528. *Quinazolines. Part I. Cations of Quinazoline.*

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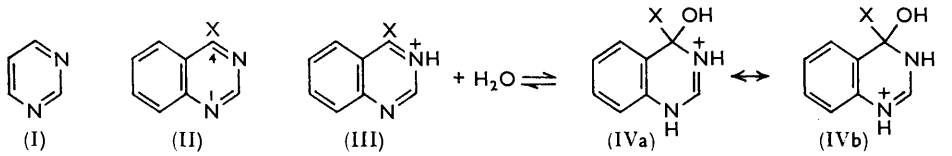
Depending on the conditions, quinazoline can form either a normal or an abnormal monocation; the latter preponderates in aqueous medium (4-substituted quinazolines form predominantly the normal monocation even in dilute aqueous acid). The abnormal ion is formed by the reaction of water with the normal ion; a possible structure is (IV; X = H) although some evidence at present appears not to be wholly in accord with this. A (normal) dication of quinazoline has also been obtained.

WHEREAS there is a great similarity in base strength [1] between pyridazine (pK_a 2·3) and cinnoline (2·3), and between pyrazine (0·6) and quinoxaline (0·7), there is a large difference between pyrimidine (I) (1·3) and quinazoline (II; X = H) (3·5); 4-methylquinazoline (2·5), by contrast, resembles 4-methylpyrimidine (2·0). Thus, quinazoline (predicted $pK_a \sim 1{\cdot}5$) is an anomalously strong base. Ultraviolet spectra show that only the cation of quinazoline is abnormal: quinoline, isoquinoline, and the eight known diazanaphthalenes [2,3] all have ultraviolet spectra like that of naphthalene; and the spectra undergo but minor changes on cation formation,[4] with the exception of that of quinazoline (also that of 2-methylquinazoline [5]) which is greatly changed on cation formation in dilute aqueous acid (Fig. 1).

[1] (*a*) Albert, "Heterocyclic Chemistry," Athlone Press, London, 1959, pp. 344—345; (*b*) Albert, Goldacre, and Phillips, *J.*, 1948, 2240; (*c*) Albert, Brown, and Wood, *J.*, 1954, 3832.
[2] Ref. 1 (*a*), pp. 300, 314—316.
[3] Albert, *J.*, 1960, 1790.
[4] Ref. 1 (*a*), p. 303.
[5] Mason, communication to Osborn *et al.*; see ref. 7.

By contrast, the spectra of 4-methyl-[5] and 2,4-dimethyl-quinazoline are little changed under these conditions.

To explain the anomaly it has been suggested[6,7] that water adds covalently to the cation of quinazoline, the hydroxyl group becoming attached to the 4-position. Nucleophilic addition of water to C=N bonds has been observed previously, *e.g.*, to azomethines,[8] but only when such bonds are not part of an aromatic ring. (However, some quaternised pyridines,[9a] and even neutral acridine[9b] and quinoxaline,[10] add various nucleophilic reagents.) The addition of water to the normal cation of quinazoline (III; X = H) can



yield a product for which stabilization by amidinium resonance (IV,a ⟷ b) has been postulated.[6,7] Several 3-methylquinazolinium derivatives contain a very firmly held alcohol molecule [11,12] which, it has been suggested,[7] is covalently bound.

Two different hydrochlorides of quinazoline have now been prepared as solids. In anhydrous ether, quinazoline was converted into a hydrochloride $C_8H_7ClN_2$; this was very hygroscopic and readily formed a hydrate $C_8H_9ClN_2O$. The latter is stable at room temperature, and relatively difficult to dehydrate even in a vacuum at 60°; infrared spectra suggested that it contained covalently bound water, as it failed to show several bands observed for $C_8H_7ClN_2$ (see Table 1), and showed extra bands at 1474 and 1240 cm.$^{-1}$

TABLE 1. *The infrared spectra * of quinazoline hydrochloride and quinazoline hydrochloride " monohydrate."*

$C_8H_7N_2Cl$: 3250ms, 3090mw, 3025mw, 2980s, 1669ms, 1599w, 1582ms, 1495ms, 1448m, **1427**m, 1332ms, 1293m, 1264m, 1218ms, **1170**mw, 1159mw, 1123vw, 1039mw, 1024ms, 965mw, 955vw, **931**m, 872vw, **838**m, 805 + 799w, 774ms, 726vw, **663**m.

