J. Indian Chem. Soc.,
Vol. LV, July 1978, pp. 726-729

Synthesis of 2-*N*,*N*-Dialkyl (or Alkylaryl) Aminoacetamido-(Substituted)-Benzothiazoles or-Thiazoles as Local Anaesthetics

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Manuscript received 7 July 1976, revised 1 August 1977, accepted 14 February 1978

Hydrochlorides of 2-*N*, *N*-dialkyl (or alkylaryl) aminoacetamido-(substituted)-benzothiazoles or -thiazoles were prepared and tested for their local anaesthetic activity on frogs. The compounds 2-*N*, *N*-diisobutylaminoacetamido-6-chlorobenzothiazole. 2-*N*-butyl-*N*-phenylaminoacetamido-4-chlorobenzothiazole; 2-*N*,*N*-diisobutylaminoacetamido-4-*p*-chlorophenyl-, -4-methyl-5-carboethoxy-thiazoles and 2-*N*,*N*-dibenzylaminoacetamido-4-methyl-5-carboethoxythiazole showed a high degree of activity.

FOR a local anaesthetic compound, a lipophilic moiety containing an aromatic nucleus, a hydrophilic moiety containing a tertiary amino group and an intermediate alkyl or substituted alkyl chain are the structural requirements. In view of the significant anaesthetising property exhibited by thiazoles[1,2] and benzothiazoles[3,4], the synthesis of hydrochlorides of several 2-*N*, *N*-dialkyl (or alkylaryl) aminoacetamido-(substituted)-benzothiazoles or -thiazoles was undertaken in order to study their local anaesthetic properties on frogs by the method of Bulbring and Wajda[5].

The melting points of the compounds were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Experimental

2-Chloroacetylamino-(substituted) benzothiazoles- These were prepared by the method of Bhargava and Ram[6].

2-Chloroacetylamino-(substituted) thiazoles—These were prepared by the method of Sharma[7].

Hydrochloride of 2-N,N-Diisobutylaminoacetamido-4-chlorobenzothiazole ;

A mixture of 2-chloroacetylamino-4-chlorobenzothiazole (2.6 g), diisobutylamine (1.9 ml) and anhydrous potassium carbonate (1.0 g) in absolute ethanol (50 ml) was refluxed on a water-bath for 6 hours. It was filtered and the excess of ethanol and diisobutylamine were distilled off on a rotavapour. The residue could not be crystallised from ethanol.

It was then transformed into its hydrochloride by passing dry hydrochloric acid gas in the ethereal solution. Recrystaliisation from benzene-ethanol (3:2) afforded white crystals, yield 68%, m.p. 242°. Found : N, 10.53 ; S, 8.02. $C_{17}H_{25}Cl_2N_3OS$ requires N, 10.76 ; S, 8.20%. NMR (D_2O, δ) : 0.95 [6H, d, J=6Hz, $-CH(CH_3)_2$], 1.05 [6H, d, J=6Hz, $-CH(CH_3)_2$], 1.62–2.26 [2H, m, two $-CH(CH_3)_2$ groups], 2.88 [2H, d, J=7Hz, $-\overset{+}{N}-CH_2-CH(CH_3)_2$], 3.29 [2H, d, J=7Hz, $-\overset{+}{N}-CH_2-CH(CH_3)_2$], 4.48 (2H, s, $-COCH_2-\overset{+}{N}-$), 7.15-7.55 (3H, m, aromatic protons) ppm. The NH and $-\overset{+}{N}-H$ proton resonances are not observed due to deuterium exchange in D_2O. IR (nujol) cm^{-1} : 3400 (m) >NH and $-\overset{+}{N}H$ bands ; 1655 (s, C=O) ; 1610 (m), 1555 (s).

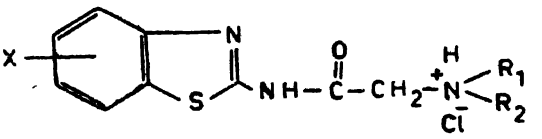
Similarly other compounds with different substitutions in benzothiazole nucleus were prepared and enlisted in Table 1.

Some other compounds were also prepared by using *n*-butylaniline instead of diisobutylamine and their physical data are given in Table 1.

