107. *Quinazolines. Part IV.*[1] *Covalent Hydration in the Cations of Substituted Quinazolines.*

By W. L. F. Armarego.

Twenty mono(*Bz*-)substituted quinazolines have been prepared, some by conventional routes, but ten of them by alkaline decomposition of appropriately substituted 4-(*N'*-toluene-*p*-sulphonylhydrazino)quinazolines made from the corresponding 4-chloroquinazolines.

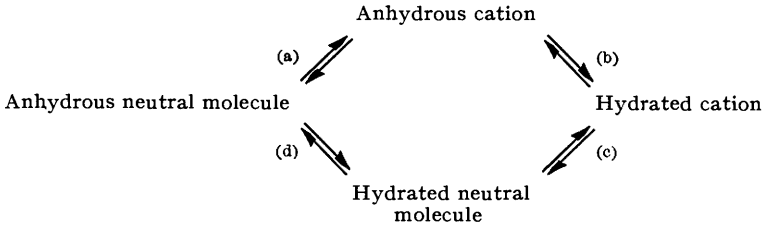
The ionization constants and ultraviolet spectra reveal many examples of stable covalent hydration in the cation. The kinetics of dehydration of some (unstable) hydrated neutral molecules have been measured and used to throw light on the degree of hydration in the cation. The relation between hydration and the positions and nature of the substituents is discussed.

That electron-donating substituents in the benzene ring of a quinazoline could inhibit hydration in a quinazoline cation was first suggested for the cations of 5-, 7-, and 8-aminoquinazoline because the ultraviolet spectra differ so much from that of the 6-isomer.[2] However, the aminoquinazolines are perhaps not the best examples for early discussion because the position of protonation (on ring- or amino-nitrogen) in each isomer was not established. The present investigation was therefore undertaken to find out mainly whether the electronic effects of simple substituents, preferably in the benzene ring of quinazoline, are relayed to the 3,4-double bond in the respective cations. Twenty mono-(*Bz*-)substituted and one (*Bz*-)disubstituted quinazolines (16 of them new) were synthesized. The substituents (methyl, chloro, methoxy, hydroxy, and nitro) were chosen so as to avoid the complication encountered in the aminoquinazolines.

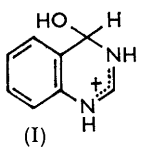
The ultraviolet spectrum of quinazoline shows the three main bands typical of azanaphthalenes but the cation, in water, shows marked hypsochromy instead of the usual bathochromic shift. The neutral molecule, in water, is anhydrous and the anomaly in the cation has been attributed to covalent hydration.[2,3] The structure (I) postulated for the cation has been confirmed [1] and hence the ultraviolet spectrum will be taken as typical for an (almost completely) hydrated quinazoline cation for purposes of comparison in the present work. Although 2-methylquinazoline also forms a similar hydrated cation, the cation of 4-methylquinazoline has a spectrum similar to that of its neutral molecule but with a small bathochromic shift of the long-wavelength band.[3a] In the present studies this is taken as an example of (predominantly—see below) the normal (anhydrous) cation. Thus the spectrum of a quinazoline whose cation contained both anhydrous and hydrated species should show features of both the above typical spectra (*e.g.*, Fig. 1, C), *i.e.*, a low-intensity band at long wavelengths due to the anhydrous cation and a high-intensity band at *ca.* 260 mμ due to the hydrated species. The ratio of anhydrous to hydrated cations should be calculable from the extinction coefficients.

[1] Part III, *J.*, 1961, 5267.
[2] Osborn, Schofield, and Short, *J.*, 1956, 4191.
[3] (*a*) Albert, Armarego, and Spinner, *J.*, 1961, 2689; (*b*) Albert, *Chem. Soc. Special Publ.* No. 3, 1955, p. 138; cf. "Heterocyclic Chemistry," Athlone Press, London, 1959, p. 121.

In quinazoline, hydrated species are involved during the determination of the ionization constants and the basic pK_a of 3·51 is an overall ionization constant (pK_a^{eq}) for the equilibria:



In the forward- and back-titrations no hysteresis was observed, indicating that the equilibrium pH values are rapidly attained and that the half-lives of the anhydrous cation



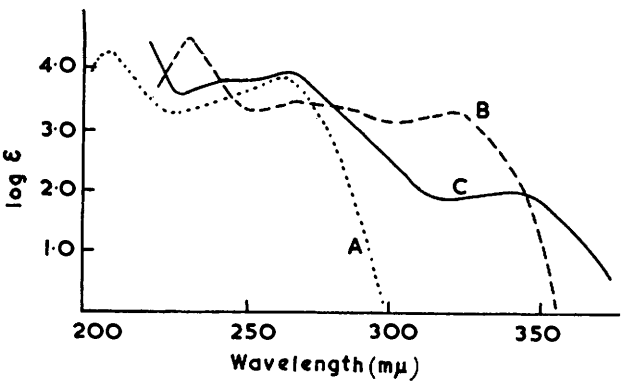


FIG. 1. Ultraviolet spectra (in water) of: A, quinazoline cation; B, 4-methylquinazoline cation and C, 6-methylquinazoline cation.

and the hydrated neutral molecule are very short. By rapidly adjusting the pH of an acid solution of quinazoline to an alkaline value above the pK_a of 3,4-dihydroquinazoline (9·19) [3a] and measuring the rate of change of absorption at 290 mμ it was possible to obtain the half-life of dehydration of the hydrated neutral molecule (which is present in the system after the very rapid loss of a proton at this pH from the hydrated cation). The

TABLE 1.

Physical properties of quinazolines.

	Ionization (H_2O, 20°) [a]			Spectroscopy in water [c]		
Quinazoline	pK_a	Spread (±)	Conc. (M)	$\lambda_{max.}$ (mμ)	log ε	pH
Unsubst.[b]...				222, 271, 305	4·57, 3·40, 3·38	7·0
	3·51	0·05	0·07	208, 260	4·20, 3·91	1·0
4-Me [b]				223, 270, 305, 314	4·62, 3·45, 3·45, 3·41	7·0
	2·52	0·02	0·07	234, 270, 279, 323	4·52, 3·47, 3·45, 3·34	0·3
5-Me				229·5, 285, 317	4·55, 3·35, 3·44	7·0
	3·63	0·03	0·005	*246* + 261 + *288*, 348	*3·79* + 3·89 + *3·48*, 2·07	0·4
6-Me				227, 268, 316 + *325*	4·60, 3·35, 3·38 + *3·33*	7·0
	3·41	0·02	0·005	*244* + 267, 340	*3·78* + 3·93, 2·06	0·7
7-Me				228, 289 + 299 + *310*	4·58, 3·52 + 3·52 + *3·44*	7·0
	3·17	0·01	0·005	*214*, 242 + 263	*4·27*, 3·89 + 3·83	0·4
8-Me				230, 286 + 314	4·55, 3·34 + 3·37	7·0
	3·20	0·05	0·005	213, 245 + 263 + *290*, 346	4·80, 3·81 + 3·87, *3·50*, 2·13	0·4

TABLE 1 (*continued*).

