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

By Prithwi Nath BHARGAVA and Suresh Chandra SHARMA

(Received September 7, 1964)

A definite antispasmodic activity of pyrazolone derivatives,[1,2] certain substituted β-aminoalkylaryl ketones,[3,4] pyridyl and thiazolyl quinoline derivatives[5,6] and quinolyl and pyrazolone derivatives of thiazolidiones,[7] has created an interest in the syntheses of thiazole and thiazolidione derivatives—Mannich bases, and also to study, how the attachment of an additional therapeutically active quinoline and pyrazolone nuclei adds to the importance of thiazole in therapy, particularly their usefulness as antihistaminics and antispasmodics.

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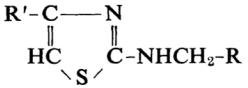
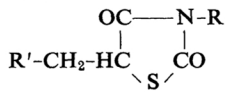
TABLE I. 2-SUBSTITUTED (R) METHYLAMINO-4-ARYL (R') THIAZOLES



Sample No.	R	Aryl group R'	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenacyl	*p*-Tolyl-	58	d. 219	$C_{19}H_{18}N_2OS$	8.65	8.70	9.85	9.94
2	8-Hydroxyquinolinyl-	*p*-Tolyl-	52	d. 116	$C_{20}H_{18}N_3OS$	11.95	12.06	9.21	9.19
3	*p*-Methylphenacyl-	*p*-Tolyl-	53	d. 215	$C_{20}H_{20}N_2OS$	8.31	8.33	9.55	9.52
4	1-Phenyl-3-methyl-5-pyrazolonyl-	*p*-Tolyl-	48	d. 178	$C_{21}H_{20}N_4OS$	14.83	14.89	8.48	8.51
5	Phenacyl-	*p*-Bromophenyl-	50	d. 214	$C_{18}H_{15}N_2OSBr$	7.15	7.23	8.30	8.27
6	*p*-Methylphenacyl-	*p*-Bromophenyl-	58	137	$C_{19}H_{17}N_2OSBr$	6.92	6.98	7.95	7.98
7	8-Hydroxyquinolinyl-	*p*-Bromophenyl-	46	d. 242	$C_{19}H_{15}N_3OSBr$	10.10	10.17	7.64	7.75
8	Phenacyl-	*p*-Methoxyphenyl-	51	d. 156	$C_{19}H_{18}N_2O_2S$	8.23	8.28	9.42	9.47
9	8-Hydroxyquinolinyl-	*p*-Methoxyphenyl-	54	212	$C_{20}H_{18}N_3O_2S$	11.46	11.54	8.75	8.79

TABLE II. 3-ARYL-5-SUBSTITUTED-METHYL-2 : 4-THIAZOLIDIONES



Sample No.	Aryl group R	R'	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenyl-	2'-Methyl-*N*-benzimidazolyl-	66	173	$C_{18}H_{15}N_3O_2S$	12.38	12.46	9.53	9.50
2	*p*-Chlorophenyl-	*N*-Benzimidazolyl-	70	196	$C_{17}H_{12}N_3O_2SCl$	11.70	11.75	8.92	8.95
3	*p*-Chlorophenyl-	2'-Methyl-*N*-benzimidazolyl-	72	188—190	$C_{18}H_{14}N_3O_2SCl$	11.24	11.31	8.62	8.61
4	*o*-Anisyl-	*N*-Benzimidazolyl-	63	82	$C_{18}H_{15}N_3O_3S$	11.83	11.90	9.02	9.06
5	*o*-Anisyl-	2'-Methyl-*N*-benzimidazolyl-	65	80	$C_{19}H_{17}N_3O_3S$	11.38	11.44	8.65	8.72
6	*p*-Phenetyl-	Methylanilino-	63	d. 95	$C_{19}H_{20}N_2O_3S$	7.81	7.86	9.04	8.99
7	*p*-Phenetyl-	2'-Methyl-*N*-benzimidazolyl-	64	d. 94	$C_{20}H_{19}N_3O_3S$	10.93	11.02	8.35	8.40
8	α-Naphthyl-	Methylanilino-	60	81	$C_{21}H_{18}N_2O_2S$	7.70	7.73	8.85	8.84
9	α-Naphthyl-	*N*-Benzylanilino-	65	116	$C_{27}H_{22}N_2O_2S$	6.31	6.39	7.28	7.31
10	α-Naphthyl-	*N*-Benzimidazolyl-	68	d. 73	$C_{21}H_{15}N_3O_2S$	11.19	11.26	8.53	8.58
11	α-Naphthyl-	2'-Methyl-*N*-benzimidazolyl-	71	d. 84	$C_{22}H_{17}N_3O_2S$	10.76	10.85	8.29	8.27
12	β-Naphthyl-	Methylanilino-	65	d. 90	$C_{21}H_{18}N_2O_2S$	7.65	7.73	8.81	8.84
13	β-Naphthyl-	*N*-Benzylanilino-	70	d. 82	$C_{27}H_{22}N_2O_2S$	6.32	6.39	7.27	7.31
14	β-Naphthyl-	*N*-Benzimidazolyl-	63	188	$C_{21}H_{15}N_3O_2S$	11.20	11.26	8.62	8.58
15	β-Naphthyl-	2'-Methyl-*N*-benzimidazolyl-	60	111	$C_{22}H_{17}N_3O_2S$	10.81	10.85	8.30	8.27

