421. *Synthesis of* NN-*Dialkyl*-N′-*arylalkyl*-N′-4-*cinnolinyl*(*or* 9-*fluorenyl or* 6-*methyl*-3-*pyridazinyl or* 1-*phthalazinyl or* 2-*quinoxalinyl*)*ethylenediamines of Potential Pharmacological Interest.*

By N. B. Chapman, K. Clarke, and K. Wilson.

Ditertiary amines of the type indicated in the title have been prepared in fair yield by interaction of an *NN*-dialkyl-*N*′-arylalkylethylenediamine with the appropriate heterocyclic chloro-compound. Attempted recrystallisation of the hydrochlorides of many of these compounds resulted in decomposition. The *NN*-dialkyl-*N*′-arylalkylethylenediamines were prepared by catalytic reduction of the anils formed from substituted benzaldehydes and *NN*-dialkylethylenediamines.

The sites of protonation of the ditertiary amines (usually containing *N*-heterocyclic substituents) have been studied spectrophotometrically; pK_a values for the salts corresponding to the two most basic centres have been measured, and an attempt has been made to relate the anti-histamine properties of the compounds with their properties as bases.

Pyrimidinyl derivatives of ethylenediamine are well-known histamine antagonists, " Hetramine " (*N*-benzyl-*N*′*N*′-dimethyl-*N*-2-pyrimidinylethylenediamine) and thonzylamine (the 4-methoxybenzyl analogue) being the most important of these. We therefore

decided to synthesise for pharmacological testing an analogous series of compounds containing a pyridazinyl group and, as Chapman and Taylor [1] have shown that the introduction of a methyl group into the pyrimidine ring has little effect on anti-histamine activity, the 6-methyl-3-pyridazinyl analogues were chosen.

Replacement of the phenyl group in " Antergan " (*N*-benzyl-*N'N'*-dimethyl-*N*-phenylethylenediamine) by a 1- or 2-naphthyl group,[2] the pyridyl group in " Pyribenzamine " (*N*-benzyl-*N'N'*-dimethyl-*N*-pyridylethylenediamine) by a 4-methyl-2-quinolyl group,[3] and the 4-pyrimidinyl group in *N*-benzyl-*N'N'*-dimethyl-*N*-4-pyrimidinylethylenediamine by a 4-quinazolinyl group [1] leads in each case to reduced anti-histamine activity. In order to establish whether the connection between the increased size of the heterocyclic group and decreased anti-histamine activity was more general, a further four series of substituted ethylenediamine derivatives were prepared. In these series the 2-quinoxalinyl, 1-phthalazinyl, 4-cinnolinyl, and 9-fluorenyl groups were introduced, and a range of substituents was used in the 4-position of the benzyl group.

The above decrease in activity might be due to the sheer bulk of the whole molecule and consequently compounds were prepared in which the benzyl group was replaced by smaller alkyl groups. In the 2-quinoxaline series, a range of alkyl groups (Me, Et, Pr^n, Pr^i, Bu^t) was used, and similarly with the 4-quinazolinyl group (the benzyl-containing compounds of this series have already been reported by Chapman and Taylor [1]). It was hoped to discern some relation between anti-histamine activity and the size of the alkyl group in these series.

Gardner and Stevens [4] have shown that in the 2-quinoxalinyl series the only successful method of preparing the required compounds is by condensing 2-chloroquinoxaline with the appropriate *NN*-dialkyl-*N'*-arylalkylethylenediamine, so this general method was adopted. Except for the 6-methyl-3-pyridazinyl and 4-quinazolinyl derivatives, the two reactants were heated together at 140° for two hours. Because 4-chloroquinazoline is more reactive it condensed in boiling nitromethane. However, no product could be obtained from 3-chloro-6-methylpyridazine and the secondary-tertiary diamines by either process; further, Chapman and Taylor's [1] procedure for condensation of 4-chloro-2- or -6-methylpyrimidine with these trisubstituted ethylenediamines, using a suspension in either water or aqueous acetic acid, also failed; yields of 30—60% were eventually obtained by condensation in boiling acetophenone in the presence of anhydrous potassium carbonate for 48—60 hours. The products were viscous, high-boiling oils or low-melting solids and were characterised as their picrates.

Attempts to isolate the products as their crystalline hydrochlorides met with little success. Those compounds containing a 1-phthalazinyl or a 4-cinnolinyl group, irrespective of the substituent in the benzyl group, decomposed with loss of the heterocyclic group on being treated with ethanolic hydrogen chloride and yielded only the hydrochlorides of the resulting secondary amines. Similarly, those 2-quinoxalinyl derivatives of *NN*-dimethylethylenediamine with a 4-alkoxy-substituent in the benzyl group were split on treatment with ethanolic hydrogen chloride.

The required secondary-tertiary diamines containing a substituted benzyl group were obtained almost quantitatively by catalytic reduction of the anils prepared from the appropriate *para*-substituted benzaldehyde and an *NN*-dialkylethylenediamine. Reduction with triethylamine formate gave 50—70% yields.

NNN'-Trimethylethylenediamine was prepared by Damiens's method [5] but for the other *N*-alkyl-*N'N'*-dimethylethylenediamines the *N*-alkyl-2-dimethylaminoacetamides were reduced with lithium aluminium hydride and aluminium chloride in ether,[6] which gave

[1] Chapman and Taylor, *J.*, 1961, 1908.
[2] Chapman and James, *J.*, 1954, 2103.
[3] Kaye, *J. Amer. Chem. Soc.*, 1949, **71**, 2322.
[4] Gardner and Stevens, *J. Amer. Chem. Soc.*, 1949, **71**, 1869.
[5] Damiens, *Ann. Chim.* (*France*), 1951, **6**, 835.
[6] Berger and Nystrom, *J. Amer. Chem. Soc.*, 1958, **80**, 2896.

higher yields (70—80%), in a faster reaction, than did lithium aluminium hydride alone. These amides were synthesised by treating chloroacetyl chloride in benzene, first with the primary amine and then with dimethylamine.

