Some Possible Antihistaminics and Antispasmodics. I. Synthesis of Mannich Bases

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In view of the findings and facts, that all the antihistaminic compounds contain the structural unit R_2N–C–C–X in which X is a group beginning with oxygen (R_2N–C–C–O), nitrogen (R_2N–C–C–N=) or carbon (R_2N–C–C–C≡), and the presence of sulphur containing groups like thienyl, thiazolidionyl, thiazolyl, etc., may promote antispasmodic activity as indicated by the observation of Blicke and Tsao,[1] Anderson and Green,[2] Bhargava and Singh[3] and Tripathi et al.[4] and also the musculotropic activity exhibited by thiazoles as described by Chance, Dirnhumber and Robinson,[5] the thiazoles have been taken as the starting material for the synthesis of a number of possible antihistaminics and antispasmodics.

Ketones containing an active methyl or

1) F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.*, **66**, 1645 (1944).
2) D. W. Adamson and A. F. Green, *Nature*, **165**, 122 (1950).
3) P. N. Bhargava and P. R. Singh (in this laboratory), Thesis submitted to Banaras Hindu University for Ph. D., March 1962 (unpublished).
4) P. Tripathi, H. K. Pujari and M. K. Rout, *J. Ind. Chem. Soc.*, **35**, 407 (1958).
5) M. R. A. Chance, P. Dirnhuber and F. A. Robinson, *Brit. J. Pharmacol.*, **1**, 153 (1946).

Table I. 2-Acetamido-4-aryl-5-substituted-methyl-thiazoles and their hydrochlorides

Sample No.	Compound	Base					Hydrochloride				
		M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % (Br., %) Found	S, % (Br., %) Calcd.	M. p. °C	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
	2-Acetamido-4-phenyl											
1	-5-dimethylaminomethyl-thiazole	129	$C_{14}H_{17}N_3OS$	15.19	15.27	11.58	11.64	—	—	—	—	—
2	-5-morpholinomethyl-thiazole	198	$C_{16}H_{19}N_3O_2S$	13.22	13.25	10.11	10.09	201	11.82	11.88	9.06	9.05
3	-5-piperidinomethyl-thiazole	158	$C_{17}H_{21}N_3OS$	13.25	13.33	10.13	10.16	196	11.89	11.95	9.01	9.10
4	-5-methylanilinomethyl-thiazole	202	$C_{19}H_{19}N_3OS$	12.35	12.46	9.37	9.49	194	11.20	11.24	8.51	8.57
5	-5-ethylanilinomethyl-thiazole	205	$C_{20}H_{21}N_3OS$	11.88	11.97	9.16	9.12	180	10.76	10.84	8.19	8.26
6	-5-*N*-benzylanilinomethyl-thiazole	196	$C_{25}H_{23}N_3OS$	10.13	10.17	7.80	7.75	198	9.28	9.34	7.03	7.12
7	-5-*N*-benzimidazolylmethyl-thiazole	121	$C_{19}H_{16}N_4OS$	16.04	16.09	9.15	9.19	—	—	—	—	—
8	-5-(2'-methyl-*N*-benzimidazolyl-methyl)-thiazole	123	$C_{20}H_{18}N_4OS$	15.40	15.47	8.87	8.84	—	—	—	—	—
9	Piperazino-1 : 4-bis(2'-acetamido-4'-phenyl-5'-methyl thiazole)	93	$C_{28}H_{30}N_6O_2S_2$	15.31	15.38	11.65	11.72	d.337	13.54	13.57	10.29	10.34
	2-Acetamido-4-*p*-bromophenyl											
10	-5-dimethylaminomethyl-thiazole	118	$C_{14}H_{16}N_3OSBr$	11.80	11.86	(22.54)	(22.60)	191	11.98	12.05	9.13	9.18
11	-5-diethylaminomethyl-thiazole	d.142	$C_{16}H_{20}N_3OSBr$	11.02	10.99	(20.86)	(20.94)	d.84	10.01	10.04	7.61	7.64
12	-5-morpholinomethyl-thiazole	d.115	$C_{16}H_{18}N_3O_2SBr$	10.53	10.61	(20.13)	(20.20)	d.197	9.62	9.71	7.41	7.40
13	-5-piperidinomethyl-thiazole	129	$C_{17}H_{20}N_3OSBr$	10.62	10.66	(20.24)	(20.30)	d.113	9.68	9.76	7.39	7.43
14	-5-methylanilinomethyl-thiazole	98	$C_{19}H_{18}N_3OSBr$	10.04	10.00	(19.15)	(19.23)	d.125	9.21	9.29	7.03	7.07
15	-5-*N*-benzylanilinomethyl-thiazole	130	$C_{25}H_{22}N_3OSBr$	8.52	8.54	(16.20)	(16.26)	d.108	7.86	7.95	6.04	6.05
16	-5-*N*-benzimidazolylmethyl-thiazole	d.136	$C_{19}H_{15}N_4OSBr$	13.06	13.11	(18.64)	(18.77)	d.194	11.97	12.08	6.85	6.90
17	-5-(2'-methyl-*N*-benzimidazolyl-methyl)-thiazole	d.134	$C_{20}H_{17}N_4OSBr$	12.63	12.70	(18.07)	(18.14)	193	11.68	11.73	6.72	6.70
18	Piperazino-1 : 4-bis(2'-acetamido-4'-*p*-bromophenyl-5'-methyl-thiazole)	d.101	$C_{28}H_{28}N_6O_2S_2Br_2$	11.85	11.93	(22.61)	(22.73)	212	10.79	10.84	8.18	8.26

