369. *Synthesis of* NN-*Dialkyl*-N′-*arylalkyl*-N′-4-*quinazolyl*(or 6-*methyl*-4-*pyrimidyl or* 4-*methyl*-2-*pyrimidyl*)*ethylenediamines of Potential Pharmacological Interest.*

By N. B. Chapman and H. Taylor.

A series of compounds of the types mentioned in the title, with methyl or ethyl as alkyl groups, and benzyl or 4-substituted benzyl as arylalkyl group, has been synthesised by condensing the appropriate chloro-heterocyclic compound with a *NN*-dialkyl-*N*′-arylalkylethylenediamine. These tertiary-secondary bases have been prepared by reduction with triethylamine formate of the anils obtained by condensation of *NN*-dimethyl- or *NN*-diethyl-ethylenediamine with benzaldehyde or *para*-substituted benzaldehydes.

The ultraviolet absorption spectra of *N*′-benzyl-*NN*-dimethylethylenediamine, of 4-benzylaminoquinazoline, and of *N*-benzyl-*N*′*N*′-dimethyl-*N*-4-quinazolylethylenediamine revealed that ditertiary amines of the type prepared undergo protonation in aqueous media first at the nitrogen atom bearing the alkyl groups, and secondly at a ring-nitrogen atom.

pK_a values of the conjugate acids so formed have been measured and the influence of molecular structure on these values is discussed. The pharmacological properties of the compounds are briefly noted and discussed.

Hetramine (*N*-benzyl-*N*′*N*′-dimethyl-*N*-2-pyrimidyl-) and Neohetramine or Thonzylamine (*N*-4-methoxybenzyl-*N*′*N*′-dimethyl-*N*-2-pyrimidyl-ethylenediamine) are well-known histamine antagonists. We therefore thought it of interest to synthesise for pharmacological evaluation two series of analogous compounds: one containing a 6-methyl-4-pyrimidyl group and the other a 2-methyl-4-pyrimidyl group in place of the 2-pyrimidyl group in the above structures, and with a range of substituents in the 4-position of the benzyl group (fluorine, chlorine, bromine, methyl, and methoxyl). As preliminary observations had shown that analogous 4-quinazolyl derivatives had analeptic properties, a group of quinazoline derivatives was also included.

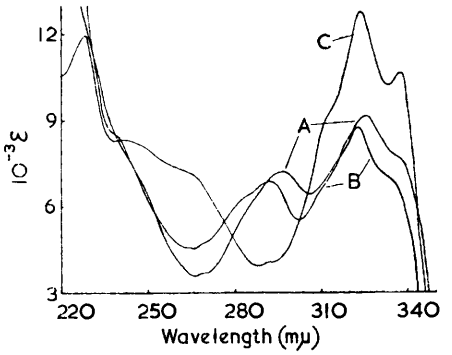
Condensation of the appropriate chloro-heterocyclic compound with a *NN*-dialkyl-*N*′-arylalkylethylenediamine under conditions detailed in the Experimental section gave, sometimes in indifferent yield, the required ditertiary amines as viscous, high-boiling oils which did not give good analyses. They were therefore characterised through analytically pure derivatives, usually picrates, and by determination of equivalent weight titrimetrically, both of the redistilled base and of the picrate. The required secondary-tertiary amines were obtained by reduction of anils obtained from benzaldehyde or a 4-substituted benzaldehyde and *NN*-dialkylethylenediamines, a method based on the work of Villani and his co-workers.[1] The anils were successfully reduced with triethylamine formate, excess of formic acid and the consequent acidic conditions being avoided. After initial experiments with a representative pure anil, it was found unnecessary to isolate the anil, so that this part of the synthesis could be achieved in virtually one stage. The necessary primary-tertiary amines were obtained by minor modifications of published methods.[2] Substituted benzaldehydes not available commercially were prepared by Beech's method,[3] *viz.*, formation of the oxime by interaction of a diazonium salt with formaldoxime and subsequent hydrolysis.

Although 4-chloroquinazoline reacted smoothly with *N*′-benzyl-*NN*-dimethylethylenediamine in boiling nitromethane to give the hydrochloride of the required product, it was found more suitable to condense the chloro-compound with the other secondary-tertiary amines without a solvent at 120—130°. Attempts to recrystallise hydrochlorides of the

[1] Villani, Sperber, Long, and Papa, *J. Amer. Chem. Soc.*, 1950, **72**, 2724.
[2] Bloom, Breslow, and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 539.
[3] Beech, *J.*, 1954, 1297.

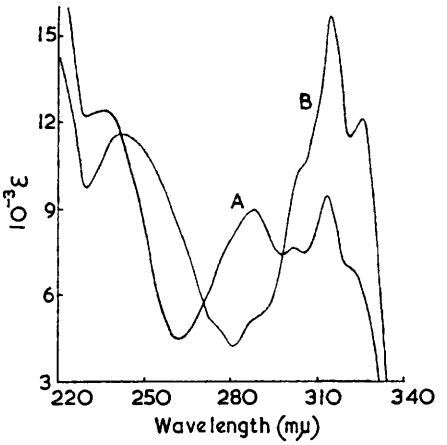
quinazoline derivatives from aqueous media led to fission of the molecule and isolation of the hydrochlorides of the corresponding secondary-tertiary amines with loss of the 4-quinazolyl group. Direct condensation of the chloropyrimidines with secondary-tertiary amines at 120—130° gave poor yields (20%) and much decomposition, and although reducing the temperature to 70—80° gave better yields (30%), decomposition, causing difficulties in purification, was still encountered. It was found best to condense the base and 4-chloro-6-methylpyrimidine in aqueous suspension, since despite extensive side reactions, the main products could readily be purified and the consumption of the chloro-compound could be followed by titration of the chloride ion formed. Aqueous acetic acid was found to be a more satisfactory medium for the analogous condensations of 4-chloro-2-methylpyrimidine. Often bases with the *NN*-dimethyl group consumed

FIG. 1. *Absorption spectra of* N-*benzyl*-N'N'-*dimethyl*-N-4-*quinazolylethylenediamine.*



A, *In* 0·1N-*sodium hydroxide.* B, *At* pH 6·8. C, *In* 0·1N-*hydrochloric acid.*

FIG. 2. *Absorption spectra of* 4-*benzylamino-quinazoline.*



A, *In* 0·1N-*sodium hydroxide.* B, *In* 0·1N-*hydrochloric acid.*

chloro-compound more rapidly than those with the *NN*-diethyl group, but from the latter better yields were obtained.

The ultraviolet absorption spectra of *N'*-benzyl-*NN*-dimethylethylenediamine, of 4-benzylaminoquinazoline (Fig. 2), and of *N*-benzyl-*N'N'*-dimethyl-*N*-4-quinazolylethylene-diamine (Fig. 1) have been determined. The pK_a values for the two most stable conjugate acids formed by each of the ditertiary amines prepared were also measured by a method detailed in the Experimental section, and the results are assembled in Table 3. The significance of the results of all these measurements is discussed later (p. 1916).

