439. *A New Phenazine Synthesis. The Phenazhydrins. Part I.*

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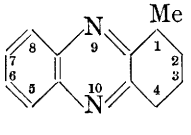
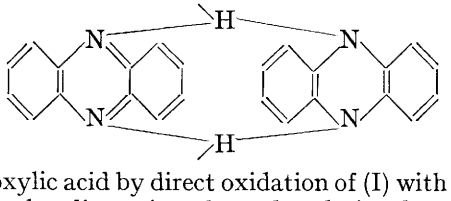
The methods for the synthesis of simple phenazines, as distinct from the complex derivatives which are dyes, have been summarised by McCombie, Scarborough, and Waters (J., 1928, 353) and by Kögl and Postowsky (*Annalen*, 1930, **480**, 284). They are distinctly limited in application and usually give low yields. The biological importance of phenazine derivatives is now realised; Kögl and collaborators (*loc. cit.*) established the bacterial pigment oxychlororaphin as the amide of phenazine-1-carboxylic acid, synthesising that acid by the somewhat drastic method of heating at 160° nitrobenzene, anthranilic acid, and solid potassium hydroxide. An independent method is described below.

Tetrahydrophenazines do not appear to have been previously described, but it has now been found that they can be readily prepared and easily dehydrogenated by iodine in glacial acetic acid to give phenazines. Thus *o*-phenylenediamine and *cyclo*hexane-1 : 2-dione give 1 : 2 : 3 : 4-*tetrahydrophenazine*, and 1-methyl*cyclo*hexane-2 : 3-dione (Wallach, *Annalen*, 1924, **437**, 174) condenses smoothly to 1-*methyl*-1 : 2 : 3 : 4-*tetrahydrophenazine* (I); as both reagents are capable of variation, the method should be of wide application. Before (I) was successfully dehydrogenated by iodine, sulphur and selenium were tried unavailingly (the latter method does not appear to have succeeded with any heterocyclic compound); the maleic acid method of Akabori and Saito (*Ber.*, 1930, **63**, 2245) gave an acid product, and Ehrenstein's platinum catalytic method (*Arch. Pharm.*, 1931, **269**, 650) gave the corresponding phenazhydrin (see under).

(I.) 



(II.)

An attempt to obtain phenazine-1-carboxylic acid by direct oxidation of (I) with chromic acid gave a dicarboxylic acid, presumably by disrupting the reduced ring between the carbon atoms 2 : 3 or 3 : 4, but the full examination of this is reserved. The methyl group of 1-methylphenazine does not condense with piperonal, but can be readily oxidised by chromic acid in acetic acid to the carboxylic acid.

We have found that the free phenazhydrins (compounds between phenazines and their dihydro-forms) can easily be obtained as highly crystalline purple or blue prisms by mixing equimolecular amounts of their components in concentrated alcoholic solution. These compounds were unknown when Hantzsch (*Ber.*, 1916, **49**, 511) stated from an optical comparison of their salts with the quinhydrones that the two classes of compounds were structurally different, and suggested that the former were free radicals (a theory recently confirmed by Michaelis *et coll.*, *J. Amer. Chem. Soc.*, 1933, **55**, 1481). The phenazhydrins

themselves are on the whole similar to the quinhydrones. They give pale yellow solutions in light petroleum or alcohol, which indicates dissociation and so prevents the determination of molecular weights; but they crystallise from these solvents and give the analytical results required for the bimolecular complexes.

The two reacting molecules show the opposing tendencies $\overset{C}{C}\!\!>\!\!\overset{\curvearrowright}{N}$ and $\overset{C}{C}\!\!>\!\!\overset{\curvearrowleft}{N}\!-\!H$ and reaction appears to involve the 9 : 10 hydrogen atoms and indicates their co-ordination or transference. The former might involve only one such link between a phenazine nitrogen atom and an imino-hydrogen atom, or two as depicted in (II), to give a Kauffler type of structure with the two imino-hydrogen atoms forming a bridge, possibly with a variation of their usual 180° angle of co-ordination. This representation is favoured rather than (III) and (IV) below. To postulate that a change of co-ordinate links occurs,

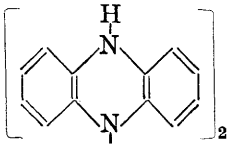
$$R_1\left\{\begin{matrix}C\\C\end{matrix}\right\}\!>\!N\longrightarrow H-N\!<\!\left\{\begin{matrix}C\\C\end{matrix}\right\}R_2 \quad\rightleftharpoons\quad R_1\left\{\begin{matrix}C\\C\end{matrix}\right\}\!>\!N-H\longleftarrow N\!<\!\left\{\begin{matrix}C\\C\end{matrix}\right\}R_2$$

to give the most stable form is only an extension of the benzene oscillatory double bond problem (Sidgwick, *Ann. Reports*, 1933, 113) and if this is granted the following observations can be explained.

