SYNTHESIS OF SOME HISTAMINE DERIVATIVES HAVING POTENTIAL HISTAMINE-LIKE OR ANTIHISTAMINE ACTIVITY

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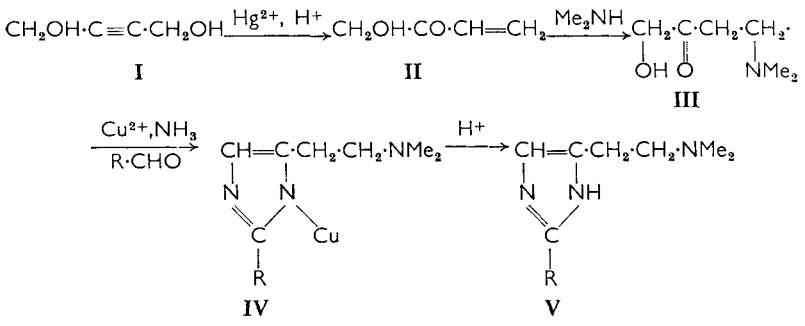
Twelve compounds derived from histamine have been prepared. In these the primary amine hydrogen atoms of histamine are replaced by methyl groups and the imidazole nucleus is substituted in the two position by a range of aliphatic and aromatic residues. Most members of the series have histamine-like pharmacological properties; two compounds have antihistamine activity.

Of the large number of compounds synthesised for possible histamine-like or antihistamine activity few have contained the imidazole nucleus and of these only a small number can be considered to be derivatives of histamine (see, e.g. Protiva, 1955). In view of the competitive antagonism to histamine shown by many antihistamine drugs it seemed that compounds closely related to histamine might possess antihistamine activity. Because many successful antihistamine compounds have an aliphatic chain terminated by a dimethylamino-group, *NN*-dimethylhistamine was chosen as the parent of a series.

Experimental Methods

The parent compound has been synthesised conveniently by Huebner (1951) using the Weidenhagen reaction (Weidenhagen and Herrmann, 1935), a method capable of general application to histamine derivatives substituted in the two position of the imidazole nucleus. In this method but-2-yne-1,4-diol (I) in ethyl acetate solution is isomerised to hydroxymethyl vinyl ketone (II) using a mercuric oxide-trichloroacetic acid-boron trifluoride catalyst (Reppe, 1949). The ketone with dimethylamine solution gives the Mannich-type base (III) which is not isolated but treated with an aldehyde and cupric acetate: ammonia solution on a heated water-bath. In the original Weidenhagen method the resulting precipitate of cuprous imidazole (IV) is separated by filtration, decomposed with hydrogen sulphide and the liberated imidazole derivative (V) obtained by suitable means. We found that improved yields are obtained when the whole of the reaction mixture is treated with hydrogen sulphide to precipitate all the copper as sulphide. This is because the cuprous imidazole compounds of this series are appreciably soluble in ammonia solution. The filtrate is then acidified, evaporated to low bulk, treated with 50 per cent potassium hydroxide solution and the liberated imidazole extracted with n-butanol. The hydrochloride is obtained either by acidification or better by first distilling the base in vacuum and then converting to the salt.



Yields (about 20 per cent) are much lower than those reported by Weidenhagen. This is probably due to the instability of the base III, which readily loses dimethylamine to revert to II, which forms polymeric compounds in ammonia solution (Huebner, 1951).

The compounds listed in Table I have been obtained by this route. The general procedure is exemplified as follows.

2-Ethyl-4(2′-dimethylaminoethyl)-imidazole

To hydroxymethyl vinyl ketone (8 g., 0·11 mole) (obtained from but-2-yne-1,4-diol (32 g., 0·44 mole) by Reppe's method (1949) was added dimethylamine (25 ml. of 33 per cent solution in ethanol, 0·17 mole) with cooling in ice-water. After allowing to stand for 15 min. the mixture was added to a solution of cupric acetate (36 g., 0·18 mole) and propionaldehyde (7 g., 0·12 mole) in ammonia solution (225 ml., s.g. 0·880). The combined solutions were heated on a boiling water-bath for 1 hr. Hydrogen sulphide was then passed in until the copper was completely precipitated, when the suspension was filtered. The filtrate was acidified with 6N hydrochloric acid, evaporated to low bulk and basified with 50 per cent potassium hydroxide. The imidazole base was extracted with n-butanol (6 portions of 20 ml.), the combined extracts dried ($MgSO_4$), the solvent removed and the residue distilled under reduced pressure to give *2-ethyl-4(2′-dimethylaminoethyl)-imidazole* (4·9 g., b.p. 140–142°/1 mm., yield 72 per cent).

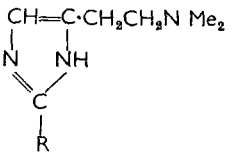
The base was dissolved in ethanolic hydrochloric acid (20 ml., 4N) and an excess of ether added to precipitate *2-ethyl-4(2′-dimethylaminoethyl)-imidazole dihydrochloride* (m.p. 181–183° after crystallisation from isopropanol-ether mixture).

In Table I the equivalent weight recorded was determined by titration with standard silver nitrate for hydrochlorides and with standard acetic-perchloric acid for picrates. Hydrochlorides were crystallised from isopropanol-ether mixture, picrates from aqueous acetone. Melting-points are uncorrected.

