Quinazolines. Part VIII.[1] Electronic Effects in 2-Substituted Quinazolines

By W. L. F. Armarego and J. I. C. Smith

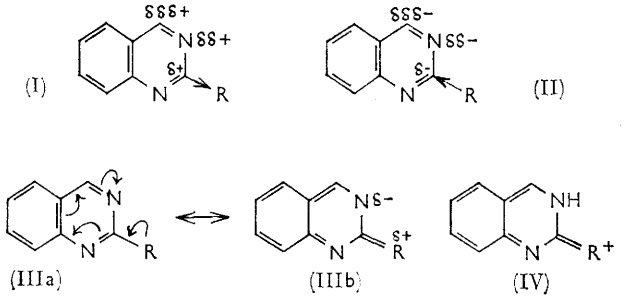
In a study of the cations of twenty 2-substituted quinazolines, it was found that covalent hydration of the 3,4-double bond decreased according to the electronic effect of the 2-substituent; *viz.*, $+I > +M > -I$. This is explained by the effect of the substituent on the polarity of the C-4,N-3 double bond. The effect of the acyl group on the rate of ring closure of *o*-acylaminoacetophenones with alcoholic ammonia at 20° is also described.

It has been stated that in the quinazoline series, substituent groups which make the pyrimidine ring more deficient in electrons also increase the tendency for covalent hydration, whereas substituents which increase the availability of electrons in the pyrimidine ring decrease this tendency.[2] This conclusion was derived from measurements of hydration in quinazolines substituted in the benzene ring. The properties of 2-substituted quinazolines, however, did not appear to comply with this general rule. Of the 2-substituted quinazolines previously examined,[2] 2-methylquinazoline cation was found to be hydrated to at least the same extent as the quinazoline cation, although the methyl group increased the availability of electrons in the pyrimidine ring. Conversely, 2-chloroquinazoline cation was mostly anhydrous. To study this anomaly we have now prepared and examined twenty 2-substituted quinazolines. We conclude that, seemingly, the governing factor is the effect of the substituent in increasing or decreasing the relative electronic charges on C-4 and N-3, and hence the polarisation of the C-4,N-3 double bond, across which covalent hydration occurs. Also, the general availability of electrons in the pyrimidine ring must remain low for water to add reversibly.

Because of its nature, the 3,4 double bond is polarised thus $-\overset{\delta+}{C}=\overset{\delta-}{N}-$. If the amount of hydration depends on this polarisation, then a 2-substituent with a $-I$ effect (*e.g.*, I; R = CF_3) must reduce the electron density at N-3 more than at C-4, act in a direction opposite to the polarisation of the 3,4 double bond, and hence decrease hydration. A 2-substituent with a $+I$ effect (*e.g.*, II; R = Et) increases the electron density at N-3 more than at C-4, assists the polarisation, and increases the amount of hydration. This is the case in the neutral

[1] Part VII, W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*, 1965, 5360.
[2] W. L. F. Armarego, *J. Chem. Soc.*, 1962, 561.

species. In the cations the polarisation is greatly enhanced by the presence of the proton on N-3 or N-1 (compare quinzoline and its cation) but it does not appear to alter the electronic effects. A 2-substituent with a $+M$ effect (*e.g.*, III; R = OMe) would tend to stabilise a canonical form which has no 3,4 double bond, and would tend to reduce the amount of hydration. Although in the latter case the polarisation is such as to enhance hydration, the contribution from the canonical form (IIIb) appears to be quite large, particularly in the cation (*e.g.*, IV compared with 7-methoxyquinazoline cation in ref. 2). It will be shown that these electronic effects influence hydration markedly in the cations (see Table 1). Although the neutral species should show



similar relative differences, they have a very small proportion of hydrated species and hence, for practical purposes have been treated as anhydrous.

TABLE 1

Electronic effects and hydration in 2-substituted quinazoline cations

% Hydration	$+I$ (with weak $+M$)	$+M$ (with weak $-I$)	$-I$
~90—100	–Me	—	—
	–Et		
	-isoPr		
	-t-Bu [a]		
	$-CH_2Cl$		
~5—50	—	$-NH_2$	—
		–NHMe	
		$-NMe_2$	
		–OMe	
		–SMe	
0	—	—	–Cl [b]
			$-CHCl_2$
			$-CF_3$ [c]

[a] This group has only a $+I$ effect. [b] This group has a weak $+M$ effect. [c] This group has a $-M$ effect (see ref. 4).