Table III. Hydrochlorides of 3-aryl-5-substituted-methyl-2 : 4-thiazolidiones

Sample No.	Aryl group R	R'	Yield %	M. p. °C	Molecular formula	N, %		S, %	
						Found	Calcd.	Found	Calcd.
1	Phenyl-	Ethylanilino-	53	134	$C_{18}H_{18}N_2O_2S\cdot HCl$	7.65	7.72	8.78	8.83
2	Phenyl-	*N*-Benzylanilino-	86	132	$C_{23}H_{20}N_2O_2S\cdot HCl$	6.52	6.60	7.58	7.54
3	Phenyl-	*N*-Benzimidazolyl-	68	136	$C_{17}H_{13}N_3O_2S\cdot HCl$	11.59	11.68	8.85	8.90
4	Phenyl-	2'-Methyl-*N*-benzimidazolyl-	81	135	$C_{18}H_{15}N_3O_2S\cdot HCl$	11.22	11.24	8.58	8.57
5	*p*-Chlorophenyl-	*N*-Benzimidazolyl-	68	191	$C_{17}H_{12}N_3O_2SCl\cdot HCl$	10.60	10.66	8.08	8.12
6	*o*-Anisyl-	Ethylanilino-	55	83	$C_{19}H_{20}N_2O_3S\cdot HCl$	7.11	7.13	8.17	8.15
7	*o*-Anisyl-	*N*-Benzimidazolyl-	50	82	$C_{18}H_{15}N_3O_3S\cdot HCl$	10.71	10.78	8.22	8.21
8	*o*-Anisyl-	2'-Methyl-*N*-benzimidazolyl-	48	79	$C_{19}H_{17}N_3O_3S\cdot HCl$	10.38	10.41	7.89	7.93
9	*p*-Phenetyl-	Ethylanilino-	57	104	$C_{20}H_{22}N_2O_3S\cdot HCl$	6.88	6.89	7.90	7.87
10	*p*-Phenetyl-	*N*-Benzylanilino-	61	129	$C_{25}H_{24}N_2O_3S\cdot HCl$	5.92	5.98	6.80	6.83
11	α-Naphthyl-	Methylanilino-	54	above 300	$C_{21}H_{18}N_2O_2S\cdot HCl$	7.01	7.03	8.06	8.03
12	α-Naphthyl-	*N*-Benzylanilino-	48	d. 201	$C_{27}H_{22}N_2O_2S\cdot HCl$	5.82	5.90	6.69	6.74
13	α-Naphthyl-	*N*-Benzimidazolyl-	60	d. 209	$C_{21}H_{15}N_3O_2S\cdot HCl$	10.23	10.26	7.78	7.81
14	α-Naphthyl-	2'-Methyl-*N*-benzimidazolyl-	43	d. 262	$C_{22}H_{17}N_3O_2S\cdot HCl$	9.81	9.92	7.49	7.56
15	β-Naphthyl-	*N*-Benzylanilino-	50	d. 87	$C_{27}H_{22}N_2O_2S\cdot HCl$	5.85	5.90	6.75	6.74
16	β-Naphthyl-	*N*-Benzimidazolyl-	55	189	$C_{21}H_{15}N_3O_2S\cdot HCl$	10.17	10.26	7.78	7.81
17	β-Naphthyl-	2'-Methyl-*N*-benzimidazolyl-	41	d. 128	$C_{22}H_{17}N_3O_2S\cdot HCl$	9.84	9.92	7.58	7.56