EXPERIMENTAL

Picrates were crystallised from aqueous ethanol containing picric acid, unless otherwise stated. Equivalent weights determined by titration of free bases are denoted by e.w. (b), and those determined by titration of amine picrates with perchloric acid in acetic acid by e.w. (p).

NN-*Dialkylethylenediamines.*—*NN*-Dimethylethylenediamine was prepared by an adaptation of the method of Bloom, Breslow, and Hauser,[2] *i.e.*, by reduction of dimethylaminomethyl cyanide (prepared by Turner's method [4]) with sodium and butan-1-ol in toluene. After steam-distillation, the amine was extracted from the toluene with hydrochloric acid, then liberated with 40% w/v aqueous sodium hydroxide. The oily base was separated and more was extracted from the aqueous layer with ether. After drying (KOH) and removal of ether, the combined

[4] Turner, *J. Amer. Chem. Soc.*, 1946, **68**, 1607.

TABLE 1. NN-*Dialkyl*-N′-*arylalkylethylenediamines*, $R_2N{\cdot}[CH_2]_2{\cdot}NH{\cdot}C_6H_4R'$-*p*.

(All compounds are new except those indicated by a reference in the last column.)

R	R′	Dipicrate (P_2) * or dihydrochloride (Cl_2)	M. p. or b. p./mm. (°c)	n_D^{18}	Found (%) C	H	N	Hal	e.w. (p)	Formula	Required (%) C	H	N	Hal	c.w.	Yield (%)	Ref.
Me	H	—	82—83/0·3 [a]	1·5183 [a]	74·3	10·0	15·7	—	90	$C_{11}H_{18}N_2$	74·1	10·1	15·7	—	89	50	11, 12
Me	,,	P_2	162—164 [b]	—	—	—	—	—	—	—	—	—	—	—	—	—	12
Me	,,	Cl_2	205—206 [c]	—	—	—	—	—	—	—	—	—	—	—	—	—	13
Me	Me	—	92—96/0·25	1·5105	75·1	10·5	14·3	—	95	$C_{12}H_{20}N_2$	74·9	10·5	14·6	—	96	55	—
Me	,,	P_2	176—176·5	—	44·3	4·0	17·2	—	—	$C_{24}H_{26}N_8O_{14}$	44·3	4·0	17·2	—	—	—	—
Me	OMe	—	114—116/0·8 [d]	1·5163 [d]	69·2	9·5	13·4	—	104	$C_{12}H_{20}N_2O$	69·4	9·6	13·5	—	104	50	*j*
Me	,,	P_2	156—157 [e]	—	43·3	3·9	16·8	—	—	$C_{24}H_{26}N_8O_{15}$	43·2	3·9	16·8	—	—	—	*k*
Me	F	—	92—95/0·7	1·4949	67·7	8·7	14·2	—	98	$C_{11}H_{17}FN_2$	67·3	8·8	14·3	—	98	52	—
Me	,,	P_2	164·5—165·5	—	42·2	3·6	17·2	—	—	$C_{23}H_{23}FN_8O_{14}$	42·2	3·5	17·1	—	—	—	—
Me	Cl	—	92—95/0·4 [f]	1·5248 [f]	61·8	7·7	13·0	16·9	107	$C_{11}H_{17}ClN_2$	62·1	8·0	13·2	16·7	106	53	*j*
Me	,,	P_2	163·5—164	—	41·0	3·6	16·9	5·3	—	$C_{23}H_{23}ClN_8O_{14}$	41·2	3·5	16·7	5·3	—	—	—
Me	Br	—	120—124/0·8	1·5405	51·8	6·7	10·6	31·4	128	$C_{11}H_{17}BrN_2$	51·4	6·6	10·9	31·1	128·5	50	—
Me	,,	P_2	192—194	—	38·9	3·3	15·3	11·3	—	$C_{23}H_{23}BrN_8O_{14}$	38·6	3·2	15·7	11·2	—	—	—
Et	H	—	112—114/0·6 [g]	1·5047 [g]	75·6	10·6	13·8	—	102	$C_{13}H_{22}N_2$	75·7	10·7	13·6	—	103	61	1
Et	,,	P_2	171·5—172	—	45·2	4·3	16·7	—	—	$C_{25}H_{28}N_8O$	45·2	4·2	16·9	—	—	—	—
Et	Me	—	131—132/6	1·5064	76·7	11·0	12·4	—	109	$C_{14}H_{24}N_2$	76·4	10·9	12·7	—	110	60	—
Et	,,	P_2	171·5—172·5	—	46·8	4·4	16·5	—	—	$C_{26}H_{30}N_8O_{14}$	46·0	4·5	16·5	—	—	—	—
Et	OMe	—	140—142/1·0 [h]	1·5108	71·6	10·3	11·6	—	118	$C_{14}H_{24}N_2O$	71·2	10·2	11·9	—	118	52	*l*
Et	,,	P_2	149·5—150·5 [i]	—	45·0	4·2	16·1	—	—	$C_{26}H_{30}N_8O_{15}$	45·0	4·4	16·1	—	—	—	*kl*
Et	F	—	96—100/0·5	1·4918	69·8	9·4	12·3	—	112	$C_{13}H_{21}FN_2$	69·7	9·4	12·5	—	112	54	—
Et	,,	P_2	150—151	—	44·3	4·0	16·4	—	—	$C_{25}H_{27}FN_8O_{14}$	44·0	4·0	16·4	—	—	—	—
Et	Cl	—	126—128/0·7	1·5190	65·0	8·8	11·7	14·7	120	$C_{13}H_{21}ClN_2$	64·8	8·8	11·6	14·7	120	63	—
Et	,,	P_2	137—139	—	43·0	3·8	16·4	5·0	—	$C_{25}H_{27}ClN_8O_{14}$	43·0	3·9	16·0	5·1	—	—	—
Et	Br	—	132—134/0·5	1·5337	54·5	7·3	9·8	26·2	142	$C_{13}H_{21}BrN_2$	54·7	7·4	9·8	26·0	143	68	—
Et	,,	P_2	155·5—157	—	40·6	3·9	14·7	11·0	—	$C_{25}H_{27}BrN_8O_{14}$	40·4	3·7	15·1	11·0	—	—	—

[a] Lit.,[11] b. p. 128—132°/18 mm.; lit.,[12], n_D^{25} 1·507. [b] Lit.,[12] m. p. 162—164°. [c] Lit.,[13] m. p. 205—207°. [d] Lit.,[j] b. p. 106—107°/0·52 mm., n_D^{25} 1·5148. [e] Lit.,[k] m. p. 151·5—153·5°. [f] Lit.,[j] b. p. 95—97°/0·47 mm., n_D^{25} 1·5198. [g] Lit.,[l] b. p. 115—119°/0·5 mm., n_D 1·499. [h] Lit.,[l] b. p. 203—205°/18 mm. [i] Lit.,[k] m. p. 150—151°; lit.[l], m. p. 140—141°. [j] U.S.P. 2,582,292/1945 (*Chem. Abs.*, 1952, **46**, 10,202). [k] Matsuka, Shirakawa, and Kawasaki, *J. Pharm. Soc. Japan*, 1951, **71**, 1316 (*Chem. Abs.*, 1952, **46**, 7101). [l] Wojahn and Erdelmeier, *Arch. Pharm.*, 1942, **200**, 215.