In an attempt to correlate changes in the properties of these compounds as bases with

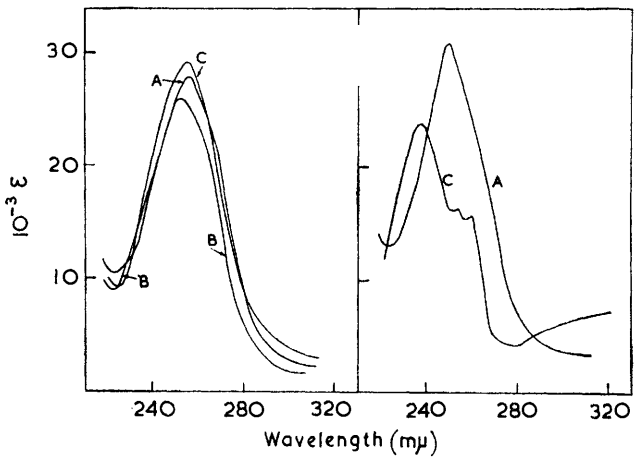


FIG. 1.

FIG. 2.

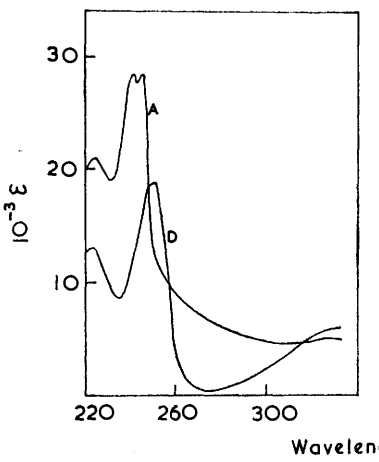


FIG. 3.

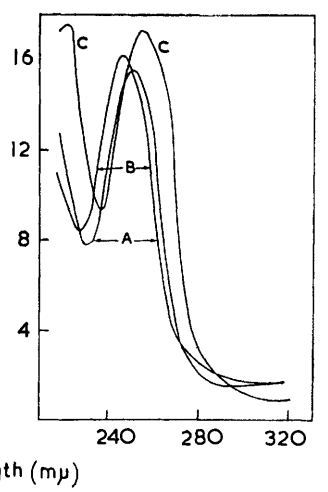


FIG. 4.

Absorption spectra of (FIG. 1) *N*-benzyl-*N'N'*-diethyl-*N*-2-quinoxalinylethylenediamine, (FIG. 2) 2-benzylaminoquinoxaline, (FIG. 3) 2-ethoxyquinoxaline, and (FIG. 4) *N*-benzyl-*N'N'*-dimethyl-*N*-(6-methyl-3-pyridazinyl)ethylenediamine.

(A) In 0·1N-NaOH. (B) At pH 6·7. (C) In 0·1N-HCl. (D) In 5N-HCl.

changes in their anti-histamine activity, the pK_a values were measured for the two most stable conjugate acids formed by each of the ditertiary amines prepared.

The site of protonation of such complex molecules is difficult to forecast and an attempt to determine it was made by measuring the ultraviolet absorption spectra of *N*-benzyl-*N'N'*-diethyl- (Fig. 1) and *NN*-dimethyl-*N'*-*p*-methylbenzyl-*N'*-2-quinoxalinylethylenediamine, of 2-benzylamino- (Fig. 2), 2-ethoxy- (Fig. 3), and 2-dimethylamino-quinoxaline, and of *N*-benzyl-*N'N'*-dimethyl-*N*-(6-methyl-3-pyridazinyl)ethylenediamine (Fig. 4).

Experimental

Substituted Benzaldehydes.—4-Ethoxy-, b. p. 130—132°/15 mm. (lit.,[7] 124—125°/8 mm.), 4-n-propoxy-, b. p. 155—157°/25 mm. (lit.,[8] 125—130°/8 mm.), and 4-isopropoxy-benzaldehyde, b. p. 141—143°/25 mm. (lit.,[9] 135—136°/16 mm.), were prepared in 90% yield by refluxing a solution of *p*-hydroxybenzaldehyde in cyclohexanone with the appropriate alkyl halide in the presence of anhydrous potassium carbonate.

p-Fluoro-, b. p. 66—67°/20 mm. (lit.,[10] 104—105°/74 mm.), and *p*-bromobenzaldehyde, m. p. 57° (lit.,[11] 57°), were prepared from the corresponding toluene by Krohnke and Borner's method [12] in 68% and 58% yield, respectively.

NN-*Dialkyl*-N′-*arylalkylethylenediamines.*—Two methods were used for the condensation of the substituted benzaldehydes with the *NN*-dialkylethylenediamine. (*a*) The aldehyde (0·1 mole) and the amine (0·12 mole) were shaken together in a stoppered flask for 10 min. (*b*) A methanolic solution of the aldehyde (0·1 mole) and the amine (0·12 mole) was heated under reflux for 30 min. The *anils* prepared by these methods are listed in Table 1.

Table 1.

Schiff bases, p-X·C_6H_4·CH:N·$[CH_2]_2$·NR_2.

