THE SYNTHESIS OF *N*-SUBSTITUTED AMIDINES OF POTENTIAL PHARMACOLOGICAL ACTIVITY

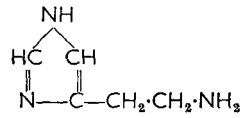
BY J. A. SMITH AND H. TAYLOR

From the Department of Pharmacy, Institute of Technology, Bradford

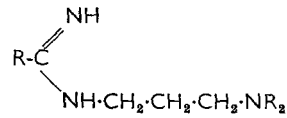
Received February 27, 1963

A series of *N*-3-diethylaminopropyl benzamidines has been prepared. The method used was the well-known Pinner synthesis (Pinner, 1892) of the imido-ester hydrochloride and then further reaction with 3-diethylaminopropylamine monohydrochloride. The compounds were tested for histamine-like, antihistamine and adrenergic neurone blocking activity. Some nonspecific antihistamine activity was found; there was no other activity.

ALTHOUGH the structure of *N*-dialkylaminopropyl amidines II bears a formal similarity to that of histamine I, little work appears to have been done in investigating the possibility of these compounds having histamine-like or antihistamine activity.



I



II

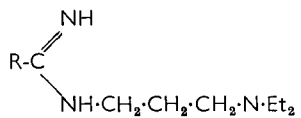
Certain *N*-dialkylaminoalkyl benzamidines have already been prepared as antimalarials (Curd and Raison, 1947), as antibacterials (Fullar, Tonkin and Walker, 1945), and also as antituberculosis agents (Charlton, Maliphant, Oxley and Peak, 1951), but no reference was made to any possible antihistamine properties of these compounds.

No attempt, however, appears to have been made to prepare a series of *N*-substituted amidines with a constant *N*-dialkylaminopropyl side chain. Therefore, it was decided to prepare such a series (Table I), varying the aromatic characteristic R in an attempt to find whether this related structure had any antihistamine activity.

EXPERIMENTAL

The method used was the Pinner synthesis (Pinner, 1892) of the imido-ester hydrochlorides which were converted into the corresponding amidines by treatment with 3-diethylaminopropylamine monohydrochloride. In this case, the reaction between the imido-ester hydrochloride and the 3-diethylaminopropylamine base as described by Curd and Raison (1947) and by Fuller and others (1945) resulted in the decomposition of the imido-ester hydrochloride, with the evolution of ammonia. It was found that on the addition of 3-diethylaminopropylamine monohydrochloride, no ammonia was evolved and the reaction proceeded to give good yields of the *N*-diethylaminopropyl benzamidines. The methods described below apply generally.

TABLE I



No.	R	Salt	m.p. °C	Formula	Found per cent				Required per cent				Found equiv. wt.	Required equiv. wt.
					C	H	N	Cl	C	H	N	Cl		
1a	C_6H_5—	di-HCl	163–4	$C_{14}H_{25}Cl_2N_3$	55·2	8·3	13·7	22·9	54·9	8·2	13·7	23·2	153	153
1b	C_6H_5—	dipicrate	166–7	$C_{26}H_{27}N_9O_{14}$	44·9	4·1	18·1	—	45·2	4·2	18·2	—	344	346
2a	*p*-Cl—C_6H_4—	di-HCl	237–9	$C_{14}H_{24}Cl_3N_3$	49·2	7·0	12·0	31·2	49·3	7·1	12·3	31·3	170	170
2b	*p*-Cl—C_6H_4—	dipicrate	193–4	$C_{20}H_{26}ClN_9O_{14}$	43·2	4·2	17·3	5·1	43·0	3·9	17·4	4·9	362	363
3a	*p*-MeO—C_6H_4—	*di-HCl*	204–5	$C_{15}H_{27}Cl_2N_3O$	53·2	8·1	12·4	21·0	53·6	8·1	12·5	21·1	169	168
3b	*p*-MeO—C_6H_4—	dipicrate	149–51	$C_{21}H_{29}N_9O_8$	44·9	4·4	17·3	—	44·9	4·3	17·5	—	364	361
4a	*p*-Me—C_6H_4—	di-HCl	195–7	$C_{15}H_{27}Cl_2N_3$	55·9	8·5	13·4	22·1	56·2	8·5	13·1	22·1	160	160
4b	*p*-Me—C_6H_4—	dipicrate	137–8	$C_{21}H_{29}N_9O_7$	45·5	4·2	17·8	—	45·9	4·4	17·9	—	352	353
5a	*p*-Br—C_6H_4	di-HCl	215–7	$C_{14}H_{24}BrCl_2N_3$	43·3	6·4	11·0	18·5	43·6	6·2	10·9	18·4	192	193
5b	*p*-Br—C_6H_4—	dipicrate	195–6	$C_{20}H_{26}BrN_9O_7$	40·4	4·1	16·0	—	40·5	3·6	16·3	—	385	385

The equivalent weights of the dihydrochlorides were determined by titration with 0·1N silver nitrate solution.
The equivalent weights of the dipicrates were determined by titration with 0·1N perchloric acid in glacial acetic acid.