$C_8H_9N_2OCl$: 3350ms, 3100s, 2975mw, 2860m, 2750m, 1665ms, 1624ms, 1599w, 1570ms, 1495ms, **1474**m, 1441ms, 1329m, 1282vw, 1266vw, **1240**mw, 1211ms, 1156w, 1120w, 1027ms, **989**w, 966mw, 951 + 945w, 880vw, 811m, 798w, 767ms, 735vw.

* Wave-numbers of absorption peaks in cm.$^{-1}$; bands not common to both spectra are in bold type.

that are possibly attributable to CH and OH bending vibrations of the CH·OH group in (IV; X = H).

The Spectrum of Quinazoline in Acidic Media of Low Water Content.—In order to ascertain whether the anomaly in the ultraviolet spectrum of the cation of quinazoline is in fact associated with the presence of water, the spectrum of quinazoline was measured in anhydrous dichloroacetic acid which has [13] an acidic pK_a value of 1·0 in water and should not undergo nucleophilic addition to a system of double bonds. The Hammett acidity function, H_0, of pure dichloroacetic acid, determined with *o*-nitroaniline as the solute, is −0·9, hence a base with a pK_a value greater than +1 would be almost completely ionized in it.

In this solvent quinazoline gives a normal cation spectrum which closely resembles

[6] Albert, *Chem. Soc. Special Publ.* No. 3, 1955, p. 138; cf. ref. 1 (*a*), p. 121.
[7] Osborn, Schofield, and Short, *J.*, 1956, 4191.
[8] Dimroth and Zoeppritz, *Ber.*, 1902, **35**, 990; Gattermann, *Annalen*, 1907, **357**, 336; Carré and Baranger, *Bull. Soc. chim. France*, 1928, **43**, 73.
[9] (*a*) Burton and Kaplan, *J. Biol. Chem.*, 1954, **206**, 283; **211**, 447; Eys and Kaplan, *J. Biol. Chem.*, 1957, **228**, 305; (*b*) Kröhnke and Honig, *Annalen*, 1959, **624**, 97.
[10] Bergstrom and Ogg, *J. Amer. Chem. Soc.*, 1931, **53**, 245.
[11] Gabriel and Colman, *Ber.*, 1904, **37**, 3643.
[12] Schöpf and Oechler, *Annalen*, 1936, **523**, 1.
[13] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.

that of 4-methylquinazoline and shows the characteristic band near 330 mμ which is absent from the quinazoline cation spectrum in dilute aqueous acid (see Table 3).

In concentrated sulphuric acid both quinazoline and its 4-methyl derivative form (stable) dications which possess normal spectra (see Table 3). The most illuminating spectra, however, are those obtained in rather concentrated aqueous sulphuric acid. The behaviour of 4-methylquinazoline is straightforward. At low acid strength (H_0 values to $-2{\cdot}5$) only the spectrum of the monocation is seen, at high acid strengths (H_0 $-6{\cdot}5$ to $-9{\cdot}4$) only the dication, and at intermediate acid strengths these two species are present in equilibrium with each other, their relative proportions varying with H_0 corresponding to proton addition to a base with a pK_a value of $-4{\cdot}4 \pm 0{\cdot}2$.

In solutions of quinazoline in sulphuric acid–water mixtures, however, *three* ionic species are observable, *viz.*: at H_0 -1 the abnormal monocation predominates; at

FIG. 1. *Ultraviolet spectra, in water, of* (A) *quinazoline* (pH 7); (B) *the abnormal cation of quinazoline* (pH 1); (C) *the cation of 4-methylquinazoline* (pH 0).

