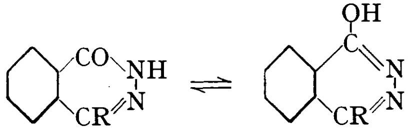
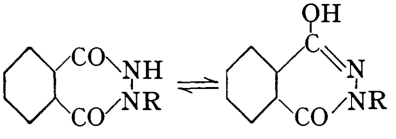
310. *Tautomerism in the Phthalazine Series. The* N- *and* O-*Derivatives of* 1-*Methylphthalaz*-4-*one and Phthalaz*-1 : 4-*dione.*

By F. M. Rowe and A. T. Peters.

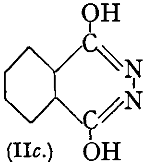
In connexion with our work on certain phthalazines and the derived amphoteric phthalazones (this vol., p. 1067, and preceding papers in that series) we have investigated the nature of the fundamental ring system with a view to examining later the influence upon it of substituents in R, where R is aryl:



(I*a*.) (I*b*.)



(II*a*.) (II*b*.)



(II*c*.)

[R = H, alkyl, or aryl.]

This was all the more necessary as the experimental data available are incomplete, and the literature contains some contradictory statements with regard to the constitution of the methylation and acetylation products of compounds of these types: nowhere is an alkoxyl determination of the ethers of simple phthalazines recorded, although this is of vital importance in determining their structure. Moreover, the possibility of forming two ethers from a suitable phthalazine by *direct* methods, which will indicate the type of tautomerism existent in the compound, does not appear to have been appreciated fully. Consequently, we have attempted to establish the structure of the above types of compounds with special reference to tautomerism by studying 1-methylphthalaz-4-one (I*a*; R = Me) or 1-hydroxy-4-methylphthalazine (I*b*), and "phthalylhydrazide" or phthalaz-1 : 4-dione (II*a*; R = H) or 1-hydroxyphthalaz-4-one (II*b*) or 1 : 4-dihydroxyphthalazine (II*c*). We have adopted the nomenclature 1-hydroxy-4-methylphthalazine and 1 : 4-dihydroxyphthalazine for the respective compounds.

1-Hydroxy-4-methylphthalazine (Gabriel and Neumann, *Ber.*, 1893, **26**, 705) is insoluble in cold, but dissolves in hot water, and the solution is neutral to litmus. It dissolves readily in mineral acids, but is not basic enough for mineral acid salts or a picrate to be isolated. It is insoluble in cold aqueous sodium carbonate, sparingly soluble in aqueous ammonia, but dissolves in hot aqueous or alcoholic potassium hydroxide, although it is not acidic enough for a potassium salt to be isolated.

1-Hydroxy-4-methylphthalazine forms two methyl ethers. Gabriel and Eschenbach (*Ber.*, 1897, **30**, 3031) obtained an ether as one of the products of distilling 1-methylphthalazine methiodide with aqueous potassium hydroxide, and also made the same compound by the action of methyl iodide and potassium hydroxide on 1-methylphthalaz-4-one. They regarded it as the *N*-ether and it is undoubtedly 1 : 3-dimethylphthalaz-4-one. We prepared it equally well by means of methyl sulphate and aqueous methyl-alcoholic sodium hydroxide, and it cannot be demethylated.

Gabriel and Neumann (*loc. cit.*) made the *O*-ethyl ether by the action of sodium ethoxide on 1-chloro-4-methylphthalazine, but did not make the corresponding *O*-methyl ether. We have made similarly from 1-chloro-4-methylphthalazine 1-*methoxy*-4-*methylphthalazine*, which is clearly the *O*-ether, and we also made it directly by the action of methyl sulphate on 1-hydroxy-4-methylphthalazine in dry nitrobenzene solution; the latter method gives no trace of 1 : 3-dimethylphthalaz-4-one. The fact that the *O*-ether can be isolated at all under the latter conditions may be due to its greater basicity in comparison with that of 1-hydroxy-4-methylphthalazine. 1-Methoxy-4-methylphthalazine is demethylated readily under any conditions, even by cold hydrobromic acid (*d* 1·7) in the attempt to make a hydrobromide from it. Both ethers are insoluble in alkalis, but extremely soluble in mineral acids; the *O*-ether is more basic than the *N*-ether and forms a well-defined *picrate*, but the latter does not.

With acetic anhydride alone, or in presence of glacial acetic acid or fused potassium acetate, 1-hydroxy-4-methylphthalazine forms only one monoacetyl derivative, which can be crystallised from dry benzene, but is hydrolysed readily by boiling alcohol, and is undoubtedly 1-*acetoxy*-4-*methylphthalazine*.

