1042. *Quinazolines. Part III.* The Structure of the Hydrated Quinazoline Cation.*

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The hydrated cation of quinazoline is shown to have the structure (I; X = OH, R = H) by comparison of its physical properties with those of the 3-methylquinazolinium ion and of the *pseudo*-base obtained from the latter. This base has been proved to have the constitution (II; X = OH, R = Me).

Quinazoline forms an abnormal cation in dilute aqueous acid.[1-3] Strong evidence was adduced[3] in support of structure (I; X = OH, R = H) for this ion, but its ultraviolet spectrum does not resemble that of the ion (I; X = R = H) as closely as would have been expected on this basis.[3] The infrared spectrum of solid quinazoline hydrochloride "monohydrate" did not yield conclusive structural information[3] and further evidence

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band near 300 mμ by 28 mμ. A comparison of the ultraviolet spectrum of the short-lived abnormal neutral species of quinazoline with that of 3,4-dihydroquinazoline shows a similar shift of 26 mμ, which strongly suggests that the former is substance (II; X = OH, R = H); in agreement with this, it has a pK_a value of 7·77, which is similar to 7·64 obtained for (II; X = OH, R = Me).

A comparison of the ultraviolet spectra of the abnormal quinazoline cation and the (also abnormal) 3-methylquinazolinium ion (see Table 1) with those of the ions (I; X = R = H)[3] and (I; X = H, R = Me) reveals hypsochromic shifts of 20 and 18 mμ, respectively, but, in view of the large spectral shifts observed on replacing X = H by X = OH in the above neutral molecules, these represent evidence for, rather than against, the structures (I; X = OH, R = H) and (I; X = OH, R = Me) for the two abnormal ions. Two further pieces of evidence against the alternative structures (III) have now been obtained.

First, on addition of a concentrated aqueous solution of quinazoline to benzidine in glacial acetic acid, the red colour characteristic of aromatic aldehydes[7] is not obtained in the cold. Secondly, the ultraviolet spectrum of quinazoline in 1·2N-hydrogen chloride in anhydrous methanol is identical with that of quinazoline in aqueous acid at pH 1, although in anhydrous methanol no cation analogous to (III) should be obtainable; however, the spectrum of the ion (I; X = OMe) should closely resemble that of the ion (I; X = OH). Further, 3-methylquinazolinium iodide "methanolate" (which, in the solid state, is known to retain the elements of $CH_3{\cdot}OH$ very tenaciously[4,5]) has the same ultraviolet spectrum[2] as 3-methylquinazolinium iodide "hydrate," but paper chromatography in aqueous solution showed the "hydrate" to be different from the "methanolate," at pH 5 and at pH 11. The "methanolate" cation must have the structure (I; X = OMe, R = Me) and the corresponding neutral molecule (the *pseudo*-base) the structure (II;

TABLE 1.

Ultraviolet spectra.

Compound	Solvent	pH (or H_0)	Species[a]	$\lambda_{max.}$ (mμ) (inflexions in italics)	log ε
3,4-Dihydro-3-methylquinazoline[b]	H_2O	11·5	N	*219* + 225 + 231; 304	*3·99* + 4·01 + 4·04; 3·90
	H_2O	7·0	C	214 + 218 + *224*; 284	4·23 + 4·24 + *4·04*; 3·79
3,4-Dihydro-4-hydroxy-3-methylquinazoline[c]	H_2O	10·0	N	<210 + *218* + *225*; 276	>4·30 + *3·99* + *3·85*; 4·06
	H_2O	2·0	AC	<207; 266	>4·38; 3·98
o-Toluidine[d]	n-C_6H_{14}		N	234; 285	3·93; 3·32
o-Aminobenzyl alcohol	n-C_6H_{14}		N	240; 290	3·80; 3·36
3,4-Dihydroquinazoline[b]	H_2O	11·5	N	*217* + 221 + *227*; 291	*4·07* + 4·09 + *3·97*; 3·76
		7·0	C	212 + 217 + *225*; 280	4·26 + 4·25 + *4·01*; 3·69
3,4-Dihydro-4-methylquinazoline[e]	H_2O	11·5	N	221 + *226*; 287	4·12 + *4·00*; 3·80
		7·0	C	212 + 216 + *223*; 277	4·24 + 4·23 + *3·99*; 3·70
3,4-Dihydroquinazolinium-4-sulphonate[f]	H_2O	4·0	Z[b]	222 + *229*; 282	4·17 + *3·93*; 3·66
	H_2O–HCl	−3·4	C	<212 + *217* + *222*; 279	>4·30 + *4·54* + *4·43*; 3·73
4-Cyano-3,4-dihydroquinazoline[f]	H_2O	1·0	C	210 + 216 + *222*; 275	4·35 + 4·29 + *4·11*; 3·80
Quinazoline	H_2O	1·0	AC[b]	208; 260	4·20; 3·91
	H_2O	9·8	AN[g]	265	3·97

[a] N = neutral molecule; AN = abnormal (short-lived) neutral molecule; C = (normal) cation; AC = abnormal cation; Z = zwitterion (I; R = H, X = SO_3^-). [b] Ref. 3. [c] pK_a value, 7·64 ± 0·03. [d] Wolf and Herold, *Z. phys. Chem.*, 1931, *B*, **13**, 201; Dede and Rosenberg, *Ber.*, 1934, **67**, 147. [e] pK_a value, 9·19 ± 0·04. [f] pK_a value for proton addition not known. [g] pK_a value, 7·77; this substance was kindly examined by Dr. D. D. Perrin.