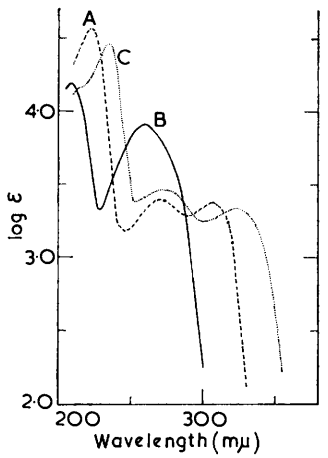
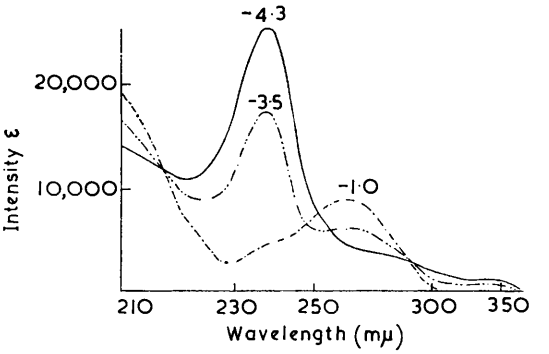


FIG. 2. *Ultraviolet spectra of solutions of quinazoline in sulphuric acid–water mixtures, at Hammett acidity functions* (H_0) *of* $-1{\cdot}0$, $-3{,}5$, *and* $-4{\cdot}5$.



H_0 $-7{\cdot}0$ to $-9{\cdot}4$ the (normal) dication is seen; but at H_0 $-4{\cdot}3$ the spectrum resembles that of 4-methylquinazoline in dilute aqueous acid, and the main species present must be the *normal* (anhydrous) monocation of quinazoline (III; X = H) already observed in anhydrous dichloroacetic acid. The value deduced for the second basic ionization constant, pK_a $-5{\cdot}5 \pm 0{\cdot}2$, as compared with $-6{\cdot}3 \pm 0{\cdot}2$ obtained for pyrimidine and $-4{\cdot}4 \pm 0{\cdot}2$ for 4-methylquinazoline, also agrees with the view that the equilibrium is mainly one between the normal dication and the normal monocation of quinazoline.

The percentage of normal monocation present increases with increasing acid strength, only slightly at low values of $-H_0$, but very markedly at higher values. The equilibrium is illustrated in Fig. 2. The estimated percentage of normal monocation present is 1—2% at H_0 $-1{\cdot}0$, 50—60% at H_0 $-3{\cdot}5$, and 80—90% at H_0 $-4{\cdot}3$ (where about 7% of the dication is also present). In mixtures of sulphuric acid and water containing more than 38% of acid ($-H_0 > 2{\cdot}3$) the activity of water is much lower than its stoicheiometric concentration would suggest, because the inner solvation shells (of water molecules held very firmly around the H_3O^+ and HSO_4^- ions) are depleted. It is therefore reasonable that in concentrated aqueous sulphuric acid an equilibrium such as that between (III; X = H) and (IV; X = H) should be strongly dependent on the solvent composition.

4-Substituted Quinazolines.—There is thus abundant evidence that the normal (anhydrous) cation of quinazoline is capable of existence, but in dilute aqueous acid it is

not the energetically preferred species. In the case of 4-methylquinazoline, on the other hand, only the normal cation (III; X = Me) is known. It must now be decided whether this resistance to hydration is due to the (weak) electron-donating effect or to the steric effect of the methyl group. Electronic effects are known to be of importance, because the (strongly electron-donating) amino-group, if present in any position in quinazoline other than at 6, causes the normal cation to predominate.[7]

However, 4-chloro-, 4-cyano-, and 4-cyanoethoxycarbonylmethyl-quinazoline, in 5·6N-hydrochloric acid, have now also been found to give mainly the normal cations (see Table 3), although here the substituent is electron-withdrawing. It is thus by their steric effect that 4-substituents cause predominance of the normal cation, and the view that the conversion of the normal into the abnormal cation involves attack at the 4-position is confirmed.

