Kinetics of Reactions in Heterocycles. Part IX.[1] Trimethylammonio- and Dimethylamino-*N*-methyl-derivatives of Quinoline, Isoquinoline, Cinnoline, Phthalazine, Quinazoline, and Quinoxaline

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Trimethylammonio-derivatives of quinoline and quinazoline have been prepared: from the corresponding chloro-compound with trimethylamine or by quaternisation of the dimethylamino-compound with methyl iodide. The kinetics of their reactions with hydroxide ion have been measured; quinazolin-4-yltrimethylammonium chloride was found to be *ca.* 700 times more reactive than 4-chloroquinazoline, at 20°.

Nuclear *N*-methyl derivatives of dimethylamino-quinoline, isoquinoline, cinnoline, phthalazine, and quinoxaline have been prepared by quaternisation.

Ionization constants, u.v. and ^{1}H n.m.r. spectra are recorded and discussed.

THE preparation of trimethylammonio-derivatives of purines, pyridine, and pyrimidine, and the kinetics of displacement of the trimethylammonio-group by hydroxide ion, have been described in Parts VII [2] and VIII [1] of this series. Here we describe the preparation and reactivity towards hydroxide ion of trimethylammonio-derivatives of quinoline and quinazoline, and the preparation of nuclear *N*-methyl derivatives of dimethylamino-quinoline, isoquinoline, cinnoline, phthalazine, and quinoxaline.

The trimethylammonio-compounds were prepared either (*a*) by the reaction of the corresponding chloro-compound with trimethylamine in benzene, or (*b*) by quaternisation of the dimethylamino-compound with methyl iodide.

Quinazolin-2- and 4-yltrimethylammonium chloride were readily prepared by the first method, but 2- and 4-chloroquinoline, 1-chloroisoquinoline, 4-chlorocinnoline, 1-chlorophthalazine, and 2-chloroquinoxaline with trimethylamine in benzene (under conditions sufficient to induce reaction but with unchanged chloro-compound present) gave only the 2-dimethylamino-quinoline and analogous compounds. The dimethylamino-compounds were formed presumably by the decomposition of the trimethylammonio-compound under the conditions required for its formation.

We were unable to repeat the preparation [3] of quinolin-2-yltrimethylammonium salts by the reaction of 2-chloroquinoline with liquid trimethylamine at 40°, and isolated only 2-dimethylaminoquinoline instead.

The quaternisation of 2-dimethylaminoquinoline with methyl iodide at 100° has been investigated by Luthy, Bergstrom, and Mosher,[4] but only 2-dimethylamino-1-methylquinolinium iodide was obtained. We have reinvestigated this reaction at 20°, and have found the major product to be quinolin-2-yltrimethylammonium iodide, which was contaminated with some isomeric 2-dimethylamino-1-methylquinolinium iodide. The trimethylammonio-compound was obtained pure by selectively hydrolysing the more reactive nuclear *N*-methyl compound. Thus, the reaction product was dissolved in 0·2M-sodium hydroxide at room temperature, and the hydrolysis product, 1-methyl-2(1*H*)-quinolone was extracted; subsequently the unchanged quinolin-2-yltrimethylammonium iodide was recovered.

All other quaternisations of dimethylamino-compounds with methyl iodide gave only ring-nitrogen methylated products. Thus 4-dimethylaminoquinoline and 1-dimethylaminoisoquinoline with methyl iodide at 20° gave 4-dimethylamino-1-methylquinolinium iodide and 1-dimethylamino-2-methylisoquinolinium iodide. These assignments were supported by their ^{1}H n.m.r. spectra.

Similarly, 4-dimethylaminocinnoline gave 4-dimethylamino-2-methylcinnolinium iodide. The identity of the product was established by hydrolysis to the known [5] anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide rather than 1-methyl-4(1*H*)-cinnolone. The ^{1}H n.m.r. spectrum was consistent with this assignment.

Likewise 2-dimethylaminoquinoxaline and 1-dimethylaminophthalazine underwent methylation at the ring nitrogen atom. The hydrolysis of 2-dimethylaminoquinoxalinium methiodide was followed spectroscopically and the u.v. spectrum of the reaction mixture at the end of the reaction differed from those of the starting material, 2-hydroxyquinoxaline and 1-methyl-2(1*H*)-quinoxalone. Elemental analysis of the product isolated from the reaction mixture corresponded to the anhydro-base of 3-hydroxy-1-methylquinoxalinium hydroxide.

Similar hydrolysis of 1-dimethylaminophthalazinium methiodide yielded a solution with an u.v. spectrum that was different from those of starting material, 1-hydroxyphthalazine and 2-methyl-1(2*H*)-phthalazone. No product could be isolated from the reaction mixture. (The evidence suggests that methylation was occurred *meta* to the dimethylamino-group. Methylation *ortho* to the dimethylamino-group cannot be discounted, however, since the hydrolysis of this methiodide need not have resulted in the replacement of the dimethylamino-group.)

The results of measuring the kinetics of the reactions of the trimethylammonio-compounds and of 4-chloroquinazoline (for comparison) with hydroxide ion are

[1] Part VIII, G. B. Barlin and A. C. Young, *J. Chem. Soc.* (*B*), 1971, 1675.
[2] G. B. Barlin and A. C. Young, *J. Chem. Soc.* (*B*), 1971, 821.
[3] C. B. Reese, *J. Chem. Soc.*, 1958, 899.
[4] N. G. Luthy, F. W. Bergstrom, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1949, **71**, 1109.
[5] D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, 1963, 4924.

