705. *Polynuclear Heterocyclic Systems. Part II.* Hydroxy-derivatives.*

By G. M. Badger, R. S. Pearce, and R. Pettit.

Phenazin-2-ol and 3 : 4-dihydroxy-1 : 2-benzophenazine (I) have been shown to exhibit lactam–lactim tautomerism. Phenazin-1-ol, on the other hand, does not undergo tautomerisation, and it is suggested that this substance is stabilised in the lactim form by hydrogen bonding between the hydroxyl group and the adjacent nitrogen atom.

Tautomerism of the keto–enol type has often been encountered in carbocyclic phenols, the classical example being that of 9-anthrol $\rightleftharpoons$ 9-anthrone, both forms being capable of isolation. In heterocyclic " phenols " for which a lactam type of structure can be written, however, an additional lactam–lactim type of tautomerism occurs, as exemplified by 2- and 4-hydroxypyridines. No lactam structures can be written for 1- and 3-hydroxyacridines, and these do not tautomerise; but 2- and 4-hydroxyacridines, for which lactam structures can be written, do exhibit this type of tautomerism (Albert and Short, *J.*, 1945, 760). The lactam form appears to be favoured by solvents of high dielectric constant, and a change from a solvent of low dielectric constant to one having a high constant is, in the case of 4-hydroxyacridine, associated both with

Fig. 1. Fig. 2.

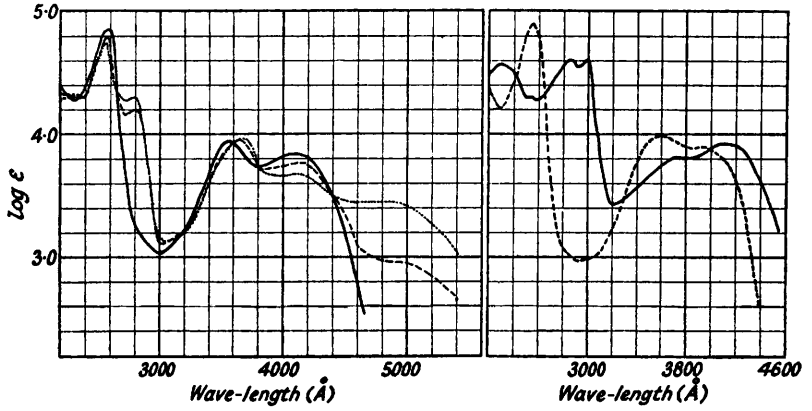


Fig. 1. *Absorption spectra of phenazin-2-ol in absolute alcohol* (———), *in* 50% (*v*/*v*) *ethanol* (– – – – –), *and in water* (. . . . .).

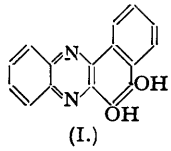
Fig. 2. *Absorption spectra of* 3 : 4-*dimethoxy*-1 : 2-*benzophenazine* (———) *and of* 2-*methoxyphenazine* (– – – – –), *both in absolute alcohol.*

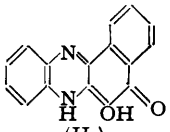
a considerable deepening in the colour of the solution and with increased absorption at long wave-lengths. Lactam–lactim structures can be written for phenazin-1- and -2-ol, and the present investigation was suggested by the observation that although these are both yellow solids resembling phenazine in colour, yet 3 : 4-dihydroxy-1 : 2-benzophenazine (I) is a deep blue-violet solid quite unlike its pale yellow parent substance, 1 : 2-benzophenazine. It therefore seemed of interest to examine the colour of these substances in solution, and also to determine their absorption spectra.

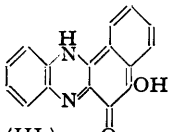
It has been found that phenazin-2-ol does show lactam–lactim tautomerism. It gave a yellow solution in alcohol and its absorption spectrum in this solvent (Fig. 1) closely resembles that of 2-methoxyphenazine in the same solvent (Fig. 2). It may be concluded therefore that phenazin-2-ol exists predominantly in the lactim form in absolute alcohol. In aqueous solvents, however, a deeper colour was apparent, and this is associated with increased absorption at long wave-lengths. In pure water, for example, phenazin-2-ol gave an orange solution, and the absorption extended as far as 5400 Å. Indeed, the curve in this solvent shows some similarities

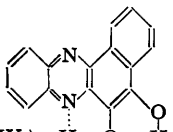
* Part I, preceding paper.

(Fig. 3) to that of phenothiazone which, of course, has a pure lactam structure. The situation clearly approximates to that observed by Albert and Short (*loc. cit.*) for 2-hydroxyacridine, and there seems no reason to doubt that the lactam form is favoured by the high dielectric constant of aqueous solvents, as suggested by these authors.


(I.)


(II.)


(III.)


(IV.)