4-Cyanoethoxycarbonylmethylquinazoline is stable in 5·6N-hydrochloric acid, but the cyano- and the chloro-derivative are rapidly hydrolysed to 4-hydroxyquinazoline (the half-reaction times being about 5 min. and 50 sec., respectively). Very probably a small amount of an ion (IV) is present in equilibrium with (III) here; however, amide cyanohydrins and chlorohydrins are not stable, and rapid elimination of hydrogen cyanide or hydrogen chloride from a form (IV; X = CN or Cl), with formation of the cation of 4-quinazolone (*i.e.*, of 4-hydroxyquinozaline), would be expected.*

Unsuccessful attempts were made to synthesize 4-acetonyl- (II; X = CH_2·COMe) and 4-cyanomethyl-quinazoline (II; X = CH_2·CN) as examples of quinazolines in which the " X " group is electron-attracting but not readily hydrolysable. In the former synthesis

TABLE 2. *Ionization constants in water, at* 20°.

Compound	pK_a	Spread (±)	Concn. (M)
Quinazoline [a] (II; X = H)	3·51	0·05	0·07
2-Methylquinazoline	4·52	0·02	0·005
4-Methylquinazoline [a]	2·52	0·02	0·07
2,4-Dimethylquinazoline	3·60	0·01	0·002
4-(α-Cyano-α-ethoxycarbonylmethyl)quinazoline	(9·78	0·05	0·005) [b]
3,4-Dihydroquinazoline	9·19	0·07	0·002
3,4-Dihydro-3-methylquinazoline	9·23	0·03	0·001
1,4-Dihydro-1-methylquinazoline	9·43	0·04	0·005
3,4-Dihydroquinazolinium-4-sulphonate (VI)	(7·1		0·002) [b,c]
3,4-Dihydro-2-methylquinazoline	10·16	0·04	0·005
1,2 3,4-Tetrahydroquinazoline	7·65	0·03	0·005
Phthalazine	3·50	0·02	0·005
1-Methylphthalazine	4·39	0·01	0·005

[a] Albert, Brown, and Wood, *J.*, 1954, 3832. [b] Proton lost; the other pK_a value is less than 1. [c] Approx.; the anion splits off sulphite ion at an appreciable rate.

benzyl sodioacetoacetate was condensed with 4-chloroquinazoline with the aim of later debenzylation and decarboxylation; however, the condensation followed the mechanism suggested by Elderfield and Serlin [14] and 4-benzyloxycarbonylmethylquinazoline and not 4-α-benzyloxycarbonylacetonylquinazoline was isolated. In the latter synthesis alkaline hydrolysis of 4-(α-cyano-α-ethoxycarbonylmethyl)quinazoline was studied but the ester resisted hydrolysis when boiled with 3 equivalents of alkali and with 3N-potassium hydroxide; this is probably due to the formation of a stable salt (cf. pK_a in Table 2), and more drastic hydrolytic conditions caused considerable decomposition. Finally 4-(α-cyano-α-benzyloxycarbonylmethyl)quinazoline was prepared, but on hydrogenolysis a mixture was obtained from which the free acid could not be isolated.

Ionization Constants.—2-Methylquinazoline has an anomalously high base strength,

* Some other 4-substituted quinazolines [*e.g.*, where X = $CEt(CO_2Et)_2$] give 4-hydroxyquinazoline when heated with acid,[14] presumably by the same mechanism.

[14] Elderfield and Serlin, *J. Org. Chem.*, 1951, **16**, 1669.

