997. *Quinazolines. Part VII.*[1] *Steric Effects in 4-Alkylquinazolines*

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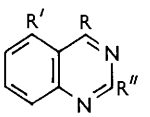
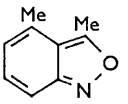
The cations of 4,5-dimethyl- and 2,4,5-trimethyl-quinazoline, unlike the cation of 4-methylquinazoline, are predominantly hydrated. This hydration is shown to take place across the 3,4-double bond as in the cation of quinazoline. The proportion of hydrated species in 4-methyl-, 4-ethyl-, and 4-isopropyl-quinazoline cations increases in that order. Both these results are explained by overcrowding of the substituents on C-4 and C-5. Catalytic reduction of 4-alkylquinazolines to the corresponding 3,4-dihydro-derivatives is described together with an improved preparation of quinazoline itself.

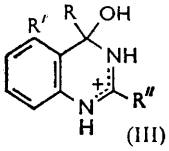
One of the most effective ways to locate the carbon atom (now known to be C-4) involved in the covalent hydration of the quinazoline cation was found to be the insertion of a methyl group which, when placed on C-4, inhibited the addition of water.[2] This effect of the methyl group has also been successfully used to diagnose the position of hydration in other heterocyclic systems.[3] Although both the steric and electronic effects of the methyl group can act in inhibiting nucleophilic attack on C-4 in 4-methylquinazoline, it was shown that in the quinazolines the former was the major influence.[2] This conclusion was based on the evidence that 4-cyano- and 4-chloro-quinazolines, in which the substituents have electronic effects opposite to that of a methyl group on C-4, also have predominantly anhydrous cations. We investigated further the effect of the 4-alkyl substituent in quinazoline in order to confirm this point because of possible objections to the validity of earlier results in view of the rapid hydrolysis of 4-chloro- and 4-cyano-quinazolines in acid solution. We now report that the cations of 4,5-dimethyl- (I; R = R′ = Me, R″ = H) and 2,4,5-trimethyl-



(I)



(II)



(III)

quinazoline (I; R = R′ = R″ = Me) (where the electronic effect of the 4-methyl group is barely altered but in which the steric effect is decreased by intramolecular overcrowding with the 5-methyl group) are predominantly hydrated across the 3,4-double bond. We have also shown that the amount of hydration in the 4-alkylquinazoline cations increases in the order Me, Et, Pr^{i}, which, contrary to the order of the electronic and direct steric effects, is in accordance with the increased steric interaction of the substituent with C-5 and H-5 of the benzene ring.

4,5-Dimethylquinazoline.—2-Methyl-6-aminoacetophenone, an intermediate common to the preparation of 4,5-dimethyl- and 2,4,5-trimethyl-quinazoline, was prepared by reduction of the corresponding nitro-compound with a large excess of tin and hydrochloric acid. Reduction under conditions used for preparing *o*-aminoacetophenone [4] gave a high yield of a compound, m. p. 82°, which proved to be 3,4-dimethylanthranil (II). Its structure was deduced from the weak basic properties (pK_a −1·22) consistent with those of anthranil and 3-methylanthranil, and by the close similarity of the ultraviolet spectra with those of the anthranils (see Table). 3,4-Dimethylanthranil, always formed during these reductions even with large excesses of the reducing agent, is possibly formed by the buttressing effect on the acetyl group by the 2-methyl group. The aminoacetophenone was then

[1] Part VI, W. L. F. Armarego and R. E. Willette, *J.*, 1965, 1258.
[2] A. Albert, W. L. F. Armarego, and E. Spinner, *J.*, 1961, 2689.
[3] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.
[4] J. C. E. Simpson, C. M. Atkinson, K. Schofield, and O. Stephenson, *J.*, 1945, 646.

acylated and the derivatives heated with ethanolic ammonia to give the required quinazolines.