The most reasonable explanation of all of these reactions is that tautomerism occurs, 1-methylphthalaz-4-one (I*a*; R = Me) existing in alkali hydroxide solution, and 1-hydroxy-4-methylphthalazine (I*b*) in neutral or acid solution.

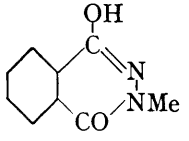
The tautomerism of "phthalylhydrazide" (II*a*; R = H) was considered briefly by Heller (*J. pr. Chem.*, 1925, **111**, 4) and in detail by Radulescu and Georgescu (*Bull. Soc. chim.*, 1925, **37**, 881). Heller stated that tautomerism occurs only to a slight extent, and Radulescu and Georgescu favoured formula (II*a*; R = H). The latter authors, by methylation with methyl sulphate in potassium hydroxide solution, prepared a mono- and a di-ether, which they regarded as the *O*-mono- and the *O*-di-methyl ether respectively, and they considered that the acetyl derivative of the former was the *O*-acetate-*O*-methyl ether. We have prepared these three compounds and have arrived at entirely different conclusions. The monomethyl ether cannot be demethylated; it is obtained readily also by condensing methylhydrazine with phthalic anhydride, and is 1-*hydroxy*-3-*methylphthalaz*-4-*one*; with acetic anhydride it forms 1-*acetoxy*-3-*methylphthalaz*-4-*one*, from which the acetyl group is hydrolysed readily by boiling aqueous alcohol. The dimethyl ether is 1-*methoxy*-3-*methylphthalaz*-4-*one*, demethylated by hydrobromic acid (*d* 1·7) at 100° to 1-hydroxy-3-methylphthalaz-4-one.

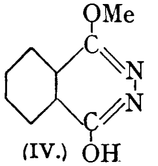
The actual *O*-monomethyl ether was made by Heller (*loc. cit.*, p. 14) by heating the silver salt, methyl iodide, and ether in a sealed tube at 100° for 2 hours, and we obtained it by refluxing the silver salt with methyl-alcoholic methyl iodide, but 1-chloro-4-hydroxyphthalazine was unaltered by heating with methyl-alcoholic sodium methoxide in a sealed tube at 120°. 4-Hydroxy-1-methoxyphthalazine is demethylated readily; and with acetic anhydride it forms 1-*methoxy*-4-*acetoxyphthalazine*, from which the acetyl group is hydrolysed readily by boiling aqueous alcohol.

In the nature of the case, we are unable to establish the constitutions of the metallic salts of 1 : 4-dihydroxyphthalazine, but the facts are of interest and present analogies with the behaviour of the metallic cyanides towards alkylating agents. The silver salt prepared *via* the ammonium salt behaves as the *O*-salt, and when prepared *via* the sodium salt also reacts with methyl iodide at 125° to give the *O*-ether; the sodium salt, however, under the same conditions gives the *N*-ether, suggesting that it is the *N*-sodium salt, since at this temperature the *O*-ether suffers little decomposition and can be obtained in lower yield from the silver salt under these conditions. 4-Hydroxy-1-methoxyphthalazine is still acidic enough to form a sodium salt, but ammonium and silver salts could not be obtained; this salt behaves as the *N*-sodium salt, since with methyl iodide at 125° it gives 1-methoxy-3-methylphthalaz-4-one.

Heller (*loc. cit.*) prepared an *O*-monoacetyl derivative by the action of acetyl chloride on the potassium salt of "phthalylhydrazide" in benzene, and stated that neither the free compound nor the silver salt reacts in this way. Radulescu and Georgescu (*loc. cit.*) described a stable diacetyl derivative obtained from "phthalylhydrazide" by the action of acetic anhydride and anhydrous sodium acetate, and a labile diacetyl derivative obtained by the use of acetic anhydride only (compare Mihăilescu and Florescu, *Bull. Acad. Sci. Roumaine*, 1923, **8**, 303). They regarded the latter as the *ON*-diacetyl derivative, because it is converted into the above *O*-monoacetyl compound by boiling alcohol, although this interpretation is not reasonable. We have prepared the monoacetyl derivative by the action of acetic anhydride and glacial acetic acid on 1 : 4-dihydroxyphthalazine and also from the silver salt of the latter by the action of acetyl chloride in dry benzene. It is hydrolysed by boiling aqueous alcohol and is undoubtedly 4-hydroxy-1-acetoxyphthalazine. We were unable to prepare the stable diacetyl derivative of Radulescu and Georgescu, as under all conditions of diacetylation we obtained only 1 : 4-*diacetoxyphthalazine*, which is hydrolysed successively to 4-hydroxy-1-acetoxyphthalazine and 1 : 4-dihydroxyphthalazine by boiling aqueous alcohol.