X	R	Method	B. p./mm.	Yield (%)	X	R	Method	B. p./mm.	Yield (%)
H	Me	1	114°/6	78	OEt	Me	2	126—130°/0·5	74
Me	Me	1	101—103°/0·7	93	OPr^n	Me	2	133—138°/0·5	80
F	Me	2	86°/0·5	97	OPr^i	Me	2	122—126°/0·3	82
Cl	Me	2	107—110°/0·7	92	H	Et	1	124—126°/0·3	93
Br	Me	2	118—120°/0·7	91	Cl	Et	2	156°/2	93
OMe	Me	2	134—136°/2	88	OMe	Et	2	138—141°/2	93

These anils were usually reduced catalytically in methanol at room pressure and temperature over 5% palladium–alumina. However, the 4-halogeno-compounds were dehalogenated under these conditions but were successully reduced with Adams platinum catalyst. Yields were 85—95%. In most cases the b. p. of the amines and the m. p. of their picrates agreed with those given by Chapman and Taylor,[1] but the following substituted *N*-benzyl-*N′N′*-dimethylethylenediamines have not been reported: 4-ethoxy-, b. p. 128—130°/1·0 mm. [*dipicrate* (from aqueous ethanol), m. p. 175—176·5° (Found: C, 43·8; H, 3·8; N, 16·3. $C_{25}H_{28}N_8O_{15}$ requires C, 44·1; H, 4·1; N, 16·5%)]; 4-n-propoxy-, b. p. 122—125° 0·3 mm. [*dipicrate*, m. p. 167—168° (Found: C, 45·1; H, 4·3; N, 16·3. $C_{26}H_{30}N_8O_{15}$ requires C, 44·9; H, 4·3; N, 16·1%)]; 4-isopropoxy-, b. p. 108—112°/0·2 mm. [*dipicrate*, m. p. 170—171° (Found: C, 44·6; H, 4·4; N, 15·8%)].

N′-*Alkyl*-NN-*dimethylethylenediamines.*—*NNN′*-Trimethylethylenediamine, prepared in 16% yield by Damiens's method,[5] had b. p. 114—117° (lit., 115—117°). The picrate (from acetone) had m. p. 206—208° (decomp.) (lit.,[13] 206—208°).

NN-*Dimethylglycine Alkylamides.*—A 50% solution of the primary amine (1·0 mole) in dry benzene was added slowly with stirring to chloroacetyl chloride (0·5 mole) in benzene at <25°. After 1 hr. the primary amine hydrochloride was filtered off and the filtrate poured slowly with stirring into a 20% w/v solution (1 l.) of dimethylamine in benzene and left overnight. The precipitate of dimethylamine hydrochloride was collected and washed with benzene, and the combined filtrates were concentrated and distilled under reduced pressure. The amides prepared in this way, and their *picrates* (crystallised from water), are listed in Table 2.

N′-*Alkyl*-NN-*dimethylethylenediamines.*—The *NN*-dimethylglycine alkylamide (0·4 mole) in sodium-dried ether (400 ml.) was added slowly to a stirred suspension of lithium aluminium hydride (0·4 mole) and aluminium chloride (0·4 mole) in dry ether (1·0 l.) with exclusion of moisture. The mixture was heated under reflux for 3 hr. The excess of hydride was destroyed by water (5 ml.), and the mixture was made strongly alkaline with 20% sodium hydroxide solution (800 ml.). The ethereal layer was separated and the white gel of sodium aluminate

[7] Hall and Hamilton, *J.*, 1934, 1779.
[8] Jones and Gray, *J.*, 1954, 1467.
[9] Weygand and Gabler, *J. prakt. Chem.*, 1940, **155**, 332.
[10] Shoesmith, Sosson, and Slater, *J.*, 1926, 2760.
[11] Adams and Vollweiler, *J. Amer. Chem. Soc.*, 1918, **40**, 1738.
[12] Krohnke and Borner, *Ber.*, 1936, **69**, 2006; 1938, **71**, 2583.
[13] Kyuji Abe, *J. Pharm. Soc., Japan*, 1955, **75**, 153.

TABLE 2.

NN-Dimethylglycine alkylamides.

			Picrate							
				Found (%)				Required (%)		
Alkyl	B. p./20 mm.	Yield (%)	M. p.	C	H	N	Formula	C	H	N
Et	104—105°	86	165—166°	40·1	4·6	19·8	$C_{12}H_{17}N_5O_8$	40·1	4·7	19·5
Pr^n	111—112	82	136—138	42·1	5·3	19·0	$C_{13}H_{19}N_5O_8$	41·8	5·1	18·8
Pr^i	102—104	77	163—164	42·1	5·3	19·0	$C_{13}H_{19}N_5O_8$	41·8	5·1	18·8
Bu^t	91—92	47	145—147	43·4	5·8	17·8	$C_{14}H_{21}N_5O_8$	43·4	5·5	18·1

TABLE 3.

N'-Alkyl-*NN*-dimethylethylenediamines.

				Picrate							
					Found (%)				Required (%)		
Alkyl	B. p.	Yield (%)	n_D^{20}	M. p.	C	H	N	Formula	C	H	N
Et ...	135—137° *	49	1·4230	187—189°	—	—	—	—	—	—	—
Pr^n ...	154—155	70	1·4270	173—174	38·6	4·0	19·2	$C_{19}H_{25}N_8O_{14}$	38·7	4·1	19·0
Pr^i ...	143—144 †	69	1·4224	193—195	—	—	—	—	—	—	—
Bu^t ...	156—158	69	1·4266	238—240 ‡	39·7	4·9	18·9	$C_{20}H_{27}N_8O_{14}$	39·8	4·3	18·6

* Ref. 5, b. p. 135°. † Ref. 14, b. p. 142—144°. ‡ With decomp.

was shaken with ether (6 × 200 ml.). The combined ethereal extracts were dried (Na_2SO_4) and distilled. The amines prepared in this way are listed in Table 3, along with their *picrates* that crystallised from acetone.