	Ionization (H_2O, 20°) [a]			Spectroscopy in water		
Quinazoline	pK_a	Spread (±)	Conc. (M)	$\lambda_{max.}$ (mμ)	log ε	pH
2-Cl	−1·6 [c]	0·2	0·25 × 10^{-4}	231, 274, 316 + *320*	4·61, 3·37, 3·33 + *3·28*	5·7
5-Cl				230, 287, 316	4·55, 3·44, 3·46	7·0
	3·75	0·02	0·005	215, 259 + *281* + *290* [j]	4·21, 3·95 + *3·56* + *3·35*	0·4
6-Cl				226, 260, 315 + *324*	4·68, 3·42, 3·34 + *3·30*	7·0
	3·55	0·01	0·0025	208, 266	4·02, 4·02	1·0
7-Cl				227·5, 277, 302 + 314	4·66, 3·61, 3·52 + 3·45	5·5
	3·29 [d]	0·03	0·4 × 10^{-5}	217·5, 261	4·47, 3·87	0·5
8-Cl				230, 285, 317	4·55, 3·39, 3·49	6·0
	3·30	0·04	0·005	216, 264	4·20, 3·91	1·0
6,8-Cl_2				233, 278, 323 + *332*	4·61, 3·40, 3·40 + *3·36*	6·0
	3·06 [a]	0·03	0·5 × 10^{-4}	218, 270	4·18, 3·99	1·0
2-OMe				222, 235, 265, 326 + *336*	4·51, 4·38, 3·51, 3·46 + *3·38*	6·0
	1·31 [f]	0·08	0·02	216·5, 238, 293, 337	4·30, 4·44, 3·81, 3·41	−1·1
4-OMe				222 + 226, 264 + *269*, 298, 310	4·47 + 4·44, 3·64 + *3·59*, 3·48, 3·50	7·2
	3·13 [f]	0·05		*228* + 235, 305 [k]	*4·23* + 4·33, 3·65	0·3
5-OMe				240, *294*, 334	4·53, *3·18*, 3·50	7·0
	3·41	0·03	0·005	218, 253, 288, 388	4·13, 3·89, 3·62, 2·40	1·3
6-OMe				233, 260, 334	4·57, 3·53, 3·49	7·0
	2·85	0·04	0·005	253, 276, 364	3·95, 3·98, 2·51	0·4
7-OMe				236, 313	4·59, 3·71	7·0
	2·89	0·02	0·005	228, 250, 321	4·18, 4·27, 3·83	0·5
8-OMe				239, 329	4·54, 3·42	7·0
	3·51	0·01	0·005	216, 259, 297	3·99, 3·86, 3·78	0·4
5-OH				239, *296*, 336 [l]	4·54, *3·15*, 3·43	5·5
	3·64	0·04	0·0025	254, 291, 395	3·76, 3·62, 2·34	1·0
	7·39 [g]	0·02	0·0025	252, 330, 396	4·44, 3·38, 3·54	10·0
6-OH [e]				231, 264, 336	4·50, 3·52, 3·51	5·65
	3·12	0·03	0·005	252 + 275, 368	3·90 + 3·95, 2·49	1·0
	8·19 [g]	0·01	0·005	248, 285, 380	4·55, 3·76, 3·53	11·0
7-OH				235, 272, 314	4·48, 3·51, 3·66	5·2
	3·22	0·03	0·0025	222 + 249, 322 + *340*	4·14 + 4·22, 3·74 + *3·67*	1·0
	7·37 [g]	0·03	0·0025	225, 253, 293, 354	4·27, 4·47, 3·66, 3·83	10·0
8-OH [h]				240, 327	4·48, 3·36	7·0
	3·41	0·01	0·01	257, 298, 376	3·85, 3·75, 1·79	1·0
	8·65 [g]	0·02	0·005	*235* + 254, 338 + 369	*4·03* + 4·39, 3·50 + 3·36	11·0
5-NO_2				215, 292 + *320*	4·51, 3·80, *3·56*	7·0
	3·75	0·01	0·005	260, 319	4·08, 3·14	1·0
				285 + *312* + *323*	3·80 + *3·58* + *3·46*	— [m]
6-NO_2				216, 249, 287	4·21, 4·32, 3·81	7·0
	4·18	0·01	0·0025	222, 306	3·99, 5·04	0·1
				241 + 246 + 253, 281 + *290*, 321	*4·34* + 4·37 + 4·25, 3·84 + *3·80*, 3·10	— [m]
7-NO_2				*215*, 242, 273, 329	*4·34*, 4·18, 3·93, 3·34	7·0
	4·05	0·01	0·0025	251, 315	4·29, 3·15	1·8
				238 + *269* + *280*, *315* + 326 + *340*	4·26 + *3·87* + *3·64*, *3·21* + 3·28 + *3·12*	— [m]
8-NO_2				218 + *269*, 316, *417*	4·59 + *3·58*, 3·63, *2·80*	7·0
	4·00	0·02	0·0025	247 + 272, 331 + *407*	4·01 + 3·91, 3·62 + *3·00*	1·7

[a] pK_a values were measured potentiometrically as by Albert and Phillips (*J.*, 1956, 1294), unless otherwise stated; basic pK_a values are overall ionization constants. [b] Ref. 3*a*. [c] Spectroscopic at 224 mμ; material kindly supplied by Dr. G. B. Barlin. [d] Spectroscopic at 260 mμ. [e] Spectroscopic at 680 mμ. [f] pK_a's from Albert and Phillips, ref. *a*; 2-methoxyquinazoline was kindly supplied by Prof. Albert. [g] Proton lost. [h] pK_a from Albert and Hampton (*J.*, 1954, 505). [i] Inflexions are underlined. [j] Absorption tails off at longer wavelengths. [k] Spectrum taken within 5 min. after preparation of solution. [l] Neutral molecule spectrum from ref. 4. [m] In cyclohexane.

half-life at pH 10·5 was 9·5 seconds.* The pK_a for the hydrated species [equilibrium (c)] was found to be 7·77 ± 0·04 [1] by using a continuous-flow technique and measuring the absorption at 290 mμ after rapid adjustment of the pH of an acid solution with various buffers.* The pK_a for the anhydrous species [equilibrium (a)] was estimated [3a] as 1·5.

* These determinations were kindly carried out by Dr. D. D. Perrin by rapid-reaction techniques.