* Dipicrates (Table 1) recryst. from aq. EtOH.

TABLE 2. NN-*Dialkyl*-N′-*arylalkyl*-N′-*heterocyclic ethylenediamines*, $R_2N{\cdot}[CH_2]_2{\cdot}NR''{\cdot}C_6H_4R'$-*p*.

R	R′	R″	Dipicrate (P_2) or mono- (Cl_1) or di-hydrochloride (Cl_2)	M. p. or b. p./mm. (°C)	Found (%) C	H	N	Hal	e.w. (b)	e.w. (p)	Formula	Required (%) C	H	N	Hal	e.w.	Yield (%)
Me	H	A	—	200—204/0·8	72·5	7·1	17·9	—	148	154	$C_{19}H_{22}N_4$	74·5	7·2	18·3	—	153	42
Me	,,	A	Cl_1	194—195·5	66·2	6·8	16·8	10·5	—	—	$C_{19}H_{23}ClN_4$	66·6	6·7	16·4	10·4	—	28
Me	,,	A	Cl_2 [a]	215—216	—	—	—	18·4	—	—	$C_{19}H_{24}Cl_2N_4$	—	—	—	18·7	—	—
Me	,,	A	P_2	214—216	48·7	3·8	18·2	—	—	—	$C_{31}H_{28}N_{10}O_{14}$	48·7	3·7	18·3	—	—	—
Me	Me	A	Cl_1	201—202	67·7	7·2	15·9	9·95	159	158	$C_{20}H_{25}ClN_4$	67·3	7·1	15·7	9·94	160	42
Me	,,	A	P_2	199—200·5	49·6	3·9	17·9	—	—	—	$C_{32}H_{30}N_{10}O_{14}$	49·4	3·9	18·0	—	—	—
Me	OMe	A	—	186—190/0·008	—	—	—	—	174	169	$C_{20}H_{24}N_4O$	—	—	—	—	168	38
Me	,,	A	P_2	193—194	48·5	3·8	17·5	—	—	—	$C_{32}H_{30}N_{10}O_{15}$	48·4	3·8	17·6	—	—	—
Me	F	A	—	172—176/0·01	68·9	6·2	16·8	—	158	162	$C_{19}H_{21}FN_4$	70·3	6·5	17·3	—	162	54
Me	,,	A	P_2	217—218	47·4	3·7	17·8	—	—	—	$C_{31}H_{27}FN_{10}O_{14}$	47·6	3·5	17·9	—	—	—
Me	Cl	A	—	170—174/0·03	—	—	—	—	178	172	$C_{19}H_{21}ClN_4$	—	—	—	—	170	33
Me	,,	A	P_2	209·5—211	46·5	3·6	17·2	4·4	—	—	$C_{31}H_{27}ClN_{10}O_{14}$	46·6	3·4	17·5	4·4	—	—
Me	Br	A	—	176—180/0·005	—	—	—	—	187	191	$C_{19}H_{21}BrN_4$	—	—	—	—	193	27
Me	,,	A	P_2	222·5—224	44·4	3·3	16·6	9·6	—	—	$C_{31}H_{27}BrN_{10}O_{14}$	44·1	3·2	16·6	9·5	—	—
Et	H	A	—	200—205/0·3	—	—	—	—	166	166	$C_{21}H_{26}N_4$	—	—	—	—	167	42
Et	,,	A	Cl_1 [a]	142·5—143·5	—	—	—	—	—	—	$C_{21}H_{27}ClN_4$	—	—	—	9·6	—	—
Et	,,	A	Cl_2 [a]	231—233	61·9	7·2	13·7	17·4	—	—	$C_{21}H_{28}Cl_2N_4$	62·1	6·9	13·8	17·4	—	—
Et	,,	A	P_2	169—170	49·4	4·2	17·8	—	—	—	$C_{33}H_{32}N_{10}O_{14}$	50·0	4·0	17·7	—	—	—
Et	Me	A	—	174—176/0·005	—	—	—	—	176	174	$C_{22}H_{28}N_4$	—	—	—	—	174	59
Et	,,	A	P_2	201—202	50·1	4·1	17·3	—	—	—	$C_{34}H_{34}N_{10}O_{14}$	50·6	4·3	17·4	—	—	—
Et	OMe	A	—	184—188/0·007	—	—	—	—	188	181	$C_{22}H_{28}N_4O$	—	—	—	—	182	35
Et	,,	A	P_2	173—174	49·6	4·4	16·8	—	—	—	$C_{34}H_{34}N_{10}O_{15}$	49·6	4·2	17·0	—	—	—
Et	F	A	—	178—180/0·008	—	—	—	—	173	178	$C_{21}H_{25}FN_4$	—	—	—	—	176	71
Et	,,	A	P_2	201·5—202	48·4	4·1	17·5	—	—	—	$C_{33}H_{31}FN_{10}O_{14}$	48·9	3·9	17·3	—	—	—
Et	Cl	A	—	192—196/0·005	—	—	—	—	181	185	$C_{21}H_{25}ClN_4$	—	—	—	—	184	68
Et	,,	A	P_2	201·5—202	48·0	4·0	17·2	4·2	—	—	$C_{33}H_{31}ClN_{10}O_{14}$	47·9	3·8	16·9	4·3	—	—
Et	Br	A	—	200—204/0·01	—	—	—	—	205	206	$C_{21}H_{25}BrN_4$	—	—	—	—	207	72
Et	,,	A	P_2	201·5—203	45·2	3·9	16·5	8·9	—	—	$C_{33}H_{31}BrN_{10}O_{14}$	45·5	3·6	16·1	9·2	—	—
Me	H	B	—	135—139/0·02	—	—	—	—	130	134	$C_{16}H_{22}N_4$	—	—	—	—	135	26
Me	,,	B	P_2	161—162·5	46·2	3·8	19·3	—	—	—	$C_{28}H_{28}N_{10}O_{14}$	46·2	3·9	19·2	—	—	—
Me	Me	B	—	134—140/0·005	—	—	—	—	144	141	$C_{17}H_{24}N_4$	—	—	—	—	142	35
Me	,,	B	P_2	184—185	47·0	4·1	18·9	—	—	—	$C_{29}H_{30}N_{10}O_{14}$	46·9	4·0	18·9	—	—	—
Me	OMe	B	—	158—166/0·01	—	—	—	—	145	149	$C_{17}H_{24}N_4O$	—	—	—	—	150	34
Me	,,	B	P_2	142—144	45·6	4·0	18·4	—	—	—	$C_{29}H_{30}N_{10}O_{15}$	45·9	4·0	18·5	—	—	—
Me	F	B	—	123—125/0·002	—	—	—	—	146	144	$C_{16}H_{21}FN_4$	—	—	—	—	144	28
Me	,,	B	P_2	189·5—190	45·2	3·6	18·8	—	—	—	$C_{28}H_{27}FN_{10}O_{14}$	45·0	3·7	18·8	—	—	—
Me	Cl	B	—	147—152/0·01	—	—	—	—	145	150	$C_{16}H_{21}ClN_4$	—	—	—	—	152	29
Me	,,	B	P_2	172·5—174·5	44·0	3·6	18·7	4·7	—	—	$C_{28}H_{27}ClN_{10}O_{14}$	44·1	3·6	18·4	4·7	—	—
Me	Br	B	—	148—152/0·01	—	—	—	—	182	174	$C_{16}H_{21}BrN_4$	—	—	—	—	175	27
Me	,,	B	P_2	139—141	41·4	3·4	17·1	10·0	—	—	$C_{28}H_{27}BrN_{10}O_{14}$	41·2	3·4	17·3	9·9	—	—
Et	H	B	—	130—136/0·001	—	—	—	—	144	146	$C_{18}H_{26}N_4$	—	—	—	—	149	54