The spectroscopic, ionisation, and rapid reaction methods used below for observing covalent hydration and for obtaining percentages of hydrated and anhydrous species were as described in ref. 5 and 6. In all cases where covalent hydration was present, negative aldehyde tests with *p*-nitrophenylhydrazine [3] indicated the absence of ring opening.

2-Substituents with a $+I$ *Effect.*—The compounds in this series were 2-methyl-, ethyl-, isopropyl-, and t-butyl-quinazoline. In addition to the $+I$ effect these substituents have a weak $+M$ effect due to hyperconjugation, which falls off with chain branching. Examination of their ultraviolet spectra (Table 2) shows that, in the cation of each, the long-wavelength band is absent, although it is present in 2,4-dimethyl- and 2-t-butyl-4-methyl-quinazoline cations. These spectra are parallel to those of the quinazoline cation, and hence the cations of the 2-alkylquinazolines are all predominantly hydrated. The methods for determining the ratio of hydrated to anhydrous cations were not sufficiently accurate to decide whether they were slightly more (or less) hydrated than the quinazoline cation, although they did show that the percentage of hydrated cation is >98.

The slight base weakening trend found in the 2-alkyl series, as the bulk and branching of the group increases, not observed in 2,4-dimethyl- and 2-t-butyl-4-methyl-quinazolines which are predominantly anhydrous, can probably be ascribed to a steric interference important only in the hydrated species.

2-Substituents with a $-I$ *Effect.*—(a) *Halogenoquinazolines.* These include 2-chloro-, dichloromethyl-, trifluoromethyl-quinazolines and their 4-methyl derivatives, and 2-monochloromethylquinazoline. The chloro-substituted compounds have in addition a weak $+M$ effect, but the trifluoromethyl group has a $-M$ effect, considered to be due to hyperconjugation.[4] Examination of the pK_a values of these quinazolines (except 2-monochloromethylquinazoline, see below) shows that they are very weak bases, and hence there is no appreciable covalent hydration in the cations and neutral species. This conclusion is substantiated by the ultraviolet spectra (see Table 2) of their cations, which closely resemble those of the neutral species and of the cations of the corresponding 4-methyl derivatives, where, as has been previously established,[5] the 4-methyl group in quinazoline is an effective block to hydration.

The ultraviolet spectra of 2-monochloromethylquinazoline, on the other hand, showed that the long-wavelength band in the neutral species had been reduced to a very weak inflexion in the cation. By making use of these spectra the cation was found to be about 90% hydrated. Thus the inductive effect exhibited by the monochloromethyl group, whilst reducing the amount of hydration found in quinazoline and 2-methylquinazoline cations, does not have the drastic dehydrating effect observed when it is replaced by the more strongly electron-withdrawing dichloromethyl group. The kinetics of the decay of the unstable hydrated neutral species were studied by the stopped-flow rapid reaction method. This showed that the reaction was both acid and base catalysed (see Table 3), but the half life of the unstable species at the appropriate pH values was too short (~1 sec.) for the ionisation constants of the hydrated or anhydrous species to be measured.

[3] A. Albert, C. F. Howell, and E. Spinner, *J. Chem. Soc.*, 1962, 2595.
[4] J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Amer. Chem. Soc.*, 1950, **72**, 408.
[5] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.
[6] D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43.

TABLE 2

Ionisation constants [a] and ultraviolet spectra of quinazolines (in water at 20°)