The general features of the ultraviolet spectra of the neutral species of 4,5-dimethyl- and 2,4,5-trimethyl-quinazoline show them to be typical quinazolines. Whereas the spectra of their cations in water differ markedly from that of the 4-methylquinazoline cation, they are similar to that of the quinazoline cation. In quinazoline itself this was shown [2] conclusively to be due to the formation of the cation (III; R = R′ = R″ = H). This fact suggested that the cations of 4,5-dimethyl- and 2,4,5-trimethyl-quinazoline, unlike the neutral species, are predominantly hydrated. Confirmatory evidence was found in their ionisation data. Thus, the difference in basic strength between 4,5-dimethyl- and 4-methyl-quinazoline (4·16 − 2·83 = 1·33 pK units), and 2,4,5-trimethyl- and 2,4-dimethyl-quinazoline (4·75 − 3·60 = 1·15) is much larger than would be expected (~0·2 pK unit) from inserting a methyl group in the 5-position. For example, a methyl group in the benzene ring of quinoline has a base-strengthening effect of 0·2—0·3 pK_a unit,[5] also a methyl group in the benzene ring of quinazoline is base-strengthening by 0·2 pK unit for the anhydrous species.[6] The large base-strengthening effect observed in the 4,5-dimethyl-quinazolines is characteristic of covalent hydration.[3] Evidence for the formation of the hydrated cations (III; R = R = R″ = Me) and (III; R = R′ = Me, R″ = H) was obtained by neutralising solutions of these cations with alkaline buffers using a rapid-reaction apparatus [7] and observing the rate of change of optical density (first-order rates) of the hydrated neutral species at 235 mμ. The half-lives at 20° were 28 sec. at pH 9·07 and 31 sec. at pH 9·01 for 4,5-dimethyl- and 2,4,5-trimethyl-quinazoline, respectively. However, these cations, although predominantly hydrated, are less hydrated than the quinazoline cation because the ultraviolet spectra show that each has a weak long-wavelength band at ~346 mμ (see Table) with extinction coefficients of 794 and 676 for the dimethyl and trimethyl derivatives, respectively. These bands must be due to a small amount of anhydrous cation because their intensities increased when the spectra were measured in strong acid solutions, and reached almost the intensity of the corresponding long-wavelength band of the neutral species when the solutions consisted mostly of the mono-cations. By using the equation $pK_a^{eq} = pK_a^{anhd} + \log(1 + r)$, where r is the ratio of hydrated to anhydrous species in the cation (see ref. 8), and 3·0 for the pK_a^{anhd} value of 4,5-dimethylquinazoline, it is found that the percentage of the hydrated species in the cation is ~90. A similar percentage is obtained for the trimethylquinazoline. Conclusive evidence for the structure (III) is shown by the fact that 2,4,5-trimethylquinazoline is hydrated to the same extent as the 4,5-dimethyl compound, which excludes the possibility of water addition across the 1,2-double bond.

4-*Alkylquinazolines.*—4-Ethyl- and 4-isopropyl-quinazolines were prepared by reaction of the appropriate alkylmagnesium halide and quinazoline to give the 3,4-dihydro-derivatives which were oxidised with potassium ferricyanide as described in the literature.[8] We isolated and anlysed the free bases of both the quinazolines and their 3,4-dihydro-derivatives. Previously only the picrates of the former were known, and the dihydro-compounds had been oxidised without purification.[9] Similarly, we prepared 4-t-butyl-3,4-dihydroquinazoline but attempts to oxidise this as above to 4-t-butylquinazoline gave quinazoline in over 50% yield, with loss of the t-butyl group. Attempted oxidation with potassium permanganate or iodine, or hydrogen transfer with ethyl cinnamate in the presence of 5% palladium–charcoal, failed. The reason for this failure was revealed by examination of molecular models (Leybold). These showed that the rotation of the alkyl group in 4-t-butylquinazoline was largely restricted by H-5 but is less restricted in

[5] R. Riccardi and M. Bresesti, *Ann. Chim.* (*Italy*), 1948, **48**, 826.
[6] J. W. Bunting and D. D. Perrin, personal communication.
[7] D. D. Perrin, *Adv. Heterocyclic Chem.*, 1965, **4**, 43.
[8] W. L. F. Armarego, *J.*, 1963, 561.
[9] T. Higashino, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 1043.

