NOTES

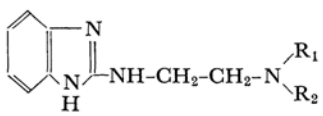
The Synthesis of Benzimidazole Derivatives as Potential Antihistaminic Compounds

S. M. DESHPANDE and Kanwal NAIN

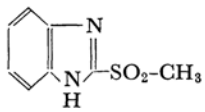
Chemistry Department, Banaras Hindu University, Varanasi, India

(Received September 14, 1965)

A general antihistaminic compound, as it acts by the competitive inhibition of histamine, has to satisfy the structural requirements[1] by having a two-carbon chain with a tertiary nitrogen on one end and a secondary or tertiary nitrogen or an ether or an ester linkage on the other end of the carbon chain. Maintaining these standard conditions, Wright[2] has shown that benzimidazole with a dialkylaminoethyl substituent on nitrogen possesses a slight antihistaminic property. This observation prompted the present authors to synthesise a series of benzimidazole derivatives (*Cf.* Table 1), with the general structure (I) and to



(I)



(II)

study their antihistaminic activities. These derivatives, when tested as histamine antagonists on a guinea-pig ileum preparation, were, however, found to be active to only a small extent.

These 2-substituted benzimidazoles have been synthesised by an interaction of 2-methanesulphonylbenzimidazole (II) with diamine according to the method of Hoggarth.[3]

Experimental

All the substituted ethylenediamines used in these preparations were synthesised by Gabriel's[4] phthalimide process, with the modification introduced by Ing and Manske[5] with respect of the hydrolysis of intermediate phthalimides. The following substituted diamines were prepared and employed in the preparation of 2-substituted benzimidazoles:

1. *N*, *N*-Dimethylaminoethylamine[6] (bp 101—104°C)
2. *N*, *N*-Diethylaminoethylamine[7] (bp 145—150°C)
3. 4-(β-Aminoethyl)morpholine[8] (bp 200—202°C)
4. *N*-Methyl-*N*-phenylaminoethylamine[9] (bp 98°C/3 mmHg)
5. *N*-Ethyl-*N*-phenylaminoethylamine[9] (bp 90—95°C/0.8—1 mmHg, bp 134—135°C/15 mmHg)
6. *N*-*o*-Tolylaminoethylamine[9] (bp 105—110°C/0.8—1 mmHg, bp 157—160°C/15 mmHg)
7. 4-(β-Aminoethyl)pyrrolidine[10] (bp 159—161°C)

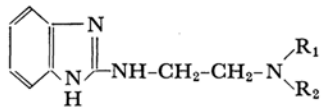
2 - 2′ - Dimethylaminoethylaminobenzimidazole Oxalate (Compd. 1). Earlier attempts to prepare this compound by condensing 2-chlorobenzimidazole and *N*, *N*-dimethylaminoethylamine in phenolic media failed to give the desired product. This compound was, however, prepared in a low yield by following the procedure of Hoggarth[3] with a slight variation in the procedure of the extraction of the final compound.

2-Methanesulphonylbenzimidazole (1.27 g, 0.0064 mol) was heated with *N*, *N*-dimethylaminoethylamine (0.8 g, 0.09 mol) for 4 hr at 140—150°C. The viscous red mass obtained after the solution had then been cooled to room temperature was extracted with dilute acetic acid. The residue, unreacted 2-methanesulphonylbenzimidazole, was filtered off. The filtrate was basified with 10% sodium hydroxide and thoroughly extracted with ether. The ethereal extract, dried over anhydrous sodium sulphate, was treated with powdered oxalic acid and stirred, whereupon the oxalate separated. The oxalate was then recrystallised from aqueous alcohol to give a crystalline salt weighing 0.3 g (a 12% yield).