Quinazolines	pK_a	Spread (±)	Concn. 10^{-5}M	λ [b] mμ	λ_{max}, (mμ) [c]	log ε [c]	Species	pH [d]
2-Amino-	4·86 [d]	0·02	8·41	285	232 + *247*; *258*; 350	4·47 + *4·19*; *3·67*; 3·41	0	9·0
	4·83 [e]	0·02	12·51	284	229 + *245* + 247; 284; 347	4·32 + *4·16* + 4·17; 3·64; 3·36	+	0·0
2-Methylamino-	5·02 [d]	0·02	9·08	285	239 + *252*; 363	4·55 + *4·33*; 3·47	0	9·0
	4·98 [e]	0·01	10·29	285	234 + *249*; 285; 350	4·48 + *4·25*; 3·79; 3·59	+	0·0
2-Dimethylamino-	5·26 [d]	0·03	8·59	290	244 + *260*; 375	4·49 + *4·32*; 3·46	0	9·0
	5·24 [e]	0·03	10·86	290	239 + *255*; 289; 365	4·45 + *4·24*; 3·76; 3·66	+	0·0
2-Amino-4-methyl-	5·36	0·04	2·09	280	236 + *245*; 260; 348	4·54 + *4·35*; 3·66; 3·42	0	10·0
					228 + 245; 280; 342	4·36 + 4·27; 3·34; 3·25	+	2·0
4-Methyl-2-methylamino-	5·48	0·04	3·04	280	241 + *250*; *266*; 358	4·57 + *4·38*; *3·90*; 3·42	0	10·0
					234 + 247; 281; 346	4·43 + 4·28; 3·56; 3·45	+	2·0
2-Dimethylamino-4-methyl	6·13	0·02	3·86	270	246 + *259*; 273; 369	4·49 + *4·34*; 4·13; 3·43	0	9·0
					239 + *252*; 282; 355	4·45 + *4·34*; 3·67; 3·64	+	2·0
2-Ethyl- [f]	4·51 [d]	0·03	100		224; 266; 310 + *320*	4·64; 3·38; 3·38 + *3·37*	0	10·0
					261	3·97	+	0·0
2-Isopropyl [f]	4·29 [d]	0·03	250		224; 265; 310 + *320*	4·62; 3·38; 3·38 + *3·27*	0	10·0
					259	3·97	+	0·0
2-t-Butyl-	4·17 [d]	0·04	4·17	260	224; 265; 310 + *320*	4·61; 3·42; 3·35 + *3·24*	0	10·0
					260	3·92	+	0·0
2-t-Butyl-4-methyl-	3·87 [d]	0·02	2·50	240	225; 259; 308 + *318*	4·65; 3·50; 3·43 + *3·38*	0	8·0
					236; 270; 320	4·56; 3·46; 3·39	+	0·0
2-Trifluoromethyl- [g]	−2·23	0·05	4·60	230	228; 280 + *316*	4·58; 3·94 + *3·71*	0	8·0
					242; 286; 334	4·51; 3·30; 3·23	+	−4·0
2-Dichloromethyl- [g]	−0·87	0·06	4·28	245	232; 267; 306 + *320*	4·66; 3·52; 3·34 + *3·25*	0	5·0
					243; 278; 318 + *330*	4·56; 3·52; 3·34 + *3·31*	+	−3·0
2-Chloromethyl-	1·81 [d]	0·05	7·94	270	230; 270; 308 + *318*	4·63; 3·40; 3·33 + *3·27*	0	6·0
					209; 270; *344*	4·16; 3·87; *2·27*	+	−1·0
4-Methyl-2-trifluoromethyl [g]	−1·75	0·03	2·18	240	228; 280; 300 + *315*	4·64; 3·40; 3·39 + *3·31*	0	6·0
					242; 282; 330	4·58; 3·41; 3·37	+	−3·0
2-Dichloromethyl-4-methyl-	+0·11	0·05	4·36	245	231; 264; 316	4·38; 3·30; 3·10	0	7·0
					244; 278; 330	4·32; 3·21; 3·27	+	−2·0
2-Chloro- [g]	−1·60	0·07	2·36	240	231; 274; 316 + *320* [h]	4·61; 3·37; 3·33 + *3·28*	0	5·7
2-Chloro-4-methyl- [g]	−0·75	0·05	4·04	243	231; 270; 314	4·67; 3·40; 3·45	0	5·0
					241; 289 ; 340	4·49; 3·70; 3·30	+	−2·0
2-Methoxy-	1·60 [d]	0·02	3·91	240	222; 235; 265; 326 + *336* [h]	4·51; 4·38; 3·51; 3·46 + *3·38*	0	6·0
					216·5; 238; 293; 337	4·30; 4·44; 3·81; 3·41	+	−1·1
2-Methoxy-4-methyl-	2·32	0·04	6·23	240	*223* + 226 + *234*; 255; 322 + *334*	*4·45* + 4·51 + *4·37*; 3·51; 3·48 + *3·33*	0	6·0
					218 + 237; 290; 330	4·31 + 4·39; 3·66; 3·31	+	0·0
2-Methylthio- [i] (for comparison)	1·60	0·03	2·50	256	257; 342	4·38; 3·43	0	7·0
					249; 269; 321; 357	4·17; 4·25; 3·32; 3·38	+	0·4
4-Methyl-2-methylthio-	1·85	0·05	5·21	255	208; 257; 338	4·43; 4·48; 3·45	0	6·0
					237; 249 + 268; 319; 353	4·09; 4·22 + 4·35; 3·42; 3·67	+	−1·0