Physical properties of anthranils and quinazolines (H_2O, 20°)

	Ionisation [a]				Spectroscopy [b]			
	pK_a	Spread (±)	Concn. (M)	A.w.l.[c]	$\lambda_{max.}$ (mμ)	log ε	Species [d]	pH or H_0
Anthranils								
Unsubstituted	−2·22	0·03	$6·85 \times 10^{-5}$	258	*215*; *247* + *252* + 257 + 262 + 267 + 273 + 279; 306	*3·58*; *3·07* + *3·12* + 3·22 + 3·29 + 3·33 + 3·32 + 3·44; 3·63	0	3·0
					220; 256 + *276*; 312	4·28; 3·82 + *3·14*; 3·32	+	−4·0
3-Methyl	−1·24	0·05	$1·16 \times 10^{-4}$	250	*215*; *252* + 256 + 260 + 266 + *271* + 278; 318	*3·73*; *3·29* + 3·33 + 3·32 + 3·31 + *3·24* + 3·26; 3·62	0	3·0
					218; 252 + *274*; 312	4·24; 3·80 + *2·77*; 3·19	+	−4·0
3,4-Dimethyl	−1·22	0·06	$1·39 \times 10^{-4}$	265	*215*; *256* + *260* + 267 + *272* + 279; 322	*3·79*; *3·06* + 3·06 + 3·11 + *3·05* + 3·11; 3·69	0	3·0
					266 + *275*; 342	3·64 + *3·54*; 3·51	+	−4·0
Quinazolines								
4-Methyl [e]	2·83	0·03	$2·87 \times 10^{-5}$	235	223; 270; 305 + *314*	4·62; 3·45; 3·45 + *3·41*	0	7·0
					234; 270 + 279; 323	4·52; 3·47 + 3·45; 3·34	+	0·3
4-Ethyl	3·07	0·04	$1·57 \times 10^{-4}$	306	224; 271; 306 + *314*	4·62; 3·43; 3·47 + *3·43*	0	7·0
					236; 261; 323	4·27; 3·68; 3·11	+	1·0
4-Isopropyl	3·06	0·04	$1·58 \times 10^{-4}$	306	224; 271; 306 + *315*	4·57; 3·42; 3·47 + *3·42*	0	7·0
					237; 267; 322	4·14; 3·67; 3·01	+	1·0
4,5-Dimethyl	4·16	0·03	$1·00 \times 10^{-5}$	234	232; 280; 317	4·57; 3·44; 3·50	0	10·0
					243; 264 + *289*; 345	4·15; 3·76 + *3·48*; 2·90	+	2·0
2,4,5-Trimethyl	4·75	0·05	$1·04 \times 10^{-5}$	235	233; 274; 319	4·59; 3·42; 3·52	0	10·0
					244; 261 + *290*; 347	4·15; 3·81 + *3·43*; 2·83	+	2·0
3,4-Dihydroquinazolines [f]								
4-Ethyl	9·21	0·05	$1·60 \times 10^{-5}$	300	217 + *228*; 291	4·07 + *4·05*; 3·80	0	12·0
					213 + *217* + *223*; 276	4·22 + *4·18* + *4·01*; 3·69	+	2·0
4-Isopropyl	9·21	0·02	$2·94 \times 10^{-5}$	290	222 + *228*; 290	4·18 + *4·08*; 3·80	0	12·0
					213 + *217* + *224*; 277	4·23 + *4·22* + *3·98*; 3·66	+	2·0
4-t-Butyl [g]	9·36	0·02	0·005		*218* + 223; 287	*4·00* + 4·06; 3·74	0	11·5
					213 + *218*; 276	4·22 + *4·19*; 3·67	+	7·0

[a] Measured spectrophotometrically as described in A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962, and buffers used had ionic strength 0·01 (see D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572). [b] Inflexions are in italics. [c] A.w.l., analytical wavelength (mμ). [d] Neutral species, 0; cation, +. [e] A. Albert, D. J. Brown, and H. C. S. Wood, *J.*, 1954, 2832 gave pK_a 2·52 by the potentiometric method. [f] For parent substance see ref. 2. [g] Determined potentiometrically.