2-N,N-Diisobutylaminoacetamido-4-phenylthiazole :

A mixture of 3,0 g of 2-chloroacetamido-4-phenylthiazole, 2.0 g of diisobutylamine and 1.0 g of anhydrous potassium carbonate in 40 ml absolute ethanol was refluxed on a water-bath for 8 hours. Ethanol was evaporated under vaccuo at room temperature and the residue was washed with sodium bicarbonate solution followed by water. The product was recrystallised from 50% ethanol, yield 60%, m.p. 95°.

TABLE 1—HYDROCHLORIDES OF 2-*N*, *N*-DIALKYL (OR ALKYLARYL) AMINOACETAMIDO-(SUBSTITUTED)-BENZOTHIAZOLES



S. No.	Substituent X	Molecular formula	M.P. (°C)	Yield (%)	Onset of anaesthesia (minute) with administration of anaesthetic[a] in hydrochloric acid of strength	
					0.05 N	0.1 N
		$R_1 = R_2$ = Isobutyl				
1.	H	$C_{17}H_{26}ClN_3OS$	210	54	25.15	29.30
2.	4-Methyl	$C_{18}H_{28}ClN_3OS$	195	62	16.20	19.15
3.	5-Methyl	$C_{18}H_{28}ClN_3OS$	264	72	19.30	22.50
4.	6-Methyl	$C_{18}H_{28}ClN_3OS$	251	65	14.10	16.55
5.	4-Chloro	$C_{17}H_{25}Cl_2N_3OS$	242 d	75	11.50	13.10
6.	5-Chloro	$C_{17}H_{25}Cl_2N_3OS$	232	70	16.20	17.55
7.	6-Chloro	$C_{17}H_{25}Cl_2N_3OS$	242 d	65	7.35	8.30
		R_1 = *n*-Butyl, R_2 = Phenyl				
8.	H	$C_{19}H_{22}ClN_3OS$	244	61	35.20	42.45
9.	4-Methyl	$C_{20}H_{24}ClN_3OS$	238	52	20.00	23.25
10.	5-Methyl	$C_{20}H_{24}ClN_3OS$	270 d	63	24.10	28.40
11.	6-Methyl	$C_{20}H_{24}ClN_3OS$	244	68	15.25	17.15
12.	4-Chloro	$C_{19}H_{21}Cl_2N_3OS$	243 d	59	7.30	8.45
13.	5-Chloro	$C_{19}H_{21}Cl_2N_3OS$	238 d	76	12.35	14.10
14.	6-Chloro	$C_{19}H_{21}Cl_2N_3OS$	210	78	11.55	13.05
	Procaine hydrochloride (0.2 %)				11.45	12.45

Satisfactory results were obtained for Sulphur and Nitrogen analyses.
a—Concentration of anaesthetic, 0.2 %
d—metts with decomposition

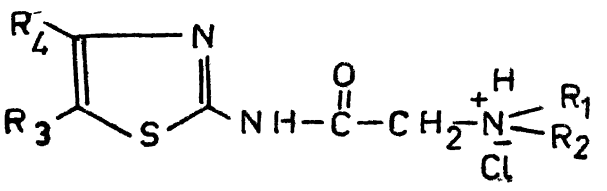
Found ; N, 12.32 ; S, 9.02. $C_{19}H_{27}N_3OS$ requires N, 12.17 ; S, 9.27%. IR (nujol) cm^{-1} : 3300 (m, >NH stretch), 1695 (s, >C=O stretch), 1540 (s). NMR ($CDCl_3$)δ : 1.0 [d, 12H, J=6Hz, two $-CH_2-CH-(CH_3)_2$ groups], 1.5-2.2 [m, 2H, two $-CH_2-CH-(CH_3)_2$ groups], 2.3 [d, 4H, J=7Hz, two $-CH_2-CH-(CH_3)_2$ groups], 3.3 (s, 2H, $-C(O)-CH_2-N<$), 7.1-8.1 (m, 6H, aromatic protons), 10.2-10.7 (br, *NH* proton) ppm.

Similarly, 2-*N*,*N*-diisobutyl-, -dibenzyl-, and -dipropylaminoacetamido -4,5-disubstituted thiazoles were prepared. Many of the above bases were obtained as semisolids. These were isolated as their solid hydrochlorides and recrystallised from benzene alcohol mixture. Their yields and melting points are recorded in Table 2.