Pharmacological Properties and Discussion

The hydrochlorides have been tested for histamine-like and anti-histamine activity on isolated guinea-pig ileum. As reported by Huebner

TABLE I



No.	R	Salt	m.p. °C	Formula	Found per cent				Required per cent				Found equiv. wt.	Required equiv. wt.
					C	H	N	Hal	C	H	N	Hal		
1a	H	di-HCl	192–4[a]	$C_7H_{15}Cl_2N_3$	—	—	—	33·5	—	—	—	33·5	106	106
1b	H	dipicrate	231–2[b]	$C_{19}H_{19}N_9O_{14}$	—	—	21·1	—	—	—	21·1	—	296	299
2a	Me	di-HCl	199–201	$C_8H_{17}Cl_2N_3$	42·1	7·5	18·2	31·6	42·5	7·5	18·6	31·4	114	113
2b	Me	dipicrate	193–4	$C_{20}H_{21}N_9O_{14}$	38·9	3·7	20·5	—	39·3	3·4	20·6	—	304	306
3a	Et	di-HCl	181–3	$C_9H_{19}Cl_2N_3$	44·6	8·0	17·5	29·4	45·0	7·9	17·5	29·6	122	120
3b	Et	dipicrate	154–6	$C_{21}H_{23}N_9O_{14}$	40·6	3·7	20·0	—	40·3	3·7	20·2	—	311	313
4a	Ph·CH_2	di-HCl	174–5	$C_{14}H_{21}Cl_2N_3$	55·2	7·0	13·5	23·4	55·6	7·0	13·9	23·5	151	151
4b	Ph·CH_2	dipicrate	161–2	$C_{26}H_{25}N_9O_{14}$	45·1	3·8	18·3	—	45·4	3·6	18·3	—	346	344
5a	Ph	di-HCl	280–2[c]	$C_{13}H_{19}Cl_2N_3$	54·1	6·9	14·5	24·6	54·2	6·6	14·6	24·7	143	144
5b	Ph	dipicrate	223–4[d]	$C_{25}H_{23}N_9O_{14}$	44·9	3·6	18·7	—	44·6	3·4	18·7	—	336	337
6a	*p*-Cl·C_6H_4	di-HCl	285–6	$C_{13}H_{18}Cl_3N_3$	48·3	5·7	13·3	33·1	48·4	5·6	13·0	33·0	162	161
6b	*p*-Cl·C_6H_4	dipicrate	219–20	$C_{25}H_{22}ClN_9O_{14}$	42·5	3·3	17·8	5·4	42·4	3·1	17·8	5·1	353	354
7a	*p*-Br·C_6H_4	di-HCl	276–8	$C_{13}H_{18}BrCl_2N_3$	42·9	5·2	11·2	—	42·5	4·9	11·5	—	185	183
7b	*p*-Br·C_6H_4	dipicrate	218–9	$C_{25}H_{22}BrN_9O_{14}$	40·3	3·2	16·6	10·6	39·9	2·9	16·8	10·6	377	376
8a	*p*-Me·C_6H_4	di-HCl	296–7	$C_{14}H_{21}Cl_2N_3$	55·2	6·9	13·8	23·5	55·6	7·0	13·9	23·5	152	151
8b	*p*-Me·C_6H_4	dipicrate	213–4	$C_{26}H_{25}N_9O_{14}$	45·9	3·8	18·3	—	45·4	3·6	18·3	—	344	344
9a	*m*-NO_2·C_6H_4	di-HCl	273–4	$C_{13}H_{18}Cl_2N_4O_2$	46·6	5·9	16·5	21·5	46·9	5·4	16·8	21·3	167	167
9b	*m*-NO_2·C_6H_4	dipicrate	221–2	$C_{25}H_{22}N_{10}O_{16}$	42·0	3·2	19·6	—	41·8	3·1	19·5	—	362	359
10a	*p*-Me_2N·C_6H_4	di-HCl	258–9	$C_{15}H_{24}Cl_2N_4$	54·0	7·3	17·4	21·4	54·3	7·3	16·9	21·2	165	166
10b	*p*-Me_2N·C_6H_4	dipicrate	222–3	$C_{27}H_{26}N_{10}O_{14}$	45·3	4·2	19·4	—	45·3	3·9	19·6	—	241	239
11a	*p*-MeO·C_6H_4	di-HCl	287–8	$C_{14}H_{21}Cl_2N_3O$	52·5	6·3	13·0	22·7	52·8	6·6	13·2	22·3	158	159
11b	*p*-MeO·C_6H_4	dipicrate	225–6	$C_{26}H_{25}N_9O_{15}$	44·4	3·5	18·1	—	44·4	3·5	17·9	—	352	352
12a	2-Furyl	di-HCl·H_2O	241–2	$C_{11}H_{16}Cl_2N_3O_2$	44·5	6·6	14·2	23·7	44·6	6·4	14·2	24·0	149	148
12b	2-Furyl	dipicrate	225–6	$C_{23}H_{22}N_9O_{15}$	41·8	3·3	19·0	—	41·6	3·2	19·0	—	331	332

(*a*) Huebner (1951) reports m.p. 184–5°. (*b*) Huebner (1951) reports m.p. 230–2°. (*c*) Huebner (1951) reports m.p. 270–5°. (*d*) Huebner (1951) reports m.p. 218–220°.

(1951) and Huebner, Turner and Scholz (1949), compounds 1a and 4a (Table I) had histamine-like activity, as did 2a, 3a, 8a, 9a, 10a, and 12a, in doses 10 to 100 times those at which histamine itself was effective. Compounds 6a and 11a were found to have a slight antihistamine activity. This is of interest in that a number of commercial antihistamine drugs have a *p*-chlorophenyl or *p*-methoxyphenyl group in the molecule. It is not to be expected that antihistamine activity will be high in these compounds as study of the reported activity of many substances synthesised for antihistamine action shows that a second aromatic or hetero-aromatic substituent is likely to be necessary for high activity.

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