TABLE 1

Reactions of hydroxide ions

Quinolin-2-yltrimethylammonium iodide at 79·6°

Hydroxide ion 0·0400M, trimethylammonio-compound 0·000296M

Time (min)	13	27	39	54	68	90	115	142	204
Reaction (%)	8·6	17·5	24·3	32·2	38·4	46·8	56·8	64·0	75·5
10^3k/l mol^{-1} s^{-1}	2·98	2·96	3·00	2·97	2·95	2·93	3·05	3·00	2·88

Mean $10^3k = 2·97 \pm 0·05$; after correction for solvent expansion, 3·05.

Quinazolin-4-yltrimethylammonium chloride at 20·4°

Hydroxide ion 0·00250M, trimethylammonio-compound 0·000032M

Time (s)	12	19	26	33	46	54	67	82	112	137	190
Reaction (%)	12·1	18·2	24·2	30·3	38·6	44·5	51·3	58·6	69·1	76·8	86·5
k/l mol^{-1} s^{-1}	4·35	4·25	4·21	4·33	4·27	4·39	4·30	4·31	4·23	4·28	4·24

Mean $k = 4·29 \pm 0·05$.

4-Chloroquinazoline at 19·85°

Hydroxide ion 0·0125M, chloro-compound 0·000212M

Time (min)	36	55	79	106	137	175	227	332	449
Reaction (%)	14·5	21·0	29·0	37·1	45·2	53·6	62·9	77·8	87·1
10^3k/l mol^{-1} s^{-1}	5·80	5·67	5·79	5·82	5·86	5·87	5·87	6·10	6·13

Mean $10^3k = 5·88 \pm 0·15$.

TABLE 2

Kinetic results for the reactions of trimethylammonio- and chloro-compounds with hydroxide ions

Temp.[a] (°C)	10^2[OH$^-$]/ M	10^4[$-\overset{+}{N}Me_3$]/ M	10^3k [b]	10^3k [c] corr.	$t_{\frac{1}{2}}$ [d]	$t_{\frac{1}{2}}/t_{\frac{1}{2}}'$ [e]	$t_{\frac{1}{2}}/t_{\frac{1}{2}}'$ [f] calc.	An λ/nm [g]	pH [h]
				Quinolin-2-yltrimethylammonium iodide					
99·8	4·00	2·96	14·0	14·6				323	4·8
89·75	4·00	4·04	6·48	6·70	44·5			323	4·8
89·75	2·00	2·02	6·53	6·75	88·5	1·99	2·00	323	4·8
79·6	4·00	2·96	2·97	3·05				323	4·8
				Quinazolin-2-yltrimethylammonium chloride					
30·05	0·477	1·91	68·0	68·2				241	5·0
20·2	0·477	1·90	28·9	28·9				241	5·0
10·2	0·477	1·91	10·1	10·1	248	2·02	2·00	241	5·0
10·2	0·954	3·81	10·8	10·8	123			241	5·0
				Quinazolin-4-yltrimethylammonium chloride					
40·0	0·250	0·245	15,700	15,800				229	*i*
31·5	0·250	0·246	9490	9520				229	*i*
20·4	0·250	0·320	4290	4290	65			229	*i*
20·4	0·125	0·140	4120	4120	135	2·08	2·00	229	*i*
				4-Chloroquinazoline					
39·65	1·25	2·13	35·0	35·2				263	7·0
29·95	1·25	2·13	16·2	16·2	57			263	7·0
29·95	0·626	1·06	16·1	16·2	114·5	2·01	2·00	263	7·0
19·85	1·25	2·12	5·88	5·88				263	7·0

[a] ±0·1° [b] In l mol^{-1} s^{-1}; the standard deviation was usually below 3%. [c] Corrected for solvent expansion. [d] Time for 50% reaction in min. except for quinazolin-4-yltrimethylammonium chloride where the units are s. [e] The ratio of $t_{\frac{1}{2}}$ for two experiments at different concentrations. [f] Calculated values from the concentration of reactants employed. [g] Analytical wavelength for determination of percentage reaction. [h] pH of buffer solutions used to stop the reactions and for spectroscopic measurements. [i] The rapid reaction 'stopped flow' technique (ref. 31), was used to study this reaction.

TABLE 3

Rate coefficients and Arrhenius parameters for reactions with hydroxide ions

Compound	Temp. (°C)	10^3k [a]	E [b] (kJ mol^{-1})	log A [c]	$\Delta H^{\ddagger}$ [b] (kJ mol^{-1})	$-\Delta S^{\ddagger}$ [d] (J mol^{-1} deg^{-1})
Quinolin-2-yltrimethylammonium iodide	20·0	0·0086 [e]	84·5	10·0	82·1	61·6
Quinazolin-2-yltrimethylammonium chloride	20·2	28·9	68·4	10·6	65·9	49·8
Quinazolin-4-yltrimethylammonium chloride	20·4	4290	49·5	9·5	47·1	72·2
4-Chloroquinazoline	19·85	5·88	69·4	10·2	67·0	58·6

[a] In l mol^{-1} s^{-1}. [b] Accurate to ±1·2 kJ mol^{-1}. [c] Accurate to ±0·3 unit. [d] Accurate to ±1 unit. [e] Calculated from the experimental results.

given in Tables 1—3. Some typical examples of these reactions are shown in Table 1; all the kinetic results are in Table 2; and, the Arrhenius parameters calculated from the kinetic results are in Table 3. These reactions were bimolecular and obeyed second-order kinetics as shown by the $t_{\frac{1}{2}}$ values.