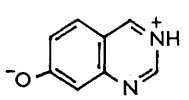
[1] Mason, *J.*, 1957, 5010.

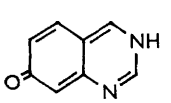
The pK_a^{eq} for quinazoline (3·51) is between these two figures and its value depends on the relative stabilities of the anhydrous and the hydrated species. Thus the pK_a^{eq} is lowered if the anhydrous cation is the more stable, and is raised if the hydrated neutral molecule is the more stable. Hence, in addition to the ultraviolet spectra, the ionization constants of quinazolines can be diagnostic of hydration.

Quinazoline has two basic centres but it is not of prime importance to know which nitrogen atom originally accepts the proton in aqueous solution because addition of water (whether 1,4 or 3,4) to the anhydrous cation must give the same stabilised structure (I). This applies to all the hydrated cations, but for the anhydrous cations the value of the ionization constant will depend on whether $N_{(1)}$ or $N_{(3)}$ is protonated. Thus a comparison of the ionization constants of anhydrous cations should be taken with some reserve.

Ultraviolet Spectra.—The quinazolines (other than nitroquinazolines) recorded in Table 1 showed the typical spectrum of quinazoline at pH 7·0. These spectra were taken at 2 pH units (at least) above the ionization constants to ensure that only neutral molecules were present. The comparison suggests that all these quinazolines form anhydrous stable neutral molecules and hence the spectral differences in the cations warrant the qualitative interpretations that follow. The cations of 5-, 6-, 7-, and 8-methylquinazolines have the type of spectrum (C) in Fig. 1, and are mixtures of hydrated and anhydrous forms. 6-, 7-, and 8-Chloro- and 6,8-dichloro-quinazoline cations are almost completely hydrated and their spectra are very similar to that of the quinazoline cation. The spectrum of 5-chloroquinazoline cation shows a very weak absorption at longer wavelengths which tails off without a distinct maximum. This indicates that it is largely hydrated but contains a trace of the anhydrous cation.

Quite unlike the above two sets of isomers, the spectra of 5-, 6-, 7-, and 8-methoxyquinazoline cations reveal that these isomers are not all similar to each other. 7-Methoxyquinazoline cation is predominantly anhydrous and its spectrum (as with 4-methylquinazoline) is similar to that of the neutral molecule except for a small bathochromic shift. 5- and 6-Methoxyquinazoline cations have spectra of the type (C) in Fig. 1, and hence are partly hydrated, but 8-methoxyquinazoline cation is almost completely hydrated and shows the spectrum of the type (A) (Fig. 1). Again, 7-hydroxyquinazoline, like 7-methoxyquinazoline, forms largely the anhydrous cation while 5-, 6-, and 8-hydroxyquinazoline cations gave spectra of the type (C). Because the spectra of the anions of 5-, 6-, 7-, and 8-hydroxyquinazoline (in aqueous alkaline solution) are of the normal type, it is likely that they are all anhydrous. A zwitterionic structure (*e.g.*, II) which can be written for the neutral molecules of all the isomers does not have a significant contribution to the structure since the spectra in water and in ethanol (*e.g.*, for the 6- and the 8-isomer cf. ref. 4) are similar. The existence of the quinonoid structure (*e.g.*, III), which is possible only for the 5- and the 7-isomer must also be ruled out because the spectra of the neutral molecules of all the isomers do not show very great differences. The close similarity of the spectrum of the neutral molecule of each of the four (*Bz*-)substituted methoxyquinazolines to that of the similar (*Bz*-)substituted hydroxyquinazolines is also in agreement with these views.


(II)


(III)

The spectra of the neutral species of the four *Bz*-nitroquinazolines are complicated, as is common for nitro-compounds. The cationic spectra of 5-, 7-, and 8-nitroquinazoline do not differ markedly from those of the neutral molecules and the 6-isomer shows a bathochromic shift. The spectra of 5-, 6-, and 7-nitroquinazoline in cyclohexane were also not very different from those of the corresponding neutral species in water, which excludes the possible complication that the neutral species are hydrated. This indicates that the cations are anhydrous; however, it is difficult to derive exact information regarding hydration in the nitroquinazolines from spectra.

Although ultraviolet spectra can clearly reveal the presence of an almost completely

hydrated cation and can also indicate that a cation is a mixture of anhydrous and hydrated species when the percentage of the former is relatively small, these spectra cannot detect a small percentage of hydrated species because the absorption of the anhydrous cation occurs where it must greatly obscure that of the hydrated species. This difficulty was overcome by taking advantage of the fact that on rapid neutralisation the short-lived hydrated neutral quinazolines are formed. The spectrum of the hydrated quinazoline cation shows a maximum at 260 mμ and that of the hydrated neutral molecule [1] (obtained by the rapid-flow technique), which resembles it very closely, is shifted 5 mμ to longer wavelength (to 265 mμ). In quinazoline the hydrated neutral molecule therefore shows a hypsochromic shift of 40 mμ as compared with the (anhydrous) neutral molecule. Similar shifts are to be expected in the hydrated neutral species of other quinazolines when hydration takes place.

If a solution containing the cation of a completely anhydrous quinazoline is immediately adjusted to pH 10 (by the rapid-mixing technique, see Experimental section), the observed

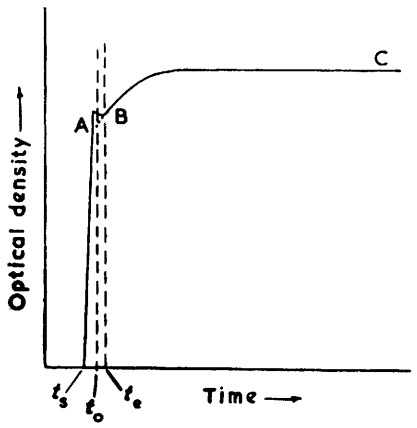


FIG. 2. Recti-riter tracing of 4-methylquinazoline. t_s, time when flow was started; t_o, extrapolated zero time; t_e, time when flow was stopped.

optical density at a fixed wavelength should not alter with time because the cation would be instantaneously converted into the stable neutral molecule and the absorption observed would be due to this stable species. On the other hand, a sudden change of pH in a solution containing a mixture of anhydrous and hydrated cations must convert it into a mixture of anhydrous and hydrated neutral molecules. Their ratio at the time of mixing at pH 10 should be the same as in the original acid solution. Since the hydrated neutral species is unstable and because the wavelength is chosen such that the absorption of this species is as small as is experimentally possible, the initial absorption should rise with time until the hydrated neutral species is completely converted into the anhydrous species. The kinetics of dehydration of the hydrated neutral quinazoline can thus be followed and by extrapolation to zero time the absorption at the time of mixing can be determined. This should be mainly due to the anhydrous neutral species and a rough estimate of the percentage of anhydrous to hydrated cation can thus be made.

