The Synthesis of Local Anaesthetics

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(Received May 2, 1964)

In view of the significant biological properties exhibited by thiazoles[1] and benzothiazoles[2], the preparation of some 2-(*N*-benzimidazolyl-acetylamino) benzothiazoles and their hydrochlorides was examined in order to ascertain their local anaesthetic properties.

The starting compound, 2-aminobenzothiazole, was prepared by the action of liquid bromine on asymmetrical phenylthiourea in an inert solvent such as chloroform.[3] Similarly, various substituted benzothiazoles have been prepared from the corresponding substituted asymmetrical thioureas. These 2-aminobenzothiazoles were condensed with chloroacetylchloride in dry benzene to obtain the corresponding 2-chloroacetylaminobenzothiazoles, which subsequently, on condensation with benzimidazole and 2-methylbenzimidazole, gave various substituted 2-(*N*-benzimidazolylacetylamino)benzothiazoles. Hydrochlorides of the above mentioned benzothiazoles have been prepared, and their local anaesthetic activity has been tested.[4]

A study of the pharmacological screening has shown that not a single compound is active. The values obtained for these compounds are more than those obtained for procaine-hydrochloride probably because of a heavier hydrophylic end in these compounds.

Experimental

2-Chloroacetylaminobenzothiazole.—To a solution of 2-aminobenzothiazole (20 g.) dissolved in dry benzene (150 ml.), a solution of chloroacetylchloride (10 ml.) in dry benzene (50 ml.) was

TABLE I. 2-CHLOROACETYLAMINOBENZOTHIAZOLES

2-Chloroacetylamino	M. p. °C	Molec. formula	N, %		S, %	
			Found	Calcd.	Found	Calcd.
-benzothiazole	156	$C_9H_7N_2OSCl$	12.32	12.36	14.21	14.13
-(4-methyl)-benzothiazole	181	$C_{10}H_9N_2OSCl$	11.46	11.64	13.61	13.30
-(5-methyl)-benzothiazole	185	$C_{10}H_9N_2OSCl$	11.42	11.64	13.49	13.30
-(6-methyl)-benzothiazole	183	$C_{10}H_9N_2OSCl$	11.48	11.64	13.71	13.30
-(4-chloro)-benzothiazole	182	$C_9H_6N_2OSCl_2$	10.67	10.73	12.61	12.26
-(5-chloro)-benzothiazole	184	$C_9H_6N_2OSCl_2$	10.39	10.73	12.31	12.26
-(6-chloro)-benzothiazole	198	$C_9H_6N_2OSCl_2$	10.48	10.73	12.57	12.26
-(6-bromo)-benzothiazole	204	$C_9H_6N_2OSClBr$	9.10	9.16	10.61	10.47
-(6-methoxy)-benzothiazole	188	$C_{10}H_9N_2O_2SCl$	10.46	10.91	12.71	12.48
-(6-ethoxy)-benzothiazole	174	$C_{11}H_{11}N_2O_2SCl$	10.63	10.35	11.70	11.82

TABLE II. 2-(*N*-BENZIMIDAZOLYLACETYLAMINO) BENZOTHIAZOLES

2-(*N*-Benzimidazolyl-acetylamino)	M. p. °C	Molec. formula	N, %		S, %	
			Found	Calcd.	Found	Calcd.
-benzothiazole	245	$C_{16}H_{12}N_4OS$	18.00	18.18	10.61	10.39
-(4-methyl)-benzothiazole	260	$C_{17}H_{14}N_4OS$	17.03	17.39	10.21	9.93
-(5-methyl)-benzothiazole	262	$C_{17}H_{14}N_4OS$	17.41	17.39	10.18	9.93
-(6-methyl)-benzothiazole	210	$C_{17}H_{14}N_4OS$	17.01	17.39	10.32	9.93
-(4-chloro)-benzothiazole	266	$C_{16}H_{11}N_4OSCl$	16.46	16.35	9.61	9.34
-(5-chloro)-benzothiazole	228	$C_{16}H_{11}N_4OSCl$	16.18	16.35	9.66	9.34
-(6-chloro)-benzothiazole	192	$C_{16}H_{11}N_4OSCl$	16.20	16.35	9.51	9.34
-(6-bromo)-benzothiazole	230	$C_{16}H_{11}N_4OSBr$	14.00	14.47	8.30	8.26
-(6-methoxy)-benzothiazole	265	$C_{17}H_{14}N_4O_2S$	16.19	16.57	9.83	9.46
-(6-ethoxy)-benzothiazole	244	$C_{18}H_{16}N_4O_2S$	15.80	15.92	9.44	9.09

1) P. N. Bhargava and P. R. Singh, *J. Indian Chem. Soc.*, 37, 241 (1960).
2) P. N. Bhargava and S. C. Sharma, This Bulletin, 35, 942 (1962).
3) A. Hugershoff, *Ber.*, 36, 3121 (1903).
4) E. Bülbring and I. Wajda, *J. Pharmacol.*, 85, 78 (1945).