TABLE 2. (*Continued.*)

R	R′	R″	Dipicrate (P_2) or mono- (Cl_1) or di-hydrochloride (Cl_2)	M. p. or b. p./mm. (°c)	Found (%) C	H	N	Hal	e.w. (b)	e.w. (p)	Formula	Required (%) C	H	N	Hal	e.w.	Yield (%)
Et	,,	B	P_2	144—145	47·6	4·3	18·5	—	—	—	$C_{30}H_{32}N_{10}O_{14}$	47·6	4·3	18·5	—	—	—
Et	Me	B	—	142—145/0·001	—	—	—	—	149	154	$C_{19}H_{28}N_4$	—	—	—	—	156	56
Et	,,	B	P_2	192—193	48·3	4·6	18·4	—	—	—	$C_{31}H_{34}N_{10}O_{14}$	48·1	4·5	18·2	—	—	—
Et	OMe	B	—	155—162/0·003	—	—	—	—	168	165	$C_{19}H_{28}N_4O$	—	—	—	—	165	76
Et	,,	B	P_2	162·5—163·5	47·0	4·4	17·7	—	—	—	$C_{31}H_{34}N_{10}O_{15}$	47·3	4·3	17·8	—	—	—
Et	F	B	—	138—140/0·002	—	—	—	—	158	160	$C_{18}H_{25}FN_4$	—	—	—	—	158	63
Et	,,	B	P_2	160·5—161·5	46·6	4·2	18·4	—	—	—	$C_{30}H_{31}FN_{10}O_{14}$	46·5	4·0	18·1	—	—	—
Et	Cl	B	—	154—156/0·003	—	—	—	—	168	165	$C_{18}H_{25}ClN_4$	—	—	—	—	166	48
Et	,,	B	P_2	163·5—166	45·6	4·1	17·9	4·7	—	—	$C_{30}H_{31}ClN_{10}O_{14}$	45·5	4·0	17·7	4·5	—	—
Et	Br	B	—	158—162/0·003	—	—	—	—	182	187	$C_{18}H_{25}BrN_4$	—	—	—	—	189	64
Et	,,	B	P_2	176—176·5	43·1	3·9	16·5	9·4	—	—	$C_{30}H_{31}BrN_{10}O_{14}$	43·1	3·7	16·8	9·6	—	—
Me	H	C	—	94—96/0·008 [b]	—	—	—	—	134	133	$C_{16}H_{22}N_4$	—	—	—	—	135	18
Me	,,	C	P_2	136—138	46·4	3·7	19·0	—	—	—	$C_{28}H_{28}N_{10}O_{14}$	46·2	3·9	19·2	—	—	—
Me	Me	C	—	94—96/0·001	—	—	—	—	144	144	$C_{17}H_{24}N_4$	—	—	—	—	142	14
Me	,,	C	P_2	164—165·5	46·7	4·1	19·0	—	—	—	$C_{29}H_{30}N_{10}O_{14}$	46·9	4·0	18·9	—	—	—
Me	OMe	C	—	122—124/0·001	—	—	—	—	158	148	$C_{17}H_{24}N_4O$	—	—	—	—	150	26
Me	,,	C	P_2	140—141	46·0	3·9	18·2	—	—	—	$C_{29}H_{30}N_{10}O_{15}$	45·9	4·0	18·5	—	—	—
Me	F	C	—	94—104/0·005	—	—	—	—	149	144	$C_{16}H_{21}FN_4$	—	—	—	—	144	40
Me	,,	C	P_2	160·5—161	44·7	3·4	18·5	—	—	—	$C_{28}H_{27}FN_{10}O_{14}$	45·0	3·6	18·8	—	—	—
Me	Cl	C	—	110—112/0·001	—	—	—	—	148	150	$C_{16}H_{21}ClN_4$	—	—	—	—	152	30
Me	,,	C	P_2	163—164	44·2	3·8	18·7	5·0	—	—	$C_{28}H_{27}ClN_{10}O_{14}$	44·1	3·6	18·4	4·7	—	—
Me	Br	C	—	110—118/0·003	—	—	—	—	176	174	$C_{16}H_{21}BrN_4$	—	—	—	—	175	26
Me	,,	C	P_2	165—166	41·9	3·1	17·7	10·0	—	—	$C_{28}H_{27}BrN_{10}O_{14}$	41·6	3·4	17·3	9·9	—	—
Et	H	C	—	106—108/0·003	—	—	—	—	150	147	$C_{18}H_{26}N_4$	—	—	—	—	149	56
Et	,,	C	P_2	138·5—140	47·4	4·4	18·2	—	—	—	$C_{30}H_{32}N_{10}O_{14}$	47·6	4·3	18·5	—	—	—
Et	Me	C	—	104—106/0·002	—	—	—	—	150	157	$C_{19}H_{28}N_4$	—	—	—	—	156	49
Et	,,	C	P_2	135—137	48·4	4·5	18·2	—	—	—	$C_{31}H_{34}N_{10}O_{14}$	48·3	4·5	18·2	—	—	—
Et	OMe	C	—	122—124/0·0005	—	—	—	—	167	166	$C_{19}H_{28}N_4O$	—	—	—	—	164	36
Et	,,	C	P_2	134—135·5	47·1	4·2	18·1	—	—	—	$C_{31}H_{34}N_{10}O_{15}$	47·3	4·4	17·8	—	—	—
Et	F	C	—	105—108/0·001	—	—	—	—	154	158	$C_{18}H_{25}FN_4$	—	—	—	—	158	53
Et	,,	C	P_2	176—176·5	46·7	4·0	18·1	—	—	—	$C_{30}H_{31}FN_{10}O_{14}$	46·5	4·0	18·1	—	—	—
Et	Cl	C	—	105—110/0·005	—	—	—	—	173	164	$C_{18}H_{25}ClN_4$	—	—	—	—	166	43
Et	,,	C	P_2	169—170	45·7	4·2	17·7	4·5	—	—	$C_{30}H_{31}ClN_{10}O_{14}$	45·5	4·0	17·7	4·5	—	—
Et	Br	C	—	128—132/0·0005	—	—	—	—	193	191	$C_{18}H_{25}BrN_4$	—	—	—	—	189	44
Et	,,	C	P_2	167—167·5	43·5	3·8	17·1	9·5	—	—	$C_{30}H_{31}BrN_{10}O_{14}$	43·1	3·8	16·8	9·6	—	—

A = 4-Quinazolyl. B = 6-Methyl-4-pyrimidyl. C = 4-Methyl-2-pyrimidyl.
Picrates were crystallised from aqueous acetone.