4-isopropylquinazoline; on the other hand, there was no restricted rotation in the 3,4-dihydro-derivatives. Other attempts to prepare 4-t-butylquinazoline failed.

A study of many substituted quinazolines showed [8] that the quinazoline cations which were a mixture of hydrated and anhydrous species had ultraviolet spectra in which the intensity of the long-wavelength band was considerably smaller than that of the long-wavelength band in the neutral species. Because this band disappeared in the predominantly hydrated cations and was of intensity comparable with that of the corresponding neutral species in the predominantly anhydrous cations, a rough estimate was made of the ratio of hydrated to anhydrous species in the cations.[8] An examination of the spectra of 4-methyl-, 4-ethyl-, and 4-isopropyl-quinazoline cations revealed that the molecular extinction coefficients of the long-wavelength band decreased in the order 2190, 1290, and 1024 (the intensity of these bands increased on increasing the acid strength of the solutions). The extinction coefficients of this band in the neutral species are 2820, 2955, and 2929, respectively. Therefore the percentages of hydrated cation in 4-methyl-, 4-ethyl-, and 4-isopropyl-quinazolines are roughly in the order 22, 57, and 65.

The n.m.r. spectra of these quinazoline cations, measured at 33° in aqueous hydrochloric acid, revealed a mixture of anhydrous and hydrated cations, but it was not possible to measure ratios because the spectra overlapped considerably. Examination of the ultraviolet spectra of 4-methylquinazolines at 20 and 33° showed that, whereas there was no change in intensity of the long-wavelength band in the neutral species, there was an increase in intensity of this band in the cation corresponding to an increase of ~5% of anhydrous species.

The pK_a (equilibrium) values of the 4-alkylquinazolines (see Table) are in the order Me $<$ Et $\simeq$ Pr^i, and when the above equation is used the percentages of hydrated cation agree with those obtained from the spectra. However, the small differences between the pK_a^{eq} and pK_a^{anhd} values discourage more accurate comparisons. It must be pointed out that percentages obtained from pK_a values only are more accurate when the amount of hydration in the cations is very large.

Catalytic Reduction of 4-Alkylquinazolines.—A qualitative study of the reduction of quinazoline, 2-methyl-, 4-methyl-, 4-ethyl-, and 4-isopropyl-quinazolines with 5% palladium–charcoal in ethanol under strictly comparable conditions was made. These reductions were followed spectrophotometrically (see the spectra of these quinazolines and the corresponding 3,4-dihydro-derivatives in the Table and refs. 10 and 11), and by paper chromatography.[10] Large differences in rate of reduction (all to 3,4-dihydro-derivatives) warrant comment. Thus, quinazoline and its 2-methyl derivative were quantitatively reduced in 45 min., but the reduction of 4-methyl and 4-ethyl derivatives was incomplete in 10 hr. and complete after 16 hr. On the other hand, 4-isopropylquinazoline was quantitatively reduced in 7 hr., *i.e.*, faster than the ethyl and methyl derivatives, and this may be attributed to the larger sp^3 character at C-4 because the molecules are non-planar. There was no evidence of the catalyst being poisoned because reduction of oxygen proceeded normally on introduction of air into the apparatus after the quinazolines were reduced. The important features of these reductions are that the alkyl group at the site of reduction considerably lowers the rate, and that the 1,2-double bond is not reduced before the 3,4-double bond because in all cases no tetrahydroquinazolines were formed when the absorption of hydrogen had almost ceased.

Experimental

Microanalyses were by Dr. J. E. Fildes and her staff. Evaporations were carried out in a rotary evaporator at 50°/15 mm. and the purity of materials was examined as before.[8] Ether (B.D.H. AnalaR) for reactions was dried over molecular sieves (Union Carbide type 4 A; 100 g. for 2·5 l.) for 24 hr. before use. Extracts were dried over anhydrous sodium sulphate. 2-Methyl- and 4-methyl-quinazolines,[2] 3,4-dihydro- and 2-methyl-3,4-dihydro-quinazolines,[10]

[10] W. L. F. Armarego, *J.*, 1961, 2697.