TABLE III. 2-[*N*-(2'-METHYLBENZIMIDAZOLYL)ACETYLAMINO]BENZOTHIAZOLES

2-[*N*-(2'-Methylbenzimidazolyl)acetylamino]	M. p. °C	Molec. formula	N, %		S, %	
			Found	Calcd.	Found	Calcd.
-benzothiazole	160	$C_{17}H_{14}N_4OS$	17.32	17.39	10.10	9.93
-(4-methyl)-benzothiazole	200	$C_{18}H_{16}N_4OS$	16.42	16.66	9.98	9.52
-(5-methyl)-benzothiazole	193	$C_{18}H_{16}N_4OS$	16.39	16.66	9.71	9.52
-(6-methyl)-benzothiazole	183	$C_{18}H_{16}N_4OS$	16.58	16.66	9.86	9.52
-(4-chloro)-benzothiazole	158	$C_{17}H_{13}N_4OSCl$	15.63	15.71	8.68	8.97
-(5-chloro)-benzothiazole	191	$C_{17}H_{13}N_4OSCl$	15.73	15.71	9.21	8.97
-(6-chloro)-benzothiazole	193	$C_{17}H_{13}N_4OSCl$	15.48	15.71	9.03	8.97
-(6-bromo)-benzothiazole	218	$C_{17}H_{13}N_4OSBr$	13.48	13.96	8.41	7.98
-(6-methoxy)-benzothiazole	214	$C_{18}H_{16}N_4O_2S$	15.87	15.92	9.60	9.09
-(6-ethoxy)-benzothiazole	198	$C_{19}H_{18}N_4O_2S$	15.00	15.30	8.69	8.74

TABLE IV. HYDROCHLORIDES OF 2-(*N*-BENZIMIDAZOLYLACETLYLAMINO)BENZOTHIAZOLES

Hydrochlorides of 2-(*N*-benzimiazolylacetylamino)	M. p. °C	Molec. formula	N, %		S, %	
			Found	Calcd.	Found	Calcd.
-benzothiazole	200	$C_{16}H_{13}N_4OSCl$	16.10	16.26	9.46	9.28
-(4-methyl)-benzothiazole	204	$C_{17}H_{15}N_4OSCl$	15.49	15.63	9.31	8.92
-(5-methyl)-benzothiazole	191	$C_{17}H_{15}N_4OSCl$	15.43	15.63	9.19	8.92
-(6-methyl)-benzothiazole	188	$C_{17}H_{15}N_4OSCl$	15.61	15.63	9.41	8.92
-(4-chloro)-benzothiazole	263	$C_{16}H_{12}N_4OSCl_2$	14.81	14.78	8.51	8.44
-(5-chloro)-benzothiazole	183	$C_{16}H_{12}N_4OSCl_2$	14.39	14.78	8.36	8.44
-(6-chloro)-benzothiazole	202	$C_{16}H_{12}N_4OSCl_2$	14.61	14.78	7.99	8.44
-(6-bromo)-benzothiazole	219	$C_{16}H_{12}N_4OSClBr$	13.21	13.22	7.63	7.55
-(6-methoxy)-benzothiazole	197	$C_{17}H_{15}N_4O_2SCl$	14.87	14.95	8.41	8.54
-(6-ethoxy)-benzothiazole	164	$C_{18}H_{17}N_4O_2SCl$	14.48	14.42	8.63	8.23

TABLE V. HYDROCHLORIDES OF 2-[*N*-(2'-METHYLBENZIMIDAZOLYL)ACETYLAMINO]BENZOTHIAZOLES

Hydrochlorides of 2-[*N*-(2'-methylbenzimidazolyl)acetylamino]	M. p. °C	Molec. formula	N, %		S, %	
			Found	Calcd.	Found	Calcd.
-benzothiazole	166	$C_{17}H_{15}N_4OSCl$	15.55	15.63	9.41	8.92
-(4-methyl)-benzothiazole	193	$C_{18}H_{17}N_4OSCl$	14.98	15.03	8.67	8.59
-(5-methyl)-benzothiazole	211	$C_{18}H_{17}N_4OSCl$	14.88	15.03	8.37	8.59
-(6-methyl)-benzothiazole	168	$C_{18}H_{17}N_4OSCl$	15.13	15.03	8.57	8.59
-(4-chloro)-benzothiazole	182	$C_{17}H_{14}N_4OSCl_2$	14.16	14.25	8.79	8.14
-(5-chloro)-benzothiazole	199	$C_{17}H_{14}N_4OSCl_2$	14.00	14.25	8.44	8.14
-(6-chloro)-benzothiazole	195	$C_{17}H_{14}N_4OSCl_2$	14.23	14.25	8.58	8.14
-(6-bromo)-benzothiazole	257	$C_{17}H_{14}N_4OSClBr$	12.88	12.79	7.18	7.31
-(6-methoxy)-benzothiazole	158	$C_{18}H_{17}N_4O_2SCl$	14.31	14.42	8.63	8.23
-(6-ethoxy)-benzothiazole	183	$C_{19}H_{19}N_4O_2SCl$	13.87	13.92	8.28	7.95