A possible disadvantage of this method is that, on neutralisation, the spectrum of the anhydrous species undergoes a hypsochromic shift and that of the hydrated species a small bathochromic shift. Thus, at the fixed wavelength chosen, the absorption by the hydrated neutral species may contribute slightly to the optical density at zero time (this is made as small as possible by working at as long a wavelength as possible). Therefore the estimated percentages of anhydrous cation in the mixture of cations represent a maximum value.

When this technique was applied to 4-methylquinazoline and the rate of change of optical density measured at 325 mμ, a curve of the type B—C in Fig. 2 was obtained. Extrapolation of B—C to zero time gave the optical density of the mixture consisting

almost entirely of the anhydrous species, and from B—C the rate of dehydration of the hydrated neutral species was calculated. This experiment showed that the amount of anhydrous cation in 4-methylquinazoline was at the most 81%. 2-Methylquinazoline gave an extrapolated optical density almost equal to zero, indicating the virtual absence of anhydrous cation. The latter is in agreement with previous spectral evidence.[3a] Table 2 shows the maximum percentages of anhydrous cation in methyl-, chloro-, and methoxy-quinazoline cations calculated from the rate curves. This method was unsuitable for the four *Bz*-hydroxyquinazolines because anions, formed in the final alkaline solution, absorb strongly at the wavelengths used.

It is also possible to calculate the approximate percentages of anhydrous cation from spectral data, by using the ratio of the extinction coefficient of the long-wavelength band in the neutral molecule to that in the cation. By using this ratio in 4-methyl- and 7-methoxy-quinazoline as standard for the respective series (the percentage of anhydrous cation for these two being taken from the kinetic experiments) and this ratio for the individual members from the spectra, the percentages of anhydrous cations in Table 2 (last column) were calculated. These percentages are in good agreement with those

TABLE 2.

Quinazoline	k_{obs} (sec.$^{-1}$) [a]	Half life (sec.) [b]	Wavelength (mμ)	% Anhydrous cation from rates	% Anhydrous cation from spectra
Unsubst. [c]	0·077	9·0	305	0	0
2-Me	0·07	10·0	328	0	0
4-Me	0·15	4·7 [d]	325	81 [e]	81 [f]
2,4-Me_2	0·19	3·6	328	76	76 [f]
5-Me	0·105	6·5	336	10	4
6-Me	0·10	6·8	330	8	5
7-Me	0·12	5·9	322	15	— [g]
8-Me	0·11	6·1	334	10	6
6-Cl	0·06	10·9	335	0	0
7-Cl	0·08	8·4	320	0	0
8-Cl	0·08	8·4	335	0	0
6,8-Cl_2	0·07	9·9 [c]	338	0	0
5-OMe	0·095	7·5	365	12	5
6-OMe	0·12	5·5	354	15	6
7-OMe	0·19	3·6	332	78	78
8-OMe	0·09	7·9	355	0	0

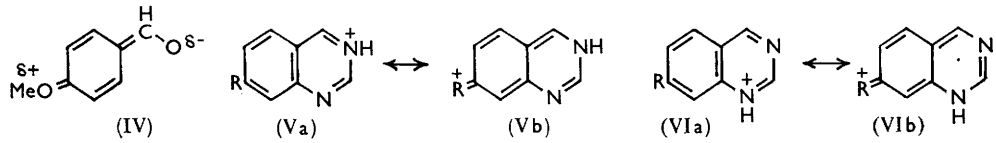
Zero percentages indicate values less than 0·5%. [a] First-order rates determined at 20° and pH 10·0. [b] Error ±0·5 sec. [c] Kindly carried out by Dr. D. D. Perrin. [d] Error ±0·8 sec. [e] Allowance was made for 3% of neutral species in the original acid solution. [f] Standard percentages taken from rates. [g] This compound shows a broad band in the long-wave region but no distinct maximum.

obtained from the kinetic experiments. The spectra of the neutral molecules and cations of 5-, 6-, and 7-hydroxyquinazoline resemble closely those of the corresponding methoxy-quinazolines. If 7-hydroxyquinazoline cation is assumed to contain 78% of anhydrous species (as with 7-methoxyquinazoline) and is taken as standard for the hydroxy-series, then by using the extinction coefficients of the long-wavelength bands, the cations of 5-, 6-, 7-, and 8-hydroxyquinazoline contain respectively 6, 7, 78, and 2% of anhydrous material, and hence present a similar pattern to the methoxy-series.

It is interesting that a methoxy-, hydroxy-, or amino-group in the 7-position can render the cation almost as anhydrous as when a methyl substituent is in position 4.[3a] The effect of these powerful $+M$ groups in the 7-position in repelling the attack of water molecules on $C_{(4)}$ is reminiscent of the effect of a *p*-methoxy-, *p*-hydroxy-, and *p*-amino-group in hindering the addition of the cyanide anion to benzaldehyde.[5] Both equilibria involve a nucleophilic attack on a polarised double bond. However, the unreactive contributor of the resonance hybrid (IV) of *p*-methoxybenzaldehyde has no exact parallel in the conventional cation of 7-methoxyquinazoline (Va; R = OMe) which bears a full

[5] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 678; Gilman, " Organic Chemistry," Vol. 1, Wiley, New York, 1943, pp. 1035—1038.

positive charge in a position corresponding to that where (IV) bears a fractional negative charge. This difficulty disappears if the cation of 7-methoxyquinazoline is considered as a resonance hybrid in which an important contribution is made by a form (Vb or VIb;



(IV) (Va) (Vb) (VIa) (VIb)

R = OMe) with a full positive charge on the 7-substituent. That (Vb or VIb; R = NH_2) applies for the cation of 7-aminoquinazoline follows from the acceptance of this hybridization for 7-aminoquinoline.[6] Cationic hybridization of this type does not occur when *ortho*-quinonoid forms are involved,[6] which agrees with the lack of dehydrating influence of $+M$ groups in the 5-position of quinazoline cations. The 5-isomers are also complicated by proximity effects, and in the 6- and 8-isomers the $+M$ effects, as in the cyanohydrin equilibrium, are absent, leaving only the $-I$ effects, making the situation closer to that found in the *Bz*-chloro-substituted quinazolines.

The correlations between the rates (first order) or half-lives (cf. Table 2) of dehydration of the hydrated neutral quinazolines and the percentage of anhydrous species in the cation mixture are in good agreement with one another. This is in accord with the prediction that a higher percentage of anhydrous cation indicates a lower stability of hydrated species and thus easier dehydration.