[a] Determined spectrophotometrically except where otherwise indicated. [b] Analytical wavelength. [c] Inflexions in italics. [d] $pK_a^{eq.}$. These compounds all exhibit some covalent hydration. [e] $pK_a^{anhyd.}$ determined by stopped-flow rapid reaction technique. [f] pK_a determined potentiometrically. [g] pH values below 0 were obtained in solutions of sulphuric acid to which Hammett's acidity functions have been assigned (M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, *57*, 1). [h] Ultraviolet spectra from W. L. F. Armarego, *J. Chem. Soc.*, 1962, 561. [i] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.

TABLE 3

$t_{0·5}$ Values in seconds (from first-order rates) of 2-substituted quinazolines at various pH values

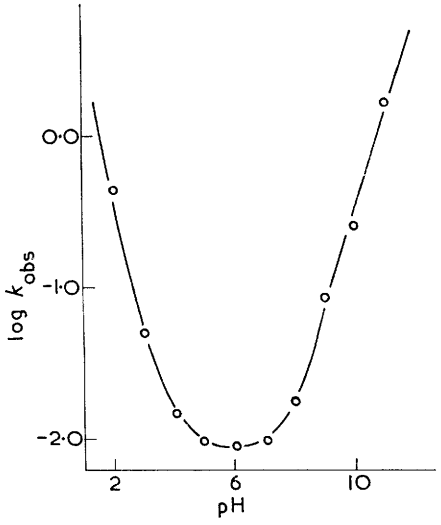
Quinazoline	2·0	3·0	4·0	5·0	6·0	7·0	8·0	9·0	10·0	11·0
Amino-	1·6	13·7	46·8	72·6	75·0	72·8	40·3	8·1	2·7	0·4
Methylamino-	1·0	9·6	—	—	42·5	41·3	29·3	—	5·6	—
Dimethylamino- *	2·1	10·0	—	—	—	—	—	—	—	—
Methylthio-	—	0·5	—	—	1·4	8·7	31·6	1·8	0·5	—
Methoxy-	—	0·6	—	—	2·2	7·5	30·5	2·0	0·7	—
Monochloromethyl-	—	1·2	—	—	1·2	12·5	17·7	11·8	1·4	—

* Change in optical density too small to calculate reliable $t_{0·5}$ values except at pH shown.

(b) *Aminoquinazolines.* The spectra of 2-amino-, methylamino-, and dimethylamino-quinazolines show that the long-wavelength band in the neutral species is also present in the cations, and from a comparison of their extinction coefficients with those of the corresponding 4-methyl compounds it appears that relatively little hydration is present in the cations. By using the stopped-flow rapid reaction method, the kinetics of the unstable hydrated neutral species were observed. From the changes in optical density observed it was calculated that the least amount of hydration in 2-amino-, 2-methylamino-, and 2-dimethylamino-quinazoline cations was 22, 5, and 3%, respectively. Unstable hydrated species were not observed in the corresponding 4-methyl derivatives when using the same method. This study was made at several wavelengths and pH values. The pH-rate (first-order kinetics) profile for 2-aminoquinazoline (Figure 1) is typical of molecules that undergo

reversible covalent hydration.[6] The other compounds measured are given in Table 3 with the rates expressed as half lives.