gradually added. The reaction mixture was then warmed at 70°C on a water bath for 1.5 hr. The benzene was distilled off, and the residue was washed with a sodium bicarbonate solution and water and then dried. The product was crystallized from alcohol; m. p. 156°C.

Similarly other substituted 2-aminobenzothiazoles were converted into 2-chloroacetylamino-derivatives. Their melting points and analytical data are recorded in Table I.

2-(*N*-Benzimidazolylacetylamino)benzothiazole.—To 2-chloroacetylaminobenzothiazole (6 g.) dissolved in absolute ethanol (50 ml.), benzimidazole (3 g.) was added, and the mixture refluxed for 8 hr. After the alcohol had been recovered and the residue washed with a sodium bicarbonate solution and water, the product was crystallized from alcohol as brown crystals; m. p. 245°C.

Similarly, various substituted 2-(*N*-benzimidazolylacetylamino)- and 2-[*N*-(2'-methylbenzimidazolyl)-acetylamino]-benzothiazoles were prepared. Their melting points and analytical data are listed in Tables II and III.

The Preparation of Hydrochlorides.—The hydrochlorides of the above-mentioned bases were prepared as usual. Their melting points and analytical data are recorded in Tables IV and V.

Pharmacological Screening.—The hydrochlorides prepared above were screened for local anaesthetic activity by the method using a frog's sciatic plexus.

TABLE VI. LOCAL ANAESTHETIC ACTIVITY OF HYDROCHLORIDES OF 2-(*N*-BENZIMIDAZOLYLACETYLAMINO)BENZOTHIAZOLES

Hydrochlorides of 2-(*N*-benzimidazolylacetylamino)	Onset of anaesthesia (min.) with administration of anaesthetic* in hydrochloric acid of strength		
	0.05 N	0.1 N	0.2 N
-benzothiazole	22	40	58
-(4-methyl)-benzothiazole	20	36	55
-(5-methyl)-benzothiazole	26	39	56
-(6-methyl)-benzothiazole	28	41	58
-(4-chloro)-benzothiazole	30	40	55
-(5-chloro)-benzothiazole	25	38	53
-(6-chloro)-benzothiazole	23	36	55
-(6-bromo)-benzothiazole	24	42	52
-(6-methoxy)-benzothiazole	27	39	58
-(6-ethoxy)-benzothiazole	26	41	56
Procaine-hydrochloride	12	15	20

* Concentration of anaesthetic, 0.2%

TABLE VII. LOCAL ANAESTHETIC ACTIVITY OF HYDROCHLORIDES OF 2-[*N*-(2'-METHYL-BENZIMIDAZOLYL)ACETYLAMINO]BENZOTHIAZOLES

Hydrochloride of 2-[*N*-(2'-methylbenzimidazolyl)-acetylamino]	Onset of anaesthesia (min.) with administration of anaesthetic* in hydrochloric acid of strength		
	0.05 N	0.1 N	0.2 N
-benzothiazole	22	40	56
-(4-methyl)-benzothiazole	19	37	51
-(5-methyl)-benzothiazole	22	40	56
-(6-methyl)-benzothiazole	25	39	56
-(4-chloro)-benzothiazole	23	41	52
-(5-chloro)-benzothiazole	26	39	55
-(6-chloro)-benzothiazole	18	42	56
-(6-bromo)-benzothiazole	21	39	58
-(6-methoxy)-benzothiazole	22	30	55
-(6-ethoxy)-benzothiazole	28	41	53
Procaine-hydrochloride	12	15	20

* Concentration of anaesthetic, 0.2%

The compounds were tested at the concentration of 0.2%, and the time taken by a given concentration of a local anaesthetic to fail to provoke the withdrawal of a foot was recorded. The results are shown in Tables VI and VII.

Results

A study of the pharmacological screening has shown that not a single compound is active.

Thanks are due to the authorities of the Banaras Hindu University for providing necessary facilities and to the University Grants Commission for the award of a Junior Research Fellowship to one of us (P. R.).

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