[a] Prepared by adding the required quantity of an ethanolic solution of hydrogen chloride to an ethanolic solution of the base and precipitating the salt with ether. The salt was crystallised from nitromethane. [b] B.P. 629,471/1946 lists b. p. 134°/1·4 mm. All the other compounds listed in Table 2 are new.

bases were distilled to give *NN*-dimethylethylenediamine, b. p. 106—109° (lit.,[4] 105—108°) [derived phenylthiourea, m. p. 82—82·5° (lit.,[4] 82·6—83°), in 48% overall yield. This base was also prepared by methylation and subsequent hydrolysis of monoacetylethylenediamine, prepared by Aspinall's method,[5] according to the method of Baldy, Naudet, and Desnouelle [6] (overall yield 46%). *NN*-Diethylethylenediamine was obtained from L. Light and Company and had b. p. 144—145°.

Substituted Benzaldehydes.—4-Bromo-, m. p. 57° (lit.,[7] 57°), and 4-fluoro-benzaldehyde, b. p. 180—181°/760 mm. (lit.,[8] 181·5°/763 mm.) [oxime, m. p. 86—87° (lit.,[8] 86·5°)], were prepared by Beech's method.[3]

NN-*Dialkyl*-N′-*arylalkylethylenediamines.*—*N*′-Benzylidene-*NN*-dimethylethylenediamine was prepared (76%) by condensing benzaldehyde with 2-dimethylaminoethylamine by Surrey's method [9] and had b. p. 83°/0·3 mm., n_D^{18} 1·5347 (lit., 132—133°/12 mm., n_D^{25} 1·5330). This was then reduced by a modification of Alexander and Wildman's method.[10] To a mixture of the anil (0·19 mole) and triethylamine (0·4 mole) was added 98—100% formic acid (0·6 mole) and, after the initial reaction had subsided, excess of triethylamine and water were distilled off through a column and the residue was heated strongly until evolution of carbon dioxide ceased. 6N-Hydrochloric acid (200 ml.) was added, and the mixture was boiled for 15 min., and, after cooling, basified with 5N-sodium hydroxide. The oily layer was separated, more oil was extracted from the aqueous layer with ether, and the ether was removed. The combined oils were distilled to give *N*′-benzyl-*NN*-dimethylethylenediamine (76%), b. p. 82—83°/0·3 mm., n_D^{18} 1·5183 (lit.,[11,12] 128—132°/18 mm., n_D^{25} 1·507) [Found: C, 74·3; H, 10·1; N, 15·7%; e.w. (p), 90. Calc. for $C_{11}H_{18}N_2$: C, 74·1; H, 10·1; N, 15·7%; e.w., 89] [dipicrate, m. p. 162—164° (lit.,[12] 162—164°); dihydrochloride (from ethanol), m. p. 205—206° (lit.,[13] 205—207°)]. This amine was also prepared by a modification of a method given in a patent [14] (yield 12%) and by Zechmeister and Truka's method [15] (yield 64%). The compounds listed in Table 1 were prepared as for *N*′-benzyl-*NN*-dimethylethylenediamine, but without isolation of the intermediate anil.

Chloro-heterocyclic Compounds.—4-Chloroquinazoline was prepared by Chapman, Gibson, and Mann's method,[16] and 4-chloro-6-methyl- and 2-chloro-4-methyl-pyrimidine according to the methods given by Chapman and Rees,[17] and had m. p.s as recorded by these authors.

NN-*Dialkyl*-N′-*arylalkyl*-N′-*heterocyclic Ethylenediamines.*—4-Chloroquinazoline (0·013 mole) and *N*′-benzyl-*NN*-dimethylethylenediamine (0·013 mole) were boiled under reflux in nitromethane (10 ml.) for 2 hr. Adding acetone (20 ml.) led to a white precipitate which was crystallised from nitromethane to give N-*benzyl*-N′N′-*dimethyl*-N-4-*quinazolylethylenediamine monohydrochloride* (28%), m. p. 194—195·5° (Found: C, 66·2; H, 6·8; Cl, 10·5; N, 16·8. $C_{19}H_{22}N_4$,HCl requires C, 66·6; H, 6·7; Cl, 10·4; N, 16·4%). Similarly 4-chloroquinazoline and the *N*-4-methylbenzylamine gave N-p-*methylbenzyl*-N′N′-*dimethyl*-N-4-*quinazolylethylenediamine monohydrochloride* (42%), m. p. 201—202° (Found: C, 67·7; H, 7·2; Cl, 9·95; N, 15·9. $C_{20}H_{24}N_4$,HCl requires C, 67·3; H, 7·1; Cl, 9·9; N, 15·7%).

4-Chloroquinazoline and *N*′-benzyl-*NN*-dimethylethylenediamine were also heated together without solvent at 120—130° for 4 hr. The semi-solid product was dissolved in hot 95% ethanol, the solution was made alkaline with sodium hydroxide and the liberated oil was extracted with ether. After drying (KOH) the ether was removed and the residue was distilled to give N-*benzyl*-N′N′-*dimethyl*-N-4-*quinazolylethylenediamine*, b. p. 200—204°/0·8 mm. [Found: C, 72·5; H, 7·1; N, 17·9%; e.w. (b) 148; e.w. (p), 154. $C_{19}H_{22}N_4$ requires C, 74·5; H, 7·2; N, 18·3%; e.w. 153] [*dipicrate* (from acetone), m. p. 214—216° (Found: C, 48·7; H, 3·8; N, 18·2. $C_{31}H_{28}N_{10}O_{14}$ requires C, 48·7; H, 3·7; N, 18·3%)]. The remaining quinazoline derivatives