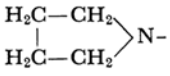
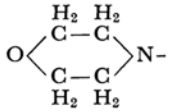
Following this procedure, compounds 2 and 7 of the table were prepared. Compound 6 of the table was also prepared by the same procedure. In this case the ether extract of the final compound, on the removal of the solvent, gave a solid base which was

1) A. Burger, "Medicinal Chemistry," 2nd Ed., Interscience Publishers, New York (1960), p. 532.
2) J. B. Wright, *J. Am. Chem. Soc.*, **71**, 2035 (1949).
3) E. Hoggarth, *J. Chem. Soc.*, **1949**, 3311.
4) S. Gabriel, *Ber.*, **20**, 2224 (1887).
5) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, **1926**, 2348.
6) E. E. Campaigne and F. Jacoby, *Chem. Abstr.*, **48**, 11321 (1954).
7) K. Miura, *ibid.*, **44**, 10161 (1950).
8) M. E. Hultquist and E. H. Northey, *J. Am. Chem. Soc.*, **62**, 447 (1940).
9) J. P. Fourneau, *Chem. Abstr.*, **42**, 3345 (1948).
10) R. H. Reitsema and J. H. Hunter, *J. Am. Chem. Soc.*, **70**, 4009 (1948).

TABLE 1



(oxalate)

S. No.	R_1	R_2	Yield %	Mp* °C (Oxalate)	Recrystallising solvent	Formula
1	CH_3	CH_3	12	189	a	$C_{11}H_{16}N_4 \cdot 2(C_2H_2O_4)H_2O$***
2	C_2H_5**	C_2H_5	49—41	188—190	a	$C_{13}H_{20}N_4 \cdot C_2H_2O_4$
3	CH_3	C_6H_5	12	143	b	$C_{16}H_{18}N_4 \cdot C_2H_2O_4$
4	H	*o*-$CH_3C_6H_4$	35	155	c	$C_{16}H_{18}N_4 \cdot C_2H_2O_4 \cdot H_2O$***
5	C_2H_5	C_6H_5	26	128	b	$C_{17}H_{20}N_4 \cdot C_2H_2O_4$
6	RR′		49	200—202	a	$C_{13}H_{18}N_4 \cdot 2(C_2H_2O_4)$
7	RR′		50	188—189	a	$C_{13}H_{18}N_4O \cdot 2(C_2H_2O_4)$

S. No.	Carbon		Hydrogen		Nitrogen	
	Calcd	Found	Calcd	Found	Calcd	Found
1	44.78	44.74	5.47	5.34	13.97	14.17
2	55.90	55.69	6.80	6.30	17.39	17.15
3	60.68	60.91	5.62	5.74	15.78	15.79
4	57.75	58.13	5.88	5.59	14.97	15.27
5	61.61	61.03	5.94	5.83	15.14	15.43
6	49.75	49.22	5.36	5.59	13.65	14.05
7	47.88	47.54	5.16	5.14	13.14	12.50

* All melting points are uncorrected.

** Free base has been reported by Hoggarth[3] which melts at 126—128°C.

*** Compounds were dried for 48 hr at 0.8 mmHg pressure over refluxing benzene. Still crystalline water is indicated.

a Aqueous ethanol b Absolute ethanol c Ethanol+Ether

converted into oxalate salt by treating it with oxalic acid in boiling alcohol.

2 - 2′ - Methylanilinoethylaminobenzimidazole Oxalate (Compd. 3). *N*-Methyl-*N*-phenylaminoethylamine (7.0 g, 0.026 mol) was heated with 2-methanesulphonylbenzimidazole (4.6 g, 0.023 mol) for 5 hr at 170—180°C. After the solution had cooled, the red, viscous mass was extracted with dilute hydrochloric acid. The extract was neutralized with 10% sodium hydroxide and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate. The ether and the excess amine were removed under reduced pressure. The residue was dissolved again in dry ether and treated with oxalic acid. On stirring, a pasty mass was obtained which solidified after having been kept for three days at room temperature. It was repeatedly crystallized from a mixture of absolute alcohol and dry ether to obtain an analytical sample.

Compounds 4 and 5 were prepared by a similar procedure and were crystallised from suitable solvents.

The authors express their grateful thanks to Professor G. B. Singh, Head of the Department of Chemistry, for providing necessary facilities and to Council of Scientific and Industrial Research, New Delhi for awarding Fellowship to one of them (K. N.). Our thanks are also due to Professor P. K. Das, Professor of Pharmacology, College of Medical Sciences, Banaras Hindu University, for testing the compounds.