The Synthesis of Local Anaesthetics

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In view of the significant biological properties exhibited by thiazoles1) and benzothiazoles²⁾, 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 2chloroacetylaminobenzothiazoles, 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 The values obtained for these comactive. pounds 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 (20g.) dissolved in dry benzene (150 ml.), a solution of chloroacetylchloride (10 ml.) in dry benzene (50 ml.) was

TABLE I.	2-Chloroacetylaminobenzothiazoles
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М.р.	Moloo formula	N, %		S, %	
°C	Molec. Iominuta	Found	Calcd.	Found	Calcd.
156	$C_9H_7N_2OSCl$	12.32	12.36	14.21	14.13
181	$C_{10}H_9N_2OSCl$	11.46	11.64	13.61	13.30
185	$C_{10}H_9N_2OSCI$	11.42	11.64	13.49	13.30
183	$C_{10}H_9N_2OSCl$	11.48	11.64	13.71	13.30
182	$C_9H_6N_2OSCl_2$	10.67	10.73	12.61	12.26
184	$C_9H_6N_2OSCl_2$	10.39	10.73	12.31	12.26
198	$C_9H_6N_2OSCl_2$	10.48	10.73	12.57	12.26
204	C ₉ H ₆ N ₂ OSClBr	9.10	9.16	10.61	10.47
188	$C_{10}H_9N_2O_2SCl$	10.46	10.91	12.71	12.48
174	$C_{11}H_{11}N_2O_2SCl$	10.63	10.35	11.70	11.82
	M. p. °C 156 181 185 183 182 184 198 204 188 174	$\begin{array}{c} \mbox{M. p.} \\ \mbox{o} \mbox{C} \end{array} \qquad \mbox{Molec. formula} \\ 156 \qquad \mbox{C}_9 \mbox{H}_7 \mbox{N}_2 \mbox{OSCl} \\ 181 \qquad \mbox{C}_{10} \mbox{H}_9 \mbox{N}_2 \mbox{OSCl} \\ 185 \qquad \mbox{C}_{10} \mbox{H}_9 \mbox{N}_2 \mbox{OSCl} \\ 183 \qquad \mbox{C}_{10} \mbox{H}_9 \mbox{N}_2 \mbox{OSCl} \\ 182 \qquad \mbox{C}_9 \mbox{H}_6 \mbox{N}_2 \mbox{OSCl} \\ 184 \qquad \mbox{C}_9 \mbox{H}_6 \mbox{N}_2 \mbox{OSCl} \\ 198 \qquad \mbox{C}_9 \mbox{H}_6 \mbox{N}_2 \mbox{OSCl} \\ 204 \qquad \mbox{C}_9 \mbox{H}_6 \mbox{N}_2 \mbox{OSCl} \mbox{I} \\ 188 \qquad \mbox{C}_{10} \mbox{H}_9 \mbox{N}_2 \mbox{OSCl} \\ 174 \qquad \mbox{C}_{11} \mbox{H}_{11} \mbox{N}_2 \mbox{OSCl} \\ \end{array}$	$\begin{array}{cccc} M_{\circ}p. & Molec. \ formula & Found \\ \hline & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$	$\begin{array}{c ccccc} M. p. & Molec. \ formula & Found & Calcd. \\ \hline & & Found & Calcd. \\ \hline 156 & C_9H_7N_2OSCl & 12.32 & 12.36 \\ \hline 181 & C_{10}H_9N_2OSCl & 11.46 & 11.64 \\ \hline 185 & C_{10}H_9N_2OSCl & 11.42 & 11.64 \\ \hline 183 & C_{10}H_9N_2OSCl & 11.48 & 11.64 \\ \hline 182 & C_9H_6N_2OSCl_2 & 10.67 & 10.73 \\ \hline 184 & C_9H_6N_2OSCl_2 & 10.39 & 10.73 \\ \hline 198 & C_9H_6N_2OSCl_2 & 10.48 & 10.73 \\ \hline 204 & C_9H_6N_2OSClBr & 9.10 & 9.16 \\ \hline 188 & C_{10}H_9N_2O_2SCl & 10.46 & 10.91 \\ \hline 174 & C_{11}H_{11}N_2O_2SCl & 10.63 & 10.35 \\ \hline \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