It appears from all of these reactions that 1 : 4-dihydroxyphthalazine (II*c*) exists in acid or neutral solution and 1-hydroxyphthalaz-4-one (II*b*; R = H) in alkali hydroxide solution; there is no evidence to support the "phthalylhydrazide" or phthalaz-1 : 4-dione formula (II*a*; R = H) first advanced by Curtius and Foersterling (*J. pr. Chem.*, 1895, **51**, 371). The formulæ of the methyl ethers are: *N*-methyl ether (III); *O*-methyl ether in acid or neutral solution (IV) and in alkali hydroxide solution (V); and the dimethyl ether (VI).


(III.)


(IV.)

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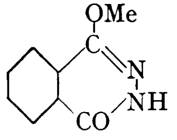
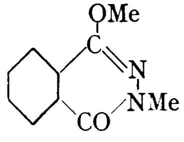

(V.)


(VI.)

Experimental.

1 : 3-*Dimethylphthalaz*-4-*one*.—(*a*) 1-Hydroxy-4-methylphthalazine (4·5 g.), methyl alcohol (33 c.c.), and 4*N*-sodium hydroxide (8 c.c.) were refluxed with methyl iodide (6 g.) for 1 hour. The alcohol was removed, ice added, the clear solution extracted with ether, and the ether removed. 1 : 3-Dimethylphthalaz-4-one crystallised from methyl alcohol in colourless large rhombohedra, m. p. 112° (yield, 4·3 g.; 88%) (Gabriel and Eschenbach, *Ber.*, 1897, **30**, 3032, gave m. p. 109—110°). It is insoluble in alkalis; is not demethylated by hydrobromic acid (*d* 1·7) and glacial acetic acid in a sealed tube at 120° during 3 hours, or by hydriodic acid (*d* 1·7) at 140° under Zeisel experimental conditions; it is very soluble in mineral acids, but does not form crystalline salts; and does not form a picrate.

(*b*) 1-Hydroxy-4-methylphthalazine (3·4 g.), methyl alcohol (60 c.c.), and 4*N*-sodium hydroxide (16 c.c.) were warmed with methyl sulphate (5 g.) on the water-bath for ½ hour. Alcohol was then removed, and excess of 4*N*-sodium hydroxide added to the warm residue. Crystalline form, yield, and m. p. as in (*a*).

1-*Methoxy*-4-*methylphthalazine*.—(a) 1-Chloro-4-methylphthalazine (4 g.) (Gabriel and Neumann, *Ber.*, 1893, **26**, 709; Gabriel and Eschenbach, *loc. cit.*, p. 3025; yield, 81%) was refluxed with sodium methoxide (1 g. sodium) and methyl alcohol (40 c.c.) for ½ hour. Sodium chloride was filtered off, alcohol removed from the filtrate, water added, the product extracted with ether, and the ether removed. 1-*Methoxy*-4-*methylphthalazine* crystallised from light petroleum in colourless prismatic needles, m. p. 53—54° (yield, 3·5 g.; 85%) (Found: C, 68·8; H, 5·75; N, 15·8; OMe, 17·8. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·7; N, 16·1; OMe, 17·8%). With an alcoholic solution of picric acid, it forms a *picrate*, small yellow needles, m. p. 198° (Found: C, 47·8; H, 3·3. $C_{16}H_{13}O_8N_5$ requires C, 47·6; H, 3·2%).

(b) 1-Hydroxy-4-methylphthalazine (5 g.) in dry nitrobenzene (50 c.c.) was heated with methyl sulphate (5 g.) at 130° for 20 minutes, the nitrobenzene then being removed with steam. The clear colourless solution was made strongly alkaline with sodium hydroxide and extracted with ether, and the ether removed. The residue (0·9 g.) was converted into the picrate, m. p. and mixed m. p. 198°, from which 1-methoxy-4-methylphthalazine, m. p. 53—54°, was isolated by treatment with alcoholic potassium hydroxide. The *N*-ether can be detected readily in presence of the *O*-ether by treating a mixture with hydrobromic acid and glacial acetic acid at 100°, then diluting the product with water, filtering off the 1-hydroxy-4-methylphthalazine, making the filtrate alkaline with sodium hydroxide, and extracting it with ether. No 1 : 3-dimethylphthalaz-4-one was obtained when the above reaction mixture was examined in this way.