N'-*Substituted* NN-*Dialkyl*-N'-*arylalkylethylenediamines*.—2-Chloroquinoxaline [15] (0·05 mole) and *N'*-benzyl-*NN*-dimethylethylenediamine (0·05 mole) were stirred together under nitrogen at 140° for 4 hr., then dissolved in ethanol (30 ml.), made alkaline with sodium hydroxide solution, and shaken with ether. The ethereal extract was dried (K_2CO_3), the ether removed, and the product isolated by distillation under reduced pressure as a dark red viscous oil, b. p. 180—185°/0·02 mm. 1-Chlorophthalazine,[16] 4-chlorocinnoline,[17] and 9-bromofluorene [18] reacted similarly.

The products obtained from 2-chloroquinoxaline and *N'*-arylalkyl-*NN*-diethylethylenediamines were isolated as the hydrochlorides. The residues from the ethereal extracts were dissolved in the volume of ethanolic hydrogen chloride of known concentration calculated to give the monohydrochlorides, which recrystallised from propan-2-ol.

The pyridazine derivatives were prepared as follows. The 3-chloro-6-methylpyridazine [19] (0·05 mole) and the appropriate trisubstituted ethylenediamine (0·05 mole) were heated in acetophenone (150 ml.) under reflux with stirring in the presence of anhydrous potassium carbonate (30 g.) for 48—60 hr. The mixture was filtered, the solvent removed, and the residue distilled under reduced pressure.

The derivatives from 4-chloroquinazoline [20] were prepared by using nitromethane as solvent, as described by Chapman and Taylor.[1]

Picrates were prepared by dissolving the free base (1 g.) in hot 1 : 1 acetone–ethanol and adding the theoretical amount of dry picric acid. They were recrystallised from the solvents indicated in the Tables.

The procedure adopted for the purification of these *bases* for the potentiometric titrations depended on the individual characteristics of each compound. Five main methods were used: (1) solid compounds were recrystallised repeatedly from light petroleum (b. p. 40—60°); (2) oils were redistilled under a high vacuum; (3) the base was chromatographed in light petroleum (b. p. 40—60°) on calcium carbonate; (4) the picrate of the base was recrystallised until pure

[14] Leonard and Anderson, *J. Amer. Chem. Soc.*, 1955, **77**, 4425.
[15] Gowenlock, Newbold, and Spring, *J.*, 1945, 622.
[16] Gabriel and Neumann, *Ber.*, 1893, **26**, 523.
[17] Keneford and Simpson, *J.*, 1947, 920.
[18] Wittig and Felletschin, *Annalen*, 1944, **555**, 133.
[19] Overend and Wiggins, *J.*, 1947, 241.
[20] Chapman, Gibson, and Mann, *J.*, 1947, 890.

and then decomposed with lithium hydroxide, and the free base was chromatographed to remove traces of picric acid; (5) the base was obtained from the carefully purified hydrochloride. The method used is indicated in Tables 4 and 5.

Measurement of Absorption Spectra.—A Unicam S.P. 500 spectrophotometer was used to measure the ultraviolet absorption of 2-benzylamino-, 2-dimethylamino-, and 2-ethoxyquinoxaline; *N*-benzyl-*N'N'*-diethyl-*N*-2-quinoxalinylethylenediamine; *N'N'*-dimethyl-*N*-*p*-methylbenzyl-*N*-2-quinoxalinylethylenediamine, and *N*-benzyl-*N'N'*-dimethyl-*N*-(6-methyl-3-pyridazinyl)ethylenediamine. For the ditertiary bases, measurements were carried out on the free base (in 0·1N-sodium hydroxide), on the singly protonated compound (in a buffered aqueous solution of pH 6·7), and on the doubly protonated compound (in 0·1N-hydrochloric acid). For 2-benzylaminoquinoxaline, solutions in 0·1N-sodium hydroxide and 0·1N-hydrochloric acid only were used. The spectrum of 2-ethoxyquinoxaline was also measured in 5N-hydrochloric acid. The results obtained are discussed below.

Determination of pK_a *Values.*—It was impossible to measure pK_a values by direct titration in aqueous solution because of solubility difficulties. Bennett, Brooks, and Glasstone [21] have, however, shown that the order of base strength of a series of compounds should remain constant irrespective of solvent, provided that no chemical side-reactions occur. We therefore used a mixture of absolute ethanol and 0·1M-lithium chloride. This provided a relatively constant ionic strength throughout the titration as advised by Wootton and Hammett.[22] This solution was stirred and titrated with standard hydrochloric acid (0·0500N). A sharp end-point was obtained for the first neutralisation stage, but the second stage showed no obvious end-point and so its value was taken as twice that obtained for the first neutralisation.

TABLE 4.

N-Benzylethylenediamines, $NR_2{\cdot}CH_2{\cdot}CH_2{\cdot}NR'{\cdot}CH_2{\cdot}C_6H_4R''$-*p*.
Picrates * (or, where stated, analyses of bases).