In contrast to the above, phenazin-1-ol does not seem to exhibit lactam–lactim tautomerism in spite of the facts that a lactam structure can be drawn and the analogous 4-hydroxyacridine shows the effect very clearly. Phenazin-1-ol gave a pale yellow solution in absolute alcohol and its colour was unchanged by dilution with water. Moreover, the absorption spectrum in aqueous alcohol was identical (within experimental error) with that in absolute alcohol (Fig. 4), and similar to that of phenazine itself. The lactam form is therefore unimportant with this compound, at least under the conditions studied : the most reasonable explanation would seem to be that its lactim form is stabilised by hydrogen bonding to the adjacent nitrogen, and this

FIG. 3. FIG. 4.

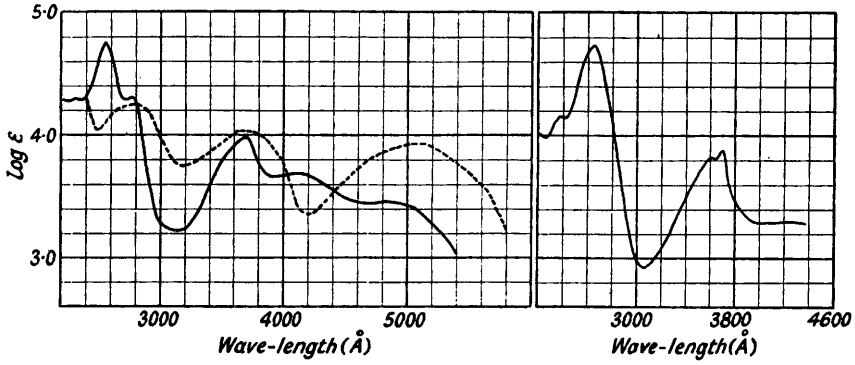


FIG. 3. *Absorption spectra of phenazin-2-ol in water* (———) *and of phenothiazone in alcohol* (– – – – –).

FIG. 4. *Absorption spectrum of phenazin-1-ol in absolute alcohol.*

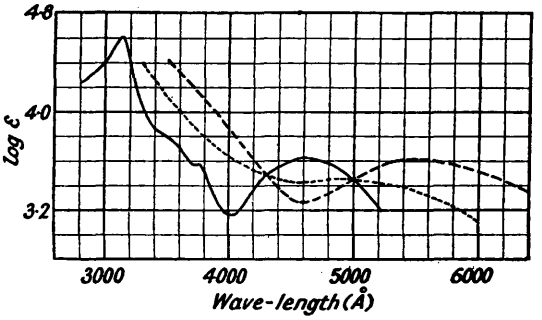
has been confirmed by an examination of the infra-red absorption spectrum of this compound kindly carried out for us by Dr. J. B. Willis of the Division of Industrial Chemistry, C.S.I.R.O., Melbourne. The substance was examined in the 1500—1800 cm.$^{-1}$ region as a " Nujol " mull, but no band corresponding to the normal carbonyl frequency (about 1670 cm.$^{-1}$) was found, so the lactam form appears to be excluded. It was also examined in the 3000—3600 cm.$^{-1}$ region as a dilute solution in carbon tetrachloride, a sharp band at 3445 cm.$^{-1}$ being found. As the normal frequency of the OH vibration is 3600—3650 cm.$^{-1}$, and that of the NH vibration is 3400—3500 cm.$^{-1}$, the results appear to indicate weak hydrogen bonding between the OH and the ring nitrogen in the lactim form. Albert and Goldacre (*J.*, 1943, 454) have suggested that hydrogen bonding occurs in the related compounds 1-hydroxy- and 1-amino-acridine, and it has often been suggested that similar hydrogen bonding occurs in the closely related compound 8-hydroxyquinoline. In this connection it is noteworthy that 8-hydroxyquinoline is volatile in steam and that its m. p. is well over 100° below that of any of the isomeric hydroxyquinolines.

Lactam–lactim tautomerism has also been confirmed with 3 : 4-dihydroxy-1 : 2-benzophenazine (I), and the blue colour of this substance in the solid state probably indicates that the compound exists predominantly as the lactam (II). The alternative lactam structure (III) is probably unimportant, for it involves an unstable 2 : 3-naphthaquinone type of bond structure. In absolute alcohol 3 : 4-dihydroxy-1 : 2-benzophenazine gives a brown solution, which however gradually fades to pale yellow in a few days. This change is caused by oxidation, the diol being converted into the yellow 1 : 2-benzophenazine-3 : 4-quinone. A freshly prepared solution became dark blue on dilution with water, evidently indicating the formation of an

increased quantity of the lactam form (II), but this blue colour faded in a few minutes, the quinone again being formed by oxidation. The lactam form (II) is evidently very readily oxidised to the quinone by dissolved oxygen in the solvent. It was impossible to obtain a sufficiently concentrated alcoholic solution of this substance for accurate spectrographic work, and dioxan was therefore tried. In dioxan, 3 : 4-dihydroxy-1 : 2-benzophenazine gave a dark reddish-brown solution, the absorption spectrum (Fig. 5) being similar to that of 3 : 4-dimethoxy-1 : 2-benzophenazine (Fig. 2), except that the former absorbs at somewhat longer wave-lengths. This indicates that the diol exists largely, but not entirely, in the lactim form in anhydrous dioxan. In aqueous dioxan a deep blue colour corresponding to the increased proportion of the lactam form was obtained, but this again faded too rapidly for the absorption curve to be determined. Recourse had to be made to the addition of a reducing agent to prevent this oxidation, and the spectrum was therefore determined in aqueous dioxan containing a little hydrazine. The curves show the increased absorption at long wave-lengths, and the existence of the isosbestic points at 4300 Å and at 5000 Å probably indicates that the addition of hydrazine has not upset the position of the equilibrium.