Ionization Constants.—The basic strengths of the various quinazolines were measured and are set out in Table 1. No hysteresis was observed during the determination of all the ionization constants, indicating that all the equilibria were rapidly established. In the titrations, hydrated and anhydrous species are involved and the overall equilibrium constant can be expressed (see also ref. 7) as:

$$K_a^{eq} = \frac{[H^+]([X] + [Y])}{[HX^+] + [HY^+]}, \quad \text{(i)}$$

where K_a^{eq} is the overall equilibrium constant, [X] the concentration of anhydrous neutral molecule, [Y] the concentration of hydrated neutral molecule, $[HX^+]$ the concentration of anhydrous cation, and $[HY^+]$ the concentration of hydrated cation. As $[Y] \ll [X]$ the relation (i) becomes

$$K_a^{eq} = [H^+][X]/([HX^+] + [HY^+]); \quad \text{(ii)}$$

and if $[HY^+]/[HX^+] = r$ (the ratio of hydrated to anhydrous species in the cation), then we have

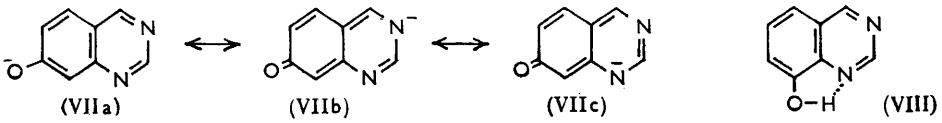
$$pK_a^{eq} = pK_a^* + \log(1 + r), \quad \text{(iii)}$$

where pK_a^* is the constant for the equilibrium $[HX^+] \rightleftharpoons [H^+] + [X]$ involving the two anhydrous species. By applying equation (iii) to 4-methylquinazoline which has pK_a^{eq} 2·52,[8] it is found that its pK_a^* is 2·43, so that the presence of 19% of hydrated species in the cation makes a difference of 0·09 pK unit. If the percentage of the hydrated cation is very small, then $pK_a^{eq} = pK_a^*$.

The pK_a^{eq} values of the four *Bz*-chloroquinazolines are higher than those of the corresponding methylquinazolines because the chloro-compounds form predominantly hydrated cations, whereas the cations of the methyl compounds have up to 15% of the anhydrous form. Thus even if the chloro-bases are assumed to form cations containing as much as 1% of anhydrous species, the calculated pK_a^* values would be smaller than those calculated for the methyl bases. The position of the substituent does not have a large effect on the basic strengths in the two series, hence the inductive effect is mainly operating.

[6] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[7] Perrin and Inoue, *Proc. Chem. Soc.*, 1960, 342.
[8] Albert, Brown, and Wood, *J.*, 1954, 3832.

In the *Bz*-methoxyquinazolines the inductive effect is not the only one operating (see p. 567) and the large percentage of hydrated cation in 5- and 8-methoxyquinazoline is reflected in the higher basic strengths. The close similarity in the basic strengths of the 6- and 7-methoxyquinazoline appears to be coincidental. In the 7-isomer the $+M$ effect predominates over the $-I$ effect, thus increasing the basic strength, but the resistance to hydration caused by this $+M$ effect (see p. 567) keeps the basic strength low. In 6-methoxyquinazoline the $-I$ effect is the main influence and it lowers the basic strength, but the resulting hydration tends to increase it.



(VIIa) (VIIb) (VIIc) (VIII)

Basic strengths of the *Bz*-hydroxyquinazolines show the same behaviour as the methoxy-series and can be similarly explained. The acidic pK_a values of the hydroxyquinazolines are readily explained by resonance in the anions. All the anions are anhydrous but only the 5- and the 7-isomer, which are the stronger acids, can be written in three resonating structure (*e.g.*, VIIa, b, c). Of the weaker acids, *e.g.*, 6- and 8-hydroxyquinazoline, the latter is weaker by 0·46 pK_a unit, which could be attributed to the difficulty in removing the proton from the hydrogen-bonded structure (VIII).

TABLE 3.

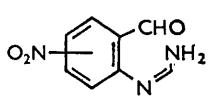
Extinction coefficients of the long-wavelength bands in aminoquinazolines (cf. ref. 2).

Quinazoline	pK_a	$\lambda_{max.}$ (mμ)	ε [a]	pH	Quinazoline	pK_a	$\lambda_{max.}$ (mμ)	ε [a]	pH
5-Amino ...		372	2818	9·2	7-Amino ...		345	6310	9·2
	3·57	462	525	2·0		4·60	373	11,480	2·0
6-Amino ...		360	2630	7·0	8-Amino ...		338	2884	7·0
	3·29	260	9550	1·7		2·81	415	331	1·1

[a] Calculated from ref. 2.

The behaviour of the aminoquinazolines discussed by Osborn, Schofield, and Short [2] can now be rationalised. The ratio of the extinction coefficients for the long-wavelength bands in the neutral molecules to those in their respective cations shows that, whereas 6-aminoquinazoline cation is mostly hydrated and 7-aminoquinazoline cation mostly anhydrous, 5- and 8-aminoquinazoline cations are mixtures containing a relatively small percentage (some 10%) of anhydrous species. Thus their cations followed the same pattern of hydration as the methoxy- and hydroxy-quinazolines, and hence the possibility of protonation on the exocyclic nitrogen atom need no longer be entertained. The high basic strength of 7-aminoquinazoline when compared with the 5-, 6-, and 8-isomers indicates the cationic resonances (Va ⟷ b; R = NH_2) or (VIa ⟷ b; R = NH_2) depending on which ring nitrogen atom is protonated.

The rather high basic strengths of the nitroquinazolines (Table 1) are not compatible with completely hydrated cations alone but suggest that the electron-attracting property of the nitro-group is large enough to cause hydration in the neutral species as well, although the spectral measurements do not reveal any hydration. The rapid-flow technique used above could not be applied here because of the complicated spectra. The ring-opened form (IX) is unlikely to be present in the neutral molecule because aldehydes having $-I$ substituents show enhanced activity towards amino-groups. In pteridine, hydration across the 3,4-double bond in the neutral species was demonstrated by a slow change in the spectrum of the neutral molecule in water.[9] As ring-nitrogen atoms can be considered as effective as nitro-groups in their electron-attracting properties,[10] the above



(IX)

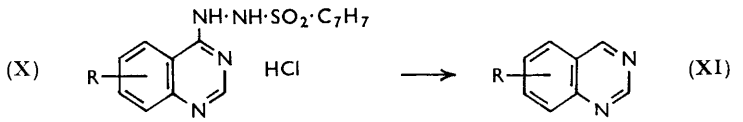
[9] Perrin, *J.*, in the press.