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[7] Feigl, "Spot Tests in Organic Analysis," Elsevier, Amsterdam, 1956, p. 210.

X = OMe, R = Me) (and any replacement of OMe by OH in aqueous medium must be slow in the neutral molecule and very slow in the cation).

The Effect of 4-*Substituents on the Ultraviolet Spectrum of* 3,4-*Dihydroquinazoline*.—The hypsochromic shift of 20—25 mμ produced by the replacement of the hydrogen atom by hydroxyl in the (non-conjugating) 4-position in molecules (II) and (I) is very remarkable and contrary to previous experience. Thus, the replacement of α-hydrogen by hydroxyl causes a bathochromic shift of the spectrum by about 5 mμ in *o*-toluidine (see Table 1), and shifts of +5·5 mμ (*K*-band, at 236 mμ) and −2 mμ (*B*-band, at 291 mμ) in *p*-toluidine,[8] of +3 mμ (*K*-band) and −4 mμ (*B*-band) in *p*-anisidine,[9] and of −2·5 mμ (*K*-band) in *p*-nitrotoluene; [8] the shift due to hydroxyl in such a position (*i.e.*, at a saturated carbon atom attached to a conjugated system) is normally smaller [8,9] than that caused by more strongly electron-withdrawing groups (such as cyano).

In the ions (I; R = H), by contrast, the replacement of X = H by other groups usually produces only small and irregular displacements of the band at 280 mμ (see Table 1), *viz.*, X = SO_3^-, +2 mμ; X = SO_3H, −1 mμ; X = CH_3, −3 mμ; X = CN, −5 mμ; as compared with X = OH, −20 mμ. For the molecules (II; R = H) the figures are X = Me, −4 mμ and X = OH, −26 mμ. (When X = CN or SO_3^- elimination of HCN or HSO_3^- is very rapid, and no spectra could be obtained.) No satisfactory explanation for the large spectral shift produced by X = OH is available.

EXPERIMENTAL

Analyses were by Dr. J. E. Fildes and her staff.

Physical Measurements.—Ionisation constants and spectra were determined as before.[3] The rapid-flow measurements [10] were carried out by means of a modified Chance apparatus from which the rapidly-mixed liquid was passed into a spectrophotometric cell inserted in a Perkin–Elmer Spectracord instrument.

Materials.—2-Aminobenzyl alcohol [11] and 4-cyano-3,4-dihydroquinazoline [12] were prepared as described in the literature.

3,4-*Dihydro*-4-*hydroxy*-3-*methylquinazoline*.—Anhydrous 3-methylquinazolinium iodide prepared [6] from 2·2 g. of resublimed quinazoline and 1·7 ml. of methyl iodide) in water (15 ml.) was treated, with cooling, with 33% aqueous potassium hydroxide (3·0 ml.). After a few minutes the *pseudo*-base that had crystallised in needles was filtered off, washed with water until the filtrate was no longer alkaline, and dried at 100° to constant weight (1·91 g., 70%). (This product could not be isolated from the action of alkali on the methanolate [4,5] of 3-methylquinazolinium iodide.) It decomposes slowly in boiling water or benzene, and is best purified by adding boiling water to the finely powdered material, filtering immediately, and quickly chilling the filtrate to initiate crystallisation. Purified in this manner it had m. p. 167—168° (Gabriel and Colman,[4] and Schöpf and Oechler,[5] gave 162—163°; Fry, Kendall, and Morgan [6] 164—165°) (Found: C, 66·8; H, 6·0; N, 17·25. Calc. for $C_9H_{10}N_2O$: C, 66·7; H, 6·2; N, 17·3%).

These compounds have been proved to be the 3- and not the 1-methylated derivatives,[5,6] and in the present work they were obtained in a chromatographically pure state. At pH 5 (3% aqueous ammonium chloride, 20 hr. at 5°) the methanolate gave only one spot, with R_F 0·89, and the *pseudo*-base one with R_F 0·79 (ascending method).

3,4-*Dihydro*-4-*methylquinazoline*.—3,4-Dihydro-4-methylquinazoline picrate [12] (prepared by the action of methylmagnesium iodide on quinazoline, followed by treatment with ethanolic picric acid) [4·8 g.; m. p. 234—236° (decomp.)], suspended in chloroform, was shaken with 5N-aqueous sodium hydroxide, and the aqueous layer was diluted with water until all the sodium picrate had dissolved. The chloroform layer was washed with 10N-aqueous sodium hydroxide and dried (K_2CO_3). The chloroform was removed at 30°/15 mm., and the residue

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[8] Burawoy and Spinner, *J.*, 1955, 2557.

[9] Spinner, *Spectrochim. Acta*, 1961, **17**, 545.

[10] Perrin, *J.*, in the press.

[11] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 2548.

[12] Higashino, *J. Pharm. Soc. Japan*, 1960, **80**, 5062.

distilled (b. p. 124°/2·5 mm.). The pale yellow viscous distillate (1·3 g., 70%) crystallised and had m. p. 78—79° (Found: C, 73·8; H, 7·0; N, 18·8. $C_9H_{10}N_2$ requires C, 73·9; H, 6·9; N, 19·2%).

The correctness of the assigned structure was proved by oxidation, with potassium ferricyanide, to 4-methylquinazoline, which was isolated as the picrate, m. p. and mixed m. p. 180—181°.

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