Preparation of ethyl benzimidate hydrochloride. A solution of dry benzonitrile (10·3 g. 0·1 mole) and "super-dry" ethanol (13·8 g. 0·3 mole) in dry chloroform (30 ml.) was saturated with dry hydrogen chloride gas at 0°. The mixture was allowed to stand for four days at room temperature and the solvent removed under reduced pressure. The residue was dried quickly at 80° and the last traces of hydrogen chloride removed in a desiccator containing sodium hydroxide pellets to give ethyl benzimidate hydrochloride (17·25 g.) m.p. 119–120°. Yield, 93·0 per cent.

Preparation of N-*diethylaminopropyl benzamidine dihydrochloride.* A solution of ethyl benzimidate hydrochloride (9·275 g. 0·05 mole), 3-diethylaminopropylamine (6·83 g. 0·053 mole) and ethanolic hydrogen chloride (9·72 ml. of 5·4N solution 0·053 mole) in 20 ml. absolute ethanol was warmed at 40° for 8 hr. The mixture was allowed to stand overnight at room temperature, filtered and the solvent removed under reduced pressure. The residue was treated with sodium hydroxide solution (85 ml. of a 5 per cent solution) and the liberated oil taken up in ether. The ethereal solution was shaken with acetic acid (125 ml. of a 5 per cent solution), and the acid layer separated. Sodium hydroxide (85 ml. of a 5 per cent solution) was added to liberate the base which was again taken up in ether. The ether layer was separated, washed with water and dried ($MgSO_4$). The solvent was removed, ethanolic hydrogen chloride (18·52 ml. of 5·4N solution), isopropanol and then ether were added to give N-*diethylaminopropylbenzamidine dihydrochloride* (10·2 g.). The yield was 66·7 per cent. On recrystallisation from isopropanol: ether, white crystals were obtained, m.p. 163–164°.

Pharmacology

The amidine dihydrochlorides were tested on guinea-pig ileum for histamine or antihistamine activity. Although compounds 2a and 5a (20 μg./20 ml. bath) reduced the response to 0·1 μg. histamine by about half, the same dose reduced the response to acetylcholine, 5-hydroxytryptamine and barium ions by a similar amount. Compound 3a also had slight spasmolytic activity but 1a and 4a showed no blocking action.

It was reported by Boura, Copp and Green (1962) that certain acetamidine derivatives have an adrenergic neurone blocking action. Our compounds structurely resembled some of these compounds and therefore, 2a and 4a were tested but were found to have no such activity.

Discussion

Although compounds 2a and 5a were found to be antagonistic to histamine, the action is nonspecific, since they also antagonise acetylcholine, 5-hydroxytryptamine and barium ions. This is not unexpected since most specific antihistamines have two aromatic ring structures.

It appears that the *para*-halogen substituent, and to a lesser extent the methoxy group, is necessary for activity in this limited series, since the unsubstituted and the *para*-methyl substituted derivatives have no activity.

This is interesting because many antihistamines have *para*-halogen and methoxy substituents.

Acknowledgements. We wish to thank the Department of Pharmacology, Institute of Technology, Bradford, and the Wellcome Research Laboratories, Beckenham, for their assistance in the testing of these compounds.

REFERENCES

Boura, A. L. A., Copp, F. C. and Green, A. F. (1962). *Nature, Lond.*, **195**, No. 4847, 1213–1214.
Charlton, P. T., Maliphant, G. K., Oxley, P. and Peak, D. A. (1951). *J. chem. Soc.*, 485–492.
Curd, F. H. S. and Raison, C. G. (1947). *Ibid.*, 160–164.
Fuller, A. T., Tonkin, I. M. and Walker, J. (1945). *Ibid.*, 633–640.
Pinner, A. (1892). Die Imidöather und ihre Derivate. Berlin: Oppenheim.