[10] Taylor and Baker, " Sidgwick's Organic Chemistry of Nitrogen," Oxford Univ. Press, 1942, p. 523.

hypothesis that the neutral molecules of the nitroquinazolines may be hydrated is, to some extent, justified. However, no change in the spectrum of an aqueous solution of 6- and 7-nitroquinazoline was observed in storage at pH 7·17 and 11·0, indicating that if hydration does occur it must be very rapid (the crystalline nitro-compounds are anhydrous). That the nitroquinazoline cations contain at least some of the 3,4-hydrated species is indicated by their ready conversion into the 4-hydroxy-compounds on mild oxidation.

The 2- and the 4-substituted chloro-, methoxy-, and hydroxy-quinazolines present a different problem. 2- and 4-Chloroquinazoline are hydrolysed too readily in acid to give reliable information, but the initial spectra revealed that the anhydrous cation predominates. The 4-methoxyquinazoline cation is also hydrolysed rapidly. The 2-methoxyquinazoline cation, relatively more stable, shows a band at 337 mμ which is at longer wavelengths than the long-wavelength band in the neutral molecule, and the intensity of these two bands is of the same order. Thus the cation has a high proportion of anhydrous species, although some of the hydrated species must be present because the band at 293 mμ is rather more intense than would be expected for a completely anhydrous cation. By using the rapid-flow technique [$\lambda_{(analytical)} = 345$ mμ] it was shown that 2-methoxyquinazoline cation contained 64% of the anhydrous species, so that the rather high intensity at 293 mμ was of some significance. 2- and 4-Hydroxyquinazoline cannot be studied by the above techniques because of their tautomerism.

Materials.—Quinazolines are conveniently prepared by (i) the catalytic reduction of 4-chloroquinazolines [11] or (ii) Riedel's synthesis [12] (reduction with zinc and acid of bisformamido-*o*-nitrobenzaldehydes. The key intermediates for method (i) are the anthranilic acids, which are readily converted into 4-hydroxyquinazolines and then into 4-chloroquinazolines, whereas the poor availability of the required *o*-nitrobenzaldehydes limits the application of method (ii). Hydrogenation of 4,6- and 4,8-dichloro- and 4,6,8-trichloro-quinazolines with palladium–charcoal, as described for quinazoline,[11] gave the corresponding 6- and 8-chloro- and 6,8-dichloro-quinazoline in good yields. Attempts to reduce 4,5- and 4,7-dichloroquinazoline by the same method gave a mixture of the starting materials and 5- and 7-chloroquinazoline, respectively, contaminated with the corresponding 3,4-dihydro- and 1,2,3,4-tetrahydro-quinazolines which were difficult to separate. Therefore a more satisfactory method was required which would also be applicable to the preparation of nitroquinazolines. By heating the *N'*-toluene-*p*-sulphonyl derivative of 4-hydrazino-6-methoxy-7-nitroquinazoline with potassium carbonate, Dewar [13] obtained 6-methoxy-7-nitroquinazoline, but only in a poor yield; however, in view of the success of a modified version of this reaction in the acridine series,[14] the use of



this reaction (X ⟶ XI) in the quinazoline series has been re-examined and conditions found that never failed to give good results. Thus, ten (cf. Table 4) of the 21 *Bz*-substituted quinazolines were obtained by this method. The intermediates were the respective anthranilic acids, mostly prepared by the Sandmeyer isatin synthesis followed by oxidation with alkaline hydrogen peroxide. The amino-acids were converted into the 4-hydroxyquinazolines by von Niementowski's method [15] and chlorinated with phosphorus pentachloride in phosphorus oxychloride. With toluene-*p*-sulphonyl hydrazide the 4-chloroquinazolines gave the corresponding 4-(*N'*-toluene-*p*-sulphonylhydrazino)quinazoline hydrochlorides in almost quantitative yields and the quinazolines were then obtained

[11] Armarego, *J. Appl. Chem.*, 1961, **11**, 70.
[12] Riedel, G.P. 1905, 174941; Bogert and McColm, *J. Amer. Chem. Soc.*, 1927, **49**, 2650.
[13] Dewar, *J.*, 1944, 619.
[14] Albert and Royer, *J.*, 1949, 1148.
[15] von Niementowski, *J. prakt. Chem.*, 1895, **51**, 564.

by decomposition with dilute alkali in ethylene glycol (with evolution of nitrogen and formation of toluene-*p*-sulphinic acid).

5-, 6-, and 8-Methoxy- and 5-hydroxy-quinazoline were prepared by the Riedel synthesis from the *o*-nitrobenzaldehydes, but 7-methoxyquinazoline required a fourteen-stage synthesis *via* 2-amino-4-methoxybenzoyl chloride and 4-hydroxy-7-methoxyquinazoline and starting from 2-nitro-*p*-toluidine. 6-, 7-, and 8-Hydroxyquinazoline were prepared by demethylation of the corresponding methoxy-compounds. 6-Nitroquinazoline was the only material prepared by direct electrophilic substitution of quinazoline.[16]

Experimental

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

The purity of materials was examined by paper chromatography in two solvent systems [17] after recrystallisation to constant m. p. before analysis and physical measurements. 3-, 4-, 5-, and 6-Methylanthranilic acid,[18] 4-hydroxy-5-, 6-, 7-, and 8-methylquinazoline,[19] 4- and 6-chloroisatin,[20] 7-chloroisatin,[21] 5-, 6-, and 8-chloro-4-hydroxyquinazoline,[19] 7-chloro-4-hydroxyquinazoline,[22] 4,6-dichloroquinazoline,[23] 4,6,8-trichloroquinazoline,[24] 4-methoxyquinazoline,[25] 2-hydroxy-6-nitrobenzaldehyde,[26] 5-hydroxy-2-nitrobenzaldehyde,[27] 4-amino- [28] and 4-hydroxy-nitrobenzoic acid,[29] 4-chloro-7-methoxyquinazoline,[30] 8-methoxy- and 8-hydroxy-quinazoline,[31] 3-nitrophthalimide,[32] 6-,[33] 4-,[34] and 3-nitroanthranilic acid,[35] 4-chloro-5- [2] and 4-chloro-7-nitroquinazoline,[16] 6-nitroquinazoline,[16] 4-chloro-8-nitroquinazoline,[16] and toluene-*p*-sulphonylhydrazide [14] were prepared as described in the literature.

Methylation of 2- and 3-hydroxy-6-nitrobenzaldehyde and of 4-hydroxy-2-nitrobenzoic acid with dimethyl sulphate was achieved in 90, 67, and 80% yield, respectively, by using the method described [36] for methylation of *m*-hydroxybenzaldehyde.