The tendency of 3 : 4-dihydroxy-1 : 2-benzophenazine to exist largely in the lactam form (II) is of some interest. Weak hydrogen bonding both between the hydroxyl groups and between the 4-hydroxyl group and the ring nitrogen atom might be expected (cf. Pauling, " The Nature of the Chemical Bond," 2nd edn., 1940, p. 325; Albert and Goldacre, *loc. cit.*). Unlike the case of phenazin-1-ol, however, this hydrogen bonding (IV) would facilitate the formation

FIG. 5.



Absorption spectra of 3 : 4-*dihydroxy*-1 : 2-*benzophenazine in anhydrous dioxan* (———), *in* 80% *aqueous dioxan containing* 1·15% *of hydrazine* (– – – – –), *and in* 50% *aqueous dioxan containing* 1·15% *of hydrazine* (— — —).

of the lactam. No doubt the lactam form (II) is also favoured by the fact that it contains an α-naphthaquinonoid structure which is much more stable than the *o*- and *p*-benzoquinonoid structures of the lactam forms of phenazin-1- and -2-ol, respectively.

EXPERIMENTAL.

Phenazin-1-ol.—This material was kindly supplied by Dr. B. Hegedüs, of F. Hoffmann-La Roche & Co., Basle (cf. Hegedüs, *Helv. Chim. Acta*, 1950, **33**, 766).

Phenazin-2-ol and 2-Methoxyphenazine.—Both compounds were kindly supplied by Dr. D. L. Vivian of the National Institute of Health, U.S.A. (compare Vivian, *J. Amer. Chem. Soc.*, 1949, **71**, 1139).

Phenothiazone.—This was prepared according to Dutch Patent, 59,559 (*Chem. Abs.*, 1947, **41**, 5557), and recrystallised from water.

3 : 4-*Dihydroxy*-1 : 2-*benzophenazine.*—A solution of 1 : 2-benzophenazine-3 : 4-quinone (Fischer and Schindler, *Ber.*, 1906, **39**, 2238) (2 g.) in chloroform (250 c.c.) at 40° was treated with phenylhydrazine (25 c.c.). A blue-violet precipitate immediately formed, and the product was collected after ½ hour. For analysis it was recrystallised from ethyl acetate and washed with acetone. It formed small violet-blue needles, m. p. indefinate at 270° (Found: C, 73·0; H, 3·9. Calc. for $C_{16}H_{10}O_2N_2$: C, 73·3; H, 3·85%) (Zincke and Wiegand, *Annalen*, 1895, **286**, 58, give m. p. 241°; Fischer, *Ber.*, 1903, **36**, 3622, gives m. p. 270°, after sintering at 240°).

3 : 4-*Diacetoxy*-1 : 2-*benzophenazine.*—This was prepared by boiling the above dihydroxy-compound with acetic anhydride. It was remarkably unstable. In the presence of a little water, or even with acetic acid, hydrolysis took place and the recrystallisation liquors always became deep red-brown. It was successfully recrystallised from acetic anhydride, the slight amount of colour in the liquors being removed with cold acetic anhydride. 3 : 4-Diacetoxy-1 : 2-benzophenazine formed beautiful pale yellow

blades, m. p. 214—216° (Found : C, 69·5; H, 4·1. Calc. for $C_{20}H_{14}O_4N_2$: C, 69·4, H, 4·1%). Zincke and Wiegand (*Annalen, loc. cit.*) give m. p. 208°.

3 : 4-*Dimethoxy*-1 : 2-*benzophenazine*.—3 : 4-Dihydroxy-1 : 2-benzophenazine was methylated at 90°, by the alternate addition of sodium hydroxide solution and methyl sulphate, in the usual way. After several recrystallisations from acetic acid, and then from alcohol (charcoal), 3 : 4-*dimethoxy*-1 : 2-*benzophenazine* formed canary-yellow needles, m. p. 160—161° (Found : C, 74·5; H, 4·6. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·9%).

Absorption Spectra.—For rapidity, the spectra of 3 : 4-dihydroxy-1 : 2-benzophenazine in aqueous dioxan were determined with a Bellingham and Stanley spectrophotometer fitted with a Hilger echelon cell and rotating sector. All other spectra were determined with a Beckman DU spectrophotometer.

We are grateful to Dr. B. Hegedus and to Dr. D. L. Vivian for gifts of phenazinols, and we also thank the Director of Chemistry (Mr. R. J. Cowan), South Australian Government Department of Chemistry, for permission to use the Beckman spectrophotometer. Microanalyses were carried out by Mr. R. T. Howard. We are also indebted to the Commonwealth Government Research Fund for maintenance grants (to R. S. P. and R. P.).

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