Examination of these data reveals that at 20°, quinazolin-4-yltrimethylammonium chloride is *ca.* 700 times more reactive than 4-chloroquinazoline due mainly to the lower energy of activation of the former (49·5 compared with 69·4 kJ mol^{-1}) although its log A value is also lower (9·5 compared with 10·2). This compares with a differential of *ca.* 1600 times between 9-methylpurin-6-yltrimethylammonium chloride and 6-chloro-9-methylpurine,[2] and *ca.* 700 times between pyrimidin-2-yltrimethylammonium chloride and 2-chloropyrimidine [1] and does not appear to be markedly affected by the partial hydration of quinazolin-4-yltrimethylammonium chloride discussed below.

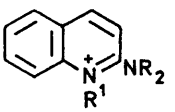
In the absence of quantitative results for the reactivity of the other chloro-compounds with hydroxide ion, it is not yet possible to compare the hydrolysis of the remaining chloro- and trimethylammonio-compounds.

Examination of the effect of annelation in quinolin-2-yltrimethylammonium iodide relative to 2-pyridyltrimethylammonium iodide [1] reveals that at 20°, the quinoline is 1100 times the more reactive. Although log A for 2-pyridyltrimethylammonium iodide (12·3) is higher than for quinolin-2-yltrimethylammonium iodide (10·0), the higher reactivity of the quinoline is due mainly to its lower energy of activation (84·5 compared with 114 kJ mol^{-1}). Likewise quinazolin-4-yltrimethylammonium chloride is 27 times more reactive than pyrimidin-4-yltrimethylammonium chloride, but in this instance the log A values are comparable (9·5 and 9·4 respectively). This higher reactivity of the annelated compounds was attributed to the larger area available for delocalisation of the charge in the transition state.[6] Relative rates of 290 and 370 have been found for the reactions of 2-chloro-quinoline and -pyridine [6] towards ethoxide and 2-methylsulphonylquinoline and -pyridine [7] towards methoxide ion.

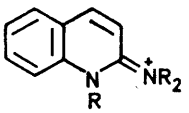
In contrast to these results, quinazolin-2-yltrimethylammonium chloride was found to be less reactive than pyrimidin-2-yltrimethylammonium chloride (the ratio of reactivities at 20° was *ca.* 0·5). The lower reactivity of the quinazoline is believed to be due to fixation of the shared bond which reduces the activating influence of N-3 by hindering its participation in the transition state. Chapman and Russell-Hill [6] proposed a similar explanation to account for the observed reactivities of 2-chloroquinazoline and 2-chloropyrimidine towards ethoxide ion.

Ionization Constants and Spectra (*Tables* 4 *and* 5).—The effect of inductive electron withdrawal by the positively charged trimethylammonio-group ($-\overset{+}{N}Me_3$) adjacent to the basic centre in quinolin-2-yltrimethylammonium iodide is to lower the pK_a to −4·54, *i.e.* by 9·48 units relative to quinoline, and is comparable with that observed in the pyridine series.[1] Ionization constants for the other trimethylammonio-compounds described here could not be determined because of their instability in strong acid.

The pK_a value of quinolin-2-yltrimethylammonium iodide is 2·94 units higher than that relating to dication formation in 2-dimethylamino-1-methylquinolinium iodide. As in the pyridine series,[1] this difference, which is of the same order, is taken as a measure of the loss in mesomeric stabilisation of the monocation (1) ⟷ (2) and any differences associated with protonation at a dimethylamino-group or ring nitrogen atom.

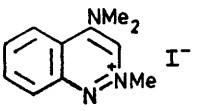


(1)

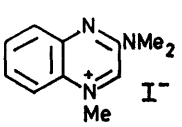


(2)

Examination of the data in Table 4 shows that 2-dimethylamino-1-methylquinolinium iodide and 1-dimethylamino-2-methylisoquinolinium iodide have comparable basicities but that 4-dimethylamino-1-methylquinolinium iodide is a much stronger base. This is compatible with the separation of the basic centre and the positively charged ring nitrogen atom. Of the three compounds 4-dimethylamino-2-methylcinnolinium iodide (3), 1-dimethylaminophthalazinium methiodide,



(3)



(4)

and 3-dimethylamino-1-methylquinoxalinium iodide (4) the quinoxaline is the strongest base. Methylation in all three compounds is thought to have taken place at the ring nitrogen atom *meta* to the dimethylamino-group. Therefore protonation of the first two compounds involves addition of a proton adjacent to a ring nitrogen atom already carrying a positive charge, but in (4) protonation is not so severely restricted and the compound shows a higher basic strength.

The u.v. spectra of the trimethylammonio-compounds were similar to those of the neutral species of compounds lacking this substituent, but different from those of the monocations of the corresponding amino-compounds in which protonation is known to involve the ring nitrogen atom. This is consistent with the optical transparency of the trimethylammonio-group.[8-11] Thus

[6] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1956, 1563.
[7] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 736.
[8] A. Wohl, *Bull. Soc. chim. France*, 1939, [5] **6**, Memoirs 1312.
[9] K. Bowden and E. A. Braude, *J. Chem. Soc.*, 1952, 1068.
[10] A. Albert, *J. Chem. Soc.*, 1960, 1020.
[11] G. B. Barlin and W. Pfleiderer, *J. Chem. Soc.* (*B*), 1971, 1425.