No.	R	R'	R''	B. p./mm. of base (or m.p. of hydrochloride)	Yield (%)	Purifn. method	M. p. of base *	pK_a'	pK_a''
1	Me	A	H	168—170°/0·003	47	4		8·35	4·02
2	Me	A	Cl	165—170°/0·01	26	4		8·27	3·94
3	Me	A	OMe	180—185°/0·005	32	4		8·36	4·03
4	Me	A	OEt	190—195°/0·015	45	4		8·34	4·00
5	Me	A	OPr^n	190—195°/0·02	27	4		8·33	3·99
6	Me	A	OPr^i	196—200°/0·05	37	4		8·32	4·00
7	Et	A	H	144—150°/0·0006	28	4		8·92	3·87
8	Et	A	OMe	160—165°/0·001	31	4		8·94	3·96
9	Me	B	H	180—185°/0·02	27	3	168°	7·89	2·78
10	Me	B	Me	186—190°/0·03	44	1	66—67	7·89	2·78
11	Me	B	F	200—204°/0·06	36	1	43—44	7·92	2·97
12	Me	B	Cl	216—220°/0·06	46	1	83·5—84	7·83	2·81
13	Me	B	Br	230—234°/0·1	41	1	80·5—82	7·77	2·83
14	Me	B	OMe	190—195°/0·005	37	4		7·86	2·85
15	Me	B	OEt	206—214°/0·01	45	3		7·86	2·85
16	Me	B	OPr^n	212—214°/0·003	34	3		7·81	2·84
17	Me	B	OPr^i	202—208°/0·007	46	3		7·84	2·78
18	Et	B	H	(183—185°)	56	5		8·39	2·81
19	Et	B	Cl	(169—171°)	54	5		8·27	2·78
20	Et	B	OMe	(160—162°)	48	5		8·36	2·78
21	Me	C	H	172—176°/0·03	15	4			
22	Me	C	OMe	200—205°/0·03	29				
23	Me	D	H	190—195°/0·02	29	4		7·33	3·96
24	Me	D	OMe	220—230°/0·02	30	4		7·43	4·11
25	Me	E	H	190—192°/0·04	42	1	60—61	8·53	2·78
26	Me	E	Cl	206—208°/0·06	47	3		8·47	
27	Me	E	Br	190—194°/0·01	32	3		8·48	2·98
28	Me	E	OMe	200—205°/0·02	51	3		8·51	3·24
29	Et	E	H	200—205°/0·02	72	3		8·88	3·06
30	Et	E	Cl	174—180°/0·002	67	3		8·87	3·23
31	Et	E	OMe	195—198°/0·01	49	3		8·89	3·54

[21] Bennett, Brooks, and Glasstone, *J.*, 1935, 1821.
[22] Wootten and Hammett, *J. Amer. Chem. Soc.*, 1935, **57**, 2289.

TABLE 4. (*Continued.*)

No.	M. p.*	Found (%) C	H	N	Formula	Required (%) C	H	N
1	178—180	46·4	3·9	19·2	$C_{28}H_{28}N_{10}O_{14}$	46·1	3·9	19·2
2	189—191	44·4	3·5	18·3	$C_{28}H_{27}ClN_{10}O_{14}$	44·1	3·6	18·4
3	158—160	45·6	4·1	18·7	$C_{29}H_{30}N_{10}O_{15}$	45·8	4·0	18·5
4	157—158	46·9	3·8	17·8	$C_{30}H_{32}N_{10}O_{15}$	46·7	4·1	18·1
5	150—151	47·3	5·0	17·7	$C_{31}H_{34}N_{10}O_{15}$	47·3	4·3	17·8
6	152—153	47·1	4·4	17·6	$C_{31}H_{34}N_{10}O_{15}$	47·3	4·3	17·8
7	169—171	47·6	4·3	18·6	$C_{30}H_{32}N_{10}O_{14}$	47·5	4·2	18·5
8	142—144	47·1	4·4	17·8	$C_{31}H_{34}N_{10}O_{15}$	47·3	4·3	17·8
9	(Base)	74·4	5·8	18·5	$C_{19}H_{22}N_4$	74·4	7·2	18·3
	140—141 (M)	55·8	4·6	18·2	$C_{25}H_{25}N_7O_7$	56·0	4·7	18·3
10	(Base)	74·9	7·6	17·9	$C_{20}H_{24}N_4$	75·0	7·5	17·5
	167—170	49·8	4·1	17·8	$C_{32}H_{30}N_{10}O_{14}$	49·4	3·9	18·0
11	(Base)	70·5	6·8	17·0	$C_{19}H_{21}FN_4$	70·4	6·5	17·3
	168—170	47·8	3·6	17·7	$C_{31}H_{27}FN_{10}O_{14}$	47·5	3·5	17·9
12	(Base)	66·8	5·9	16·2	$C_{19}H_{21}ClN_4$	66·9	6·1	16·4
	193—194	46·3	3·1	17·4	$C_{31}H_{27}ClN_{10}O_{14}$	46·0	3·4	17·5
13	(Base)	59·2	5·1	15·0	$C_{19}H_{21}BrO_4$	59·2	5·4	14·5
	189—190	43·8	3·0	16·7	$C_{31}H_{27}BrN_{10}O_{14}$	44·2	3·2	16·7
14	148—150 (d)	48·0	4·0	18·1	$C_{32}H_{30}N_{10}O_{15}$	48·3	3·8	17·7
15	141—143 (d)	49·2	4·1	17·2	$C_{33}H_{32}N_{10}O_{15}$	49·0	4·0	17·3
16	102—104	49·3	4·2	17·1	$C_{34}H_{34}N_{10}O_{15}$	49·6	4·1	17·1
17	127—128 (d)	49·7	4·0	17·2	$C_{34}H_{34}N_{10}O_{15}$	49·6	4·1	17·1
		68·3	7·3	—	$C_{21}H_{27}ClN_4$ †	68·2	7·5	—
18	156—157 (M)	57·1	5·2	17·4	$C_{27}H_{29}N_7O_7$	57·4	5·1	17·4
		61·8	6·3	—	$C_{21}H_{26}Cl_2N_4$ ‡	62·3	6·4	—
19	179—181 (M)	54·5	4·7	16·9	$C_{27}H_{28}ClN_7O_7$	54·2	4·7	16·4
		65·3	7·3	—	$C_{22}H_{29}ClN_4O$ §	65·9	7·2	—
20	139—141 (M)	56·9	4·9	17·0	$C_{28}H_{30}N_7O_8$	56·7	5·2	16·5
21	209—211 (d)	48·8	4·0	18·2	$C_{31}H_{28}N_{10}O_{14}$	48·7	3·7	18·4
22	162—164 (d)	48·7	3·9	17·6	$C_{32}H_{30}N_{10}O_{15}$	48·3	3·8	17·7
23	202—204 (d)	48·6	3·5	18·8	$C_{31}H_{28}N_{10}O_{14}$	48·7	3·7	18·4
24	137—139 (M)	55·4	5·3	18·2	$C_{26}H_{27}N_{10}O_{15}$	55·3	4·8	17·4
25	(Base)	84·0	7·4	8·5	$C_{24}H_{26}N_2$	84·2	7·6	8·2
	203—205 (d) (M)	63·2	5·4	12·2	$C_{30}H_{29}N_5O_7$	63·0	5·1	12·2
26	214—215 (d)	51·7	3·9	13·6	$C_{36}H_{31}ClN_8O_{14}$	51·8	3·7	13·5
27	158—160	55·4	4·3	10·8	$C_{36}H_{31}BrN_8O_{14}$	55·4	4·3	10·8
28	168—170 (d)	53·5	4·2	13·8	$C_{37}H_{33}N_8O_{15}$	53·5	3·1	13·5
29	153—155 (d)	54·7	4·5	13·3	$C_{38}H_{36}N_8O_{14}$	55·1	4·4	13·5
30	191—193 (d)	52·8	4·2	13·0	$C_{38}H_{35}ClN_8O_{14}$	52·9	4·1	13·0
31	181—182	54·4	4·5	12·9	$C_{39}H_{37}N_8O_{15}$	54·6	4·4	13·1