TABLE 3. *Ultraviolet spectra.*

Compound	Solvent	pH (or H_0)	Species [a]	$\lambda_{max.}$ (mμ) (inflections in italics)	log $\varepsilon_{max.}$
Quinazoline	H_2O	7·0	N	222; 271; 305	4·57; 3·40; 3·38
	H_2O	1·0	AC	208; 260	4·20; 3·91
	$CHCl_2{\cdot}CO_2H$ [b]	−0·9	C	297; *309*; 333	3·44; *3·36*; 3·36
	H_2O–H_2SO_4	−4·3	C	238; *284*; *299*; *309*; 333	4·40; *3·51*; *3·30*; *3·22*; 3·10
	H_2SO_4	−9·4	DC	252; 307; *314*; 363	4·54; 3·57; *3·55*; 3·10
4-Methylquinazoline	H_2O	7·0	N	223; 270; 305; 314	4·62; 3·45; 3·45; 3·41
	H_2O	0·3	C	234; 270; 279; 323	4·52; 3·47; 3·45; 3·34
	$CHCl_2{\cdot}CO_2H$ [b]	−0·9	C	298; 328	3·41; 3·44
	H_2SO_4	−9·4	DC	253; 305; *313*; 353	4·50; 3·55; *3·54*; 3·20
Pyrimidine	H_2O–H_2SO_4	−3·6	C [c, d]	*238* + 242 + *248*	*3·57* + 3·64 + *3·52*
	H_2O–H_2SO_4	−8·9	DC [d, e]	*242* + 246 + *252*	*3·73* + 3·77 + *3·62*
2-Methylquinazoline	H_2O	7·0	N	223; 268; 310; *320*	4·60; 3·41; 3·40; *3·31*
	H_2O	1·0	AC	207; 258	4·28; 3·96
2,4-Dimethylquinazoline	H_2O	7·0	N	226; 266; 309; *318*	4·67; 3·45; 3·49; *3·45*
	H_2O	1·0	C	236; 265; *277*; *302*; 322	4·46; 3·49; *3·45*; *3·29*; 3·29
4-Chloroquinazoline [f]	H_2O	5·5	N	228; 274; 309; *317*	4·62; 3·41; 3·50; *3·47*
	H_2O–HCl	−1·9	C [g]	242; 310	4·62; 3·75
4-Cyanoquinazoline [f]	H_2O	7·0	N	237; 324	4·49; 3·58
	H_2O–HCl	−1·9	C	246; 328	4·39; 3·78
4-(α-Cyano-α-ethoxycarbonylmethyl)-quinazoline	H_2O–EtOH (1 : 1)	7·0	N	209; 234 + 239 285 + *292*; 348; 363 + 382	4·54; 3·88 + 3·89 3·97 + *3·95*; 4·17; 4·39 + 4·36
	H_2O–HCl	−1·9	C	216; 238 + 244; 282; *343*; 358 + 376	4·33; 3·84 + 3·86; 4·26; *4·23*; 4·40 + 4·36
3,4-Dihydroquinazoline	H_2O	11·5	N	*217* + 221 + *227*; 291	*4·07* + 4·09 + *3·97*; 3·76
	H_2O	7·0	C	212 + 217 + *225*; 280	4·26 + 4·25 + *4·01*; 3·69
3,4-Dihydro-3-methylquinazoline	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
1,4-Dihydro-1-methylquinazoline	H_2O	11·5	N	? [h] + *220* + *225*; 289	? + *4·04* + *3·97*; 3·64
	H_2O	7·0	C	213 + 218 + *224*; 282 + 292	4·20 + 4·19 + *3·99*; 3·61 + 3·60
3,4-Dihydro-2-methylquinazoline	H_2O	12·5	N	*217* + 220 + *226*; 290	*4·12* + 4·13 + *4·02*; 3·82
	H_2O	7·0	C	211 + 215 + *221*; 276	4·30 + 4·31 + *4·08*; 3·74
3,4-Dihydroquinazolinium-4-sulphonate (VI)	H_2O	4·0	"N" [i]	222 + *229*; 282	4·17 + *3·93*; 3·66
1,2,3,4-Tetrahydroquinazoline	H_2O	10	N	239; 287	3·80; 3·19
		5	C	237; 287	3·82; 3·16
Phthalazine	H_2O	7	N	218; 261; 292; *297*; 305	4·83; 3·53; 3·18; *3·11*; 3·11
	H_2O	0	C	229; 273; 314	4·61; 3·35; 3·45
1-Methylphthalazine	H_2O	7	N	219; 262; *270*; 292; 305	4·70; 3·59; *3·57*; 3·21; 3·18
	H_2O	2	C	230; 271; *304*; 312	4·62; 3·40; *3·40*; 3·46

[a] N = neutral molecule; C = (normal) cation; AC = abnormal cation; DC = dication. [b] Transmission limit, 290 mμ. [c] This spectrum is practically unchanged between H_0 −1·12 and H_0 −4·5. [d] Near H_0 −6·3 pyrimidine shows only a broad uninflected band ($\lambda_{max.}$ ~243·5 mμ). [e] The wavelength of this spectrum is only slightly changed between H_0 = −8·5 ($\lambda_{max.}$ 246 mμ) and −9·35 ($\lambda_{max.}$ 245·5 mμ). [f] Estimated basic pK_a value between 0 and −0·5. [g] Determined within about 2 seconds after acidification (by mixing in a specially designed apparatus utilising a rapid-flow technique; see acknowledgments). [h] Peak below 210 mμ. [i] Zwitterion (VI).