4-methyl-3,4-dihydroquinazoline,[11] and t-butylmagnesium chloride [12] were prepared as in the references cited.

2-Methyl-6-nitrobenzoic Acid.—2-Amino-3-nitrotoluene [13] was converted into 2-amino-6-nitrobenzonitrile by diazotisation and reaction with cuprous cyanide as before.[14] The nitrile (3·0 g.) in sulphuric acid (20 ml.; 62% v/v) was heated at 100—110° for 1 hr., poured into boiling water (75 ml.), decolourised, cooled, and the precipitate collected, dried, and recrystallised from benzene–light petroleum (b. p. 40—60°) to give 2-methyl-6-nitrobenzamide (2·9 g., 80%), m. p. 158° (lit.,[14] 158°) (Found: C, 53·4; H, 4·4; N, 15·9. Calc. for $C_8H_8N_2O_2$: C, 53·3; H, 4·4; N, 15·6%). Conditions previously described [14] gave a tar. Reduction of the amide with saturated potassium nitrite solution as before [14] gave 2-methyl-6-nitrobenzoic acid (90%), m. p. 155° (lit.,[14] 151—152°) (Found: C, 53·4; H, 3·9; N, 7·9. Calc. for $C_8H_7NO_4$; C, 53·0; H, 3·9; N, 7·7%).

2-Methyl-6-nitroacetophenone.—2-Methyl-6-nitrobenzoyl chloride [4·7 g., prepared from the acid with thionyl chloride and recrystallised from light petroleum (b. p. 60—80°)] in dry ether (20 ml.) was added slowly to a stirred ethereal solution of diethyl ethoxymagnesium malonate (prepared [15] from 5 ml. of ethyl malonate), refluxed for 1½ hr., and decomposed with 4N-sulphuric acid. The ethereal layer was separated, evaporated, and the residue in acetic acid (10 ml.), water (6 ml.), and sulphuric acid (2 ml.; *d* 1·84) was refluxed for 4 hr. After being cooled and, basified with sodium hydrogen carbonate, the solution was extracted with ether and the dried extract evaporated. Distillation of the residue gave *2-methyl-6-nitroacetophenone* (3·2 g., 70%), b. p. 108°/1 mm., and m. p. 37° after sublimation at 35°/0·5 mm. and recrystallisation from light petroleum (b. p. 40—60°) (Found: C, 60·1; H, 4·9; N, 7·7. $C_9H_9NO_3$ requires C, 60·3; H, 5·1; N, 7·8%).

2-Methyl-6-aminoacetophenone.—To 2-methyl-6-nitroacetophenone (2 g.) in boiling hydrochloric acid (18 ml.; *d* 1·18) was added tin (3·6 g.) in small portions and boiling continued until the metal dissolved. The cooled solution was made strongly alkaline with 5N-sodium hydroxide and extracted with ether, and the ethereal solution washed with water and extracted with 0·1M-sulphuric acid. The acid solution (some anthranil which was always formed remained in the ethereal solution because of its weak basic properties) was then basified with N-sodium hydroxide and extracted again with ether. The dried extract was evaporated and the residue distilled to give *2-methyl-6-aminoacetophenone* (1·75 g., 90%), b. p. 81°/0·2 mm., and m. p. 60° after sublimation at 50°/0·3 mm. and recrystallisation from light petroleum (b. p. 60—80°) (Found: C, 72·3; H, 7·4; N, 9·3. $C_9H_{11}NO$ requires C, 72·3; H, 7·4; N, 9·4%).

3,4-Dimethylanthranil.—2-Methyl-6-nitroacetophenone (0·16 g.) in acetic acid (3 ml.) was treated with tin (0·5 g.) and refluxed for 1 hr., cooled, basified with sodium hydrogen carbonate, and extracted with chloroform. The residue from the extract was sublimed at 75°/0·3 mm. and recrystallised from light petroleum (b. p. 60—80°) to give *3,4-dimethylanthranil* (0·1 g., 78%), m. p. 82° (Found: C, 73·4; H, 6·1; N, 9·4. C_9H_9NO requires C, 73·45; H, 6·1; N, 9·5%).