The following typical preparations were used for new substances:

(A) *4-Chloroquinazolines.* Dry 4-hydroxyquinazoline (0·1 mole) and phosphorus pentachloride (0·1 mole) in phosphorus oxychloride (100 ml.) were refluxed with stirring until the hydroxy-compound dissolved (½—3 hr.). Boiling was continued for a further 30 min. The phosphorus oxychloride was removed in a vacuum and the residue kept in a vacuum desiccator (KOH) overnight. The solid was shaken in chloroform (100 ml.) with saturated aqueous sodium carbonate until the supernatant liquid was neutral to litmus. The lower layer was dried (Na_2SO_4) and evaporated to dryness in a vacuum at room temperature. The crystalline residue was passed in benzene (150 ml.) through alumina (5″ × 1″; B.D.H.) and charcoal (2″ + 1″; B.D.H.) and eluted with benzene. The eluates, on evaporation in a vacuum at 40°, gave a solid which was recrystallised. The yields of 4-chloroquinazolines were 40—90%.

(B) *Quinazolines by reduction of 4-chloroquinazolines.* The chloroquinazoline (10 mmoles) in anhydrous benzene (75 ml.), and anhydrous sodium acetate (15 mmole) in methanol (30 ml.), were added to a hydrogenated suspension of 5% palladium–charcoal (1·5 g.) in anhydrous benzene (25 ml.). The mixture was shaken with hydrogen at room temperature and atmospheric pressure, and reduction was stopped after absorption of 10 mmoles of hydrogen.

[16] Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405.
[17] Armarego, *J.*, 1961, 2697.
[18] Mayer, Schäfer, and Rosenbach, *Arch. Pharm.*, 1929, **267**, 571.
[19] Baker, Schaub, Joseph, McEvoy, and Williams, *J. Org. Chem.*, 1952, **17**, 141.
[20] Senear, Sargent, Mead, and Koepfli, *J. Amer. Chem. Soc.*, 1946, **68**, 2695.
[21] Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 234.
[22] Price, Leonard, and Curtin, *J. Amer. Chem. Soc.*, 1946, **68**, 1305.
[23] Endicott, Alden, and Sherill, *J. Amer. Chem. Soc.*, 1946, **68**, 1303.
[24] Sen and Singh, *J. Indian Chem. Soc.*, 1959, **36**, 787.
[25] Breukink, Krol, Verkade, and Wepster, *Rec. Trav. chim.*, 1957, **76**, 401.
[26] Perkin, Robinson, and Ashley, *J.*, 1930, 382.
[27] Heilbron, Kitchen, Parkes, and Sutton, *J.*, 1925, **127**, 2167.
[28] Schofield and Simpson, *J.*, 1945, 512.
[29] Drain, Martin, Mitchell, Seymour, and Spring, *J.*, 1949, 1498.
[30] Chapman, Gibson, and Mann, *J.*, 1947, 890.
[31] Albert and Hampton, *J.*, 1952, 4985.
[32] Shirley, " Preparation of Organic Intermediates," Wiley, New York, 1951, p. 233.
[33] Kahn, *Ber.*, 1902, **35**, 3857.
[34] Iguchi, *J. Pharm. Soc. Japan*, 1952, **72**, 131.
[35] Chapman and Stephen, *J.*, 1925, **127**, 1791.
[36] Icke, Redemann, Wisegraver, and Alles, *Org. Synth.*, 1949, **29**, 63.

The catalyst was filtered off and the filtrate evaporated at 40°/15 mm. The residue was strongly basified with aqueous ammonia (15 ml.; *d* 0·880) and extracted with benzene (4 × 25 ml.), the extract was dried (Na_2SO_4), and the solvent removed at 20°/15 mm. The solid residue recrystallised from light petroleum and sublimed at 0·2 mm. The yields of quinazolines were 40—70%.

(C) *Quinazolines by alkaline decomposition of* 4-(N′-*toluene*-p-*sulphonylhydrazino*)*quinazoline hydrochlorides.* The 4-chloroquinazoline (1 mol.) dissolved in the least volume of cold chloroform was treated with a solution of toluene-*p*-sulphonylhydrazide (1 mol.) in the least volume of cold chloroform. Separation of the 4-(*N*′-toluene-*p*-sulphonylhydrazino)quinazoline hydrochlorides usually began after 1 hr. at room temperature, but if no solid separated dry hydrogen chloride was bubbled through the solution for a few minutes. In all cases the mixture was left at room temperature overnight. When no solid separated, the whole solution was evaporated to dryness in a vacuum desiccator (KOH) until free from hydrogen chloride. The yield of solid obtained was almost quantitative. All the hydrochlorides melted with decomposition over a range and were used without further purification.

The hydrochloride (5 mmoles) was heated with alkali (see Table 4) in water (30 ml.) and ethylene glycol (70 ml.), with occasional shaking, on a steam bath until it had dissolved and nitrogen evolution ceased (1—2 hr.). The solution was cooled, diluted with water (100 ml.), and extracted with ether (6 × 75 ml.). The extract was dried (Na_2SO_4) and the solvent distilled off. The pasty residue was passed in benzene through alumina (5″ × 1″; B.D.H.) and eluted with benzene. The fractions which gave an oily residue, on evaporation in a vacuum, were cooled, and those which solidified were combined, sublimed at 0·2 mm., and recrystallised. The yields of quinazolines calculated on the chloro-compound were 15—67% (cf. Table 4).

TABLE 4.

Quinazolines prepared from 4-(*N*′-toluene-*p*-sulphonylhydrazino)quinazoline hydrochloride derivatives.

Deriv.	Quinazoline yield (%)	Conditions	Deriv.	Quinazoline yield (%)	Conditions
5-Cl	60	0·5N-NaOH 100°/2 hr.	7-OMe ...	65	0·5N-NaOH 100°/1 hr.
7-Cl	30	1·0N-NaOH 100°/2 hr.			
			5-NO_2 ...	25	0·125N-Na_2CO_3 100°/2 hr.
5-Me	63	0·5N-NaOH 100°/2 hr.	7-NO_2 ...	30	0·125N-Na_2CO_3 100°/2 hr.
6-Me	62	0·5N-NaOH 100°/1 hr.	8-NO_2 ...	15	0·125N-Na_2CO_3 100°/2 hr.
7-Me	67	0·5N-NaOH 100°/1 hr.			
8-Me	62	0·5N-NaOH 100°/1 hr.			

(D) *Quinazolines by Riedel's synthesis.* (i) Bisformamido-*o*-nitrobenzaldehydes. A vigorous stream of dry hydrogen chloride was passed through a suspension of the methoxy- or hydroxy-*o*-nitrobenzaldehyde (3·0 g.) in formamide (7·5 ml.). The temperature rose to 110° and the solid dissolved. The mixture was then cooled to 80—90° and after 5 min. the bisformamido-compound separated but hydrogen chloride was bubbled through for a further 10 min. to ensure saturation and the mixture was left at room temperature overnight. The mixture was triturated with ether to remove unchanged starting material and then washed with cold water, filtered, crystallised, and dried at 100°. The yield of bisformamido-methoxy- or -hydroxy-*o*-nitrobenzaldehyde was 90% or more.

