

810. *Studies of the Amino-isoquinolines, -cinnolines, and -quinazolines.*(A) *The Basic Strengths and Ultraviolet Absorption Spectra.*

By A. R. OSBORN and K. SCHOFIELD.

(B) *The Infrared Spectra.*

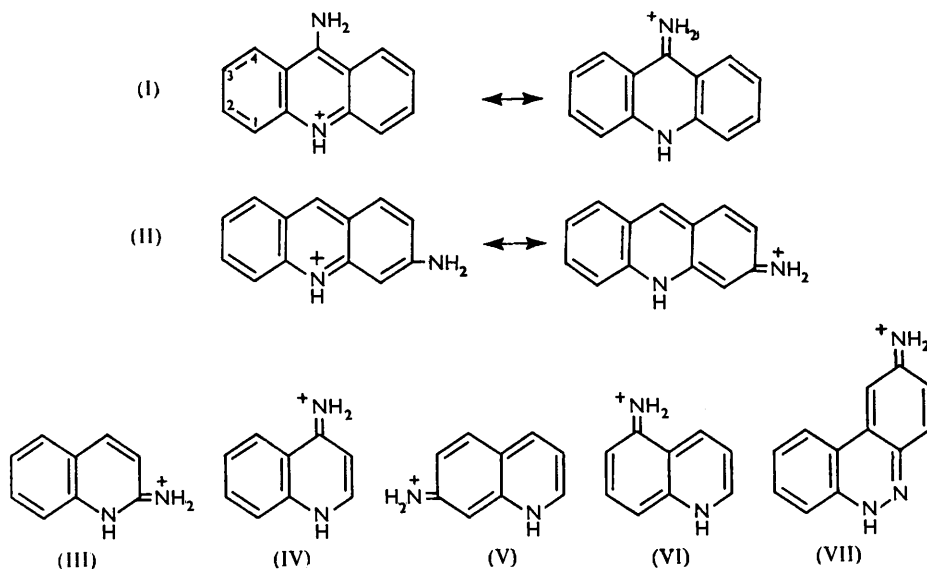
By L. N. SHORT.

The basic strengths and ultraviolet absorption characteristics of the amino-isoquinolines, -cinnolines, and -quinazolines have been determined. The ionisation constants in the first two series can, with minor qualifications, be discussed satisfactorily in terms of the resonance theory, but difficulties arise in the quinazoline group.

The connection between N-H group frequencies and force constants and interaction of the amino-group with the aromatic ring in the above compounds is discussed. Evidence of lack of interaction between N₍₁₎ and a 5-amino-group is noted and used to qualify the idea of "additional ionic resonance."

THE ultraviolet extinction curves of heteroaromatic amines such as the aminoacridines¹ and aminoquinolines,² like those of acridine and quinoline, show in general a marked bathochromic shift when the base is converted into its monocation. This behaviour contrasts with that of typical aromatic amines³ and proves that in forming monocations the heteroaromatic amines accept the proton on the ring-nitrogen atom.

This information has made possible the rationalisation⁴ of the observed basic strengths of a large number of heteroaromatic amines. Thus, the aminoacridines fall into three



groups: those (3- and 4-aminoacridine) of roughly the same basic strength as acridine, those (2- and 5-aminoacridine) considerably stronger than acridine, and an isomer (1-aminoacridine) distinctly weaker than the parent. Base-strengthening is attributed to an

¹ Craig and Short, *J.*, 1945, 419.

² Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397.

³ Harberts, Heertjes, van der Hulst, and Waterman, *Bull. Soc. chim. France*, 1936, **3**, 643; de Borst, Heertjes, van der Hulst, and Waterman, *ibid.*, 1938, **70**, 3397.

⁴ Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

"additional ionic resonance effect" (see I and II) (a similar situation, formally possible in 4-aminoacridine, would involve less stable *o*-quinonoid forms: but see Short⁵ and Discussion below). Infrared studies⁵ suggest that base-weakening in the 1-isomer is due to intramolecular hydrogen bonding.

Gore and Phillips,⁶ seeking regularities in ΔpK_a (the difference between pK_a for the amine and for the parent base), classified the possible ionic structures as *ortho*-quinonoid, e.g., (III), *para*-quinonoid (IV), *ortho-para*-quinonoid (V), *ortho-ortho*-quinonoid (VI), and *para-para*-quinonoid [their only available example being "2-aminobenzocinnolinium," the benzocinnolinylideneammonium compound (VII)]. They concluded "that the ΔpK_a associated with any particular quinonoidal structure is reasonably constant for several heterocyclic nuclei," and on this premise predicted pK_a values for the three "*para-para*"-types: 6-amino-*iso*quinoline, -phthalazine, and -phenanthridine.

Our present aim was further to test the various ideas mentioned above by examining the amino-*iso*quinolines, and then to investigate the use of pK_a and spectroscopic studies in throwing light on the problem of the basic centre in diazines, especially the amino-cinnolines and -quinazolines.

DISCUSSION

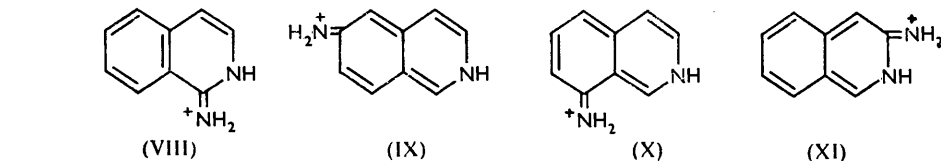
(A) Basic strengths and ultraviolet absorption spectra.

Results are summarised in Tables 1 and 2.

(a) *iso*Quinolines.—The assignment by Lewis and Calvin⁷ of the three main absorption bands in the spectrum of naphthalene (310, 280—260, 220 $m\mu$) to electronic transitions polarised parallel to (x), parallel to (y), and parallel to (z) respectively, received support from Kiss's work⁸ on the effect of substituents upon these bands. Tombacz⁹ related the three main bands in the *iso*quinoline spectrum to those of naphthalene, and indicated that the bathochromic displacement of the long-wavelength band observed in *iso*quinoline (but not in quinoline) was due to the position of the nitrogen atom which produced an effect similar to β -substitution in naphthalene.

The spectra of the amino-*iso*quinolines (neutral molecules) show shifts relative to that of *iso*quinoline which are roughly in accord with these views. Thus, the 3- and the 7-amino-groups produce considerable bathochromic shifts in the long- and short-wavelength bands, but only small changes in the medium-wavelength band. In contrast, substitution at C₍₁₎, C₍₄₎, or C₍₅₎ causes considerable bathochromic shifts in the middle band, small bathochromic shifts in the long-wavelength band, and hypsochromic shifts in the short-wavelength band.

8-Amino-*iso*quinoline is partly anomalous, for whilst it shows the expected big bathochromic shift in the middle band, and a hypsochromic effect is found with the short-wavelength band, yet the long-wavelength band also shows a large bathochromic shift. 6-Amino-*iso*quinoline is also anomalous: here all three bands suffer bathochromic shifts, considerable



only with the medium-wavelength one; further, a decrease in intensity is noticed with the short-wavelength band, and an increase with the middle band.

In solutions sufficiently acid to convert them into monocations all the amino-*iso*quinolines show bathochromic shifts of their ultraviolet extinction curves. Following Craig and

⁵ Short, *J.*, 1952, 4584.

⁶ Gore and Phillips, *Nature*, 1949, **163**, 690.

⁷ Calvin and Lewis, *Chem. Rev.*, 1939, **25**, 273.

⁸ Kiss, *Compt. rend.*, 1949, **229**, 762.

⁹ Tombacz, *Magyar Kém. Folyóirat*, 1950, **56**, 175.

Short¹ we take this to indicate that the amines accept the first protons on their ring-nitrogen atoms.

This conclusion, together with Albert's idea of additional ionic resonance, makes it possible to rationalise the ΔpK_a values observed for the aminoisoquinolines (Table 2). Thus amines with monocations from which additional ionic resonance is absent (4-, 5-, and 7-aminoisoquinolinium) give values for ΔpK_a smaller than 1 unit. In contrast, 1-, 6-, and 8-aminoisoquinoline [cations (VIII), (IX), and (X)] give ΔpK_a values considerably greater than 1 unit. 6-Aminoisoquinoline thus parallels 7-aminoquinoline.⁴ The case of 3-aminoisoquinoline is particularly interesting. If the evidence of the ultraviolet absorption spectra is accepted as indicating that this amine receives its first proton on the ring-nitrogen atom, then the *ortho*-quinonoid ionic resonance form (XI) clearly does not increase the stability of the cation relative to that of the free base. Presumably the destruction of conjugation between the nucleus and the amino-group which would result from cationisation of the latter is even less favourable energetically. Infrared examination (see below) shows the amine itself to be normal.