[5] Aspinall, *J. Amer. Chem. Soc.*, 1941, **63**, 853.
[6] Baldy, Naudet, and Desnouelle, *Bull. Soc. chim. France*, 1955, 518.
[7] Kjellin and Kuylenstjerna, *Ber.*, 1897, **30**, 1899.
[8] Shoesmith, Sosson, and Slater, *J.*, 1926, 2760.
[9] Surrey, *J. Amer. Chem. Soc.*, 1949, **71**, 3105.
[10] Alexander and Wildman, *J. Amer. Chem. Soc.*, 1948, **70**, 1187.
[11] B.P. 594,603, 606,181—2/1945.
[12] U.S.P. 2,440,703/1948; cf. *Chem. Abs.*, 1949, **43**, 1914.
[13] Gardner and Stevens, *J. Amer. Chem. Soc.*, 1949, **71**, 1869.
[14] B.P. 433,625/1934.
[15] Zechmeister and Truka, *Ber.*, 1930, **63**, 2883.
[16] Chapman, Gibson, and Mann, *J.*, 1947, 890.
[17] Chapman and Rees, *J.*, 1954, 1190.

listed in Table 2 were prepared in this way, as was N-*benzyl*-N'N'-*dimethyl*-N-6-*methyl*-4-*pyrimidylethylenediamine*. The remaining pyrimidine derivatives listed in Table 2 were prepared by boiling the appropriate chloroheterocyclic compound and amine under reflux in sufficient 0·5N-acetic acid to neutralise one basic centre in the amine for the 4-methyl-2-pyrimidyl derivatives, and in water for the 6-methyl-4-pyrimidyl derivatives. The products were worked up as for *N*-benzyl-*N'N'*-dimethyl-*N*-4-quinazolylethylenediamine.

Measurement of Absorption Spectra.—Ultraviolet absorption was measured for *N'*-benzyl-*NN*-dimethylethylenediamine, *N*-benzyl-*N'N'*-dimethyl-*N*-4-quinazolylethylenediamine, and for 4-benzylaminoquinazoline (m. p. 169—169·5°) with a Unicam S.P. 500 spectrophotometer. The two ethylenediamine derivatives were investigated in three states: as the free base (in 0·1N-sodium hydroxide), as the singly protonated ion (in a buffer solution of pH 6·8), and as the doubly protonated ion (in 0·1N-hydrochloric acid), the solvents having been chosen from titration results. For 4-benzylaminoquinazoline the solvents used were 0·1N-sodium hydroxide and 0·1N-hydrochloric acid.

The absorption curves obtained for *N*-benzyl-*N'N'*-dimethylethylenediamine in all three solvents were very similar to each other and to that of benzylamine in acid solution.[18] Those obtained for the two quinazoline compounds are shown in Figs. 1 and 2.

Determination of pK_a *Values and Equivalent Weights of Bases.*—In order to approximate to physiological conditions the pK_a values of the conjugate acids of the ditertiary bases were determined by titration in aqueous solution at 37°. To keep the free bases in solution during titration, dilute solutions were necessary, requiring a small volume of titrant which was added from an Agla micrometer syringe. To ensure complete dissolution of the base it was dissolved in hydrochloric acid, and the solution was diluted with water and then titrated with 0·1N-barium hydroxide, the liquid being stirred with a stream of nitrogen.

To calculate dissociation constants, Gage's method [19] was adapted for dibasic acids (although four potentially basic centres are present in the ditertiary amines, only two become protonated in dilute aqueous solution). The dissociation of unsymmetrical dibasic acids has been considered by Adams [20] whose analysis, combined with conservation of mass and charge, leads to equation (i) (cf. Barton,[21] from whose equation the same relation may be derived):

$$(c - x) = x[\mathrm{H}]/(K_1 + K'_1) - K_2K'_2(2c - x)/[\mathrm{H}](K_2 + K'_2) \quad . \quad . \quad . \quad \text{(i)}$$

where c = total molar concentration of acid and derived species, $x = [\mathrm{M}] + [\mathrm{H}] - [\mathrm{OH}]$, [M] = normality in the titrated liquid of added titrant cation, [H] = hydrogen-ion concentration, [OH] = hydroxyl-ion concentration. K_1 and K'_1 are dissociation constants for the alternative first stages of ionisation of the dibasic acid. K_2 and K'_2 are dissociation constants for the alternative second stages of ionisation of the dibasic acid. Equation (i) is inexact in that activity coefficients have not been introduced. At concentrations used (~0·0001N), the error is not significant.

The dibasic acids investigated in this work have as one acid centre a protonated aromatic amino-group and as the other a protonated aliphatic amino-group. It is expected that the dissociation constant of the former would be much greater than that of the latter which could thus reasonably be neglected in their sum. If K_1 and K'_2 refer to the aromatic basic centre and K_2 and K'_1 to the aliphatic basic centre then equation (i) reduces to (ii)

$$c - x = x[\mathrm{H}]/K_1 - K_2(2c - x)/[\mathrm{H}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(ii)}$$

When $K_1 \gg K_2$ for dibasic acids the two stages of neutralisation are virtually separate. When this is so, the two terms on the right-hand side of equation (ii) correspond to the two stages of neutralisation, the first term being negligible during the second stage and the second term during the first stage. Equation (ii) can thus be modified to (iii) and (iv) which apply to the two successive stages of neutralisation:

$$(c - x) = x[\mathrm{H}]/K_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(iii)}$$

$$(c - x) = -K_2(2c - x)/[\mathrm{H}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{(iv)}$$

[18] Controulis, Rebstock, and Crooks, *J. Amer. Chem. Soc.*, 1949, **71**, 2463.
[19] Gage, *Analyst*, 1957, **82**, 219.
[20] Adams, *J. Amer. Chem. Soc.*, 1916, **38**, 1503.
[21] Barton, *Nature*, 1947, **160**, 752.

Equation (iii) is identical with that given by Gage [19] for a monobasic acid. As shown by him, a plot of x[H] against x should give a straight line of slope $-K_1$ and extrapolation to x[H] = 0 should give $x = c$, from which the equivalent weight may be calculated. Similarly a plot of $-(c - x)$[H] against x should be linear and of slope $-K_2$. Extrapolation to $-(c - x)$[H] = 0 should give $x = 2c$ to serve as a check on c.

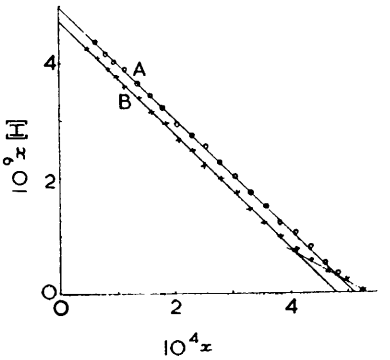


FIG. 3. *Derived curves for first stage of titration of* N-*benzyl*-N'N'-*dimethyl*-N-4-*quinazolylethylenediamine.*

A, *Crystalline dihydrochloride.* B, *Neutralised distilled base.*

TABLE 3. *Physical data, etc., for* NN-*dialkyl*-N'-*arylalkyl*-N'-*heterocyclic ethylenediamines,* $R_2N{\cdot}[CH_2]_2{\cdot}NR'R''$.

