium), the dichlorophthalazine (2·5 g.) was added, and the mixture heated under reflux for 10 hr. After filtration of the mixture and evaporation, the residue was sublimed at 80—90°/1·5 mm. to yield prisms, m. p. 93°, of 1,4-*dimethoxyphthalazine* (Found: C, 63·2; H, 5·4; N, 14·8; OMe, 33·0; *N*-Me, 0. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7; OMe, 32·7%).

The Isomers (II) *and* (III).—(*a*) Methylhydrazine, obtained in 42% aqueous solution by distillation of the sulphate [16] with soda-lime and sodium hydroxide [17] (Found: C, 10·9; H, 12·0. Calc. for $CH_6N_2,3\frac{1}{2}H_2O$: C, 11·0; H, 11·9%), was treated with phthalic anhydride to yield 1,2-dihydro-4-hydroxy-2-methyl-1-oxophthalazine [2] (VI) as plates, m. p. 238—240° (from methanol–water) (Found: C, 61·55; H, 4·5; OMe, 0; *N*-Me, 9·05. Calc. for $C_9H_8O_2N_2$: C, 61·4; H, 4·6; *N*-Me, 8·5%). The identical compound was formed from phthalhydrazide with dimethyl sulphate and alkali.[2] Further methylation of the derivative (VI) (2 g.) for 4 hr. with a boiling mixture of dimethyl sulphate (4·6 c.c.) and water (8 c.c.) containing sodium hydroxide (1·6 g.) afforded, by isolation in ether (2 × 200 c.c.), a gum which solidified on trituration with dry ether. After several washings with boiling ether, the solid remaining (600 mg.), m. p. *ca.* 170°, crystallised from water to give 1,2,3,4-tetrahydro-2,3-dimethyl-1,4-dioxophthalazine (III) as needles, m. p. 174—175° (cf. ref. 5) (Found: C, 63·1; H, 5·3; OMe, 0;

[12] *E.g.*, Ferns and Lapworth, *J.*, 1912, **101**, 273; Sekara and Marvel, *J. Amer. Chem. Soc.*, 1933, **55**, 345; Shirley, Zietz, and Reedy, *J. Org. Chem.*, 1953, **18**, 378.
[13] Roberts, DeWolfe, and Ross, *J. Amer. Chem. Soc.*, 1951, **73**, 2277.
[14] *E.g.*, Keneford, Schofield, and Simpson, *J.*, 1948, 358; Morley and Simpson, *ibid.*, p. 360; Simpson and Wright, *ibid.*, p. 1707.
[15] Radulescu and Georgescu, *Bull. Soc. chim. France*, 1925, **37**, 881.
[16] Hatt, *Org. Synth.*, **16**, 51.
[17] von Brüning, *Annalen*, 1889, **253**, 5.

N-Me, 15·3. Calc. for $C_{10}H_{10}O_2N_2$: C, 63·2; H, 5·3; *N*-Me, 15·0%). Evaporation of the ethereal washings and sublimation of the residue (650 mg.), m. p. 85—90°, at 80°/0·4 mm. afforded 1,2-dihydro-4-methoxy-2-methyl-1-oxophthalazine (II), m. p. 93° (cf. ref. 2) (Found: C, 63·5; H, 5·5; OMe, 16·3; *N*-Me, 8·1. Calc. for $C_{10}H_{10}O_2N_2$: C, 63·2; H, 5·3. OMe, 16·3; *N*-Me, 7·9%).

(*b*) Phthalhydrazide was converted into the silver derivative and treated with methyl iodide.[2] Sublimation (twice) of the crude product at 100—130°/0·15 mm. gave 1,2-dihydro-4-methoxy-1-oxophthalazine (VII), m. p. 189° (Found: C, 61·5; H, 5·0; OMe, 17·2; *N*-Me, 0. Calc. for $C_9H_8O_2N_2$: C, 61·4; H, 4·6; OMe, 17·6%). This monomethoxy-compound (450 mg.) was heated under reflux with dimethyl sulphate (1·12 c.c.) and 20% potassium hydroxide solution (2 c.c.) for 2 hr. The mixture was made alkaline and extracted continuously with ether. Evaporation of the extract afforded a colourless solid, m. p. 93° undepressed on admixture with the *ON*-dimethyl derivative (II) above.

A mixture of the dimethyl derivatives (I) and (II) had m. p. *ca.* 70°.

Methylations by (I) *and* (VII).—(*a*) 1,4-Dimethoxyphthalazine (I) (300 mg.) was heated with freshly dried morpholine (5 c.c.) in a sealed tube at 204° for 20 hr. Evaporation of the liquid under reduced pressure and addition of ether gave a solid (250 mg.), identified as phthalhydrazide by m. p. and mixed m. p. and crystalline form (rosettes from dimethylformamide). A small portion of the recovered " morpholine " was examined by gas–liquid chromatography (at 184° in nitrogen over powdered brick loaded with Silicone grease). The record of the chromatogram exhibited a small peak, immediately preceding the morpholine peak, due to 4-methylmorpholine as shown by comparison with chromatograms of an authentic mixture and of morpholine alone.

(*b*) The monomethoxy-compound (VII) (100 mg.) was heated with aniline (0·60 c.c.) at 200° for 24 hr. After being washed with dry ether, the solid product (66 mg., 72%) had m. p. 332—335° (decomp.), undepressed by phthalhydrazide. The oil from evaporation of the ethereal washings and filtrate was warmed on the steam-bath with pyridine (10 c.c.) and toluene-*p*-sulphonyl chloride (1·23 g.) for 1 hr., the solution was evaporated to small bulk under reduced pressure, an excess of 2N-sodium hydroxide was added, and the mixture extracted with benzene. Acidification and cooling of the aqueous solution afforded toluene-*p*-sulphonanilide (1·348 g., 90% of theoretical recovery), m. p. 100—101° and mixed m. p. 101—103° (authentic specimen, m. p. 103°). The benzene extract was washed with 2N-sodium hydroxide and with water, and was evaporated. Trituration of the residue with ether afforded a solid which was taken up in boiling ether. Clarification of the solution and evaporation then yielded toluene-*p*-sulphon-*N*-methylanilide (131 mg., 87·5%), m. p. 88—89° and mixed m. p. 91—92° with authentic material (m. p. 93°).

1,4-*Diphenoxyphthalazine* (VIII).—To molten phenol (10 g., redistilled), sodamide (380 mg.) was added, and subsequently 1,4-dichlorophthalazine (720 mg.). After being kept at 120—130° for 2 hr., the mixture was poured into 40% aqueous sodium hydroxide (25 c.c.). Water (75 c.c.) was added and the precipitate (1·32 g.), m. p. *ca.* 200°, collected and washed with water. Recrystallisation from aqueous dimethylformamide (charcoal) gave prisms of 1,4-*diphenoxyphthalazine*, m. p. 222° (cf. ref. 18) (Found: C, 76·3; H, 4·3; N, 8·8. $C_{20}H_{14}O_2N_2$ requires C, 76·5; H, 4·5; N, 8·9%).

1,4-*Dimorpholinophthalazine* (IX).—The diphenoxy-compound (300 mg.) was heated at 205° with morpholine (5 c.c.; dried), overnight. Evaporation of the solution and crystallisation of the residue (250 mg.), m. p. *ca.* 206°, from dimethylformamide yielded needles of 1,4-*dimorpholinophthalazine*, m. p. 204° (Found: C, 64·0; H, 6·6; N, 18·4. $C_{16}H_{20}O_2N_4$ requires C, 64·0; H, 6·7; N, 18·7%).

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[18] Druey, U.S.P. 2,484,785/1949.