	2-Acetamido-4-*p*-tolyl											
19	-5-dimethylaminomethyl-thiazole	107	$C_{15}H_{19}N_3OS$	14.48	14.53	11.10	11.07	—	—	—	—	—
20	-5-diethylaminomethyl-thiazole	205	$C_{17}H_{23}N_3OS$	13.23	13.25	10.02	10.09	200	11.81	11.88	8.97	9.05
21	-5-morpholinomethyl-thiazole	d.186	$C_{17}H_{21}N_3O_2S$	12.61	12.69	9.55	9.67	d.177	11.40	11.43	8.68	8.71
22	-5-piperidinomethyl-thiazole	124	$C_{18}H_{23}N_3OS$	12.68	12.77	9.65	9.73	115	11.43	11.49	8.65	8.75
23	-5-methylanilinomethyl-thiazole	184	$C_{20}H_{21}N_3OS$	11.93	11.97	9.13	9.12	185	10.79	10.84	8.21	8.26
24	-5-*N*-benzylanilinomethyl-thiazole	135	$C_{26}H_{25}N_3OS$	9.75	9.84	7.43	7.49	117	9.02	9.06	6.87	6.90
25	-5-*N*-benzimidazolylmethyl-thiazole	97	$C_{20}H_{18}N_4OS$	15.42	15.47	8.80	8.84	—	—	—	—	—
26	Piperazino-1 : 4-bis(2′-acetamido-4′-*p*-tolyl-5′-methyl-thiazole)	71	$C_{30}H_{34}N_6O_2S_2$	14.51	14.63	11.18	11.15	d.65	12.95	13.02	9.86	9.92
	2-Acetamido-4-*p*-methoxyphenyl											
27	-5-dimethylaminomethyl-thiazole	d. 96	$C_{15}H_{19}N_3O_2S$	13.71	13.77	10.45	10.49	—	—	—	—	—
28	-5-diethylaminomethyl-thiazole	123	$C_{17}H_{23}N_3O_2S$	12.52	12.61	9.52	9.61	d.146	11.37	11.37	8.59	8.66
29	-5-morpholinomethyl-thiazole	d. 90	$C_{17}H_{21}N_3O_3S$	12.04	12.10	9.18	9.22	196	10.86	10.95	8.30	8.34
30	-5-piperidinomethyl-thiazole	d. 87	$C_{18}H_{23}N_3O_2S$	12.15	12.17	9.30	9.27	d. 65	10.94	11.01	8.32	8.39
31	-5-methylanilinomethyl-thiazole	d.199	$C_{20}H_{21}N_3O_2S$	11.33	11.44	8.68	8.72	d. 61	10.30	10.41	7.86	7.93
32	-5-ethylanilinomethyl-thiazole	d. 85	$C_{21}H_{23}N_3O_2S$	10.94	11.02	8.33	8.40	199	10.01	10.06	7.70	7.66
33	-5-*N*-benzylanilinomethyl-thiazole	203	$C_{26}H_{25}N_3O_2S$	9.39	9.48	7.25	7.22	d. 73	8.68	8.76	6.63	6.67
34	-5-*N*-benzimidazolylmethyl-thiazole	d.141	$C_{20}H_{18}N_4O_2S$	14.75	14.81	8.42	8.47	203	13.47	13.51	7.69	7.72
35	-5-(2′-methyl-*N*-benzimidazolyl-methyl)-thiazole	d.107	$C_{21}H_{20}N_4O_2S$	14.21	14.29	8.19	8.16	d.143	12.99	13.07	7.39	7.47
36	Piperazino-1 : 4-bis(2′-acetamido-4′-*p*-methoxyphenyl-5′-methylthiazole)	d.214	$C_{30}H_{34}N_6O_4S_2$	13.80	13.86	10.58	10.56	d.109	12.36	12.41	9.39	9.45
	2-Acetamido-4-α-naphthyl											
37	-5-diethylaminomethyl-thiazole	137	$C_{20}H_{23}N_3OS$	11.85	11.90	9.03	9.06	202	10.72	10.78	8.20	8.22
38	-5-morpholinomethyl-thiazole	d. 98	$C_{20}H_{21}N_3O_2S$	11.40	11.44	8.66	8.72	d. 72	10.34	10.41	7.94	7.93
39	-5-piperidinomethyl-thiazole	d. 92	$C_{21}H_{23}N_3OS$	11.39	11.51	8.80	8.77	d.112	10.39	10.46	7.89	7.97
	2-Acetamido-4-β-naphthyl											
40	-5-dimethylaminomethyl-thiazole	d. 91	$C_{18}H_{19}N_3OS$	12.85	12.92	9.77	9.84	187	11.58	11.62	8.81	8.85
41	-5-diethylaminomethyl-thiazole	d. 96	$C_{20}H_{23}N_3OS$	11.87	11.90	9.01	9.06	176	10.71	10.78	8.25	8.22
42	-5-morpholinomethyl-thiazole	152	$C_{20}H_{21}N_3O_2S$	11.37	11.44	8.62	8.72	—	—	—	—	—
43	-5-piperidinomethyl-thiazole	d.121	$C_{21}H_{23}N_3OS$	11.47	11.51	8.69	8.77	190	10.38	10.46	10.99	7.97
44	-5-methylanilinomethyl-thiazole	123	$C_{23}H_{21}N_3OS$	10.87	10.85	8.31	8.27	d.105	9.84	9.92	7.48	7.56
45	-5-*N*-benzylanilinomethyl-thiazole	d.115	$C_{29}H_{25}N_3OS$	9.01	9.07	6.88	6.91	180	8.36	8.41	6.39	6.41
46	-5-*N*-benzimidazolylmethyl-thiazole	d. 93	$C_{23}H_{18}N_4OS$	14.02	14.07	8.06	8.04	d. 65	12.81	12.89	7.40	7.36
47	-5-(2′-methyl-*N*-benzimidazolyl-methyl)-thiazole	d. 95	$C_{24}H_{20}N_4OS$	13.50	13.59	7.68	7.76	191	12.38	12.49	7.08	7.13
48	Piperazino-1 : 4-bis(2′-acetamido-4′-β-naphthyl-5′-methyl-thiazole)	d.130	$C_{36}H_{34}N_6O_2S_2$	12.89	13.00	9.87	9.91	d.194	11.68	11.71	8.89	8.93