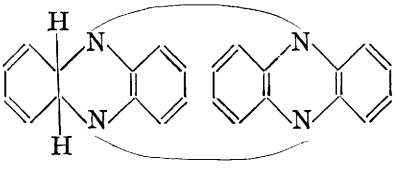
The phenazhydrins formed by (a) phenazine and 1-methyl-9 : 10-dihydrophenazine and (b) 9 : 10-dihydrophenazine and 1-methylphenazine form identical prisms, m. p. 159°. This indicates the establishment of an oxidation–reduction equilibrium between each phenazine and its dihydro-form, with the formation of the stablest complex, and corresponds to the related phenomenon in the quinhydrones (Valeur, *Ann. Chim. Phys.*, 1900, **21**, 470). In the above case the stable state is methylphenazine–dihydrophenazine, for it is methylphenazine which is removed from the complex by steam distillation in the first instance, while phenazine only comes over freely after the addition of an oxidising agent such as ferric chloride.

The fact that acridine and dihydroacridine do not similarly form a bimolecular complex may be taken to favour (II), which would also explain the formation of a dihydrochloride, although phenazine only forms a monohydrochloride, and also the ready dissociation of the complex into its components in solution.

(III.)



(IV.)



On the basis of actual hydrogen transfer, formulæ (III) and (IV), the latter the analogue of the quinhydrone acetal, may be advanced. Of these, the former with its quinonoid structure might be taken to explain the colour of the complexes, were it not that the highly quinonoid 9 : 9′-dianthryl-10 : 10′-quinone exists as canary-yellow needles, and tetraphenylhydrazine is almost colourless. A rather unlikely possibility is that the complex is (III) containing free ions in its crystal lattice. Formula (IV) is not favoured, because such a complex would not be likely to be easily resolved into its components.

The work is being actively extended, but it will probably be just as difficult as in the rather simpler case of the quinhydrones to reach finality on the structure of the complexes.

Experimental.

1 : 2 : 3 : 4-*Tetrahydrophenazine*.—*cyclo*Hexane-1 : 2-dione (Wallach, *Annalen*, 1924, **437**, 174) (9 g.), *o*-phenylenediamine (9·3 g.), fused sodium acetate (12 g.), and glacial acetic acid (30 c.c.) were refluxed for 2 hours and the product was poured into water (50 c.c.), made alkaline with sodium hydroxide, and extracted with ether. Removal of the ether left a solid (9 g.), which crystallised from light petroleum in faintly yellow plates, m. p. 92·5° (Found : C, 78·6; H, 6·6. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5%). The *compound* is easily soluble in dilute acids and in the usual organic solvents.

Phenazine.—1 : 2 : 3 : 4-Tetrahydrophenazine (1 g.), glacial acetic acid (20 c.c.), and iodine (3·5 g.) were refluxed for 8 hours, water added, and the solution made alkaline and steam-distilled. The distillate was extracted with ether, the ether removed, and the residue recrystallised from alcohol, giving yellow needles, m. p. 171°; mixed m. p. with phenazine, 171°.

1-*Methyl*-1 : 2 : 3 : 4-*tetrahydrophenazine.*—1-Methyl*cyclo*hexane-2 : 3-dione (25 g.), *o*-phenylenediamine (22 g.), freshly fused sodium acetate (33 g.), and glacial acetic acid (75 c.c.) were refluxed for 2 hours. The product was poured into 150 c.c. of water, made alkaline, and extracted with ether. The ether was removed, and the residue fractionated; the fraction, b. p. 160—165°/20 mm., solidified and then crystallised from light petroleum as faintly yellow plates (35 g.), m. p. 37° (Found: C, 78·8; H, 7·1. $C_{13}H_{14}N_2$ requires C, 78·8; H, 7·1%).