TABLE 4

pK_a Values and u.v. spectra

Compound	Ionization (water; *ca.* 20°) Charged species [a]	pK_a	Spectroscopy in water [b] $\lambda_{max.}$ (nm)	log ε	pH [c]
Quinoline	0		226, 275, 299, 312 [d]	4·36, 3·51, 3·46, 3·52	
	+	4·94 [d]	233, 313 [d]	4·50, 3·80	
2-Aminoquinoline	0		210, 310 [f]	4·5, 3·7	
	+	7·30 [e]	210, 230, 260, 308 [f]	4·3, 4·2, 3·8, 3·9	
Quinolin-2-yltrimethylammonium iodide	+		229, *279*, 288, *294*, 301, 314 [h]	4·65, *3·49*, 3·51, *3·49*, 3·50, 3·45	4·94
	++	−4·54 [g]	246, *308*, 321, 345 [h,i]	4·65, *3·77*, 3·93, *3·43*	−7·0
2-Dimethylamino-1-methylquinolinium iodide	+		210, 251, *264*, 301, 355, *370* [h]	4·56, 4·18, *4·08*, 3·76, 4·07, *3·95*	5·1
	++	−7·48 [j]	246, 323, *353* [i]	4·61, 3·87, *3·50*	−9·3
4-Aminoquinoline	0		195, 290 [f]	4·3, 3·8	
	+	9·13 [e]	195, 210, 300, 318 [f]	4·4, 4·4, 4·1, 4·1	
4-Dimethylamino-1-methylquinolinium iodide	+		221, 243, 251, *352*, 360 [h]	4·45, 4·11, 4·12, *4·25*, 4·27	5·1
	++	−4·29 [k]	242, *318*, 326 [h,i]	4·60, *3·86*, 3·93	−7·0
Isoquinoline	0		216, 267, *278*, 306, 319 [l]	4·81, 3·57, *3·41*, 3·38, 3·47	
	+	5·40 [l]	227, 266, 273, 332 [l]	4·66, 3·30, 3·31, 3·63	
1-Aminoisoquinoline	0		*240*, 290, 325 [f]	*4·0*, 3·8, 3·6	
	+	7·59 [e]	235, 270, 280, 330 [f]	4·3, 3·8, 3·8, 3·8	
1-Dimethylamino-2-methylisoquinolinium iodide	+		223, 253, *283*, 296, 361 [h]	4·62, 3·80, *3·69*, 3·75, 3·89	4·94
	++	−7·22 [m]	244, *282*, 293, 305, 353 [i]	4·71, *3·38*, 3·62, 3·26, 3·68	−9·3
Cinnoline	0		226, 283, 290, 321 [l]	4·64, 3·38, 3·38, 3·44	
	+	2·29 [l]	237, 294, 305, 353 [l]	4·59, 3·31, 3·32, 3·40	
4-Aminocinnoline	0		212, 238, *255*, *310*, 338 [l]	4·52, 4·18, *3·77*, *3·71*, 4·03	
	+	6·85 [l]	211, 236, 262, 295, 345, *360* [l]	4·45, 4·16, 3·83, 3·24, 4·12, *4·03*	
4-Dimethylamino-2-methylcinnolinium iodide	+		220, 248, *253*, *263*, *327*, *341*, 388 [h]	4·52, 4·05, *4·02*, *3·91*, *3·48*, *3·64*, 4·12	5·1
	++	−4·54 [n]	218, 253, *265*, 317, 403, *411* [h,i]	4·26, 4·27, *4·09*, 3·54, 4·01, *3·98*	−7·0
Phthalazine	0		218, 261, 292, *297*, 305 [o]	4·83, 3·53, 3·18, *3·11*, 3·11	
	+	3·47 [o]	229, 273, 314 [o]	4·61, 3·35, 3·45	
1-Dimethylaminophthalazinium methiodide	+		217, *232*, *245*, *279*, 288, 333 [h]	4·56, *4·15*, *3·92*, *3·78*, 3·86, 3·82	5·1
	++	−3·62 [p]	241, *285*, 321 [h,i]	4·63, *3·40*, 3·51	−6·0
Quinazoline	0		222, 271, 305 [o]	4·57, 3·40, 3·38	
	+	3·43 [e]	238, *284*, *299*, *309*, 333 [o]	4·40, *3·51*, *3·30*, *3·22*, 3·10	
Quinazoline (hydrated)	+		208, 260 [o]	4·20, 3·91	
2-Aminoquinazoline	0		233, *246*, *259*, 352 [l]	4·57, *4·32*, *3·75*, 3·50	
	+	4·82 [e]	229, 245, 284, *339*, 348 [e]	4·41, 4·26, 3·72, *3·45*, 3·49	
Quinazolin-2-yltrimethylammonium chloride	+		228, 275, 305	4·65, 3·39, 3·33	7·02
	++	*q*			
4-Aminoquinazoline	0		206, *214*, *228*, *278*, 283, *300*, 312, 323 [l]	4·52, *4·38*, *4·18*, *3·81*, 3·82, *3·66*, 3·78, 3·65	
	+	5·85 [l]	217, 238, *252*, 273, 284, *303*, 311, 324 [l]	4·26, 4·13, *3·99*, 3·58, 3·62, *3·87*, 3·98, 3·87	
Quinazolin-4-yltrimethylammonium chloride	+		228, *277*, *281*, 310, *317*	4·59, *3·34*, *3·36*, 3·50, *3·47*	7·02
	++	*q*			
Quinoxaline	0		234, 316 [d]	4·47, 3·79	
	+	0·8 [e]	242, 331 [d]	4·44, 3·93	
2-Aminoquinoxaline	0		240, *290—310*, 353 [p]	4·33, *3·39*, 3·80	
	+	3·96 [e]	231, 252, 257, *310—326*, 348—352 [p]	4·25, 4·05, 4·07, *3·76*, 3·84	
3-Dimethylamino-1-methylquinoxalinium iodide	+		211, *259*, 263, *274*, 323, 455 [h]	4·33, *4·37*, 4·39, *4·05*, 3·46, 3·69	5·1
	++	−1·07 [r]	248, *266*, 269, 361, 435 [h,i]	4·21, *4·29*, 4·30, 3·72, 3·78	−3·4