When *o*-nitroacetophenone was reduced as above, 3-methylanthranil (80%), b. p. 91°/1 mm. (lit.,[16] 117°/15 mm.) was obtained. Similarly *o*-nitrobenzaldehyde gave anthranil (20%), b. p. 75°/1 mm. (lit.,[17] 93°/9 mm.).

2,4,5-Trimethylquinazoline.—2-Methyl-6-aminoacetophenone (1·5 g.) in dry pyridine (5 ml.) at 5° was treated with acetyl chloride (0·95 ml., 1·2 equiv.) and kept at room temperature for 1 hr. Water (20 ml.) was added and the solution extracted with chloroform. The residue from the dried extract was sublimed at 80°/0·5 mm. and recrystallised from light petroleum (b. p. 60—80°) to give *2-methyl-6-acetylaminoacetophenone* (1·3 g., 80%), m. p. 97° (Found: C, 69·0; H, 7·2; N, 7·4. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·85; N, 7·3%). The acetyl derivative (0·8 g.) in saturated ethanolic ammonia (20 ml.) was heated in a sealed tube at 130° for 5 hr., the solvent evaporated, and the residue sublimed at 70°/0·3 mm. and recrystallised from light petroleum (b. p. 60—80°) to give *2,4,5-trimethylquinazoline* (0·52 g., 70%), m. p. 83° (Found: C, 76·5; H, 6·7; N, 16·1. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0; N, 16·3%).

4,5-Dimethylquinazoline.—2-Methyl-6-aminoacetophenone (0·2 g.) and anhydrous formic

[11] A. Albert, W. L. F. Armarego, and E. Spinner, *J.*, 1961, 5267.
[12] S. V. Puntambeker and E. A. Zoellner, *Org. Synth.*, 1941, Coll. Vol. I, 524.
[13] J. C. Howard, *Org. Synth.*, 1955, **35**, 3.
[14] S. Gabriel and A. Thieme, *Ber.*, 1919, **52**, 1079.
[15] G. A. Reynolds and C. R. Hauser, *Org. Synth.*, 1950, **30**, 70.
[16] K. von Auwers, *Ber.*, 1924, **27**, 461.
[17] J. W. Brühl, *Ber.*, 1903, **36**, 3634.

acid (0·06 g.) was boiled for 15 min., evaporated, and distilled, b. p. 170—180°/1 mm. This, in ethanolic ammonia as above, gave 4,5-*dimethylquinazoline* (0·12 g., 50%), m. p. 88°, which was hygroscopic (Found: C, 75·1; H, 6·8; N, 17·4. $C_{10}H_{10}N_2 \cdot \frac{1}{8}H_2O$ requires C, 75·1; H, 6·4; N, 17·5%).

4-*t-Butyl*-3,4-*dihydroquinazoline*.—t-Butylmagnesium chloride [12] (from 27 ml. of t-butyl chloride and 6·1 g. of magnesium in 130 ml. of dry ether) was added slowly to a stirred solution of quinazoline (6·5 g.) in dry ether (50 ml.) and the sludge boiled for 1 hr. then kept at 20° overnight. The mixture was decomposed with 20% aqueous sulphuric acid, the ether separated, and the aqueous layer basified and extracted with chloroform. Evaporation of the extract gave a pasty residue which was treated with an excess of saturated ethanolic picric acid. The picrate, which finally solidified, was collected and recrystallised from methanol to give 4-t-*butyl*-3,4-*dihydroquinazoline picrate* (7·0 g., 35%), m. p. 190—191° (Found: C, 52·0; H, 4·5; N, 16·9. $C_{18}H_{19}N_5O_7$ requires C, 51·8; H, 4·6; N, 16·8%). This was decomposed in the usual manner [11] and 4-*t-butyl*-3,4-*dihydroquinazoline*, b. p. 141—143°/0·2 mm. (25% overall yield) was isolated as a thick hygroscopic oil which solidified on standing (Found: C, 76·5; H, 8·5; N, 14·7. $C_{12}H_{16}N_2$ requires C, 76·55; H, 8·6; N, 14·9%).