Although the half life of the unstable neutral species was too short in the appropriate pH range for the ionisation constant of the hydrated species to be determined reliably, that of the anhydrous species was measured accurately for all three 2-aminoquinazolines. This was possible in these examples because the high basic strength of the anhydrous species permitted the kinetic measurements to be carried out in a pH region where they were slow enough to give reliable optical densities at zero time (see ref. 5 and 6). The closeness of the $pK_a^{eq.}$ values and $pK_a^{anhyd.}$ values (for these terms see ref. 5) shows that the amount of hydration in the cations of 2-amino-, methylamino-, and dimethylamino-quinazolines is not more than 30%.



pH-Rate profile for 2-aminoquinazoline

The increase in basic strength from 2-amino-4-methyl- to 2-dimethylamino-4-methyl-quinazolines is larger than the increase in $pK_a^{eq.}$ values from 2-amino- to 2-dimethylamino-quinazoline, and can be attributed to a decrease in hydration between the latter two, thus making the contribution of the more weakly basic anhydrous species to the $pK_a^{eq.}$ values larger. This is more prominent in the 2-aminopteridines, which are considerably more hydrated than 2-aminoquinazolines (cf. 2-amino-, 2-methylamino-, and 2-dimethylamino-pteridine have $pK_a^{eq.}$ values 4·29, 3·62, and 3·03 respectively).[3] This is in agreement with the larger increase in the $+M$ effect over the decrease in $-I$ effect in the series $-NH_2$, $-NHMe$, $-NMe_2$.

(c) *2-Methoxy- and 2-methylthio-quinazoline.* The pH-rate profile for these two compounds is consistent with hydration (see Table 3), and no unstable neutral species was observed in the 4-methyl derivatives when the measurements were made at various pH values and wavelengths. While an accurate determination of the amount of hydration was not possible (because the kinetics were too fast at the required pH values) a comparison of the ionisation constants with those of the corresponding 4-methyl derivatives indicated that 2-methoxyquinazoline cation was hydrated to about the same degree as 2-aminoquinazoline cation, whereas 2-methylthioquinazoline cation was slightly more hydrated. This is in agreement with ratios obtained from a comparison of the intensities of the long-wavelength bands, and with the larger $-I$ and $+M$ effects of the $-OMe$ over the $-SMe$ group.

The above results extend knowledge of the mechanism of hydration. It is generally agreed (cf. ref. 5) that the first step is a nucleophilic attack by OH^- or H_2O on the 4-position, but it now appears that the addition (and retention) of a proton on N-3 (or N-1) makes a significant contribution to the result.

Materials.—2-Methylamino-, 2-dimethylamino-, and 2-methylthio-quinazoline[7] were prepared by replacement of the labile chlorine of 2-chloroquinazoline[7] by the appropriate nucleophile. The reaction with trimethylamine gave a high yield of 2-dimethylaminoquinazoline presumably with loss of chloromethane. 2-Hydroxy-4-methylquinazoline was prepared by reaction of *o*-ethoxycarbonylaminoacetophenone, prepared from *o*-aminoacetophenone and ethylchloroformate, with alcoholic ammonia in a sealed tube. Fusion of *o*-aminoacetophenone with urea gave a charred mass. 2-Chloro-4-methyl-, and from this, 2-amino-, methylamino-, dimethylamino-, methoxy-, and methylthio-4-methyl-quinazoline were then prepared as for the 2-substituted quinazolines.

Attempts to convert *o*-aminobenzaldehyde to the corresponding acylamino derivatives with n-propionic, isobutyric, or pivalic anhydrides at 20° yielded chiefly a high melting material which, by infrared spectral comparison with an authentic sample,* proved to be "trimerised" *o*-aminobenzaldehyde. Traces of acid in the anhydride must have catalysed the trimerisation reaction in preference to acylation. Acylation was therefore carried out with the acid chlorides in the presence of pyridine. With acetic and trifluoroacetic anhydrides the acylation reaction was predominant. 2-Alkyl-, 2-trifluoromethyl-, 2-dichloromethyl-, and 2-monohloromethylquinazoline were prepared from the corresponding *o*-acylaminobenzaldehydes by reaction with saturated alcoholic ammonia at 20°. In each case the reaction was complete within 12 hr. Previously, heating in sealed tubes at high temperatures for long periods has been used.[8] In the ring closure of *o*-acylaminoacetophenones with alcoholic ammonia, it was observed that if the acyl group was trifluoromethyl or dichloromethyl, ring closure was complete within 12 hr. at 20°. *o*-Formylaminoacetophenone required 18 hr. for this ring closure, and when the acylamino group was acetamido or trimethylacetamido, the reaction was complete only after four to five days. The course of

* Kindly supplied by Mr. H. Yamamoto.