Apart from the case of 8-aminoquinoline, where intramolecular hydrogen bonding is important, negative values of ΔpK_a have hitherto been observed only with 4- and 7-aminopteridine,¹⁰ derivatives of a heterocyclic nucleus with a much higher N : C ratio than has isoquinoline. Further reference will be made to this point below.

(b) *Cinnolines*.—The absorption spectrum of cinnoline in cyclohexane¹¹ differs from that of, say, isoquinoline¹² in showing a further low-intensity band ($\log \epsilon_{\max}$, 2.42) at 390 m μ . We discuss the effect of substituents on this band in an accompanying paper but it may be noticed here that its disappearance from the spectrum of cinnoline in water or acid (Table 1) is in keeping with its origin in an $n \rightarrow \pi$ transition.¹³

In the aminocinnolines the conjugation of the substituent with the heterocyclic nucleus generally causes such considerable modification of the absorption spectrum that even the degree of regularity observed with the isoquinolines is not discernible here. The band due to the $n \rightarrow \pi$ transition is of course obscured, and the spectra of the neutral molecules in aqueous solutions all show large bathochromic shifts of the first long-wavelength band, as compared with cinnoline. The magnitude of the shift decreases in the order 8- > 7-, 5-, 3- > 6- > 4-, which, except for the position of the 8-isomer, is roughly that observed with the isoquinolines. The bathochromic shifts of the middle band decrease in the order 5-, 8- > 4- > 3-, with 7-aminocinnoline possibly showing a slight hypsochromic effect. The order is that expected if the band is connected with polarisations along the short axis of the molecule. As in the isoquinoline series, the 6-isomer is anomalous. Conversion into the monocations produces further bathochromy in the long-wavelength band in all cases (solutions containing the monocations of 5- or 8-aminocinnoline are violet-red, solutions containing those of 6- and 7-aminocinnoline are yellow). Again, this is taken to indicate that in the monocations the protons are attached to ring-nitrogen atoms.

In attempting to use this evidence from absorption spectra, in conjunction with the observed values of ΔpK_a (Table 2), to decide which ring-nitrogen atom in an aminocinnoline is the basic centre we should perhaps state that we realise that an equilibrium must always exist between the two possible cations, one having the proton at N₍₁₎, the other at N₍₂₎. By "basic centre," we mean the nitrogen atom which acts as such in the predominating cation. It is interesting to notice that 6-aminoquinolinium, from which additional ionic resonance is absent, shows an elevation in pK_a (compared with quinolinium) smaller by about 1 unit than that observed with 7-aminoquinolinium, in which additional ionic resonance first becomes important. A similar or larger difference exists between the values for 7-aminoisoquinolinium (no additional ionic resonance) and 6-aminoisoquinolinium, and between 5-aminocinnolinium (for which the resonance theory would postulate the unfavourable *ortho-ortho*-quinonoid form) and 8-aminocinnolinium, the member of the series

¹⁰ Albert, Brown, and Cheeseman, *J.*, 1951, 474; Albert, Brown, and Wood, *J.*, 1954, 3832.

¹¹ Hearn, Morton, and Simpson, *J.*, 1951, 3318.

¹² Friedel and Orchin, "Ultra-violet Spectra of Aromatic Compounds," Wiley and Sons, New York, London, 1951.

¹³ (a) Mason, "Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.*, No. 3, 1955, p. 139; (b) Badger and Walker, *J.*, 1956, 122.

TABLE I.

Substance	Ionisation (H ₂ O; 20°)	pK _a	Concn.	Spectroscopy (in water). λ _{max.} (mμ) (log ₁₀ ε _{max.})	pH
isoQuinoline	5.40 ± 0.01 ^a	316	319(3.47) + 306(3.38); 332(3.63);	278 ^b (3.41) + 267(3.57); 216(4.81) 273(3.31) + 266(3.30); 227(4.66)	9.22 2.0
isoQuinoline methochloride	—	—	336(3.62) + 330 ^b (3.61);	287 ^c (3.12) + 277(3.41) + 269(3.40); 231(4.70)	ca. 7.0
3-Aminoisoquinoline	5.05 ± 0.01	400	353(3.42); 390(3.62);	288 ^b (3.58) + 278(3.73) + 269(3.67); 231(4.74) 296(3.21) + 285(3.52) + 277(3.53); 237(4.76)	9.21 2.54
4-	6.28 ± 0.01	400	332(3.74); 354(3.94);	310 ^b (3.64); 316 ^b (3.55);	9.21 3.28
5-	5.59 ± 0.01	400	332(3.70); 378(3.53) + 340(3.53);	238(4.22); 259(4.18);	9.21 3.07
6-	7.17 ± 0.04	1000	326 ^b (3.47); 352(4.03) + 337(4.01);	304(3.84) + 296(3.83); 266(4.32);	9.21 3.22
7-	6.20 ± 0.02	1000	349(3.40); 385(3.35);	273(3.90); 289(3.82);	9.21 3.22
8-	6.06 ± 0.01	400	345(3.68) + 307 ^c (3.51); 224(4.36); 417(3.66) + 325(3.41);	207(4.61) 209(4.54)	9.21 3.05
Cinnoline	2.29 ± 0.03 ^d	225	321(3.44); 353(3.40);	290(3.38) + 283(3.38); 305(3.32) + 294(3.31);	7.0 0.3
Cinnoline methochloride	—	—	357(3.43); 308(3.46) + 296(3.47); 241(4.64)	231(4.56) 254(4.58); 218(4.14)	ca. 7.0
4-Methylcinnoline	—	—	330 ^c (3.47) + 320(3.54) + 308 ^c (3.42); 292(3.52) + 283(3.50); 225(4.68) 349(3.52); 306(3.44) + 300 ^b (3.40); 235(4.58)	237(4.61); 211(4.08) 238(4.18); 212(4.5) 236(4.16); 211(4.45)	7.0 0.3
4-Methylcinnoline methochloride	—	—	354(3.57); 308(3.49) + 297(3.49); 239(4.63)	237(4.59)	ca. 7.0
3-Aminocinnoline ^e	3.70 ± 0.03	1000	374(3.44); 405(3.47);	304 ^c (2.93) + 283 ^c (3.29); 234(4.61); 211(4.30) 327(2.71) + 314(2.87);	7.0 2.02
4-	6.85 ± 0.04	400	338(4.03) + 310 ^c (3.71); 255 ^c (3.77); 255(3.88); 360 ^b (4.03) + 345(4.12) + 295(3.24); 262(3.83);	238(4.18); 212(4.5) 236(4.16); 211(4.45)	9.21 4.35
5-	2.70 ± 0.06	1000	382(3.34); 490(3.00);	254(4.36) + 235 ^c (4.14) 280(4.00) 236(4.25)	7.0 0.3
6-	5.04 ± 0.04	1000	362(3.74); 416(4.02);	256(4.50); 206(4.36) 276(4.34); 220(4.36)	9.22 2.02
7-	4.85 ± 0.01	400	385(3.43); 446(3.07);	249(4.60); 206(4.43) 268(4.61); 210(4.36)	9.22 2.02
8-	3.68 ± 0.01	400	395(3.40); 520(3.48);	251(4.41) 260(4.22) + 245 ^b (4.18)	9.22 0.3
Quinazoline ^f	3.51 ± 0.01	277	306(3.38); 259(3.94);	222(4.58) 207(4.27)	7.0 1.0
Quinazoline methochloride	—	—	272(3.41);	207(4.27)	0.3

2-Aminoquinazoline ^a	4.82 ± 0.03	1000	352(3.50); 348(3.49)	339 ^b (3.45); 259 ^c (3.75); 284(3.72)	246 ^c (4.32) + 233(4.57) 245(4.26) + 229(4.41)	9.20 2.02
4- "	5.85 ± 0.06	1000	323(3.65); 324(3.87)	311(3.98) + 303 ^c (3.87); 284(3.62)	278 ^b (3.81); 228 ^b (4.18) + 214 ^c (4.38) + 206(4.52)	9.21 2.87
5- "	3.87 ± 0.01	1000	372(3.45); 462(2.72)	305(3.40); 260 ^b (4.03) + 245(4.09)	277(3.70); 207(4.31)	9.20 2.02
6- "	3.29 ± 0.02	1000	360(3.42); 310 ^c (2.70)	260(3.98); 208(4.26)	242(4.54)	7.0 1.7
7- "	4.60 ± 0.03	1000	345(3.80); 373(4.06)	328(3.71); 270(3.32); 231(4.21)	293(3.73); 251(4.48); 238 ^b (4.32); 204(4.37)	9.20 2.02
8- "	2.81 ± 0.03	1000	338(3.46); 415(2.52)	310(3.23); 265(3.90); 215(4.28)	238(4.42)	7.0 1.07
6-Chloroquinazoline	—	—	325(3.32); 265(3.90)	227(4.68)	263(3.50)	7.0 0.3
5-Aminoquinaxaline	—	—	380(3.14); 330(3.20)	322(3.21); 261(4.39); 230(3.76)	207(4.04)	7.0 0.0
6- "	—	—	372(3.74); 286 ^c (3.40); 358(3.82)	254(4.42); 207(4.46)	214(4.33)	7.0 0.3
Phenanthridine	4.52 ± 0.01 [*]	—	346(3.24); 366(3.45)	330(3.26); 296 ^c (3.75) + 290(3.79); 268 ^c (3.99); 247(4.62); 218(4.12)	247(4.66); 216 ^c (4.36) + 209(4.40)	9.21 2.01
6-Aminophenanthridine	6.88 ± 0.02 [†]	—	365 ^b (3.56) + 357(3.57); 322 ^b (3.86) + 316(3.89)	247(4.13); 207(4.38)	207(4.38)	0.0 9.22
Quinoline methochloride	—	—	321(4.13); 278 ^c (3.94); 316(3.89)	251(4.63) + 223 ^c (4.27)	237(4.56)	ca. 7.0