methylene group have been shown by Mannich[6-8] to condense with formaldehyde and secondary bases. Compounds other than ketones but containing methyl or methylene group, may be induced to go under Mannich reaction.[9] The hydrogen atom at 5-C in thiazole nucleus is very reactive to be a key point for the preparation of Mannich bases from thiazoles.

In the present study 2-acetylamino-4-aryl-thiazoles have been condensed with ten different secondary bases and formalin in absolute ethanol. Mannich base was precipitated out on treatment of the reaction mixture with the saturated solution of potassium carbonate. The bases have been converted into their hydrochlorides by the usual method. The results of the pharmacological tests will be published elsewhere after proper screening.

Experimental

2-Amino-4-phenyl-, -4-*p*-bromophenyl-, -4-*p*-tolyl, -4-*p*-methoxyphenyl-, -4-α-naphthyl-, and -4-β-naphthyl-thiazoles were prepared by the method of Dodson and King.[10]

2-Acetylamino-4-aryl-thiazoles were prepared by acetylation of 2-amino-4-aryl-thiazoles with acetic anhydride.

2-Acetamido-4-phenyl-5-diethylaminomethylthiazole.—In a dry flask 2.2 g. of 2-acetamido-4-phenyl-thiazole was taken and 1 ml. of diethylamine in 5 ml. of acetic acid and 1 ml. of formalin were added into it. The reaction mixture was refluxed for five hours on a water bath. After cooling, 15 ml. of water was added and the reaction mixture was then treated with the saturated solution of potassium carbonate. The precipitate, thus obtained, was filtered, washed well with water and finally recrystallised from ethanol and dried in vacuum desiccator, m. p. 129°C, yield 68% (Found: C, 52.89; H, 5.30; S, 11.58. Calcd. for $C_{14}H_{17}ON_3S$: C, 53.00; H, 5.38; N, 15.27; S, 11.64%).

Similarly other 2-acetamido-4-aryl-thiazoles were condensed with diethylamine, morpholine, piperidine, methylaniline, ethylaniline, *N*-benzylaniline, benzimidazole, 2-methyl-*N*-benzimidazole and piperazine. The bases, obtained on condensation, were converted into their hydrochloride by the usual method. The properties and analytical data of these bases as well as their hydrochlorides are recorded in Table I.

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6) C. Mannich and B. Kather, *Ber.*, **53**, 1368 (1920).
7) C. Mannich and G. Heilner, ibid., **55**, 356 (1922).
8) C. Mannich, *Arch. Pharm.*, **264**, 741 (1926); **265**, 589 (1927).
9) W. O. Kermack and W. Muir, *J. Chem. Soc.*, **1931**, 3089.
10) R. M. Dodson and L. C. King, *J. Am. Chem. Soc.*, **67**, 2242 (1945).