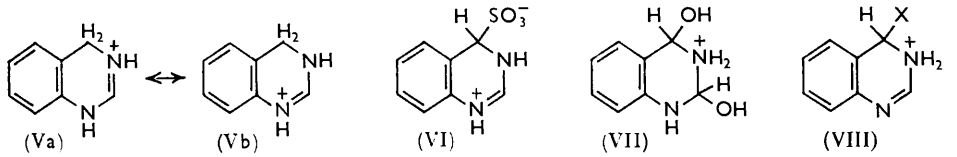
but the 2,4-dimethyl derivative has not, in agreement with the view that abnormal cation formation entails attack on an unhindered 4-position.

Spectral Shifts.—When substance (II; X = H, Me, Cl, or CN) forms the normal monocation, there is a small shift of the whole electronic spectrum to longer wavelengths; formation of the dication (when X = H or Me) results in a bigger shift, in the same direction.

As regards substituent effects (relative to that of hydrogen), the spectrum of neutral quinazoline is displaced to longer wavelengths by 4-substituents in the order (H <)Me < Cl < CN. However, 4-substituents in the normal monocation (III) displace the long-wavelength band (near 330 mμ) to *shorter* wavelengths, which is very remarkable; the displacements increase in the order (H <)CN < Me < Cl. The long-wavelength band in the dication is similarly moved to shorter wavelengths when $H_{(4)}$ is replaced by Me.

The group $-CH(CN)\cdot CO_2Et$ in the 4-position of quinazoline greatly modifies, and complicates, the spectrum. There is complete correspondence between the bands observed for the cation and those appearing for the neutral molecule, but cation formation does not affect the whole spectrum uniformly.

Spectral Comparison between the Abnormal Monocation of Quinazoline and Substances related to Reduced Quinazolines.—That the formation of the abnormal cation of quinazoline does not entail ring fission is indicated by: (*a*) the very rapid reversibility of abnormal cation formation; (*b*) the electronic spectrum of the abnormal cation, which is not what would be expected for an *ortho*-substituted aniline or an *ortho*-substituted benzaldehyde (either of which should show an absorption maximum above 290 mμ); (*c*) the ready oxidation of quinazoline in 2N-sulphuric acid (in which ~98% is present as the abnormal cation), by hydrogen peroxide or chromic acid at 20°, giving a high yield of 4-hydroxyquinazoline (cf. a similar demonstration of covalent hydration in 2- and 6-hydroxypteridine [15]).



If, on the other hand, the structure of the abnormal cation is given by (IV), its spectrum should be similar to that of the cation (V) of 3,4-dihydroquinazoline; the replacement of a hydrogen atom in the saturated portion of (V) by hydroxyl should only produce small band shifts. Actually, there is a general resemblance between the two spectra (see Table 3); however, the band of the cation (V) at 280 mμ appears to be displaced to 260 mμ in the abnormal quinazolinium ion, *i.e.*, the shift is too large to be wholly in accord with structure (IV) for the ion.

In order to ascertain the effect of substituents on the spectrum of the cation (V), we examined the 1-, 2-, and 3-methyl derivatives of the cation (V), also the product (VI) of nucleophilic addition of sulphurous acid to quinazoline. The spectra of all these resemble that of the cation (V) closely, the above-mentioned band maximum being located near 282 mμ. Thus a 4-hydroxyl group in the cation (V) is unlikely to produce a hypsochromic shift of 20 mμ, and this throws further doubt on the proposed structure (IV) for the abnormal cation.

It is also conceivable that the abnormal cation is the dihydrate (VII), formed by addition of two molecules of water to the normal ion (III; X = H). However, the cation of 1,2,3,4-tetrahydroquinazoline has a spectrum closely resembling that of aniline (as expected), and quite different from that of the abnormal quinazoline ion, for which structure (VII) is therefore ruled out.