^a Kolthoff (*Biochem. Z.*, 1925, **102**, 289) gave 5.14. Albert (*Chem. Soc. Special Publ.* No. 3, 1955, p. 138) gave 5.46. ^b Shoulder. ^c Inflection. ^d Albert *et al.*⁴ gave 2.70. ^e Alford and Schofield (*J.*, 1953, 1811) gave 3.63. ^f Albert *et al.*⁴ gave 6.84. ^g Albert *et al.*⁴ gave 3.51. ^h Albert *et al.*⁴ gave 4.43. A new determination by Professor Albert (personal communication) gave 4.78. ⁱ Albert *et al.*⁴ gave 5.73. ^j Elderfield *et al.* (*J. Org. Chem.*, 1947, **12**, 406) gave 3.2 and 2.4 (in 50% ethanol) for 6- and 8-aminoquinazoline respectively. ^k Isobestic point 301 m μ , log₁₀ ϵ 3.71; Albert *et al.*⁴ gave pK_a 3.30 in aqueous ethanol. [†] Curves at pH 9.22, 7.52, 6.35, and 4.0 gave an isobestic point at 341 m μ , log₁₀ ϵ 3.89.

TABLE 2. ΔpK_a values.*

Aminoquinoline		Aminoisoquinoline		Aminocinnoline		Aminoquinazoline	
NH ₂	ΔpK_a	NH ₂	ΔpK_a	NH ₂	ΔpK_a	NH ₂	ΔpK_a
2-	2.40	1-	2.22	3-	1.41	2-	1.31
3-	0.01	3-	-0.35	4-	4.56	4-	2.34
4-	4.23	4-	0.88	5-	0.41	5-	0.06
5-	0.52	5-	0.19	6-	2.75	6-	-0.22
6-	0.69	6-	1.77	7-	2.56	7-	1.09
7-	1.71	7-	0.80	8-	1.39	8-	-0.70
8-	-0.95	6-Aminophenanthridine	1.66				
			2.36				

* The figures for aminoquinolines and 1-aminoisoquinoline are from Albert, Goldacre, and Phillips.⁴

least favoured by additional ionic resonance. It does not seem unreasonable, therefore, to suppose that in an amino-compound containing two ring-nitrogen atoms, even in unfavourable circumstances the nitrogen atom capable of taking part in additional ionic resonance would be the predominantly cation-forming one (a difference in pK_a of 1 unit producing 90% of the preferred species).

The ultraviolet extinction curve for cinnoline cation at pH 0.3 (Fig. 1) is very similar to that for "cinnoline methochloride" prepared from the methiodide as described in the Experimental section. The slight bathochromic and hypsochromic differences are very similar to those between *isoquinoline* cation at pH 2.0 and *isoquinoline* methochloride (Table 1), and both sets of curves are very different from those for quinolinium and *N*-methylquinolinium (Table 1). This situation is unexpected, for Atkinson and Taylor¹⁴

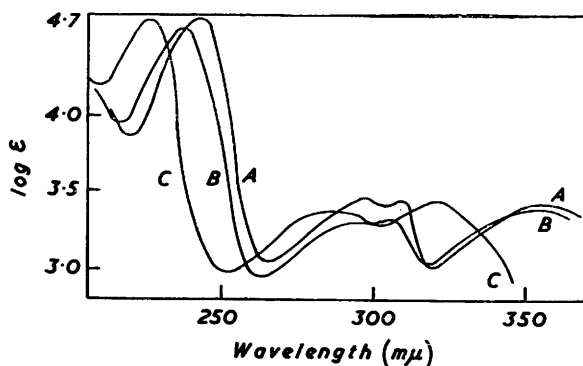
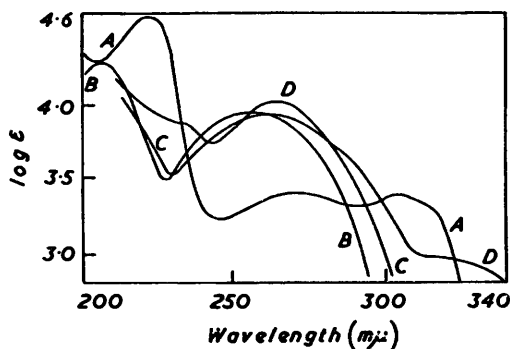


FIG. 1. A, Cinnoline methochloride; B, cinnoline cation (pH 0.3); C, cinnoline (pH 7).

FIG. 2. A, Quinazoline (pH 7); B, quinazoline cation (pH 1.0); C, quinazoline methochloride (pH 0.3); D, quinazoline methohydroxide (pH 7).



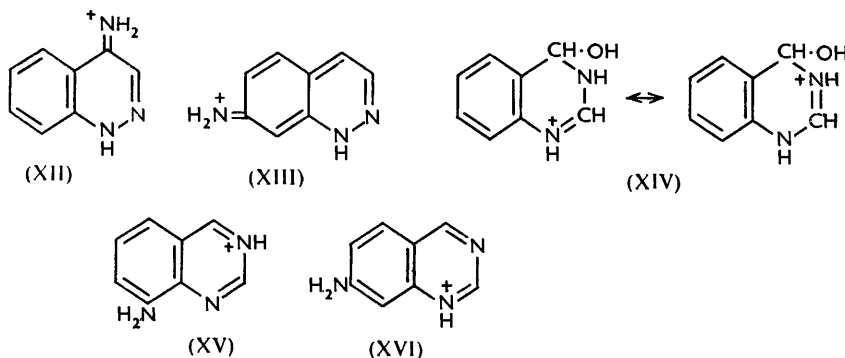
recently concluded from degradative studies that methyl iodide reacts with cinnoline at $N_{(1)}$. Nevertheless, without evidence of spectroscopic differences, if any, between unambiguously constituted $N_{(1)}$ - and $N_{(2)}$ -methylcinnolinium salts, the possibility remains that the extinction curve for cinnoline in acid is that of a mixture of cations.

With the aminocinnolines the situation is generally much clearer. Thus, for 4-aminocinnoline the large ΔpK_a value must indicate that $N_{(1)}$ is the basic centre,⁴ the cation (XII) being highly stabilised. The resonance theory would predict a low value of ΔpK_a for 5-aminocinnoline, the only cationic form which could possess additional ionic resonance being the unfavourable *ortho-ortho*-quinonoid one analogous to (VI). A low value of ΔpK_a is found, but there is evidence (see below) of peculiarity in the structure of the free base itself. $N_{(1)}$ is presumably the more favoured basic centre, but a clear-cut choice cannot be made. The monocation of 6-aminocinnoline is clearly much stabilised, and the ΔpK_a value is readily understood if $N_{(2)}$ is the basic centre, the case being analogous to that of 6-amino*isoquinoline* (cf. IX). Similarly, 7-aminocinnoline must be analogous to 7-aminoquinoline, with the basic centre now shifted to $N_{(1)}$ (XIII). 8-Aminocinnoline is

¹⁴ Atkinson and Taylor, *J.*, 1955, 4236.

interesting since in it the effect of intramolecular hydrogen-bonding (see below), which in 8-aminoquinoline results in a negative ΔpK_a , has been avoided by cation formation at $N_{(2)}$. This suggestion is strengthened by the similarity of the ultraviolet extinction curves of 8-aminocinnoline and 8-aminoisoquinoline, and by the way in which those curves change on cation formation. From earlier measurements which gave $\Delta pK_a \sim 1$ for 3-aminocinnoline, Alford and Schofield¹⁵ concluded that in this compound $N_{(2)}$ is the basic centre. The somewhat higher value of ΔpK_a now observed strengthens this conclusion. However, the compound contrasts strongly with 3-aminoisoquinoline. In the cations of both *ortho-ortho*-quinonoid forms are involved, and the differing values of ΔpK_a show the difficulty of attaching significance to the absolute value of this quantity (see below).