[7] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.

[8] J. Siegel and B. E. Christiansen, *J. Amer. Chem. Soc.*, 1951, **73**, 5777.

this reaction was followed by periodic sampling and examination of the ultraviolet spectra and chromatography. It can be concluded that an electron-withdrawing substituent on the acyl group enhances ring closure, whereas an electron-releasing substituent retards it. Although *o*-monochloroacetamidobenzaldehyde gave a 46% yield of 2-chloromethylquinazoline, *o*-monochloroacetamidoacetophenone, under a variety of conditions, failed to yield the required quinazoline. An almost quantitative yield of ammonium chloride was obtained, and as this indicated replacement of the labile chlorine, the investigation was carried no further.

EXPERIMENTAL

Ionisation measurements were made as described in A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, 1962. Microanalyses were by Dr. J. E. Fildes and her staff. Evaporations were carried out in a rotary evaporator at 50°/15 mm., and the alumina used for chromatography was Fluka grade 507c neutral. 2-Amino-[9] and 2-methoxy-[10] quinazolines were prepared as in the references cited.

Analyses, yields, and physical properties of compounds are in Table 4.

2-Alkylquinazolines.—To *o*-aminobenzaldehyde [11] or *o*-aminoacetophenone [12] (0·01 mole) in benzene (10 ml.) containing pyridine (2 ml.) and cooled to 5° was added a solution of the appropriate acid chloride (1·2 equiv.) (or acid anhydride when the substituent was methyl or trifluoromethyl) in benzene (5 ml.), and the mixture was kept at 20° for 15 min. The solution was extracted with water (3 × 20 ml.), the benzene layer dried (Na_2SO_4), and evaporated. The residue in benzene was passed through an alumina column, the eluates evaporated, and the residue crystallised from light petroleum (b. p. 60—80°) if solid, or fractionally distilled if liquid, to yield the appropriate acyl derivatives. The acyl derivative (0·01 mole) in saturated ethanolic ammonia (10 ml.) was kept at 20° for 12 hr. or longer (cf. *Materials*, above) and evaporated. The residue, dissolved in benzene, was passed through an alumina column and the eluates evaporated. The residue was crystallised from light petroleum (b. p. 60—80°) if solid, or distilled if liquid, to give the required 2-alkyl substituted quinazolines.