Reactions similar to the above but with 1·2 equivalent of alkylmagnesium halide gave: 4-*ethyl*-3,4-*dihydroquinazoline picrate* (36%), m. p. 192—194° (Found: C, 49·35; H, 4·0; N, 18·2. $C_{16}H_{15}N_5O_7$ requires C, 49·4; H, 3·9; N, 18·0%) and 4-*ethyl*-3,4-*dihydroquinazoline* (34% overall yield), b. p. 138°/0·5 mm. (Found: C, 74·7; H, 7·5; N, 17·3. $C_{10}H_{12}N_2$ requires C, 75·0; H, 7·55; N, 17·5%); and 3,4-*dihydro*-4-*isopropylquinazoline picrate*, m. p. 139—140 and 160° (dimorphic, 52% yield) (Found: C, 50·3; H, 4·1; N, 17·7. $C_{17}H_{17}N_5O_7$ requires C, 50·6; H, 4·25; N, 17·4%) and 3,4-*dihydro*-4-*isopropylquinazoline* (43% overall yield), b. p. 152—154°/0·6 mm. (Found: C, 75·8; H, 8·0; N, 16·2. $C_{11}H_{14}N_2$ requires C, 75·8; H, 8·1; N, 16·1%). The bases were stored as their more stable picrates from which they were liberated and distilled before use.

4-*Ethylquinazoline*.—4-Ethyl-3,4-dihydroquinazoline (1·43 g.) in benzene (75 ml.) and potassium ferricyanide (9 g.) in potassium hydroxide solution (5 g. in 38 ml. water) were shaken at room temperature for 3 hr. The benzene layer was dried and passed through an alumina column and the residue from the eluate distilled to give 4-*ethylquinazoline* (0·68 g., 48%), b. p. 94—96°/0·6—0·7 mm., m. p. 15—16° (Found: C, 76·15; H, 6·4; N, 17·5. $C_{10}H_{10}N_2$ requires C, 75·9; H, 6·4; N, 17·7%).

A similar oxidation gave 4-*isopropylquinazoline* (65%), b. p. 96°/0·7 mm. (Found: C, 76·4; H, 7·0; N, 16·2. $C_{11}H_{12}N_2$ requires C, 76·7; H, 7·0; N, 16·3%). The picrates of 4-ethyl- and 4-isopropyl-quinazolines had m. p.s as described in the literature.[9]

Catalytic Reduction of Quinazolines.—The quinazolines (5×10^{-4} mole) in ethanol (10 ml.) and 5% palladium–charcoal [18] (50 mg. by the formaldehyde method) were hydrogenated at 20° and 710—720 mm. in a micro-apparatus. Aliquot portions were withdrawn at intervals and examined both spectrophotmetrically and by paper chromatography. At the end of the reductions the catalyst and solvent were removed and the 3,4-dihydro-derivatives were converted into the picrates which did not depress the melting points of authentic samples.

Quinazoline.—4-Chloroquinazoline [19] (73 g., 1 mole) in chloroform (140 ml., B.P. grade) was treated with a warm solution of toluene-*p*-sulphonylhydrazine (82·7 g., 1 mole) in chloroform (250 ml.) and set aside overnight at 20°. The hydrazino-derivative that separated was filtered off and dried in air. This was added with stirring during 1 hr. to an aqueous solution of N-sodium hydroxide (3500 ml.) in a beaker containing powdered glass wool (1 g.) at 85—90°, and maintained at this temperature for 2½ hr. until nitrogen evolution ceased. The solution was cooled by addition of crushed ice (500 g.), filtered, and extracted with chloroform (4 × 500 ml.). The dried extract was evaporated to dryness and the residue (in benzene) was passed through an alumina column (10 × 1 in., B.D.H.) and eluted with benzene. Distillation of the residue from the eluates gave quinazoline, b. p. 121—122°/19—20 mm. (35 g., 60%), which crystallised on cooling, m. p. 47—48° (lit.,[19] b. p. 120—121°/17—18 mm., m. p. 48°) (Found: C, 73·6; H, 4·7; N, 21·0. Calc. for $C_8H_6N_2$: C, 73·8; H, 4·65; N, 21·5%).

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