1-*Methylphenazine.*—1-Methyl-1 : 2 : 3 : 4-tetrahydrophenazine (10 g.), iodine (25 g.), and glacial acetic acid (50 c.c.) were refluxed for 8 hours, the mixture cooled and made alkaline with dilute sodium hydroxide solution, and the 1-methylphenazine distilled in superheated steam. It crystallised from light petroleum in lemon-yellow needles (4·5 g.), m. p. 108° (Found: C, 80·25; H, 5·5. Calc. for $C_{13}H_{10}N_2$: C, 80·4; H, 5·2%).

Phenazine-1-*carboxylic Acid.*—1-Methylphenazine (1 g.) and chromic acid (1 g.) were refluxed for 1 hour in glacial acetic acid (10 c.c.), the mixture made alkaline, and unchanged methylphenazine (0·3 g.) extracted with ether; the aqueous solution was acidified with sulphuric acid, and the acid product extracted in ether and crystallised from methylated spirits, giving yellow needles (0·4 g.), m. p. 239°, not depressed by admixture with a specimen of the 1-carboxylic acid prepared by the method of Kögl and Postowsky.

An Attempt to prepare Phenazine-1-*carboxylic Acid by Chromic Acid Oxidation of* 1-*Methyl*-1 : 2 : 3 : 4-*tetrahydrophenazine.*—1-Methyl-1 : 2 : 3 : 4-tetrahydrophenazine (5 g.) was warmed at 100° with a solution of potassium dichromate (12·5 g.) and dilute sulphuric acid (100 c.c. of 25% v/v) for 1 hour. An excess of sodium carbonate was added, the precipitated chromium hydroxide filtered off, the solution made just acid with hydrochloric acid, and an excess of copper carbonate added. The resulting brown precipitate was collected, suspended in alcohol, and treated with hydrogen sulphide. On concentration of the alcoholic filtrate, crystals separated, which when recrystallised from water (charcoal) gave almost colourless plates with a slight greenish tinge, m. p. 114—117° (with evolution of water). When the acid was sublimed at 1 mm., and the product crystallised from benzene, plates were obtained, m. p. 187° [Found for the *acid*, m. p. 114—117°: C, 56·2; H, 5·15; equiv., 139·5; *M* (Rast), 300. $C_{11}H_{10}N_2(CO_2H)_2,H_2O$ requires C, 56·1; H, 5·0%; equiv., 142; *M*, 284. Found for the *acid*, m. p. 187°: C, 59·8; H, 4·15. $C_{11}H_{10}N_2(CO_2H)_2$ requires C, 60·0; H, 4·6%].

Phenazhydrin between Methylphenazine and its Dihydro-form.—(a) 1-Methyl-1 : 2 : 3 : 4-tetrahydrophenazine (5 g.) was melted and allowed to drop during ½ hour down a tube containing platinised asbestos at 325°, in an atmosphere of hydrogen. The products were expelled by the hydrogen, and solidified in a receiver to a dark purple crystalline mass, which when recrystallised from light petroleum gave dark purple prisms, m. p. 116° [Found: C, 79·8; H, 5·8. $C_{13}H_{10}N_2,C_{13}H_{12}N_2$ requires C, 80·0; H, 5·6%].

(b) 1-Methylphenazine (0·5 g.) and 1-methyldihydrophenazine (0·5 g.) were each dissolved in the least quantity of hot light petroleum, and the solutions were mixed. On cooling, a compound separated identical with the above. This compound is oxidised in air at room temperature in a few days, or at a 100° in a few minutes, producing only 1-methylphenazine.

The Phenazhydrin between Phenazine and Dihydrophenazine.—This was prepared as in (b) above, and formed blue prisms, m. p. 209° (decomp.) (Found: C, 79·5; H, 5·3. $C_{12}H_{10}N_2,C_{12}H_8N_2$ requires C, 79·6; H, 5·0%).

The Phenazhydrin from Phenazine and Methyldihydrophenazine.—Prepared as in (b) above, this formed purple prisms, m. p. 157—160° (Found: C, 79·4; H, 5·8. $C_{12}H_8N_2,C_{13}H_{10}N_2$ requires C, 79·9; H, 5·4%). An identical compound resulted from the combination of dihydrophenazine and 1-methylphenazine. On steam-distilling this compound until all the volatile matter had passed over, only methylphenazine was obtained (m. p. 108°, from alcohol). After addition of ferric chloride, phenazine was removed in steam (m. p. 171°).

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