(c) 1-Hydroxy-4-methylphthalazine (0·7 g.), methyl alcohol (6 c.c.), and methyl sulphate (3 c.c.) were heated in a sealed tube at 150° for 3 hours. Although much was unaltered, some 1-methoxy-4-methylphthalazine was isolated as the picrate, m. p. and mixed m. p. 198°.

1-*Acetoxy*-4-*methylphthalazine*.—1-Hydroxy-4-methylphthalazine (2 g.) was heated with acetic anhydride (6 c.c.) (i) alone, (ii) with addition of glacial acetic acid (10 c.c.), and (iii) with addition of freshly fused potassium acetate (2 g.); the mixtures were concentrated, and the crystals dried on tile. 1-*Acetoxy*-4-*methylphthalazine* only was formed in each case and crystallised from dry benzene in almost colourless needles, m. p. 130—132° (Found: C, 64·45; H, 5·0; N, 13·9. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·8%). It can be kept without decomposition, but is hydrolysed readily by boiling alcohol and more readily by aqueous alcohol.

1 : 4-Dihydroxyphthalazine, prepared by the method of Mihăilescu and Florescu (*Bull. Acad. Sci. Roumaine*, 1923, **8**, 303), crystallised from glacial acetic acid in colourless needles, m. p. 333—337°, according to the rate of heating.

1-*Hydroxy*-3-*methylphthalaz*-4-*one*.—1 : 4-Dihydroxyphthalazine (18 g.), methyl alcohol (150 c.c.), methyl sulphate (28 g.), and 20% aqueous potassium hydroxide (70 c.c.) were refluxed for 1 hour, then concentrated and precipitated by neutralisation. 1-*Hydroxy*-3-*methylphthalaz*-4-*one* crystallised from methyl alcohol in small needles, with a faint pink tinge, m. p. 238° (yield, 15 g.; 77%) (Found: C, 61·4; H, 4·4; N, 15·6; OMe, 0·0. $C_9H_8O_2N_2$ requires C, 61·35; H, 4·5; N, 15·9%). It was readily obtained also by boiling a solution of methylhydrazine sulphate (1 mol.) in aqueous sodium acetate with a glacial acetic acid solution of phthalic anhydride (1 mol.) for a few minutes, m. p. and mixed m. p. 238°. Radulescu and Georgescu (*Bull. Soc. chim.*, 1925, **37**, 887) gave m. p. 232° for this compound and regarded it as the *O*-ether. It dissolves in hot concentrated hydrochloric acid and in sodium hydroxide solution, and is not demethylated by hydrobromic acid (*d* 1·7) or by hydriodic acid (*d* 1·7) at 140°. With acetic anhydride, it formed 1-*acetoxy*-3-*methylphthalaz*-4-*one*, which crystallised from dry alcohol in colourless, large, flat, rectangular prisms, m. p. 142° (Found: C, 60·4; H, 4·6. $C_{11}H_{10}O_3N_2$ requires C, 60·55; H, 4·6%), which Radulescu and Georgescu (*loc. cit.*) regarded as the *O*-acetate-*O*-methyl ether. Although it can be crystallised from alcohol, it is hydrolysed readily by boiling aqueous alcohol, or by dilute acid or alkali, with formation of 1-hydroxy-3-methylphthalaz-4-one.

1-*Methoxy*-3-*methylphthalaz*-4-*one*.—1 : 4-Dihydroxyphthalazine (10 g.), 20% aqueous potassium hydroxide (40 c.c.), and methyl sulphate (30 g.) were refluxed for 1 hour, then diluted with water and extracted with ether, and the ether removed. 1-*Methoxy*-3-*methylphthalaz*-4-*one* crystallised in colourless prisms, m. p. 93° (yield, 6·8 g.; 58%) (Found: C, 63·0; H, 5·1; N, 14·3; OMe, 16·3. $C_{10}H_{10}O_2N_2$ requires C, 63·15; H, 5·3; N, 14·7; OMe, 16·3%); Radulescu and Georgescu (*loc. cit.*) gave m. p. 77° for this compound and regarded it as the di-*O*-methyl ether. It dissolves in dilute hydrochloric acid, but is insoluble in alkalis, and is demethylated by heating with hydrobromic acid (*d* 1·7) at 100°, forming 1-hydroxy-3-methylphthalaz-4-one, m. p. and mixed m. p. 238°. A smaller quantity of the latter compound also was isolated from the residue of the dimethylation mixture after the ether extraction.