[a] 0, Neutral species; +, cation; ++, dication. [b] Shoulders and inflexions in italics. [c] Values below 0 have been obtained in solutions of sulphuric acid for which the H_0 scale of M. A. Paul and F. A. Long (*Chem. Rev.*, 1957, **57**, 1) has been used for convenience. [d] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1951, 474. [e] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240. [f] E. A. Steck and G. W. Ewing, through 'Organic Electronic Spectral Data,' 1946—1952, vol. 1, p. 244, edited by M. J. Kamlet, Interscience, New York, 1960. [g] The results were within ±0·14 when the pK_a was determined spectroscopically on 0·00001M-solutions at λ 320 nm. [h] Reference cell compensated with iodide ion. [i] Careful neutralisation gave the spectrum of the monocation. [j] The results were within ±0·1 when the pK_a was determined spectroscopically on 0·00002M-solutions at λ 355 nm. [k] The results were within ±0·15 when the pK_a was determined spectroscopically on 0·00001M solutions at λ 355 nm. [l] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 1956, 4191. [m] The results were within ±0·08 when the pK_a was determined spectroscopically on 0·00003M-solutions at λ 365 nm. [n] The results were within ±0·09 when the pK_a was determined spectroscopically on 0·00002M solutions at λ 420 nm. [o] Ref. 12. [p] Ref. 28. [q] The compound was unstable in solutions of strong acid and it was not possible to determine the pK_a value. [r] The results were within ±0·05 when the pK_a was determined spectroscopically on 0·0002M-solutions at λ 360 nm.

the spectrum of quinolin-2-yltrimethylammonium iodide was similar to that of the neutral molecule of quinoline but different from that of 2-aminoquinoline monocation. Although the spectrum of quinazolin-2-yltrimethylammonium chloride is similar to that of the neutral species of quinazoline, that of the isomeric quinazolin-4-yltrimethylammonium chloride was quite different. The ^1H n.m.r. spectrum of this trimethylammonio-compound, which will be discussed below, suggests strongly that hydration has occurred, and this would adequately explain the lack of similarity in its u.v. spectrum to that of the neutral species of quinazoline

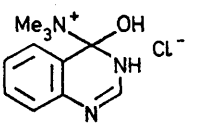
(The quinazoline cation is known to undergo hydration.[12])

Comparison of the spectra of the methiodides of 4-dimethylaminocinnoline and 2-dimethylaminoquinoxaline and those of the monocations of 4-aminocinnoline and 2-aminoquinoxaline revealed that they were different This lack of similarity is consistent with methylation occurring at the *N*-2 and *N*-4 nitrogen atoms respectively, but protonation is expected to occur at *N*-1 in each case.

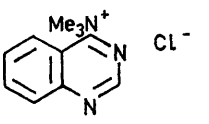
The spectra of the dications of quinolin-2-yltrimethylammonium iodide and 2- and 4-dimethylamino-1-methylquinolinium iodide were similar to that of the quinoline monocation, as expected, but the spectrum of the dication of 1-dimethylamino-2-methylisoquinolinium iodide differed from that of isoquinoline cation. This is probably due to steric inhibition (by the *peri*-proton) to mesomeric interaction of the dimethylamino-group and the ring nitrogen atom.

The ^{1}H n.m.r. spectra of the trimethylammonio- and ring-nitrogen methylated compounds (Table 5) showed signals due to the $-\overset{+}{N}Me_3$ group at τ 5·92—6·20 (except for quinazolin-4-yltrimethylammonium chloride which is discussed below), nuclear $\overset{+}{N}$-Me group at τ 5·31—5·97, and the dimethylamino-group in the methiodides at τ 6·37—6·62, together with signals due to ring protons.

However, the ^{1}H n.m.r. spectrum of quinazolin-4-yltrimethylammonium chloride showed peaks at τ 0·51 and 2·52, and at τ 5·92 and 7·00, both pairs in the ratio of 3 : 1, as well as signals due to the remaining ring protons. It was found that the H-2 proton of quinazoline is shifted upfield from τ 0·49 to 1·65 in the hydrated quinazoline cation.[13] Thus the ^{1}H n.m.r. spectrum indicates that quinazolin-4-yltrimethyl ammonium chloride exists in aqueous solution as a mixture of the hydrated and anhydrous cations [presumably (5) and (6)] in the approximate ratio of 1 : 3. This interpretation also accounts for the lack of similarity observed in the u.v. spectrum of quinazolin-4-yltrimethylammonium chloride and quinazoline.



(5)



(6)

TABLE 5

Nuclear magnetic resonance spectra of salts of quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, and quinoxaline

Compound	Chemical shifts (τ) of protons [a] 2-H	Other ring protons	$-\overset{+}{N}Me_3$	$-\overset{+}{N}Me$	$-NMe_2$
Quinoline					
2-$\overset{+}{N}Me_3$ [b]	1·30—2·00	1·30—2·00	6·20		
2-NMe_2-1-Me [b]	1·50—2·20	1·50—2·20		5·82	6·50
4-NMe_2-1-Me [b]	1·60—2·30, 3·10—3·20	1·60—2·30, 3·10—3·20		5·95	6·53
Isoquinoline					
1-NMe_2-2-Me [b]		1·50—2·80		5·97	6·62
Cinnoline					
4-NMe_2-2-Me [b]		1·15, 1·70—2·00 [d]		5·31 [d]	6·37 [d]
Phthalazine					
1-NMe_2-?-Me [b]		0·59, 1·50—1·90		5·58	6·58
Quinazoline					
2-$\overset{+}{N}Me_3$ [c]		0·05, 1·60—1·80	6·10		
4-$\overset{+}{N}Me_3$ [c]	0·51, 2·52	1·10—1·80	5·92, 7·00		
Quinoxaline					
3-NMe_2-1-Me [b]		0·75, 1·90—2·20		5·32 [d]	6·46 [d]

[a] Spectra were determined in D_2O solution unless otherwise stated, and at 33·5° with sodium 3-trimethylsilylpropanesulphonate as internal standard. [b] This salt was present as its iodide. [c] This salt was present as its chloride. [d] DCl was added to shift the signal due to H_2O downfield.