(c) *Quinazolines*.—The ultraviolet extinction curve of the neutral quinazoline molecule (Fig. 2) exhibits the three main bands characteristic of such bicyclic systems, and appears to be in no way abnormal. Surprisingly, however, the extinction curve of the cation shows marked hypsochromy, and above 200 $m\mu$ only two bands remain, both of high intensity. The more usual effect, observed with the cations of quinoline,¹⁰ isoquinoline, cinnoline, pteridine,¹⁰ acridine,¹⁶ and the diazines,¹⁷ is a slight bathochromic shift. (The extinction curve for pyridine is substantially unchanged on cationisation.) There is at present no evidence to suggest that the behaviour of quinazoline is due to any disruptive change in acid solution. If ring-opening were occurring, a slow movement to equilibrium might be evident on titration of quinazoline with acid. This is not observed. Nor is the possibility, mentioned to us by Professor A. Albert, that quinazoline exists in aqueous solution in a form having water added to the 3:4-double bond in agreement with the normal extinction curve of the neutral molecule, or with the tendency for the extinction curve of 3-methylquinazolinium (Fig. 2) to move, at higher pH values, away from the quinazoline spectrum. The alternative possibility that the quinazoline cation is in the same sense hydrated¹⁸ cannot at present be excluded, although the properties of *pseudo*-bases derived from quaternary heteroaromatic salts¹⁹ would make stability in acid solution a surprising attribute of such a cation were it not for the new possibilities of resonance stabilisation in such a structure (XIV). Nevertheless, Gabriel and Colman²⁰ observed that



3-methylquinazolinium iodide when recrystallised from methanol could not be freed from one molar equivalent of the latter without causing decomposition, and Schöpf and Oechler²¹ encountered similar difficulties in freeing 3-methyl- and 3-allyl-quinazolinium picrate from ethanol. For these reasons, and because the cationic spectrum of quinazoline points to a modification of the aromatic system, we shall assume as a working hypothesis that the quinazoline cation should be represented as the resonance-stabilised hydrated form (XIV).

¹⁵ Alford and Schofield, *J.*, 1953, 1811.

¹⁶ Albert, "The Acridines," Arnold, London, 1951.

¹⁷ Halverson and Hirt, *J. Chem. Phys.*, 1951, 19, 711.

¹⁸ Albert, see ref. 13a, p. 138.

¹⁹ Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 575.

²⁰ Gabriel and Colman, *Ber.*, 1904, 37, 3643.

²¹ Schöpf and Oechler, *Annalen*, 1936, 523, 1.

In the first place we have looked for other examples of this type of behaviour. Irving and Rossotti²² have recorded the hypsochromy produced in the spectrum of 8-hydroxyquinazoline by cationisation and we found similar changes for 6-chloroquinazoline and 6:7-benzoquinazoline. Dr. S. F. Mason (personal communication) found the same to be true of 2-methylquinazoline, but between 4-methylquinazoline and its cation (as also with 8-hydroxy-2:4-dimethylquinazoline²²) the more usual bathochromic relation exists. The extinction curve of "3-methylquinazolinium" (Fig. 2) resembles very closely that of quinazoline cation, showing the expected small bathochromic shift. In this case, as in the others quoted, we should, in terms of the working hypothesis, regard the cation as

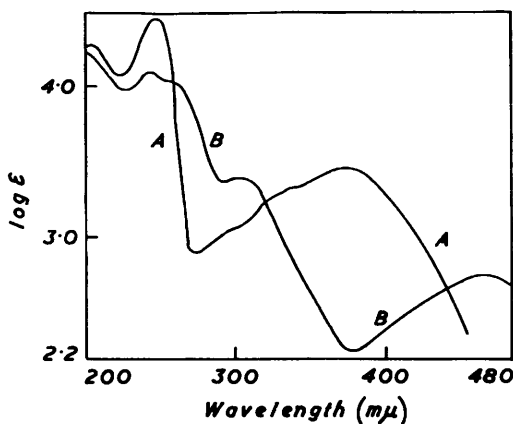
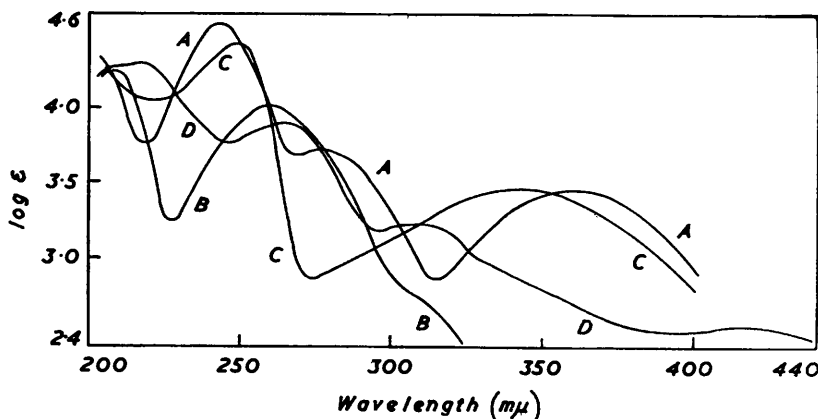


FIG. 3. A, 5-Aminoquinazoline (pH 9.20); B, 5-aminoquinazoline cation (pH 2.02).

FIG. 4. A, 6-Aminoquinazoline (pH 7); B, 6-aminoquinazoline cation (pH 1.7); C, 8-aminoquinazoline (pH 7); D, 8-aminoquinazoline cation (pH 1.07).



having a structure of the type (XIV) (Me instead of H at $N_{(3)}$), whilst 4-methyl- and 8-hydroxy-2:4-dimethyl-quinazoline presumably form cations without hydration. Only in such cases as these last two is it meaningful to enquire whether $N_{(1)}$ or $N_{(3)}$ is the basic centre.

The extinction curves of the neutral molecules of all the aminoquinazolines show in the long-wavelength bands the expected bathochromic shift relative to quinazoline, but are not amenable to further rationalisation. With regard to the behaviour of their extinction curves upon cationisation, the amines fall into three groups. Thus, with 4-aminoquinazoline the long-wavelength band is substantially stationary (though showing increased

²² Irving and Rossotti, *J.*, 1954, 2910.

intensity), whilst 2-aminoquinazoline shows only slight hypsochromy. The two compounds recall the behaviour of 4- and 2-aminoquinoline.² In contrast marked hypsochromy results from cationisation of 6-aminoquinazoline (Fig. 4) and, finally, cationisation of 5- (Fig. 3), 7-, and 8-aminoquinazoline (Fig. 4) produces the more familiar bathochromy, though intensity changes are not similar in all three cases. Pursuing the argument outlined above, and bearing in mind the similarity to the quinoline series, we assume further that 2- and 4-aminoquinazoline are compounds which are not hydrated on cationisation. The same appears to be true of the 5-, 7-, and 8-isomers, but 6-aminoquinazoline is presumably hydrated.

It is necessary to see how far these tentative deductions fall in with the evidence from ΔpK_a values (Table 2). Phillips (quoted by Albert²³) considered $N_{(3)}$ to be the basic centre in 4-aminoquinazoline since the amino-group produces "too little exaltation of basic strength over quinazoline to be γ to the basic nitrogen atom." It seems to us, in view of the quantity of evidence now available (see below also), that the idea of a ΔpK_a value's being fairly constant from series to series and associated with a particular quinonoid structure cannot be generally sustained. For this reason we cannot attach much weight to the argument, especially in the present instance, where the pK_a of the reference compound (quinazoline) may be that of a modified structure (XIV). In this connection it has been observed²⁴ that quinazoline appears to be a stronger base than expected, a fact which is understandable if the quinazoline cation does in fact possess a structure such as (XIV). It is known²⁵ that 3:4-dihydroquinazolines are much stronger bases than quinazolines, and reference to 4-aminoquinazoline to a structure such as (XIV) would give too small a value for ΔpK_a . It should also be noted that derivatives of 4-aminoquinazoline are known²⁶ to quaternise at $N_{(1)}$. The balance of evidence thus appears to favour $N_{(1)}$ as the basic centre in 4-aminoquinazoline.

Comments on the neutral molecules of 5- and 8-aminoquinazoline will be found below, but the difficulty of attaching real significance to ΔpK_a values in the quinazoline series makes impossible a choice of basic centres in these cases. The considerable negative ΔpK_a value found for 8-aminoquinazoline might arise from the lack of stabilisation in the cation (XV) and the elevated basic strength of quinazoline rather than from the adoption of $N_{(1)}$ as basic centre in the face of the chelation revealed by the infrared spectrum. However, with 7-aminoquinazoline the situation seems to be clear-cut. As stated, the spectroscopic evidence suggests that the cation is normal, and the relatively large ΔpK_a value can confidently be referred to the cation (XVI).

6-Aminoquinazoline is especially interesting. The ultraviolet extinction curve might have been expected to throw some light on the nature of the cation and so reveal the significance of the small negative value of ΔpK_a (in 50% ethanol 6-aminoquinazoline is not weaker than the parent²⁵). In fact, however, the marked hypsochromy produced by cationisation of 6-aminoquinazoline results in a curve very closely similar to that of the quinazoline *cation*! Such a change would ordinarily occur only if the amine had taken up two protons, one on a ring-nitrogen atom and one on the amino-group. This case requires further investigation.