A = 6-Methyl-3-pyridazinyl. B = 2-Quinoxalinyl. C = 1-Phthalazinyl. D = 4-Cinnolinyl. E = 9-Fluorenyl. * Picrate were recrystallised from 1 : 1 ethanol–acetone; free bases from light petroleum (b. p. 40—60°). (M) = Monopicrates. (d) = With decomp. Hydrochlorides were crystallised from propan-2-ol. pK_a' refers to the dialkylamino-group, and pK_a'' to a ring-nitrogen atom in the heterocyclic compounds and to the remaining nitrogen atom in the fluorenyl compounds. † Found: Cl, 9·2. Reqd.: Cl, 9·5%. ‡ Found: Cl, 8·8. Reqd.: Cl, 8·8%. § Found: Cl, 8·7. Reqd.: Cl, 8·7%.

The second ionisation constant (pK_a'') was calculated from the equation:

$$pK_a'' = pH - \log [(B + H^+)/(BH^+ - H^+)], \quad (1)$$

where B = concentration of free base, H^+ = hydrogen-ion concentration, BH^+ = concentration of protonated base.

For the first ionisation constant (pK_a'), the end-point lay within the region of pH 5—6, and the above equation could be reduced to the Henderson equation:

$$pK_a' = pH - \log (B/BH^+). \quad (2)$$

Procedure.—A mixture of a 0·00500M-solution (25 ml.) of the base in absolute ethanol and a 0·1M-solution (25 ml.) of lithium chloride in carbon dioxide-free, de-ionised water was introduced into the water-jacketed (20° ± 0·2°) titration beaker. The solution was stirred and a stream of nitrogen which had first been passed through a column of " Carbosorb," filtered, and bubbled through 50% aqueous ethanol was passed over its surface. The base was titrated

by the simultaneous addition, beneath the surface, of equal volumes of absolute ethanol and standard hydrochloric acid (0·0500N), the pH being read after each 0·1 ml.

Pharmacological Results.—The pharmacological properties of these ditertiary amines have been studied. Their activities against histamine and acetylcholine are listed in Table 6 and are compared with the activity of thonzylamine and "Antistine."

TABLE 5.

Bases, $Me_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NR{\cdot}R'$.

No.	R	R'	B. p./mm.	Yield (%)	Purifn. method	pK_a'	pK_a''
1	B	Me	125—130°/0·004	36	4	8·06	2·84
2	B	Et	135—138°/0·0005	35	4	8·12	2·84
3	B	Pr^n	142—145°/0·0005	40	4	8·10	2·87
4	B	Pr^i	145—148°/0·0005	43	4	8·12	2·65
5	B	Bu^t	135—140°/0·002	30	4	7·98	2·77
6	C	Et	150—155°/0·1	16	4	8·59	3·56
7	D	Et	140—148°/0·05	12	—	—	—
8	E	Et	130—134°/0·02	50	3	8·61	3·19
9	F	Me	125—128°/0·001	58	3	8·03	5·12
10	F	Et	130—135°/0·02	48	3	8·09	5·06
11	F	Pr^n	136—138°/0·03	51	3	8·00	4·99
12	F	Pr^i	138—142°/0·03	47	4	8·09	4·67