IABLE II. 2-(<i>N</i> -BENZIMIDAZOLYLACETYLAMINO)BENZOTHIAZ
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2-(N-Benzimidazolyl-	М.р.	Moloo formula	N, %		S, %	
acetylamino)	°C	Molec. Iomiula	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 ₄ OS	17.01	17.39	10.32	9.93
-(4-chloro)-benzothiazole	266	C ₁₆ H ₁₁ N ₄ OSCl	16.46	16.35	9.61	9.34
-(5-chloro)-benzothiazole	228	C ₁₆ H ₁₁ N ₄ OSCl	16.18	16.35	9.66	9.34
-(6-chloro)-benzothiazole	192	C ₁₆ H ₁₁ N ₄ OSCl	16.20	16.35	9.51	9.34
-(6-bromo)-benzothiazole	230	C ₁₆ H ₁₁ N ₄ OSBr	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).

A. Hugershoff, Ber., 36, 3121 (1903).
 E. Bülbring and I. Wajda, J. Pharmacol., 85, 78 (1945).

2-[N-(2'-Methylbenzimida- zolyl)acetylamino]	M. p. Molec formula	N, %		S, %		
	°Ċ	Molec. formula	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	C17H13N4OSCI	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 ₄ OSCl	15.48	15.71	9.03	8.97
-(6-bromo)-benzothiazole	218	C ₁₇ H ₁₃ N ₄ OSBr	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 III. 2-[N-(2'-METHYLBENZIMIDAZOLYL)ACETYLAMINO]BENZOTHIAZOLES