It is clear from present and previously available data that the basic strength of hetero-aromatic amines can to a large degree be rationalised by resonance theory, qualified in some cases by the effects of chelation, and in others, where a *peri*-amino-group is in question (see below), by the recognition that abnormalities are to be referred to the amine molecule rather than its cation. Other considerations enter the argument in cases where a 1:3-diazine system is present, permitting modification of the aromatic system in the cation whilst still allowing a considerable degree of resonance stabilisation. Such a case is presented by the quinazolines discussed here, and by the pteridines.¹⁰ The observation that 4-methylquinazoline and 4-methylpteridine are weaker bases than their parents¹⁰ is understandable if, for reasons discussed above, the parents seem to be too strongly basic.

²³ Albert, *Quart. Rev.*, 1952, **6**, 202.

²⁴ Schofield, see ref. 13a, p. 137.

²⁵ Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405.

²⁶ Morley and Simpson, *J.*, 1948, 360.

We propose to study further the interaction of the 3,4-dihydroquinazoline in pursuit of support for the ionic structure.

In another diazine series, the quinazoline, the relative basic strengths of the parent and the amines⁴ are understandable, and cationization of quinoxaline¹⁰ produces the familiar small bathochromic shift in the absorption curve. We find (Table 1) that 6-aminoquinoxaline also follows the usual pattern, but that 5-aminoquinoxaline gives upon cationization a curve which shows marked hypsochromy and only two bands. In contrast to the case of 6-aminoquinazoline, however, this curve is closely similar to that of quinoxaline,¹⁰ and 5-aminoquinoxaline appears to be the first example of a heteroaromatic amine which takes up the first proton on its amino group.

(d) *para-para-Quinonoid systems*.—The quinonoid systems which belong to this category are 6-aminoisoquinoline, 6-aminoquinoline, and 6-aminoacridine (pK_a 7.17, 5.04, and 6.88; ΔpK_a 1.77, 2.75, and 2.36 respectively). The constancy of ΔpK_a among a group of miscellaneous derived amines, related only by the formal similarity of their cations,⁶ cannot be maintained with any accuracy. These figures show however that "2-aminobenzocinnoline" (pK_a 6.68, ΔpK_a 4.48)⁶ is a much stronger base than would be expected, and support Calderbank and Le Fèvre's observations²⁷ in throwing doubt on the structure of this compound.

B. Infrared spectra.

In a previous paper⁵ it was shown that the N-H bond-stretching frequencies of the monoamino-acridines and -quinolines could be interpreted in terms of the electromeric effect produced by the ring-nitrogen atom. In general, for those positions of the amino-group for which interaction with the ring-nitrogen atom is possible, the N-H group frequencies and corresponding force constants were found to be significantly higher and to parallel values calculated for the extra electron density on the ring-nitrogen atom. The N-H force constants in these groups of isomeric heteroaromatic amines indicate the extent to which the amino-group interacts with the aromatic ring and increases the electron density at the ring-nitrogen atom. The N-H bond-stretching frequencies of the aminoisoquinolines, -cinnolines, and -quinazolines have now been determined, and along with those for the aminopyrimidines and 5-aminoquinoline (kindly supplied by Dr. D. J. Brown and Mr. A. Bryson respectively) are collected in Table 3. The force constants were calculated as previously described.⁵

It seems reasonable to expect electromeric interaction to occur in those cases for which it is formally possible. In the isoquinoline series this would apply to 3-, 6-, and 8-aminoisoquinoline.

It is seen, however, that the force constant for 8-aminoisoquinoline is only very slightly higher than that of the 7-isomer, while 3- and 6-aminoisoquinoline give significantly higher values. In the quinoline series the 2-, 4-, 5-, and 7-isomers should give high values but the force constant for 5-aminoquinoline is almost equal to that of 3-aminoquinoline and 4-aminoacridine (6.55 , 6.54 , and 6.55×10^5 dyne cm.⁻¹ respectively). These results find no explanation in the published electron-density calculations.²⁸

Some doubt is thrown on the "extra ionic resonance" explanation⁴ of such facts as the low pK_a value of 4-aminoacridine relative to that of acridine, namely, that it is due to the instability of the *o*-quinonoid forms. Since 4-aminoacridine has an anomalous N-H force constant, the lowest for the aminoacridines, the abnormal basic strength is almost certainly related to the structure of the base rather than that of the ion. Similar considerations apply to 5-aminoquinoline.

The aminocinnolines also provide evidence of the lack of interaction between N₍₁₎ and C₍₅₎. The two adjacent ring-nitrogen atoms should lead to higher N-H bond-stretching force constants for all positions of substitution. However, if the 1:5-effect operates as in 5-aminoquinoline, 5-aminocinnoline should have the force constant characteristic of non-interacting systems. The value obtained (6.56×10^5 dyne cm.⁻¹) is almost identical with

²⁷ Calderbank and Le Fèvre, *J.*, 1951, 649.

²⁸ Daudel and Chalvet, *J. Chim. phys.*, 1949, **46**, 332; Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

that for 5-aminoquinoline. 5-Aminoquinazoline should resemble 8-aminoisoquinoline in the characteristics of the amino-group, and this is found to be so.

The effect of two ring-nitrogen atoms adjacent to the amino-group is shown in 2-aminoquinazoline. As is to be expected, the N-H force constant is very high and similar to that for 2-aminopyrimidine.

In view of previous results for 8-aminoquinoline and 1-aminoacridine it was expected

TABLE 3.

Compound	In CCl ₄			In CHCl ₃			In pyridine	
	ν_a	ν_b	k^a	ν_a	ν_b	k^a	ν_a	ν_b
3-Aminoisoquinoline	3507	3407	6.62	3503	3405	6.61	—	—
4- "	3474	3393	6.53	3477	3397	6.54	—	—
5- "	3484	3401	6.56	3481	3399	6.55	—	—
6- "	3500	3407	6.61	3500	3410	6.61	—	—
7- "	3489	3402	6.58	3481	3401	6.56	—	—
8- "	3490	3407	6.59	3484	3405	6.57	3361	3230
2-Aminoquinazoline	3543	3431	6.73	3531	3421	6.69	—	—
4- " ^b	3537	3423	6.61	—	—	—	—	—
5- "	3489	3406	6.58	3489	3407	6.59	—	—
6- "	3495	3405	6.59	3495	3406	6.59	—	—
7- "	3506	3411	6.63	3504	3414	6.63	3349	3203
8- "	3502	3395	6.59	3497	3393	6.57	3457	3319
3-Aminocinnoline	3510	3405	6.62	3505	3403	6.61	—	—
4- "	Insol.	—	—	3505	3421	6.64	—	—
5- "	3481	3397	6.55	3481	3401	6.56	—	—
6- "	Insol.	—	—	3506	3413	6.63	—	—
7- "	3501	3410	6.62	3502	3410	6.62	3345	3211
8- "	3509	3399	6.61	3505	3398	6.60	3458	3316
2-Aminopyrimidine	3541	3431	6.68	—	—	—	—	—
4- "	3535	3423	6.64	—	—	—	—	—
5- "	3486	3401	6.52	—	—	—	—	—
5-Aminoquinoline	3477	3397	6.54	3479	3400	6.55	—	—

^a N-H force constant (10^5 dyne cm.⁻¹). ^b Slightly sol. in cold; saturated solution at 50–60° used.

that intramolecular hydrogen bonding would occur in 8-amino-quinazoline and -cinnoline. As before,⁵ it was found that the lowering of N-H frequencies in pyridine solution was very much less for these compounds than for other isomers, indicating the existence of hydrogen bonds which prevent bonding with the solvent. In other cases (*e.g.*, 1-aminoacridine, 8-aminoquinoline) such hydrogen bonding is associated with lowering of the pK_a value. The failure of 8-aminocinnoline to show such lowering clearly indicates N₍₂₎ as the basic centre. Lowering is observed with 8-aminoquinazoline and might be taken to indicate that N₍₁₎ is the basic centre, but the case is complicated as is discussed above.

MATERIALS

The aminocinnolines have been described elsewhere.²⁹

The amino-isoquinolines and -quinazolines were known previously, so that frequently we merely describe purification procedures, but in certain cases modified preparations require comment.

3-Aminoisoquinoline was recently synthesised by a somewhat elaborate route from 3-methylisoquinoline.³⁰ 3-Chloroisoquinoline, obtained from 1:3-dichloroisoquinoline³¹ (catalytic reduction gave only isoquinoline), has now been aminated. A similar sequence of reactions with 1:3-dibromoisoquinoline, obtained from homophthalimide, was not advantageous. 5-Nitroisoquinoline was best reduced to the amine with palladised charcoal in methanol. Although we improved the preparation of *m*-methoxy- ω -nitrostyrene we could not reduce it satisfactorily,³² and resorted to the laborious but very efficient preparation of the amine and derived 1:2:3:4-tetrahydro-6-methoxyisoquinoline described by

²⁹ Osborn and Schofield, *J.*, 1955, 2100.