TABLE 4

Compound	M. p. or b. p.	Yield [a] (%)	Found (%) C	H	N	Formula	Requires (%) C	H	N
o-Aminobenzaldehyde:									
N-Trifluoroacetyl-	69°	55	49·8	2·8	6·5	$C_9H_6F_3NO_2$	49·8	2·8	6·5
N-n-Propionyl-	46	66	67·5	6·0	8·1	$C_{10}H_{11}NO_2$	67·8	6·2	7·9
N-Isobutyryl-	118/0·35 mm.	60	68·8	6·7	7·2	$C_{11}H_{13}NO_2$	69·1	6·9	7·3
N-Trimethylacetyl-	98/0·5 mm.	60	70·3	7·3	7·0	$C_{12}H_{15}NO_2$	70·2	7·4	6·8
N-Monochloroacetyl-	107	61	54·9	4·1	7·2	$C_9H_8ClNO_2$	54·7	4·1	7·1
N-Dichloroacetyl-	72	31	46·6	3·0	6·0	$C_9H_7Cl_2NO_2$	46·6	3·0	6·0
N-Trichloroacetyl-	78	89	41·2	2·3	5·4	$C_9H_6Cl_3NO_2$	41·5	2·3	5·3
o-Aminoacetophenone:									
N-Trimethylacetyl-	75	50	71·3	7·9	6·4	$C_{13}H_{17}NO_2$	71·2	7·8	6·4
N-Trifluoroacetyl-	115	70	51·9	3·5	6·0	$C_{10}H_8F_3NO_2$	52·0	3·5	6·1
N-Monochloroacetyl-	81	77	57·1	4·6	6·9	$C_{10}H_{10}ClNO_2$	56·7	4·7	6·6
N-Dichloroacetyl-	96	60	48·7	3·7	5·8	$C_{10}H_9Cl_2NO_2$	48·8	3·7	5·7
N-Ethoxycarbonyl-	90	75	63·9	6·2	6·7	$C_{11}H_{13}NO_3$	63·8	6·3	6·8
Quinazoline:									
2-Ethyl	77/0·9 mm.[b]	90	75·5	6·2	17·9	$C_{10}H_{10}N_2$	75·9	6·4	17·7
2-Isopropyl-	95/0·5 mm.[c]	85	77·0	7·1	16·2	$C_{11}H_{12}N_2$	76·7	7·0	16·3
2-t-Butyl-	74/0·3 mm.	70	77·7	7·8	14·7	$C_{12}H_{14}N_2$	77·4	7·6	15·0
2-Trifluoromethyl-	72/0·2 mm. / 63	80	54·4	2·5	14·3	$C_9H_5F_3N_2$	54·5	2·5	14·2
2-Monochloromethyl-	93	46	60·4	3·9	15·7	$C_9H_7ClN_2$	60·5	3·9	15·7
2-Dichloromethyl-	132	63	50·6	2·9	13·0	$C_9H_6Cl_2N_2$	50·7	2·8	13·1
2-Methylamino-	92	52	68·0	5·8	26·3	$C_9H_9N_3$	67·9	5·7	26·4
2-Dimethylamino-	86	67	69·6	6·3	24·1	$C_{10}H_{11}N_3$	69·4	6·4	24·3
2-Hydroxy-4-methyl-	230	75	66·4[d]	5·0	17·1	$C_9H_8N_2O$	67·5	5·0	17·5
2-Chloro-4-methyl-	112	48	60·6	3·9	15·7	$C_9H_7ClN_2$	60·5	3·9	15·7
2-Methoxy-4-methyl-	116/1·0 mm.	30	68·8	5·8	15·9	$C_{10}H_{10}N_2O$	69·0	5·8	16·1
4-Methyl-2-methylthio-	71	20	63·3	5·1	14·7	$C_{10}H_{10}N_2S$	63·2	5·3	14·7
2-Amino-4-methyl-	155	80	67·5	5·7	26·2	$C_9H_9N_3$	67·8	5·7	26·4
4-Methyl-2-methylamino-	103	70	69·0	6·5	24·5	$C_{10}H_{11}N_3$	69·3	6·4	24·3
2-Dimethylamino-4-methyl-	124/1·0 mm.	80	70·2	7·2	22·8	$C_{11}H_{13}N_3$	70·5	7·0	22·4
2-t-Butyl-4-methyl	118/1·0 mm.	50	77·6	8·1	14·3	$C_{13}H_{16}N_2$	78·0	8·1	14·0
4-Methyl-2-trifluoromethyl-	50	87	56·5	3·4	13·0	$C_{10}H_7F_3N_2$	56·6	3·3	13·2
2-Dichloromethyl-4-methyl-	141	65	52·7	3·6	12·1	$C_{10}H_8Cl_2N_2$	52·9	3·5	12·3

[a] Yields quoted are of analytically pure material. [b] A. Bischler and M. Lang, *Ber.*, 1895, **28**, 279, gave b. p. 247—249°/722 mm. [c] A. Bischler and M. Lang, ref. *b*, gave b. p. 253—255°/722 mm. [d] Low carbon due to difficulties in combustion.

2-Methylamino- and 2-Dimethylamino-quinazolines.—2-Chloroquinazoline (0·4 g.) and the appropriate ethanolic amine solution (10 ml., 30%) was heated at 130° for 6 hr. in a sealed tube. The solvent was evaporated, the residue

[9] H. J. Rodda, *J. Chem. Soc.*, 1956, 3508.
[10] M. T. Bogert and C. E. May, *J. Amer. Chem. Soc.*, 1909, **31**, 507.
[11] L. I. Smith and J. W. Opie, *Org. Synth.*, 1955, Coll. Vol. **3**, 56.
[12] G. A. Reynolds and C. R. Hauser, *Org. Synth.*, 1950, **30**, 70.

was passed through an alumina column as before, sublimed at 90°/0·5 mm., and recrystallised from light petroleum (b. p. 60—80°).