4-*Hydroxy*-1-*methoxyphthalazine*.—Aqueous silver nitrate (1·1 mol.) was added to an ammoniacal solution of 1 : 4-dihydroxyphthalazine, from which excess of ammonia had been removed by boiling, and the white precipitate was filtered off and dried in a vacuum. The silver salt (10 g.), methyl iodide (10·5 g.), and methyl alcohol (200 c.c.) were refluxed for 2 hours, and the filtered solution concentrated. 4-Hydroxy-1-methoxyphthalazine crystallised in colourless needles, m. p. 188° (Heller, *J. pr. Chem.*, 1925, **111**, 14, gave m. p. 187°) (yield, 4·3 g.; 66%) (Found: C, 61·2; H, 4·5; N, 16·1; OMe, 17·4. Calc. for $C_9H_8O_2N_2$: C, 61·35; H, 4·5; N, 15·9; OMe, 17·6%). It was formed also by refluxing with methyl-alcoholic methyl iodide the silver salt prepared from the sodium salt, obtained in fine colourless needles by crystallising a solution of 1 : 4-dihydroxyphthalazine in 50% aqueous alcohol containing sodium (1 atom). It is insoluble in cold mineral acids or alkalis, but dissolves in hot concentrated hydrochloric acid or boiling dilute sodium hydroxide solution; a sodium salt crystallised from aqueous-alcoholic sodium hydroxide in glistening leaflets, decomposed by hot water. It is demethylated by hydrobromic acid (*d* 1·7) or hydriodic acid (*d* 1·7) at 100°, forming 1 : 4-dihydroxyphthalazine, m. p. and mixed m. p. 335—337°, whilst refluxing with methyl iodide in aqueous methyl-alcoholic potassium hydroxide solution gave 1-methoxy-3-methylphthalaz-4-one, m. p. and mixed m. p. 93°, obtained also by the action of methyl-alcoholic methyl iodide on the sodium salt of 4-hydroxy-1-methoxyphthalazine in a sealed tube at 125°.

When the silver salt of 1 : 4-dihydroxyphthalazine prepared *via* the ammonium salt was heated with methyl iodide (2 mols.) and methyl alcohol at 125°, 4-hydroxy-1-methoxyphthalazine was obtained in lower yield, but the sodium salt of 1 : 4-dihydroxyphthalazine under the same conditions gave 1-hydroxy-3-methylphthalaz-4-one. Thus the sodium salt behaves as the *N*-salt, although transformation may occur, but the silver salt behaves as the *O*-salt.

With acetic anhydride, 4-hydroxy-1-methoxyphthalazine formed 1-*methoxy*-4-*acetoxyphthalazine*, which crystallised from dry benzene in colourless needles, m. p. 137° (Found: N, 12·8. $C_{11}H_{10}O_3N_2$ requires N, 12·8%), hydrolysed readily by boiling aqueous alcohol to 4-hydroxy-1-methoxyphthalazine, m. p. and mixed m. p. 188°.

Acetylation of 1 : 4-*Dihydroxyphthalazine*.—1 : 4-Dihydroxyphthalazine (3 g.), acetic anhydride (3 c.c.), and glacial acetic acid (10 c.c.) were refluxed for 20 minutes and then cooled; the product, recrystallised from dry benzene, formed colourless prisms, m. p. 173° (Mihăilescu and Florescu, *loc. cit.*, and Radulescu and Georgescu, *loc. cit.*, gave m. p. 170°, and Heller, *loc. cit.*, gave m. p. 164·5°) (Found: C, 59·1; H, 4·0. Calc. for $C_{10}H_8O_3N_2$: C, 58·8; H, 3·9%). 4-Hydroxy-1-acetoxyphthalazine was obtained also from the silver salt of 1 : 4-dihydroxyphthalazine by the action of acetyl chloride in dry benzene. Further acetylation, or treatment of 1 : 4-dihydroxyphthalazine with excess of acetic anhydride, gave 1 : 4-*diacetoxyphthalazine*, which crystallised from dry benzene in colourless needles, m. p. 134° (Found: N, 11·0. $C_{12}H_{10}O_4N_2$ requires N, 11·3%); Radulescu and Georgescu (*loc. cit.*) regarded this compound as the 1 : 3-diacetyl derivative. It is converted into 4-hydroxy-1-acetoxyphthalazine rapidly by boiling with aqueous alcohol, whilst both compounds are hydrolysed to 1 : 4-dihydroxyphthalazine by boiling with aqueous alcohol for ½ hour.

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