³⁰ Teague and Roe, *J. Amer. Chem. Soc.*, 1951, **73**, 688; Case, *J. Org. Chem.*, 1952, **17**, 471.

³¹ Haworth and Robinson, *J.*, 1948, 777.

³² Cardwell and McQuillin, *J.*, 1949, 708.

Helfer.³³ Robinson³⁴ dehydrogenated the tetrahydro-compound with Raney nickel in naphthalene: this we could not repeat, but found palladised charcoal a satisfactory catalyst. 6-Methoxyisoquinoline was converted into the amine by known methods.^{34,35} Robinson³⁴ prepared 7-aminoisoquinoline from the hydroxy-compound, and we merely report experimental details. As a possible alternative route 4-nitrohomophthalic acid was converted into 1:3-dihydroxy-7-nitroisoquinoline by the general method of Bergstrom and Wirth.³⁶ Chlorination gave 1:3-dichloro-7-nitroisoquinoline, but subsequent attempts to reproduce the reaction failed, possibly because the initial experiment was carried out with a very old specimen of phosphorus oxychloride. Lack of material precluded careful study of the reduction of the dichloro-compound. Previous preparations^{34,37} of 8-aminoisoquinoline were impracticable. Catalytic reduction of 5-chloro-8-nitroisoquinoline with palladised calcium carbonate in methanol, in the presence of sodium acetate, gave only a moderate yield of 8-aminoisoquinoline, but excellent recovery was obtained when ammonium acetate replaced the sodium salt. Other reductions of 5-chloro- and 5-bromo-8-nitroisoquinoline are described below.

2-Chloroquinazoline was converted into 2-phenoxyquinazoline, which with fused ammonium acetate provided the corresponding amine. More convenient was Macbeth and Rodda's method³⁸ for details of which we are indebted to Dr. Rodda. Naff and Christensen³⁹ obtained 5-aminoquinazoline by catalytic reduction of 4-chloro-5-nitroquinazoline followed by dehydrogenation of the dihydro-compound (not isolated) with palladised charcoal; these workers found it necessary to shake the chloro-compound with Raney nickel in ethylene glycol monomethyl ether before carrying out reduction with palladised calcium carbonate, and were troubled by the instability of the dihydro-compound; we found that, provided pure 4-chloro-5-nitroquinazoline was used, preliminary treatment with Raney nickel was unnecessary and the dihydroquinazoline could be oxidised in the usual way with potassium ferricyanide. 6-, 7-, and 8-Aminoquinazoline were prepared by the methods of Elderfield *et al.*²⁵ and of Naff and Christensen³⁹ with the difference that the catalytic reductions were effected at atmospheric pressure with a 6% palladised-charcoal catalyst.

Attempts to prepare 6-aminophthalazine failed. Reduction of 1-chloro-7-methoxyphthalazine with red phosphorus and hydriodic acid gave 6-hydroxyphthalazine,⁴⁰ but under the conditions of the Bucherer reaction this gave only traces of diazotisable material.

6:7-Benzoquinazoline was described by Etienne and Legrand⁴¹ who obtained it from its 4-chloro-derivative. From the same source Legrand⁴² prepared 4-amino-6:7-benzoquinazoline. No experimental details of any of these reactions have been given, and these we supply below. With the aim of synthesising 4-methyl-6:7-benzoquinazoline by the method used by Elderfield and Serlin⁴³ in the quinazoline series, 4-chloro-6:7-benzoquinazoline was converted into diethyl 6:7-benzoquinazol-4-ylmalonate which with methanolic potassium hydroxide gave methyl 6:7-benzoquinazol-4-ylacetate. Hydrolysis of the latter provided only a trace of what appeared to be a hydrated form of the desired 4-methyl compound.

Quinoline and isoquinoline methochlorides were obtained by treating the aqueous solutions of the methiodides with silver chloride. Similarly, the products obtained by treating cinnoline and 4-methylcinnoline with methyl iodide were converted into chlorides. A similar attempt to prepare 4-methylquinazoline methochloride gave a pale orange glass. 3-Methylquinazolinium chloride was prepared *in situ* by dissolving the related hydroxide²⁰ in hydrochloric acid as required. We confirmed the identity of this compound with the

³³ Helfer, *Helv. Chim. Acta*, 1924, **7**, 945.

³⁴ Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1939, 1944.

³⁵ Manske and Kulka, *ibid.*, 1950, **72**, 4997.

³⁶ Bergstrom and Wirth, U.S.P., 2,351,391/1944.

³⁷ Andersag, *Med. Chem. Abhandl. a. med. chem.*, 1934, **2**, 377.

³⁸ Macbeth and Rodda, *Nature*, 1945, **156**, 207.

³⁹ Naff and Christensen, *J. Amer. Chem. Soc.*, 1951, **73**, 1372.

⁴⁰ Cf. Gabriel, *Ber.*, 1903, **36**, 3373.

⁴¹ Etienne and Legrand, *Compt. rend.*, 1949, **229**, 220.

⁴² Legrand, *ibid.*, 1950, **231**, 1318.

⁴³ Elderfield and Serlin, *J. Org. Chem.*, 1951, **16**, 1669.

unambiguously synthesised 3-methyl compound,²¹ and observed that the m. p. of "3-methylquinazolinium picrate" was extremely sensitive to the presence of moisture (see above).

EXPERIMENTAL

After purification the compounds used in physical measurements were thoroughly dried *in vacuo* over phosphoric anhydride. 4-Aminoisoquinoline gave cream nodules, m. p. 108—109.5°, from benzene-cyclohexane. 6-Aminoisoquinoline formed small cream crystals, m. p. 211—212°, from benzene. 4-Aminoquinazoline gave colourless needles, m. p. 271—272°, from ethanol. 6-Aminoquinazoline formed yellow rhombs, m. p. 213—214°, from benzene. 7-Aminoquinazoline, sublimed twice (160°/0.5 mm.) and crystallised from benzene, formed cream leaflets, m. p. 190—191°. Similar purification of 8-aminoquinazoline (sublimation at 120°/0.5 mm.) gave bright yellow prisms, m. p. 150—151°.

Catalytic Reduction of 1 : 3-Dichloroisoquinoline.—When the dichloro-compound (0.5 g.), methanol (25 c.c.), potassium hydroxide (0.4 g.), and Raney nickel (3 c.c.) were shaken with hydrogen, 2 equivs. of the latter were quickly absorbed. The filtered solution was acidified and freed from methanol. The ether extract of the basified residue gave, with ethereal picric acid, isoquinoline picrate, m. p. and mixed m. p. 225—226°. 1 : 3-Dibromoisoquinoline behaved similarly.

1 : 3-Dibromoisoquinoline.—Homophthalimide (5 g.) and phosphorus tribromide (50 c.c.) were refluxed for 5 hr. Removal of excess of phosphorus tribromide under reduced pressure, and treatment of the residue with alkali, gave colourless 1 : 3-dibromoisoquinoline (3.4 g.), m. p. 147—147.5° (Found : C, 38.85; H, 1.9. $C_9H_8NBr_2$ requires C, 37.8; H, 1.75%), from methanol.

3-Bromoisoquinoline.—The dibromo-compound (3 g.), reduced by Haworth and Robinson's method,²¹ gave 3-bromoisoquinoline (1.75 g.), m. p. 63—64° (from aqueous methanol) (Found : C, 52.5; H, 3.0. Calc. for C_9H_8NBr : C, 51.9; H, 2.9%).

3-Aminoisoquinoline.—3-Chloroisoquinoline (8.8 g.), aqueous ammonia (*d* 0.88; 100 c.c.), and copper sulphate (1 g.) were heated at 140° for 30 hr. in an autoclave. The cold mixture was strongly basified and extracted with chloroform. The extract provided 3-aminoisoquinoline (5.3 g.), m. p. 174—177°. Several recrystallisations from benzene gave bright yellow plates, m. p. 176—177° (Found : C, 74.9; H, 5.6; N, 19.6. Calc. for $C_9H_8N_2$: C, 75.0; H, 5.6; N, 19.4%). 3-Bromoisoquinoline was aminated similarly.

5-Aminoisoquinoline.—5-Nitroisoquinoline (20 g.), shaken in methanol (500 c.c.) with palladised charcoal (2 g., 5%) and hydrogen, was reduced in 2 hr. The residue from filtration and evaporation, when dissolved in chloroform and poured into light petroleum (b. p. 40—60°), gave the amine (93%), m. p. 128—129°. This was purified by repeated crystallisation from benzene-cyclohexane, and obtained as straw-coloured plates which changed to blades, m. p. 129.5—130.5°, in the presence of the solvent.

m-Methoxy- ω -nitrostyrene.—*m*-Methoxybenzaldehyde (35.5 g.), nitromethane (18 g.), acetic acid (125 c.c.), and ammonium acetate (12.5 g.) were refluxed gently for 2 hr. The solution was poured into iced water and the precipitate was recrystallised from benzene, giving yellow plates (27 g.), m. p. 91—92°.