Dipicrates.*

		Found (%)				Required (%)		
No.	M. p.	C	H	N	Formula	C	H	N
1	187—189° (M)	50·0	4·7	21·4	$C_{19}H_{21}N_7O_7$	49·5	4·6	21·4
2	179—181 (M)	50·8	4·8	20·8	$C_{20}H_{23}N_7O_7$	50·8	4·9	20·7
3	180—182	45·1	3·7	19·8	$C_{27}H_{28}N_{10}O_{14}$	45·2	3·9	19·6
4	193—195 (d)	45·3	4·0	19·7	$C_{27}H_{28}N_{10}O_{14}$	45·2	3·9	19·6
5	198—199 (d) (M)	52·9	5·2	19·7	$C_{22}H_{27}N_7O_7$	52·7	5·4	19·6
6	193—195 (d)	44·4	3·8	20·6	$C_{26}H_{26}N_{10}O_{14}$	44·5	3·7	19·9
7	205·5—208 (d)	44·3	3·7	19·9	$C_{30}H_{23}N_7O_7$	44·5	3·7	19·9
8	207—209 (d)	50·7	4·2	15·5	$C_{31}H_{30}N_8O_{14}$	50·4	4·1	15·2
9	207—209	43·5	3·4	20·1	$C_{25}H_{24}N_{10}O_{14}$	43·6	3·5	20·3
10	226—228 (d)	44·5	3·8	19·8	$C_{26}H_{26}N_{10}O_{14}$	44·5	3·7	19·9
11	190—192	46·5	4·8	17·5	$C_{27}H_{28}N_{10}O_{14}$	45·2	3·9	19·6
12	218—221 (d)	45·5	3·8	19·6	$C_{27}H_{28}N_{10}O_{14}$	45·2	3·9	19·6

B, C, D, E, as for Table 4. F = 4-Quinazolinyl. * Crystallised from 10 : 1 acetone–dimethylformamide. (d) = with decomposition. (M) = Monopicrate.

DISCUSSION

Spectrophotometric Results and Structure.—Figs. 1 and 2 show that the strong absorption in the region 230—280 mμ is due to the 2-aminoquinoxaline part of the molecule. Protonation of both 2-benzyl- and 2-dimethyl-aminoquinoxaline leads to a hypsochromic shift of 12 mμ and to a decrease in intensity. The spectra approximate closely to that found by Bohlmann [23] for quinoxaline itself. It appears that in both cases the amino-group has been protonated, thus destroying its conjugation with the heterocyclic ring and causing a reversion to the spectrum of quinoxaline. The spectra of *N*-benzyl-*N'N'*-diethyl-*N*- and *NN*-dimethyl-*N'*-*p*-methylbenzyl-*N'*-2-quinoxalinylethylenediamine show a small hypsochromic shift (4 and 3 mμ, respectively) and a slight decrease in peak intensity on monoprotonation, consistent with protonation of the dialkylamino-group. The addition of a second proton to those two compounds causes a small bathochromic shift (3 and 2 mμ, respectively) and an increase in peak intensity compared with the monoprotonated species, and these changes are not consistent with the protonation of the nitrogen atom adjacent to the heterocyclic ring. The changes are similar to those observed by Steck and Ewing [24]

[23] Bohlmann, *Chem. Ber.*, 1951, **84**, 490.
[24] Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397.

TABLE 6.

Pharmacological results for bases $NR_2 \cdot CH_2 \cdot CH_2 \cdot NR'R''_2$. Percentage reduction in contraction produced by various concentrations of antagonist.

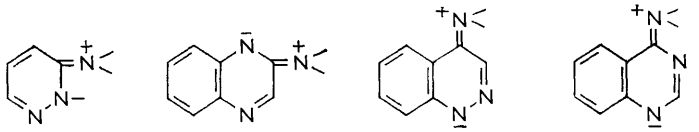
				Histamine Concn. of antagonist (g./l.)				Acetylcholine Concn. of antagonist (g./l.)		
No.	R	R′	R″	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-5}	10^{-6}	10^{-7}
1	Me	A	Benzyl	100	10	0	—	50	—	—
2	Me	A	*p*-Chlorobenzyl	100	66	5	—	30	25	—
3	Me	A	*p*-Methoxybenzyl	100	70	0	—	50	10	0
4	Me	A	*p*-Ethoxybenzyl	100	25	0	—	90	5	0
5	Me	A	*p*-n-Propylbenzyl	100	25	5	—	85	0	—
6	Me	A	*p*-Isopropylbenzyl	100	10	0	—	75	10	0
7	Et	A	Benzyl	90	10	0	—	25	0	—
8	Et	A	*p*-Methoxybenzyl	100	10	0	—	80	10	0
9	Me	B	Benzyl	100	80	0	—	75	25	5
10	Me	B	*p*-Methylbenzyl	100	85	15	10	75	0	—
11	Me	B	*p*-Chlorobenzyl	100	75	25	0	90	40	0
12	Me	B	*p*-Methoxybenzyl	100	80	10	—	100	45	10
13	Me	B	*p*-Isopropoxybenzyl	100	50	0	—	100	0	—
14	Et	B	Benzyl	100	65	10	—	70	15	0
15	Et	B	*p*-Methoxybenzyl	100	60	0	—	90	25	0
16	Et	B	*p*-Chlorobenzyl	100	50	0	—	95	60	0
17	Me	B	Methyl	0	—	—	—	15	0	—
18	Me	B	Ethyl	75	0	—	—	25	0	—
19	Me	B	n-Propyl	5	0	—	—	40	0	—
20	Me	B	Isopropyl	95	15	0	—	25	0	—
21	Me	B	t-Butyl	100	65	0	—	75	10	0
22	Me	C	Benzyl	95	10	0	—	66	33	0
23	Me	D	Benzyl	100	80	10	—	65	5	—
24	Me	E	Benzyl	100	60	0	—	100	40	0
25	Et	E	Benzyl	100	75	5	—	95	60	25
26	Me	E	Ethyl	100	60	0	—	100	15	5
27	Me	F	Methyl	75	25	0	—	0	—	—
28	Me	F	Ethyl	50	10	0	—	0	—	—
29	Me	F	Isopropyl	60	10	0	—	0	—	—
			Thonzylamine	100	100	50	50	0	10	0
			Antistine	100	100	50	10	0	0	—