No.	R	R'	R''	n_D^{18}	Dissociation Constant pK_{a_1}	Dissociation Constant pK_{a_2}	Potency [a] 10^3 ED_{50}
1	Me	Benzyl	A	1·6027	5·0	8·5	8·0
2	Me	*p*-Methylbenzyl	A	—	5·0	8·5	in.
3	Me	*p*-Methoxybenzyl	A	1·6133	5·0	8·5	6·7
4	Me	*p*-Fluorobenzyl	A	1·6055	4·8	8·5	5·1
5	Me	*p*-Chlorobenzyl	A	1·6208	4·8	8·5	2·7
6	Me	*p*-Bromobenzyl	A	1·6290	4·9	8·4	0·8
7	Et	Benzyl	A	1·5975	4·9	9·0	4·8
8	Et	*p*-Methylbenzyl	A	1·5994	4·8	8·9	p.
9	Et	*p*-Methoxybenzyl	A	1·6048	4·8	8·9	in.
10	Et	*p*-Fluorobenzyl	A	1·5927	4·7	8·9	in.
11	Et	*p*-Chlorobenzyl	A	1·6083	4·8	8·8	4·9
12	Et	*p*-Bromobenzyl	A	1·6190	4·8	8·6	1·6
13	Me	Benzyl	B	1·5565	5·2	8·3	0·4
14	Me	*p*-Methylbenzyl	B	1·5500	5·1	8·3	—
15	Me	*p*-Methoxybenzyl	B	1·5644	5·1	8·3	0·15
16	Me	*p*-Fluorobenzyl	B	1·5442	5·2	8·2	—
17	Me	*p*-Chlorobenzyl	B	1·5603	5·2	8·1	—
18	Me	*p*-Bromobenzyl	B	1·5688	5·2	8·0	0·2
19	Et	Benzyl	B	1·5498	5·2	8·8	1·7
20	Et	*p*-Methylbenzyl	B	1·5517	5·2	8·8	—
21	Et	*p*-Methoxybenzyl	B	1·5538	5·1	8·8	—
22	Et	*p*-Fluorobenzyl	B	1·5402	5·2	8·8	—
23	Et	*p*-Chlorobenzyl	B	1·5503	5·1	8·7	—
24	Et	*p*-Bromobenzyl	B	1·5667	5·2	8·7	0·9
25	Me	Benzyl	C	1·5576	2·9	8·6	2·0
26	Me	*p*-Methylbenzyl	C	1·5548	2·9	8·7	—
27	Me	*p*-Methoxybenzyl	C	1·5621	2·9	8·6	0·1
28	Me	*p*-Fluorobenzyl	C	1·5438	3·1	8·5	—
29	Me	*p*-Chlorobenzyl	C	1·5619	3·0	8·4	—
30	Me	*p*-Bromobenzyl	C	1·5690	3·0	8·3	1·0
31	Et	Benzyl	C	1·5490	2·8	9·2	10
32	Et	*p*-Methylbenzyl	C	1·5480	2·8	9·1	—
33	Et	*p*-Methoxybenzyl	C	1·5542	2·8	9·1	—
34	Et	*p*-Fluorobenzyl	C	1·5413	2·8	8·9	—
35	Et	*p*-Chlorobenzyl	C	1·5508	2·8	8·9	—
36	Et	*p*-Bromobenzyl	C	1·5672	2·9	8·8	4·5
		Thonzylamine	—	—	—	—	0·093

A, B, C, as for Table 2. in. = inactive. p. = potentiates the action of histamine.

[a] Antihistamine activity determined by the guinea-pig aerosol method, ED_{50} in millimoles per kg. pK_{a_2} refers to the dialkylamino-group, and pK_{a_1} refers to a ring nitrogen atom.

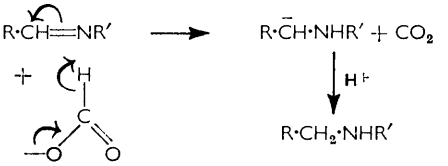
These predictions were found to be correct in practice, straight lines being obtained from the two plots. Moreover, the presence of small amounts of other basic impurities in the ditertiary bases did not invalidate the method, their presence being shown by a break in the straight line near the end of each stage of neutralisation. This is illustrated in Fig. 3 which shows the curves obtained by titrating separately the crystalline dihydrochloride and the distilled base (dissolved in hydrochloric acid) of *N*-benzyl-*N'N'*-dimethyl-*N*-4-quinazolylethylenediamine.

Procedure. The free base was dissolved in a quantity of N-hydrochloric acid calculated to form the dihydrochloride, and an equal volume of acetone. 0·8 ml. of this solution was added to distilled water (39·0 ml.) at 37° and titrated with 0·1N-barium hydroxide, the pH being read after each 0·01 ml.

Pharmacological Results.—A range of pharmacological properties of a number of the ditertiary amines of this series has been studied and has been reported elsewhere.[22] The antihistaminic potencies are listed in Table 3. The compounds studied have toxicities similar to that of Thonzylamine and in addition those derived from 2-aminopyrimidine have marked local anæsthetic activity.

Discussion

Reduction of Anils by Formic Acid.—In this work reduction has always taken place in the presence of an excess of free base and has been shown to do so when base is present in large excess (by adding formic acid dropwise during the reduction). Thus it is probably the formate ion which is the reducing species. The excess of free base and the anhydrous conditions used make it unlikely that either of the mechanisms postulated by Staple and Wagner [23] (initial protonation or hydration to an aminohydrin) is correct. It is suggested that the first step is a hydride-ion transfer from formate ion to the polarised reaction centre, following by proton uptake to complete the reduction.

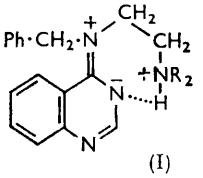


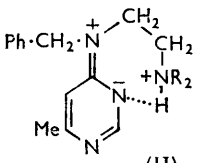
Dissociation Constants and Structure.—The pK_a values listed in Table 3 show expected trends in the main. The pK_{a_2} values in each diethylamine are greater than for the corresponding dimethylamines, as is usual. The effect of the heterocyclic group, as found in pK_{a_1} values, is in accord with the results of Albert, Goldacre, and Phillips,[24] and of Brown and Short.[25] However the effect of the heterocyclic group on the pK_{a_2} values is unexpected. This is large enough and constant enough for each heterocyclic group for an explanation to be sought. Comparison of pK_{a_1} and pK_{a_2} values for the three heterocyclic groups shows that a given group affects the two dissociation constants in the opposite direction, *e.g.*, the 4-methyl-2-pyrimidyl group gives the lowest pK_{a_1} values and the highest pK_{a_2} values. The effect is therefore unlikely to be due to an inductive mechanism which would affect both acid centres in the same way. It may however be explained in terms of an intramolecular hydrogen-bonded structure for the monoprotonated bases (I, II, III); these represent one of the contributing canonical forms of each heterocyclic aminocompound. The negative polarisation of ring-nitrogen atoms, due to conjugation of the exocyclic nitrogen atom with the aromatic ring structure (with consequent protonation of a ring nitrogen in acid solution), has been postulated for several heterocyclic amine

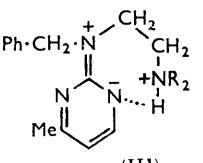
[22] Graham, *Arch. Internat. Pharmacodynam.*, 1960, **123**, 419.
[23] Staple and Wagner, *J. Org. Chem.*, 1949, **14**, 559.
[24] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[25] Brown and Short, *J.*, 1953, 331.

systems, *e.g.*, 4-aminopyridine,[26] 4-aminoquinazoline,[27] and 2- and 4-aminopyrimidines.[23] Such polarisation will tend to stabilise the postulated hydrogen bond, which in turn stabilises the protonated base.