6-Hydroxyisoquinoline.—1 : 2 : 3 : 4-Tetrahydro-6-methoxyisoquinoline (2.42 g.) (Helfer²³) and palladised charcoal (0.8 g.; 30% Pd) were heated at 180—190° for $\frac{1}{4}$ hr. in a stream of nitrogen. Treatment with ether, filtration and removal of the solvent gave a pale brown oil (2.1 g.) which was treated in acetone (10 c.c.) with picric acid (3 g.) in the same solvent. The bright yellow picrate (2.9 g.) was decomposed with aqueous lithium hydroxide, and the product was recovered by ether-extraction. The resulting pale yellow oil (1.03 g.) was refluxed for 2 hr. with concentrated hydrobromic acid (25 c.c.), excess of which was then removed under reduced pressure. The residue in water (10 c.c.) was treated with sodium carbonate solution, and the product [0.85 g.; m. p. 220° (decomp.)] was collected and washed.

1 : 3-Dihydroxy-7-nitroisoquinoline.—4-Nitrohomophthalic acid (56 g.) and *o*-dichlorobenzene (8 parts) were treated as described by Bergstrom and Wirth.²⁶ During the reaction a red solid separated which was collected and washed with dichlorobenzene, hot water, alcohol, and ether. The deep red powder (52 g.), m. p. *ca.* 291° (decomp.), could not be purified by crystallisation or sublimation. It dissolved in alkali, forming a carmine-red solution. Acidification afforded a brownish-yellow precipitate which became brown in air and deep red in the presence of ammonia.

1 : 3-Dichloro-7-nitroisoquinoline.—The above (2 g.) and phosphorus oxychloride (20 c.c.) were heated for 4 hr. on the steam-bath. Decomposition with ice and basification (pH 10) gave a khaki-coloured solid which formed greenish-yellow crystals (1.18 g.), m. p. 179—182°, from

acetic acid. Further crystallisation gave the *dichloro-compound*, m. p. 185° (decomp.) (Found: C, 45.3; H, 1.7. $C_9H_4O_2N_2Cl_2$ requires C, 44.5; H, 1.7%).

7-Aminoisoquinoline.—7-Hydroxyisoquinoline (1.25 g.), saturated ammonium hydrogen sulphite solution [4 c.c.; prepared from aqueous ammonia (d 0.88) and sulphur dioxide], and aqueous ammonia (20 c.c.; d 0.88) were heated at 140–150° for 16 hr. The product was washed with 2*N*-sodium hydroxide and water, yielding a fawn powder (1.1 g.), m. p. 204°. Sublimation (150°/0.3 mm.) and two crystallisations from benzene gave pale yellow needles, m. p. 203–205°.

5-Bromoisoquinoline.—5-Aminoisoquinoline (4.8 g.) in concentrated hydrobromic acid (12 c.c.) and water (13 c.c.) was diazotised at 0° with sodium nitrite (2.3 g.) in water (15 c.c.). The diazonium solution was added slowly to a stirred solution of cuprous bromide (5.8 g.) in hydrobromic acid (48 c.c.) at 75°. After 24 hr. at room temperature the solution was basified and steam-distilled, giving 5-bromoisoquinoline (5.1 g.), m. p. 82–84° after recrystallisation from light petroleum (b. p. 40–60°).

5-Bromo-8-nitroisoquinoline.—Potassium nitrate (2.4 g.) in concentrated sulphuric acid (20 c.c.) was added during 5 min. to 5-bromoisoquinoline (4.15 g.) in the same acid (24 c.c.) stirred at 20°. After 1 hr. at room temperature the solution was poured on ice and basified with aqueous ammonia. Crystallisation from methanol of the washed and dried precipitate gave 5-bromo-8-nitroisoquinoline (5.05 g.), m. p. 139–141°.

8-Aminoisoquinoline.—Palladised calcium carbonate (2 g.; 6% Pd) and absolute methanol were shaken for a short time with hydrogen. Pure 5-chloro-8-nitroisoquinoline (2 g.) and ammonium acetate (12 g.) were then added and shaking was continued. In 1 hr. hydrogen (10% in excess of the theor.) was absorbed. The filtered solution was acidified with concentrated hydrochloric acid and methanol was removed under reduced pressure on the steam-bath. The solution of the orange-yellow residue in water was basified with saturated aqueous sodium carbonate and extracted with chloroform. The dried extract provided felted needles (1.36 g.) which from ethyl acetate formed very pale yellow needles (1.02 g.), m. p. 168–172°. Very pale fawn prisms of pure 8-aminoisoquinoline, m. p. 171–172° (Found: C, 75.2; H, 5.5. Calc. for $C_9H_8N_2$: C, 75.0; H, 5.6%), were obtained by further crystallisation from ethyl acetate. Andersag³⁷ gave m. p. 174°. From a similar reduction in which sodium acetate was used a lower yield of impure amine was obtained. Reduction with palladised charcoal in methanol in the presence of sodium acetate merely produced 8-amino-5-chloroisoquinoline in high yield. The chlorine atom in this compound could not be removed by hydrogenation in presence of Raney nickel in alkaline solution. When 5-bromo-8-nitroisoquinoline in methanol was hydrogenated in presence of palladised calcium carbonate the solution became red and then green, and a green precipitate, probably of the intermediate hydroxylamine, was formed. A similar experiment in the presence of potassium hydroxide produced a small yield of 8-aminoisoquinoline after elaborate purification.

2-Aminoquinazoline.—2-Chloroquinazoline (0.5 g.) was added slowly to a solution of potassium hydroxide (0.4 g.) in phenol (5 g.) on the steam-bath. The mixture was heated for 3 hr. at 70°. Basification and filtration gave a light-brown solid (0.58 g.) which from light petroleum (b. p. 60–80°) formed colourless needles of 2-phenoxyquinazoline, m. p. 124–126°. This (0.5 g.) was heated with ammonium acetate (5 g.) at 170–180° for 2 hr. After cooling, water and 2*N*-sodium hydroxide were added and the product (0.35 g.) was crystallised from ethanol. It formed yellow crystals, m. p. 200°.

4-Hydroxy-5-nitroquinazoline.—6-Nitroanthranilic acid (14.84 g.) and formamide (29.4 c.c.) were heated at 155–160° (bath-temp.) for 4½ hr. The product was triturated with a little water and crystallised from the same solvent (charcoal), giving matted needles (12.2 g.), m. p. 252–256°.

4-Chloro-5-nitroquinazoline.—The hydroxy-compound (7 g.) was chlorinated as described by Naff and Christensen.³⁹ Excess of phosphorus oxychloride was removed under reduced pressure and the residue, after treatment with ice and excess of 4*N*-sodium hydroxide, was extracted rapidly with ether. The solid (5.17 g.) so recovered was sublimed (140°/0.5 mm.), giving pure 4-chloro-5-nitroquinazoline as a cream solid, m. p. 142°.

5-Aminoquinazoline.—The chloro-compound (1 g., resublimed), dry ethylene glycol mono-methyl ether (150 c.c.) and palladised calcium carbonate (0.5 g.; 6% Pd) were shaken with hydrogen. Reduction was complete in ½ hr., and the solution was filtered and evaporated under reduced pressure with gentle warming. The residue was oxidised by the method of Elderfield *et al.*,²⁵ and the brown gum isolated by chloroform-extraction of the oxidation solution was chromatographed on alumina, being eluted successively with benzene, benzene-ether, and ether. The yellow band removed by the last solvent arose from an orange-yellow solid

(0.265 g.) which formed long orange needles, m. p. 195—197°, from benzene. For physical measurements it was recrystallised several times and sublimed (160°/1 mm.), giving chrome-yellow needles, m. p. 195—196.5°.

1-Chloro-7-methoxyphthalazine (cf. Vaughan and Bird⁴⁴).—The hydroxy-compound (8.8 g.) and phosphorus oxychloride (40 c.c.) were heated on the steam-bath until dissolution occurred, and then refluxed for $\frac{1}{2}$ hr. more. The cooled liquid was poured on ice and basified. The precipitate [7.4 g.; m. p. 142° (decomp.)] was not further purified.

6-Hydroxyphthalazine.—The above compound (0.5 g.), red phosphorus (0.2 g.), and hydriodic acid (b. p. 127°; 5 c.c.) were refluxed for 1 hr. The mixture was diluted with water (5 c.c.) and after filtration evaporated to dryness under reduced pressure. The solution of the dark brown solid residue in warm water (5 c.c.) was adjusted to pH 7 with aqueous ammonia. The resulting precipitate gave the product (0.3 g.), m. p. ca. 300° (decomp.) (in a bath preheated to 290°), when crystallised from water. Recrystallisation gave 6-hydroxyphthalazine as yellow crystals of unchanged m. p. (Found: C, 60.1; H, 4.5; N, 17.3. $C_8H_6ON_2, \frac{1}{2}H_2O$ requires C, 60.8; H, 4.7; N, 17.7%). This compound was readily soluble in alkali and gave a faint red-brown colour with ferric chloride.