Pharmacological screening :

The hydrochlorides summarised in Table 1 and 2 were screened for their local anaesthetic activity by frog's sciatic plexus test. Each compound was tested on the frogs at 0.2% concentration in 0.7% saline solution. The time taken at the given concentration of a local anaesthetic to fail to provoke withdrawal of both the feet was recorded and compared with that of procaine hydrochloride (0.2%) as a standard substance. The results are recorded in Table 1 and 2.

TABLE 2—HYDROCHLORIDES OF 2-*N*, *N*-DIALKYL (OR ALKYLARYL) AMINOACETAMIDO-4, 5-(DISUBSTITUTED) THIAZOLES



S. No.	4-Substituent (R_4)	5-Substituent (R_5)	Molecular formula	M. P.[a] (°C)	Yield (%)	Onset of anaesthesia (minute) with administration of anaesthetic[b] in hydrochloric acid of strength	
						0.05 N	0.1 N
			$R_1=R_2=$ Isobutyl				
1.	*p*-Methylphenyl	H	$C_{20}H_{30}ClN_3OS$	228	60	13	15
2.	*p*-Chlorophenyl	H	$C_{19}H_{27}Cl_2N_3OS$	102	50	7	7.5
3.	Phenyl	CH_3	$C_{20}H_{30}ClN_3OS$	115 (172)	70	9.5	10
4.	*p*-Methoxyphenyl	H	$C_{20}H_{30}ClN_3O_2S$	105 (225)	60	8	9
5.	Methyl	$COOC_2H_5$	$C_{17}H_{30}ClN_3O_3S$	190	70	4	5
			$R_1=R_2=n$-Propyl				
6.	Phenyl	H	$C_{17}H_{24}ClN_3OS$	170 (88)	50	12	13
7.	*p*-Methylphenyl	H	$C_{18}H_{26}ClN_3OS$	140	40	13	13
8.	p-Chlorophenyl	H	$C_{17}H_{23}Cl_2N_3OS$	148	45	8.5	10
9.	Phenyl	CH_3	$C_{18}H_{26}ClN_3OS$	193	50	12	14
10.	*p*-Methoxyphenyl	H	$C_{18}H_{26}ClN_3O_2S$	130	40	10	12
11.	Methyl	$COOC_2H_5$	$C_{15}H_{26}ClN_3O_3S$	220 (d)	45	9	10
			$R_1=R_2=$ Benzyl				
12.	Phenyl	H	$C_{25}H_{24}ClN_3OS$	150	30	18	20
13.	*p*-Methylphenyl	H	$C_{26}H_{26}ClN_3OS$	180	40	13	13
14.	*p*-Chlorophenyl	H	$C_{25}H_{23}Cl_2N_3OS$	140 (d)	45	9	10
15.	Phenyl	CH_3	$C_{26}H_{26}ClN_3OS$	260[c] (d)	50	12	14
16.	*p*-Methoxyphenyl	H	$C_{26}H_{26}ClN_3O_2S$	232	40	8	8.5
17.	Methyl	$COOC_2H_5$	$C_{23}H_{26}ClN_3O_3S$	200 (d)	45	7	7.5
	Procaine hydrochloride (0.2 %)					11.5	13

Satisfactory results were obtained for Sulphur and Nitrogen analyses.

[a]—Melting points of the corresponding bases, wherever isolated, are given in parentheses.

[b]—Concentration of anaesthetic, 0.2 %.

[c]—melts with decomposition.

The screening results show that the hydrochlorides of 2-*N*,*N*-diisobutylaminoacetamido-6-chloro-benzothiazole ; 2-*N*-butyl-*N*-phenylaminoacetamido-4-chlorobenzothiazole ; 2-*N*,*N*-diisobutylaminoacetamido, 4-*p*-chlorophenyl-, -4-methyl-5-carboethoxythiazoles and 2-*N*,*N*-dibenzylaminoacetamido-4-methyl-5-carboethoxythiazozoles are significantly more active as compared to the standard substance procaine hydrochloride.

Acknowledgement

Thanks are due to the Council of Scientific and Industrial Research, New Delhi, for the award of a Junior Research Fellowship to one of us (S. P.).

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