Regarding other possibilities, the abnormal ion could have structure (VIII; X = OH), but this seems very unlikely because, for the cations of 3,4-dihydroquinazoline and its 3-methyl and 4-sulphonate derivatives, the tautomers of type (V) and (VI) are energetically preferred to (VIII). Alternatively, the relative contributions of the canonical forms (a) and (b) could be different for the ion (IV) on the one hand, and the ion (V) and the *N*-methyl and 4-sulphonate derivatives on the other; but this, too, is somewhat unlikely.

[15] Brown and Mason, *J.*, 1956, **3443**.

However, there is no conclusive evidence in this regard, and the precise structure of the abnormal quinazoline cation is still unsettled; it is hoped that further work will shed more light on it.

The Structure of " 3,4 "-Dihydroquinazoline.—This is not settled unambigously from the syntheses because prototropic rearrangement, giving the 1,4-dihydro-tautomer, could have occurred. Also the similarity in base strength between 1,4-dihydro-1-methyl- and 3,4-dihydro-3-methyl-quinazoline suggests that in aqueous solution " 3,4 "-dihydroquinazoline could be appreciably tautomerized to the 1,4-dihydro-isomer. However, the electronic spectrum of the substance, especially in the short-wavelength region (peak at 221 mμ), resembles that of 3,4-dihydro-3-methylquinazoline (double peak at 225 + 231 mμ) more closely than that of 1,4-dihydro-1-methylquinazoline (peak not observed because below 210 mμ).* It is therefore concluded that this substance is probably largely 3,4- rather than 1,4-dihydroquinazoline.

The Cation of Phthalazine.—The only other instance of a diazanaphthalene with a considerably higher base strength than that of its parent diazine is phthalazine (2,3-diazanaphthalene), its pK_a value being 3·5 as compared with 2·3 for pyridazine. This could simply be due to the high single-bond character of the N–N bond in phthalazine and it is to be noted that, while a stronger base than cinnoline (pK_a 2·3), phthalazine is still a much weaker base than isoquinoline (pK_a 5·4). The alternative possibility that phthalazine might form an abnormal cation, like quinazoline, is ruled out by the electronic spectrum of the phthalazine cation which is now shown to be normal and similar to that of 1-methylphthalazine (see Table 3).

Experimental

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

Syntheses of Compounds.—Quinazoline [16] and its 2-methyl-,[17] 4-methyl-,[18] 2,4-dimethyl-,[19] 4-(α-cyano-α-ethoxycarbonylmethyl)-,[14] 4-chloro-,[20] 3,4-dihydro-,[17] 3,4-dihydro-3-methyl-,[11] 1,4-dihydro-1-methyl-,[21] 3,4-dihydro-2-methyl-,[21] and 1,2,3,4-tetrahydro-derivative,[22] phthalazine,[23] and 1-methylphthalazine [24] were prepared as described in the literature, examined chromatographically, and purified for analysis.

Quinazoline hydrochloride. Dry hydrogen chloride was bubbled through a solution of quinazoline (500 mg.) in anhydrous ether (30 ml.) until separation of the white needles was complete. The apparatus was flushed with dry nitrogen and filtration carried out in a dry box. The anhydrous salt was heated at 100° for 15 min. to remove excess of hydrogen chloride. This product readily absorbed atmospheric moisture, almost liquefying, then resolidifying, to give a non-hygroscopic salt (71%), m. p. 127—128°, which contained the elements of water (Found: C, 52·2; H, 4·9; Cl, 19·3. $C_8H_9ClN_2O$ requires C, 52·05; H, 4·9; Cl, 19·2%). It was not dehydrated at 25°/15 mm. (over KOH) in 4 days, but lost 58% of its water at 60°/15 mm. (over P_2O_5) in 16 hr.

3,4-Dihydroquinazolinium-4-sulphonate. A 10% solution of sodium sulphite in water was added to aqueous quinazoline (650 mg. in 1 ml. of water) and the whole was left at 20—25° for 1 hr. The white solid (A) was filtered off, triturated with water, then with a little ethanol, and dried (882 mg., 76%). It had m. p. 181—182° (effervescence) and contained sodium. Recrystallisation from boiling water gave white needles (B) which sublimed at 210—212° [lit.,[25]

* Whatever the structure of the substance, a bathochromic shift is expected for the corresponding *N*-methyl derivative.