(ii) Quinazoline. Crushed ice (55 g.) was added to a mixture of thoroughly ground bisformamido-hydroxy- or -methoxy-*o*-nitrobenzaldehyde (3·4 g.) and zinc dust (10·6 g.). This stirred suspension was treated dropwise with glacial acetic acid (14·2 ml.) during 5 min. and the suspension stirred for a further hour during which small portions of zinc dust (4·3 g. in all) were added and stirring was continued at room temperature for 3 hr. The zinc dust was filtered off and washed with 5% acetic acid, and the filtrates were combined and treated, with cooling, with sodium hydroxide (34 g.). The alkaline solution was extracted with ether (6 × 75 ml.), and the extracts were dried (Na_2SO_4) and evaporated. The residue was sublimed at 0·2 mm. and recrystallised. The yields of methoxyquinazolines were 70—100%. The working-up with the hydroxy-compounds was more complicated: this was done by adjusting the pH to 5—6, 6—7, and 7— 8 and extracting these solutions with ether (6 × 75 ml.) in each case; the yields of hydroxyquinazolines were always low (20—50%).

(E) *Hydroxyquinazolines by demethylation of methoxyquinazolines.* The methoxyquinazoline (1·0 g.) and anhydrous aluminium chloride (3·0 g.) were ground together and heated in a

steam bath for 10 min., then at 135—140° for 3 hr. The resulting paste was cooled and treated with water (4 ml.), the pH adjusted to 4—5, and the whole extracted with ether (10 × 25 ml.). The extracts were dried (Na_2SO_4) and the residue obtained from it was recrystallised. The yields of hydroxyquinazolines were 42—50%.

Table 5 records the products.

TABLE 5.

Compound	Prep.[a]	Cryst. from [b]	M. p.	Found (%) C	H	N	Required (%) C	H	N
4,8-Dichloroquinazoline	A	M	175—176°	48·5	1·9	14·0	48·3	2·0	14·1
4,6,8-Trichloroquinazoline	A	O	139—140 [c]	41·25	1·3	12·1	41·1	1·3	12·0
4-Chloro-5-methylquinazoline	A	M	104·5—105·5	60·3	3·7	15·4	60·4	3·95	15·7
4-Chloro-6-methylquinazoline	A	N	105—106	60·7	3·9	15·6	60·4	3·95	15·7
4-Chloro-7-methylquinazoline	A	M	88—89	60·7	3·7	15·6	60·4	3·95	15·7
4-Chloro-8-methylquinazoline	A	N	129—130	60·6	4·0	15·6	60·4	3·95	15·7
Bisformamido-2-hydroxy-6-nitrobenzaldehyde	D(i)	H_2O	207—208 [c]	45·1	3·9	17·5	45·2	3·8	17·6
Bisformamido-2-methoxy-6-nitrobenzaldehyde	D(i)	EtOH	233—235 [c]	47·1	4·4	16·8	47·4	4·4	16·6
Bisformamido-5-methoxy-2-nitrobenzaldehyde	D(i)	H_2O	202—203	47·2	4·5	16·9	47·4	4·4	16·6
5-Chloroquinazoline	C	M	87·5—88	58·4	3·0	16·8	58·4	3·1	17·0
7-Chloroquinazoline	C	M	93—94	58·1	3·0	16·8	58·4	3·1	17·0
8-Chloroquinazoline	B	M	119—120	58·6	3·0	16·9	58·4	3·1	17·0
6,8-Dichloroquinazoline	B	P	165—166	48·2	2·0	13·9	48·3	2·0	14·1
5-Methylquinazoline	C	M	58—59	74·9	5·5	19·3	75·0	5·6	19·4
6-Methylquinazoline	C	M	62—63	75·4	5·7	19·2	75·0	5·6	19·4
7-Methylquinazoline	C	M	65—66	74·9	5·7	19·1	75·0	5·6	19·4
8-Methylquinazoline [d]	C	M	47—48	74·7	5·7	19·3	75·0	5·6	19·4
5-Methoxyquinazoline	D(ii)	N	84—85	67·5	5·1	17·3	67·5	5·0	17·5
6-Methoxyquinazoline	D(ii)	N	71—72	67·55	4·9	17·3	67·5	5·0	17·5
7-Methoxyquinazoline	D(ii)	M	87	67·2	4·9	17·3	67·5	5·0	17·5
5-Hydroxyquinazoline	D(ii)	EtOH	229—230 [c]	65·45	4·1	19·1	65·75	4·1	19·2
7-Hydroxyquinazoline	E	H_2O	251—252 [c]	65·5	4·0	19·0	65·75	4·1	19·2
5-Nitroquinazoline	C	EtOH	107—108	54·7	2·9	23·9	54·9	2·9	24·0
7-Nitroquinazoline	C	EtOH	156—157	54·5	2·7	24·1	54·9	2·9	24·0
8-Nitroquinazoline	C	EtOH	153—154	54·9	3·0	23·6	54·9	2·9	24·0

[a] Methods described in the text. [b] M = light petroleum (b. p. 40—60°). N = light petroleum (b. p. 60—80°). O = light petroleum (b. p. 80—100°). P = benzene–light petroleum (b. p. 40—60°). [c] Sen and Singh [24] give 236—237°. [d] Hygroscopic, sampled in a dry box. [e] Decomp.

Kinetic Measurements.—All runs were carried out under the same conditions and at 20°. The quinazoline solutions were prepared by dissolving 20 mg. of solid in 0·1N-hydrochloric acid (50 ml.). The acid solution was rapidly mixed with an equal volume of a buffer (sodium carbonate–sodium hydrogen carbonate) containing an equivalent quantity of 0·1N-sodium hydroxide to give a final solution of pH 10·0. This was done in a special mixing chamber [9] (kindly provided by Dr. D. D. Perrin) before running the solution into the spectrophotometer cell (1 cm.) situated directly below it. The flow was then suddenly stopped and the change of optical density from the spectrophotometer (Perkin–Elmer Spectracord-model 4000A) with time was traced on a Recti-riter (Texas Instruments Incorporated). The initial rapid rise of the optical density (see Fig. 2) represents the displacement of the buffer from the cell by the acid solution of the quinazoline and the neutralization process concurrently. The kink in the curve is due to overshooting of the pen recorder.

The absorption was observed at the longest possible wavelength to give a final optical density between 0·8 and 1·2. The rates were calculated from the tracings. The optical densities at zero time (t_0) we obtained from extrapolations of the plots and hence the percentages of anhydrous cations from the extrapolations were derived.

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