2-*Hydroxy*-4-*methylquinazoline*.—Ethyl chloroformate (5·4 g., 0·5 mol.) was added cautiously, with stirring, to *o*-aminoacetophenone (4·45 g., 0·3 mol.). When a heavy precipitate had formed (~10 min.), a solution of sodium hydroxide (2 g., 0·5 mol.) in water (10 ml.) was added, and the mixture stirred for 1 hr. It was extracted with chloroform (3 × 10 ml.); the extract was dried, evaporated, and the residue crystallised from light petroleum (b. p. 60—80°) and sublimed at 85°/0·5 mm. to give o-*ethoxycarbonylaminoacetophenone*. This (7·0 g.) was heated with ethanolic ammonia (10 ml.) in a sealed tube at 110° for 6 hr., evaporated, and the residue dissolved in a large volume of boiling ethanol; decolorisation with charcoal, filtration, and dilution of the filtrate with light petroleum (b. p. 40—60°) gave 2-*hydroxy*-4-*methylquinazoline*.

2-*Chloro*-4-*methylquinazoline*.—2-Hydroxy-4-methylquinazoline (3 g.) was refluxed with phosphorus pentachloride (3·5 g., 1 equiv.) and phosphoryl chloride (10 ml.) until all the solid had dissolved, then for a further 10 min. Excess phosphoryl chloride was evaporated, and the residue in chloroform (20 ml.) was washed with saturated aqueous sodium hydrogen carbonate until the washings were alkaline. The dried (Na_2SO_4) chloroform layer was evaporated, and the residue passed through an alumina column as before, sublimed at 100°/0·5 mm., and recrystallised from light petroleum (b. p. 60—80°) to give 2-*chloro*-4-*methylquinazoline*.

2-*Methoxy*-4-*methylquinazoline*.—To a solution of sodium (0·1 g.) in methanol (7 ml.) was added 2-chloro-4-methylquinazoline (0·5 g.); the mixture was heated gently for 10 min., then kept overnight at 20°. The sodium chloride was filtered off, the filtrate evaporated, and the residual oil was passed through an alumina column as before, and fractionally distilled to give 2-*methoxy*-4-*methylquinazoline*.

4-*Methyl*-2-*methylthioquinazoline*. — 2-Chloro-4-methylquinazoline (0·5 g., 0·4 mol.), thiourea (0·5 g., 0·6 mol.), and methanol (10 ml.) were heated under reflux for 1 hr., the solvent evaporated, and the residue was heated at 100° for 1 hr. in 2·5N-sodium hydroxide (10 ml.). This solution was acidified with acetic acid, and the crude 2-mercapto-4-methylquinazoline which precipitated was filtered off, washed free from acid, dissolved in N-sodium hydroxide (20 ml.), shaken with methyl iodide (1 ml.) for 30 min., and extracted with chloroform (3 × 20 ml.); the chloroform layer was dried (Na_2SO_4) and evaporated. The residue was passed through an alumina column as before, and 4-*methyl*-2-*methylthioquinazoline* sublimed at 65°/0·5 mm. and recrystallised from light petroleum (b. p. 60—80°).

2-*Amino*-, 2-*Methylamino*-, *and* 2-*Dimethylamino*-4-*methylquinazoline*.—2-Chloro-4-methylquinazoline (0·25 g.) with a saturated ethanolic solution of ammonia, methylamine, or dimethylamine was heated at 130° for 6 hr. as described above for 2-aminoquinazoline, giving 2-*amino*- and 2-*methylamino*-4-*methylquinazoline*, which were sublimed at 150 and 100° (both at 0·5 mm.), respectively, and recrystallised from benzene–light petroleum (b. p. 40—60°), and 2-*dimethylamino*-4-*methylquinazoline*, which was distilled.

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Department of Medical Chemistry
Institute of Advanced Studies,
Australian National University,
Canberra, A.C.T., Australia.

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