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195—199° (decomp.)] (Found: C, 45·2; H, 4·1; N, 13·1; S, 15·3; Ash, 0. Calc. for $C_8H_6N_2O_3S$: C, 45·3; H, 3·8; N, 13·2; S, 15·1%). Materials (A) and (B) have identical R_F values at pH 5.

4-Cyanoquinazoline. This was obtained in 2% yield by fusing 4-chloroquinazoline with cuprous cyanide, although it had been claimed [25] that no cyanoquinazoline could be obtained by this method. It was also prepared in the same overall yield, by converting 4-chloroquinazoline into trimethyl-4-quinazolinylammonium chloride and fusing the latter with sodium cyanide in acetamide according to the general method of Klötzer.[26] 4-Cyanoquinazoline had m. p. 115—116° (lit.,[25] 118—119°) (Found: C, 69·9; H, 3·5; N, 26·8. Calc. for $C_9H_5N_3$: C, 69·7; H, 3·25; N, 27·1%). These specimens proved to be identical with the cyanoquinazoline prepared recently, in better yield, by Higashino [27] by oxidation of the quinazoline–hydrogen cyanide adduct.

4-Benzyloxycarbonylmethylquinazoline. 4-Chloroquinazoline (3·5 g., 1 mol.) in dry benzene (75 ml.) was added slowly to a stirred suspension of benzyl sodioacetoacetate [prepared from 480 mg. of sodium and 3·84 g. of benzyl acetoacetate [28] in ether; the solvent was then removed *in vacuo*] in dry benzene (75 ml.). The mixture was stirred and refluxed for 28 hr. The solvent was distilled off and the residue dissolved in the minimum volume of water and acidified to pH 2. The precipitated *ester* (3·1 g., 52%) recrystallised from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 139—140° (Found: C, 73·6; H, 5·1; N, 9·9. $C_{17}H_{14}N_2O_2$ requires C, 73·4; H, 5·1; N, 10·1%).

4-(α-Cyano-α-benzyloxycarbonylmethyl)quinazoline. To a stirred solution of 4-chloroquinazoline (6·6 g., 1 mol.) in dry benzene (70 ml.) was added a suspension of benzyl sodiocyanoacetate (from 925 mg. of sodium and 7·0 g. of benzyl cyanoacetate [29]) in dry benzene (125 ml.). The mixture was refluxed for 25 hr. and worked up as above. The *ester* (5·4 g., 44%) crystallised from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 150—151° (Found: C, 71·35; H, 4·4; N, 13·8. $C_{18}H_{13}N_3O_2$ requires C, 71·3; H, 4·3; N, 13·9%).

Oxidation of the Abnormal Quinazoline Cation.—Hydrogen peroxide (100-vol.; 2·3 ml., 2 equiv.) was added to a solution of quinazoline (1·30 g., 1 mol.) in 2N-sulphuric acid (10 ml.). After 2 days at room temperature the solution was made alkaline (pH ~10) and then acidified to pH ~4 with glacial acetic acid. 4-Hydroxyquinazoline gradually separated; recrystallised from ethanol–light petroleum (b. p. 40—60°), it (1·21 g., 83%) had m. p. alone or mixed with 4-hydroxyquinazoline 217—218°. Paper chromatography in 3% aqueous ammonium chloride and in butan-1-ol–5N-acetic acid (3 : 1) showed that the two substances were identical and that no quinazoline was left in the mother-liquors. Oxidation of quinazoline in 2N-sulphuric acid with chromic oxide (4 equiv.) gave 4-hydroxyquinazoline which was isolated in 95% yield.

Ionization Constants.—In the range pK_a 1—12·5 these were measured by the potentiometric method.[30] Second basic ionization constants were determined spectrophotometrically.

Spectra.—Infrared spectra were taken with a Perkin–Elmer 21 double-beam spectrophotometer, ultraviolet spectra with a Perkin–Elmer Spectracord model 4000-A double-beam spectrophotometer, and the maxima checked with a Hilger Uvispek Mark V manual instrument.

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