In the 2-aminopyrimidine derivatives, either ring-nitrogen atom may form the hydrogen bond, which will thus be formed in the most stable way. If this bond is stronger than


(I)


(II)


(III)

those formed in the 4-aminopyrimidine and 4-aminoquinazoline derivatives its effect on pK_{a_2} will be greatest, so explaining the values found. This is not unlikely in view of the probable protonation of the 4-aminoquinazolines at position 1 (see below).

Albert's explanation of the low basicity of 2-aminopyrimidine can be interpreted as an equal sharing by the ring-nitrogen atoms of the negative charge produced by conjugation of the amino-group with the ring, so that protonation is not preferred at either site. In 4-aminopyrimidine, where the extent of conjugation may be a little greater, the enhanced basicity must be due to concentration of the negative charge at one ring-nitrogen atom. If this is at position 1, then the hydrogen-bonding tendency at position 3 is smaller than in 2-aminopyrimidines. Extension of this argument to derivatives of 2-aminopyrimidine and 4-aminopyrimidine (and the similar 4-aminoquinazoline) will explain the pK_{a_2} values found.

Spectrophotometric Results and Structure.—Comparison of the absorption spectra of 4-benzylaminoquinazoline (Fig. 2), *N*-benzyl-*N*′*N*′-dimethyl-*N*-4-quinazolylethylenediamine (Fig. 1), *N*-benzyl-*N*′*N*′-dimethylethylenediamine and 4-aminoquinazoline [27] shows that in the first two the absorption at wavelengths greater than 250 mμ is due to the 4-aminoquinazoline part of the molecule.

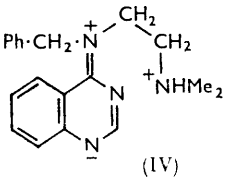
Protonation of 4-benzylaminoquinazoline causes an increase in the intensity of the 313 mμ band and a small (2 mμ) shift to longer wavelength. The 288 mμ peak is reduced to a low-intensity shoulder at a slightly longer wavelength. There is no marked hypsochromic change to give a curve characteristic of the parent aromatic system. The changes observed are similar to those found by Steck and Ewing [26] for protonation of 2- and 4-aminopyridine and interpreted by them as being due to protonation of a ring-nitrogen atom. The spectra of *N*-benzyl-*N*′*N*′-dimethyl-*N*-4-quinazolylethylenediamine show that the first proton is taken up by the aliphatic amino-group and that the second causes the same kind of change as for *N*-benzylaminoquinazoline and so likewise is attached to a ring-nitrogen atom. The protonation of a ring-nitrogen atom in these compounds suggests that the postulated conjugation and resultant polarisation do occur. This view is supported by the enhanced basicity of the quinazoline nucleus when an amino-group is present in the 4-position.[24]

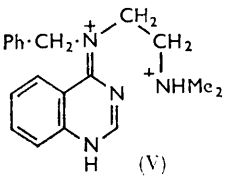
Polarisation to give structure (I) produces an *o*-quinonoid arrangement of the hetero-ring of the quinazoline nucleus while the alternative (IV) has a *p*-quinonoid structure. In the free base and monoprotonated ion the actual structure will be a hybrid of these and other canonical forms. Addition of a proton to a ring-nitrogen atom will tend to fix the structure as (I) or (IV) according to which nitrogen accepts the proton. The addition of a proton in this way increases the intensity of the long-wavelength (324 mμ) band of *N*-benzyl-*N*′*N*′-dimethyl-*N*-4-quinazolylethylenediamine (Fig. 1) so that this band

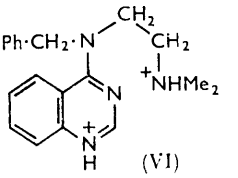
[26] Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397.
[27] Hearn, Morton, and Simpson, *J.*, 1951, 3318.

may be assigned to the quinonoid form present in the doubly charged ion The shorter-wavelength band (292 mμ) may then be assigned to the other quinonoid form.

In the free base excitation of the polar ground state will give a non-polar benzenoid structure (cf. Mason [28]). Of the two quinonoid forms the one which releases the greater strain on excitation (*i.e.*, in which the charge separation is the greater) will require the


(IV)


(V)


(VI)

less energy. This is the *para*-quinonoid form and the long-wavelength band can thus be assigned to this form. Support for this view is offered by a comparison of the two band intensities. The long-wavelength band has the greater intensity, as would be expected in view of the greater change in dipole moment which occurs on excitation of the *para*-quinonoid form. Excitation of the doubly charged ion will cause an even greater change in dipole moment (V ⟶ VI), so accounting for the increased intensity found. Thus the evidence points to protonation of position 1 of the quinazoline ring, as required for the explanation of pK_a values given above.

Structure, pK_a Values, and Anti-histamine Activity.—Compound no. 27 (Table 3) has almost the same activity as Thonzylamine and differs from it only in having a methyl group in the 4-position in the pyrimidine ring. This substituent has therefore little effect on anti-histamine activity, unlike its effect with pyridine derivatives [29] 6-Methyl-4-pyrimidyl derivatives as a group have the highest activity, 4-methyl-2-pyrimidyl the next, and the bicyclic 4-quinazolyl group the least, the last observation conforming with previous results in this field.[30] The retention of activity on altering the point of attachment of the basic side chain from the 2- to the 4-position in the pyrimidine ring is in strong contrast to the analogous change in the pyridine series.[29] It probably arises because the 4-position in the pyrimidine ring, unlike that of the pyridine ring, is a neighbour of a ring-nitrogen atom. All substituents save methyl in the 4-position of the benzyl group enhance activity, methoxyl having the greatest effect.

The pK_a values show that at physiological pH protonation occurs only at the dialkylamino-group and that the proportion of free base to salt is rather small, varying between 1% for compound no. 31 to 16% for compound no. 18. There is some indication from the pK_a values and ED_{50} values that the free base is the species active against histamine, but no further conclusions can be drawn from these results.

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[28] Mason, *Chem. Soc. Spec. Publ.* No. 3, 1955.
[29] Adamson, *Chem. and Ind.*, 1951, 2.
[30] Chapman, James, and Williams, *J.*, 1952, 4024.