EXPERIMENTAL

Solids for analysis were dried at 20° and 20 mmHg unless otherwise stated. M.p.s were taken in Pyrex capillaries. All compounds were recrystallised where possible to constant melting point and were further examined for the presence of impurities and isomers by paper chromatography on Whatman No. 1 paper with (*a*) 3% aqueous ammonium chloride, and (*b*) butan-2-ol–5M-acetic acid (7 : 3) as solvent. All trimethylammonio-compounds and nuclear *N*-methyl compounds were also examined for the presence of possible isomers by ^{1}H n.m.r. spectroscopy.

Ionization constants, and u.v. and ^{1}H n.m.r. spectra were determined as described in Part VIII.[1]

Quinolin-2-yltrimethylammonium Iodide.—A solution of

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2-dimethylaminoquinoline [14] (1·20 g) in methyl iodide (6·0 ml) was set aside at 20° for 30 days. The precipitate (2·10 g), containing a mixture of quinolin-2-yltrimethylammonium iodide and 2-dimethylamino-1-methylquinolinium iodide, was filtered off and recrystallised from water. It had m.p. 166—167° (lit.,[3] 168°) (Found: C, 45·7; H, 5·0; N, 8·9. Calc. for $C_{12}H_{15}IN_2$: C, 45·9; H, 4·8; N, 8·9%). This product (0·50 g), dissolved in 0·2M-sodium hydroxide (35 ml), was set aside at 20° for 3·5 h. The reaction mixture was exacted with ether, extracts dried (Na_2SO_4) and the solvent removed to give 1-methyl-2(1*H*)-quinolone (0·10 g), m.p. 72° [from light petroleum (b.p. 60—80°)] (lit.,[15] 74°).

The aqueous solution was adjusted to pH 6, evaporated to dryness at 20°, and the residue extracted with warm propan-2-ol. The product obtained was recrystallised from a small volume of water with addition of potassium iodide to give quinol-2-yltrimethylammonium iodide (0·22 g), m.p. 171° (lit.,[3] 168°) (Found: C, 45·7; H, 4·9; N, 8·8%).

Quinazolin-2-yltrimethylammonium Chloride.—A mixture of trimethylamine (0·7 g) and a cold solution of 2-chloroquinazoline [16] (0·20 g) in benzene (10 ml) was set aside at 5° for 24 h. The *quinazolin-2-yltrimethylammonium chloride* (0·25 g) was filtered off, washed with benzene, and dried. It had m.p. 160—161° [Found (for material dried at 100°/1 h): N, 18·8. $C_{11}H_{11}ClN_3$ requires N, 18·8%]. Aqueous lithium picrate (prepared from saturated aqueous picric acid by addition of lithium carbonate) was added to a solution of the above salt (0·002 g) in water and the precipitate of *quinazolin-2-yltrimethylammonium picrate* (0·0015 g) was collected and washed with cold water. It had m.p. 179—180° (Found: C, 48·9; H, 4·1; N, 19·9. $C_{17}H_{16}N_6O_7$ requires C, 49·0; H, 3·9; N, 20·2%).

Quinazolin-4-yltrimethylammonium Chloride.—A mixture of trimethylamine (3·0 g) and a solution of 4-chloroquinazoline [17] (1·5 g) in benzene (45 ml) was set aside at 4° for 5 days. The precipitate of *quinazolin-4-yltrimethylammonium chloride* (2·0 g) was filtered off, washed with benzene, and dried. It had m.p. 98—99° (decomp.) (Found: Cl, 15·7. $C_{11}H_{14}ClN_3$ requires Cl, 15·9%). This salt (0·050 g) with aqueous lithium picrate gave the *picrate* (0·067 g), m.p. 178—180° (decomp.) [Found (for material dried at 100° for 1 h): C, 49·1; H, 4·0; N, 20·2. $C_{17}H_{16}N_6O_7$ requires C, 49·0; H, 3·9; N, 20·2%).

Mercuric chloride (0·120 g) dissolved in methanol (5 ml) was added to a solution of quinazolin-4-yltrimethylammonium chloride (0·050 g) in methanol (2 ml) and the precipitate of *quinazolin-4-yltrimethylammonium trichloromercurate* (0·089 g) was filtered off. It had m.p. 170—172° [Found (for material dried at 100°/1 h): C, 26·8; H, 2·9; N, 8·4. $C_{11}H_{14}Cl_3HgN_3$ requires C, 26·7; H, 2·9; N, 8·5%].

Reaction of 2-Chloroquinoline with Trimethylamine.—At 40° according to the method of Reese [3] this reaction gave only 2-dimethylaminoquinoline and no trimethylammonio-compound.