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

M. p. Molec formula		N, %		S, %	
°Ĉ	Molec. Iorinula	Found	Calcd.	Found	Calcd.
200	$C_{16}H_{13}N_4OSCl$	16.10	16.26	9.46	9.28
204	$C_{17}H_{15}N_4OSCl$	15.49	15.63	9.31	8.92
191	$C_{17}H_{15}N_4OSCl$	15.43	15.63	9.19	8.92
188	$C_{17}H_{15}N_4OSCl$	15.61	15.63	9.41	8.92
263	$C_{16}H_{12}N_4OSCl_2$	14.81	14.78	8.51	8.44
183	$C_{16}H_{12}N_4OSCl_2$	14.39	14.78	8.36	8.44
202	$C_{16}H_{12}N_4OSCl_2$	14.61	14.78	7.99	8.44
219	$C_{16}H_{12}N_4OSClBr$	13.21	13.22	7.63	7.55
197	$\mathbf{C_{17}H_{15}N_4O_2SCl}$	14.87	14.95	8.41	8.54
164	$C_{18}H_{17}N_4O_2SCl$	14.48	14.42	8.63	8.23
	M. p. °C 200 204 191 188 263 183 202 219 197 164	$\begin{array}{c} \underset{C}{\text{M. p.}} & \text{Molec. formula} \\ \underset{C}{\text{OC}} & \text{C}_{16}\text{H}_{18}\text{N}_4\text{OSCl} \\ 200 & \text{C}_{17}\text{H}_{15}\text{N}_4\text{OSCl} \\ 204 & \text{C}_{17}\text{H}_{15}\text{N}_4\text{OSCl} \\ 191 & \text{C}_{17}\text{H}_{15}\text{N}_4\text{OSCl} \\ 188 & \text{C}_{17}\text{H}_{15}\text{N}_4\text{OSCl} \\ 263 & \text{C}_{16}\text{H}_{12}\text{N}_4\text{OSCl}_2 \\ 263 & \text{C}_{16}\text{H}_{12}\text{N}_4\text{OSCl}_2 \\ 202 & \text{C}_{16}\text{H}_{12}\text{N}_4\text{OSCl}_2 \\ 219 & \text{C}_{16}\text{H}_{12}\text{N}_4\text{OSCl}\text{Br} \\ 197 & \text{C}_{17}\text{H}_{15}\text{N}_4\text{O}_2\text{SCl} \\ 164 & \text{C}_{18}\text{H}_{17}\text{N}_4\text{O}_2\text{SCl} \end{array}$	$\begin{array}{cccc} M. p. & Molec. \ formula & Found \\ \hline & C & Molec. \ formula & Found \\ \hline & 200 & C_{16}H_{18}N_4OSCl & 16.10 \\ 204 & C_{17}H_{15}N_4OSCl & 15.49 \\ 191 & C_{17}H_{15}N_4OSCl & 15.43 \\ 188 & C_{17}H_{15}N_4OSCl & 15.61 \\ 263 & C_{16}H_{12}N_4OSCl_2 & 14.81 \\ 183 & C_{16}H_{12}N_4OSCl_2 & 14.39 \\ 202 & C_{16}H_{12}N_4OSCl_2 & 14.61 \\ 219 & C_{16}H_{12}N_4OSClBr & 13.21 \\ 197 & C_{17}H_{15}N_4O_2SCl & 14.87 \\ 164 & C_{18}H_{17}N_4O_2SCl & 14.48 \end{array}$	$\begin{array}{cccc} M. p. & Molec. \ formula & Found & Calcd. \\ \hline & & Found & Calcd. \\ \hline & & Found & Calcd. \\ \hline & & & & \\ 200 & C_{16}H_{18}N_4OSCl & 16.10 & 16.26 \\ \hline & & & & \\ 204 & C_{17}H_{15}N_4OSCl & 15.49 & 15.63 \\ \hline & & & & \\ 191 & C_{17}H_{15}N_4OSCl & 15.43 & 15.63 \\ \hline & & & & \\ 188 & C_{17}H_{15}N_4OSCl & 15.61 & 15.63 \\ \hline & & & & \\ 263 & C_{16}H_{12}N_4OSCl_2 & 14.81 & 14.78 \\ \hline & & & & \\ 183 & C_{16}H_{12}N_4OSCl_2 & 14.39 & 14.78 \\ \hline & & & & \\ 202 & C_{16}H_{12}N_4OSCl_2 & 14.61 & 14.78 \\ \hline & & & & \\ 219 & C_{16}H_{12}N_4OSClBr & 13.21 & 13.22 \\ \hline & & & & \\ 197 & C_{17}H_{15}N_4O_2SCl & 14.87 & 14.95 \\ \hline & & & \\ 164 & C_{18}H_{17}N_4O_2SCl & 14.48 & 14.42 \\ \hline \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

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

Hydrochlorides of	M . p.	Moleo formula	N, %		S, %	
imidazolyl)acetylamino]	°Ć	Molec. Iormula	Found	Calcd.	Found	Caled.
-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 ₄ OSCl	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	C17H14N4OSCIBr	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-benzimidazol-ylacetylamino)- 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.

Hydrochlorides of 2-(<i>N</i> -	Onset of anaesthesia (min.) with administration of anaesthetic* in hydrochloric acid of strength			
Senzimazory lacety lamino)	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	

Table VI. Local anaesthetic activity of hydrochlorides of 2-(N-benzimidazolylacetylamino)benzothiazoles

* Concentration of anaesthetic, 0.2%

TABLE VII. Local anaesthetic activity of hydrochlorides of 2-[N-(2'-methylbenzimidazolyl)acetylamino]benzothiazoles

Hydrochloride of 2-[N-(2'- methylbenzimidazolyl)-	Onset of anaesthesi anaesthetic* in	a (min.) with a hydrochloric aci	dministration of d of strength
acetylamino]	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.

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