A few 2-amino-4-aryl thiazoles have been condensed with acetophenone, *p*-methyl-acetophenone, 8-hydroxy-quinoline and 1-phenyl-3-methyl-5-pyrazolone along with paraformaldehyde and hydrochloric acid in absolute ethanol. Another series of derivatives starting from 3-aryl-2 : 4-thiazolidiones has also been synthesised by condensing thiazolidiones with different secondary amine-hydrochlorides and paraformaldehyde. These thiazoles and thiazolidiones were prepared as per procedures laid down by Dodson and King[8] and Bhargava et al.[9-11] respectively. The results of the pharmacological screening of these compounds for antihistaminics and antispasmodic activities will be published elsewhere.

Experimental

Condensation of 2-Amino-4-*p*-tolylthiazole with Formaldehyde and Acetophenone.—In a r. b. flask a mixture of 1.9 g. of 2-amino-4-*p*-tolylthiazole, 1.2 g. of acetophenone and 0.9 g. of paraformaldehyde in 3 ml. of hydrogen chloride and 30 ml. of ethanol was heated on a water bath under reflux for two hours. An addition amount of 0.6 g. of paraformaldehyde was then added and refluxing was continued for three hours more. Ethanol was distilled off and the residue solidified on keeping in contact with ammonia for four hours. It was washed with water and crystallized from ethanol m. p. d. 219°C, yield 58%.

In the case of 1-phenyl-3-methyl-5-pyrazolone, the mixture was heated directly over an asbestos wire gauge for eight hours.

The properties and analytical data of the other products obtained on condensation of acetophenone, *p*-methylacetophenone, 8-hydroxy quinoline and 1-phenyl-3-methyl-5-pyrazolone with different 2-amino-4-arylthiazoles are mentioned in Table I.

5-(2'-Methyl-*N*-benzimidazolyl-methyl)-3-phenyl-2 : 4-thiazolidione.—A mixture of 1.9 g. of 3-phenyl-2 ; 4-thiazolidione, 1.3 g. of 2-methyl-*N*-benzimidazolyl, 1.2 g. of paraformaldehyde and 3 ml. of hydrogen chloride in 25 ml. of absolute ethanole was heated under reflux on a water bath for eight hours. The solvent was distilled off and the pasty mass was obtained which on keeping in contact with concentrated ammonia for one to two hours solidified. It was washed well with water and then crystallised from ethanol, m. p. 173°C, yield 66% (Found : C, 63.92 ; H, 4.43 ; N, 12.38 ; S, 9.53. Calcd. for $C_{18}H_{15}O_2N_3S$: C, 64.09 ; H, 4.45 ; N, 12.46 ; S, 9.50%).

Similarly, other 3-aryl-2 : 4-thiazolidiones were condensed with *N*-benzimidazole, methyl-, ethyl-, and benzyl-anilines. The properties and analytical data of these compounds are reported in Table II.

It is experienced during the course of work that the isolation of the bases sometimes becomes very difficult specially with products obtained on condensation with methyl-, and ethylanilines. A few compounds were obtained as hydrochlorides only because their bases could not be isolated from the reaction product.

Preparation of the Hydrochlorides of the Above Bases. — The hydrochlorides of the bases were prepared by the usual procedure of passing dry hydrogen chloride gas into the solution of the base in benzene, or dry ether. These hydrochlorides are recorded in Table III.

Thanks are due to the authorities of the Banaras Hindu University for providing necessary facilities and also to the Council of Scientific and Industrial Research, New Delhi, India for the award of a Junior Research Fellowship to one of us (S. C. S.).

Department of Chemistry
College of Science
Banaras Hindu University
Varanasi, India

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