1-Chloro-7-methoxyphthalazine, refluxed with hydrobromic acid, gave 4 : 6-dihydroxyphthalazine, m. p. 310° (decomp.) (Found: C, 56.1; H, 4.0. $C_8H_6O_2N_2$ requires C, 56.1; H, 4.1%). which separated as a cream solid from water. The m. p. was strongly depressed on admixture with 6-hydroxyphthalazine.

6 : 7-Benzoquinazoline.—By Niemetowsky's method⁴⁵ 3-amino-2-naphthoic acid (10 g.) gave 4-hydroxy-6 : 7-benzoquinazoline (8.5 g.), which separated from water as a pale yellow solid, m. p. 278°. This compound (1.3 g.) and phosphorus oxychloride (20 c.c.) were refluxed for 2 hr. The product, a bright yellow solid (0.98 g.), m. p. 173°, was isolated in the usual way. Sublimation (160°/0.1 mm.) gave the almost pure product, m. p. 176—178°.

Reduction of the chloro-compound (0.44 g.) in ethylene glycol monomethyl ether (50 c.c.) with palladised calcium carbonate (0.5 g.; 8% Pd) and hydrogen was complete in $1\frac{1}{2}$ hr. The catalyst was removed and the solution was evaporated under reduced pressure, with gentle warming. The residue was boiled with water, the solution was filtered, and oxidation with potassium ferricyanide (1.4 g.) was effected in the usual way. From the oxidation solution chloroform removed a dark brown solid which gave bright yellow crystals (0.19 g.; m. p. 150—160°) on sublimation (110°/1 mm.). From cyclohexane it gave bright yellow crystals, m. p. 163—165°. Etienne and Legrand⁴¹ gave m. p. 160°.

4-Amino-6 : 7-benzoquinazoline.—The chloro-compound (0.23 g.) and saturated anhydrous methanolic ammonia (25 c.c.) were refluxed for 2 hr. The precipitate, combined with material obtained by evaporating the solvent, was washed with warm water and dried, giving a yellow solid (0.18 g.), m. p. ca. 300° (decomp.). Three sublimations (130°/0.1 mm.) and recrystallisation from ethanol gave the amine, m. p. ca. 365° (decomp.) (in a bath preheated to 360°). Legrand⁴² gave m. p. 363°.

Diethyl 6 : 7-Benzoquinazol-4-ylmalonate.—4-Chloro-6 : 7-benzoquinazoline (2.1 g.) in warm benzene (100 c.c.) was added to a suspension of sodiomalonic ester (2 equivs.) in benzene (100 c.c.). After being refluxed for 3 hr. and left overnight the deep orange mixture was poured into water. Evaporation of the dried (Na_2SO_4) organic layer and crystallisation of the residue from ethanol gave diethyl 6 : 7-benzoquinazol-4-ylmalonate (2.29 g.) as bright yellow needles, m. p. 172—175° (Found: C, 68.1; H, 5.5. $C_{19}H_{18}O_4N_2$ requires C, 67.4; H, 5.4%).

Methyl 6 : 7-Benzoquinazol-4-ylacetate.—The above product (1.5 g.), potassium hydroxide (0.6 g.), and methanol (60 c.c.) were refluxed for 3 hr. The orange-red solution quickly became yellow, and, on cooling, deposited yellow needles (0.58 g.). Recrystallisation from methanol gave ginger-yellow needles of the ester, m. p. 207—209° (forming a red melt) (Found: C, 71.6; H, 4.9; N, 11.5. $C_{15}H_{12}O_2N_2$ requires C, 71.4; H, 4.8; N, 11.1%). No pure product was isolated from the reaction mother-liquor.

Hydrolysis of this ester with boiling aqueous sodium hydroxide gave only traces of a steam-volatile, benzene-soluble compound, which formed pale yellow crystals, m. p. 124—126° after repeated crystallisation from light petroleum (b. p. 40—60°), and appeared to be hydrated 4-methyl-6 : 7-benzoquinazoline (Found: C, 70.1; H, 6.0. $C_{13}H_{10}N_2, 1.5H_2O$ requires C, 70.6; H, 5.9%).

isoQuinoline Methochloride.—isoQuinoline (5 g.), methyl iodide (10 c.c.), and methanol were

⁴⁴ Vaughan and Bird, *J. Amer. Chem. Soc.*, 1946, **68**, 1314.

⁴⁵ Niemetowsky, *J. prakt. Chem.*, 1895, **51**, 565.

refluxed for 2 hr. Removal of the solvent and crystallisation from ethanol gave lemon-yellow needles, m. p. 160—161.5°, which were shaken with water (50 c.c.) and excess of freshly precipitated silver chloride for 12 hr. Filtration and evaporation at reduced pressure gave glistening needles which were crystallised from ethanol-ether and collected on a sintered-glass plate in an apparatus from which moisture was excluded.

In the same way quinoline methochloride was obtained as thick deliquescent needles.

Cinnoline Methochloride.—Cinnoline methiodide was prepared from cinnoline in the usual way and freed from unchanged starting material by extraction (Soxhlet) with light petroleum (b. p. 40—60°). The lilac-coloured solution obtained after conversion into the *methochloride*, when evaporated *in vacuo* at 20° gave a lilac-coloured solid which after three crystallisations (charcoal) from dry ethanol-ether gave very pale yellow plates (Found: C, 56.9; H, 5.3; N, 18.6. $C_9H_8N_2Cl \cdot \frac{1}{2}H_2O$ requires C, 57.1; H, 5.6; N, 18.7%). These were very deliquescent, changing in air to a deep-blue liquid. They were manipulated in a filtration apparatus protected from moisture, and stored without difficulty over phosphoric anhydride in a vacuum-desiccator.

4-Methylcinnoline methochloride obtained in the same way and with the same precautions formed very pale blue-green needles (Found: C, 56.8; H, 6.0; N, 16.9. $C_{10}H_{11}N_2Cl \cdot H_2O$ requires C, 56.5; H, 6.1; N, 16.7%), which were very deliquescent and formed a dark green liquid when exposed to the atmosphere.

Physical Measurements.—The ultraviolet measurements were made in the usual way, with a Unicam S.P. 500 instrument. The buffer solutions used (which, when possible, had a constant strength of 0.01M) were: glycine-hydrochloric acid (pH 2.5—3.7), sodium acetate-acetic acid (pH 4.0—5.6), potassium dihydrogen phosphate-sodium borate (pH 7.0—9.2), sodium borate (pH 9.21). The pH values of all solutions above pH 2 were measured by means of a meter. For values below pH 2.5 standard solutions of hydrochloric acid were used.

The deliquescent methochlorides were made up as approximately 0.01M-solutions in water, and concentrations were then determined by titrating the chloride ion with silver nitrate. For both spectroscopic and pK_a determinations cinnoline and isoquinoline were purified by repeated vacuum-distillation, specimens being collected finally in small glass bulbs of known weight which were immediately sealed and subsequently broken under water when solutions were being prepared.

Ionisation constants were determined by potentiometric titrations of aqueous solutions with hydrochloric acid in a thermostat at $20^\circ \pm 0.05^\circ$. pH measurements were made with a Cambridge instrument in conjunction with a glass electrode. The latter was standardised by means of 0.05M-sodium borate (pH 9.23) and 0.05M-potassium hydrogen phthalate (pH 4.00) [British Standard pH Scale, 1647 (1950)]. pK_a values were calculated from the titration curves at 30, 40, 50, 60, and 70% neutralisation by using the equation $pK_a = pH + \log x/(100 - x)$ ($x = \%$ neutralisation), or with weaker bases $pK_a = pH + \log ([HCl] - [H^+])/([B^+] - [HCl] + [H^+])$.⁴⁶ pK_a values for phenanthridine, 6-aminophenanthridine, and 6:7-benzoquinazoline were determined spectrophotometrically. Ultraviolet extinction curves were determined for the compounds in a number of buffer solutions, and calculations made by the method of Irvin and Irvin.⁴⁷ In the case of 6:7-benzoquinazoline true isosbestic points were not obtained (probably because of intense fluorescence). Calculations at the longest wavelength gave $pK_a \sim 5.2$.

Infrared measurements were made in dried and distilled solvents, a Perkin-Elmer instrument with a lithium fluoride prism being used.

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⁴⁶ Britton, "Hydrogen Ions," Chapman and Hall, London, 1942.

⁴⁷ Irvin and Irvin, *J. Amer. Chem. Soc.*, 1947, **69**, 1091.