Reaction of 4-Chloroquinoline with Trimethylamine.—A mixture of 4-chloroquinoline [18] (0·1 g) and trimethylamine (0·35 g) in benzene (5 ml) was heated in a sealed tube at 195° for 19 h. The reaction mixture on t.l.c. (alumina; benzene) gave 4-dimethylaminoquinoline (0·04 g), picrate, m.p. 189—192° (from ethanol) (lit.,[19] 192°) [Found (for material dried at 100°/1 h): C, 50·9; H, 3·7; N, 17·4. Calc. for $C_{17}H_{15}N_5O_7$: C, 50·9; H, 3·7; N, 17·5%] and unchanged 4-chloroquinoline (0·05 g).

When the reaction mixture was heated at 53° for 4 days, no reaction took place.

Reaction of 1-Chloroisoquinoline and Trimethylamine.—1-Chloroisoquinoline in an excess of trimethylamine according to Reese,[3] and treatment with potassium iodide, gave tetramethylammonium iodide and no trimethylammonio-compound.

1-Dimethylaminoisoquinoline.— 1-Chloroisoquinoline [20] (1·2 g) and ethanolic dimethylamine (10 ml, 16%) were heated in a sealed tube at 155° for 16 h. The mixture was concentrated, made alkaline, and extracted with chloroform to give 1-dimethylaminoisoquinoline (75%), b.p. 101—102° at 2 mmHg (lit.,[21] 124—125° at 5 mmHg). The picrate, prepared in and recrystallised from benzene, had m.p. 165° (lit.,[21] 165—166°).

Reaction of 4-Chlorocinnoline with Trimethylamine.—4-Chlorocinnoline [22] (0·300 g) and trimethylamine (1·00 g) in benzene (6·0 ml) were heated in a sealed tube at 145° for 7·5 h. The tetramethylammonium chloride was filtered off and the filtrate subjected to t.l.c. (alumina; benzene) to give unchanged 4-chlorocinnoline (0·17 g) and 4-dimethylaminocinnoline (0·10 g), characterised as the picrate, m.p. 202—204° (from ethanol) undepressed on admixture with an authentic sample as prepared below.

4-Dimethylaminocinnoline.—4-Chlorocinnoline (0·20 g) and ethanolic dimethylamine (3·0 ml; 33%) were heated in a sealed tube at 100° for 24 h. The solvent was evaporated and the product subjected to t.l.c. (alumina; chloroform) to give *4-dimethylaminocinnoline* (0·20 g). The *picrate*, prepared in and recrystallised from ethanol, had m.p. 205—207° [Found (for material dried at 100°/1 h): C, 48·3; H, 3·5; N, 20·8. $C_{16}H_{14}N_6O_7$ requires C, 47·8; H, 3·5; N, 20·9%].

Reaction of 1-Chlorophthalazine with Trimethylamine.—1-Chlorophthalazine [23] (0·2 g) and trimethylamine (0·3 g) in benzene (4 ml) were heated in a sealed tube at 150° for 12 h. The precipitate, which showed no significant u.v. absorption and contained no trimethylammonio-compound, was filtered off and the filtrate concentrated. The residue was subjected to t.l.c. (alumina; ether); it yielded unchanged 1-chlorophthalazine (0·09 g) and *1-dimethylaminophthalazine* (0·10 g), which was characterised as the *picrate*, m.p. 175—176° (from ethanol) undepressed on admixture with an authentic sample prepared as described below (Found: C, 47·4; H, 3·6; N, 20·7. $C_{16}H_{14}N_6O_7$ requires C, 47·8; H, 3·5; N, 20·9%).

1-Dimethylaminophthalazine.—1-Chlorophthalazine [23] (3·9 g) and ethanolic dimethylamine (42 ml; 33%) were heated at 105° for 7 h. The solvent was evaporated and the residue made alkaline and extracted with benzene. The oil was chromatographed in chloroform over alumina

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(10 in × 2·5 in diam.) to give 1-dimethylaminophthalazine (2·9 g), picrate, m.p. 175—176° (from ethanol).

Reaction of 2-Chloroquinoxaline with Trimethylamine.—2-Chloroquinoxaline [24] (0·100 g) and trimethylamine (0·8 g) in benzene (6·0 ml) were heated in a sealed tube at 150° for 3·5 h. The tetramethylammonium chloride was filtered off and the filtrate was subjected to t.l.c. (alumina; 1 : 1 cyclohexane–benzene) to give unchanged 2-chloroquinoxaline (0·040 g) and 2-dimethylaminoquinoxaline (0·052 g), m.p. 94° (from chloroform) (lit.,[25] 94—95°) [Found (for material dried at 80°/710 mm for 1 h): C, 69·3; H, 6·4; N, 24·7. Calc. for $C_{10}H_{11}N_3$: C, 69·3; H, 6·4; N, 24·3%].

4-Dimethylamino-1-methylquinolinium Iodide.—A solution of 4-dimethylaminoquinoline [26] (0·10 g) in methyl iodide (2·0 ml) was set aside at 20° for 14 h. The precipitate, filtered off and recrystallised from ethanol–ethyl acetate, gave *4-dimethylamino-1-methylquinolinium iodide* (0·10 g), m.p. 216—218° (Found: C, 45·7; H, 4·8; N, 8·8. $C_{12}H_{15}IN_2$ requires C, 45·9; H, 4·8; N, 8·9%).

1-Dimethylamino-2-methylisoquinoline.—A solution of 1-dimethylaminoisoquinoline (0·50 g) in methyl iodide (5 ml) was set aside at 20° for 19 days. The precipitate (0·49 g), collected and recrystallised from ethanol, gave *1-dimethylamino-2-methylisoquinolinium iodide*, m.p. 189—190° [Found (for material dried at 100°/1 h): C, 45·8; H, 5·0; N, 8·7. $C_{12}H_{15}IN_2$ requires C, 45·9; H, 4·8; N, 8·9%].