A, B, C, D, E, F, as for Tables 4 and 5.

for the protonation of 2- and 4-aminopyridine and thought to be due to protonation of a ring-nitrogen atom. Also, protonation of 2-ethoxyquinoxaline with 5N-hydrochloric acid causes a small bathochromic shift (6 mμ) (Fig. 3). It appears, therefore, that, although protonation of 2-benzylamino- and 2-dimethylamino-quinoxaline occurs at the external nitrogen atom, with the more complex ditertiary bases the first proton is added to the dimethylamino-group and the second to a ring-nitrogen atom. Similar arguments also apply to the 6-methyl-3-pyridazine derivatives (Fig. 4). The presence of the positive charge on the dimethylamino-group may so diminish the basic strength of the other external nitrogen atom that one of the ring-nitrogen atoms becomes the second most basic centre. The magnitude of this effect is illustrated by the difference in the basic strengths of 9-*N*-benzylaminofluorene and *N*-benzyl-*N'N'*-dimethyl-*N*-9-fluorenylethylenediamine. The relevant pK_a values are 6·66 and 2·78, a difference of 3·88 pK_a units.

Dissociation Constants and Structure.—The pK_a values listed in Tables 4 and 5 usually show the expected trends. Thus the pK_a' values of the diethylamino-compounds are greater than those of the corresponding dimethylamino-compounds. It can be seen that the heterocyclic group influences both the pK_a' and the pK_a'' value, but in the opposite direction. Thus *N*-ethyl-*N'N'*-dimethyl-*N*-4-quinazolinylethylenediamine has the highest pK_a' value (8·1) of the *N*-ethyl compounds, but has the lowest pK_a'' value (5·1). This may best be understood by considering the various polar canonical forms which contribute to the structure of the heterocyclic amino-compounds. The most important of these

forms are those in which a negative charge is located at a ring-nitrogen atom (I, II, III, IV). It can be shown that the contributions of these canonical forms to the structures are greater for bicyclic than for monocyclic compounds, and that in bicyclic systems *para*-quinonoid forms have lower energy and consequently are more important than the



(I) (II) (III) (IV)

corresponding *ortho*-quinonoid forms. The importance of such charged canonical forms therefore increases from (I) to (IV). As a result, the inductive electron-withdrawal (—*I*) from the dialkylamino-group by the positive pole will be least in the pyridazinyl series (it should therefore exhibit the highest pK_a' value) and progressively greater from the quinoxalinyl to the cinnolinyl and quinazolinyl group, in accord with experiment. For the second protonation, which has been shown to occur at a ring-nitrogen atom, the greater the importance of these charged canonical forms the greater the basic strength of the ring-nitrogen atom, again in accord with most of the experimental findings. The *para*-substituents in the attached benzyl groups also exert a small influence on the basic strength (pK_a') of the remote nitrogen atom and it appears that a long-range inductive effect operates, similar to that found by Dippy [25] for β-phenylpropionic acids. Within the series of *N*-alkyl compounds there appears to be no correlation between the inductive effect of the alkyl group and its influence on either the pK_a' or the pK_a'' value.

Structure, pK_a *Values, and Antihistamine Activity.*—Although none of the compounds prepared exhibited anti-histamine activity comparable with that of thonzylamine, several conclusions may be drawn from the results listed in Table 6. In the substituted benzyl series of compounds, *para*-substituents enhance activity, methoxy- and chloro-groups having the greatest effect. The dimethylamino-compounds are generally more active than the corresponding diethylamino-compounds and also more specific. Within a given heterocyclic or fluorene series there is no apparent correlation between anti-histamine activity and pK_a' value. However, consideration of the results as a whole shows that the four most active compounds (nos. 10, 11, 12, and 23) have four of the lowest pK_a' values, whereas the least active compounds (nos. 1 and 7) possess high pK_a' values. This suggests that it is the free base which is the active species against histamine as compounds with low pK_a' values would have the highest ratio of free base to salt under the test conditions.

The activity of the cinnolinyl compound no. 23 is particularly interesting since the position of attachment of the ethylenediamine unit is not adjacent to a ring-nitrogen atom—a structural feature which previous workers in this field have deemed necessary for activity. Again this compound has a low pK_a' value and its anomalously high activity may be due to the higher proportion of the free base available at a given concentration of the compound. The low activity of the pyridazinyl compounds may be due either to their high pK_a' values or to the presence of the methyl group for, although Chapman and Taylor [1] have shown that such a substituent does not reduce the activity of some pyrimidinyl derivatives of ethylenediamine, the introduction of a methyl group into the analogous pyridine series [26] markedly decreases activity.

It does not appear possible to compensate for an increase in the size of the heterocyclic group in these compounds by replacing the benzyl group by a smaller alkyl group, since such a replacement leads to a marked reduction in activity (the fluorene system is the only exception to this generalisation). Only for the t-butyl compound no. 21 is the

[25] Dippy, *Chem. Rev.*, 1939, **25**, 151.
[26] Huttrer, Djerassi, Beears, Mayor, and Scholz, *J. Amer. Chem. Soc.*, 1946, **68**, 1999.

activity comparable with that of the benzyl compound no. 9, and this appears to indicate the necessity for a large group in this position.

The anti-histamine activity of the *N*-alkyl-*N'N'*-dimethyl-*N*-4-quinazolinylethylenediamines is of interest, since although it is low it is highly specific and the compounds have no anti-acetylcholine activity even at high concentrations.

We thank the Department of Scientific and Industrial Research for a research studentship (to K. W.) and the Nicholas Research Institute Ltd. for the pharmacological results.

THE UNIVERSITY, HULL. [*Received, September 27th*, 1962.]