4-Dimethylamino-2-methylcinnolinium Iodide.—A solution of 4-dimethylaminocinnoline (0·15 g) in methyl iodide (1·0 ml) was set aside at 20° for 12 h. The precipitate (0·280 g), recrystallised from water gave *4-dimethylamino-2-methylcinnolinium iodide*, m.p. 274—275° (Found: C, 41·7; H, 4·6; N, 12·9. $C_{11}H_{14}IN_3$ requires C, 41·9; H, 4·5; N, 13·3%).

1-Dimethylaminophthalazinium Methiodide.—A solution of 1-dimethylaminophthalazine (2·0 g) in methyl iodide (8·0 ml) was set aside at 20° for 3 days. The precipitate, filtered off and recrystallised from ethanol, gave *1-dimethylaminophthalazinium methiodide* (2·38 g), m.p. 217—218° (Found: C, 42·3; H, 4·7; N, 13·2. $C_{11}H_{14}IN_3$ requires C, 41·9; H, 4·5; N, 13·3%).

3-Dimethylamino-1-methylquinoxalinium Iodide.—2-Dimethylaminoquinoxaline [25] (0·10 g) and methyl iodide (2·0 ml) were set aside at 20° for 12 days. The precipitate, collected and recrystallised from ethanol–light petroleum (b.p. 60—80°), gave *3-dimethylamino-1-methylquinoxalinium iodide* (0·15 g), m.p. 245—246° (Found: C, 42·0; H, 4·9; N, 13·2. $C_{11}H_{14}IN_3$ requires C, 41·9; H, 4·5; N, 13·3%).

Anhydro-base of 4-Hydroxy-2-methylcinnolinium Hydroxide.—4-Dimethylamino-2-methylcinnolinium iodide (0·010 g) and sodium hydroxide (5 ml; 0·1M) were refluxed for 1 h. The mixture was extracted with chloroform, the extract was dried (Na_2SO_4), and the solvent was evaporated. The product, recrystallised from benzene, gave the anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide (0·002 g), m.p. 163—164° (lit.,[5] 163—165°), identical on paper chromotography (3 solvent systems) with an authentic specimen.[5] The u.v. spectrum was identical with that previously recorded.[27]

Hydrolysis of 1-Dimethylaminophthalazinium Methiodide.—1-Dimethylaminophthalazinium methiodide (0·002 g) and sodium hydroxide (50 ml; 0·02M) were refluxed for 1 h. A portion (10 ml) of the reaction mixture was buffered to pH 7 and diluted to 50 ml to afford a u.v. spectrum that was different from that of starting material, 1-hydroxyphthalazine [16] and 2-methyl-1(2*H*)-phthalazone.[16]

Anhydro-base of 3-Hydroxy-1-methylquinoxalinium Hydroxide.—3-Dimethylamino-1-methylquinoxalinium iodide (0·10 g) and sodium hydroxide (40 ml; 0·1M) were refluxed for 1·5 h, cooled, and extracted with chloroform. The extract was dried (Na_2SO_4), the solvent evaporated, and the residue subjected to t.l.c. (alumina; chloroform) to give the product (0·020 g) which, after recrystallisation from light petroleum (b.p. 60—80°), gave a white solid (0·007 g), m.p. 249—250° (Found: N, 17·8%). The u.v. spectrum of this compound was different from that of starting material, 2-hydroxyquinoxaline [28] and 1-methyl-2(1*H*)-quinoxalone.[28] The product is thought to be the *anhydro-base of 3-hydroxy-1-methylquinoxalinium hydroxide* ($C_9H_8N_2O$ requires N, 17·5%).

2(1H)-Quinolone.—Quinolin-2-yltrimethylammonium iodide (0·10 g) and sodium hydroxide (5·0 ml; 3M) were heated at 100° for 20 min. The mixture was adjusted to pH 7, chilled, and filtered and the product recrystallised from water to give 2(1*H*)-quinolone (0·040 g), m.p. 198° (lit.,[29] 198—199°), undepressed on admixture with an authentic specimen.

2-Quinazolone.—A solution of quinazolin-2-yltrimethylammonium chloride (0·050 g) in sodium hydroxide (5·0 ml; 0·4M) was set aside at 20° for 60 min. The mixture was adjusted to pH 5, chilled, and the 2-quinazolone (0·020 g) collected. It was identical on paper chromatography with an authentic specimen.[30]

4-Quinazolone.—(*a*) Quinazolin-4-yltrimethylammonium chloride (0·050 g) was dissolved in sodium hydroxide (5·0 ml; 1M); after 5 min the solution was adjusted to pH 7 and evaporated to dryness. The residue was extracted with ethyl acetate (50 ml) and the product obtained was recrystallised from ethanol to give 4-quinazolone (0·022 g), m.p. 215° (lit.,[17] 215—216°), undepressed on admixture with an authentic specimen.[17]

(b) 4-Chloroquinazoline [17] (0·10 g) was shaken with sodium hydroxide (5·0 ml; 3M) until all had dissolved (*ca.* 10 min). The mixture was then adjusted to pH 7 and evaporated to dryness. The product was extracted in boiling ethyl acetate, and recrystallised from ethanol to give 4-quinazolone (0·070 g), m.p. 215°, undepressed on admixture with an authentic specimen.[17]

Kinetic Procedure.—This procedure was similar to that described in Part VII [2] except for the reactions of quinazolin-4-yltrimethylammonium chloride when the rapid reaction ' stopped flow ' technique [31] was used.

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