Agric. Biol. Chem., **48** (6), 1441～1444, 1984

Local Anaesthetic Activity and Synthesis of 2-(*N*-Substituted or *N,N*-Disubstituted aminoacetamido)-4-aryl Thiazoles†

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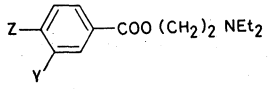
Received October 18, 1983

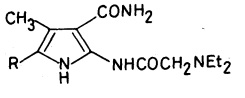
Some new 2-(*N*-substituted or *N,N*-disubstituted aminoacetamido)-4-*p*-nitrophenyl, 4-*m*-nitrophenyl and 4-(2′,5′-dimethoxy)phenyl thiazoles were synthesised. Their hydrochlorides were screened for local anaesthetic activity by Frog's sciatic plexus method and this activity compared with that of procaine hydrochloride. Among them, the 2-(*N*-substituted aminoacetamido)-4-*m*-nitrophenylthiazole hydrochlorides are the most potent: almost twice in terms of the onset of anaesthesia in comparison with procaine–HCl.

Various analogues of the well-known local anaesthetic procaine [2-(diethylamino)ethyl *p*-aminobenzoate] are still used in clinical practice. Of these, Ambucaine (**1a**)[2] and Paraethoxycaine (**1b**)[3] are of special interest not only because these compounds exhibit a low order of positional specificity for activity but functional groups may even be interchanged at will (*e.g.* ethoxy for amino). Lidocaine [(2-diethylamino)-*N*-(2,6-dimethylphenyl)acetamide] is considered one of the most satisfactory local anaesthetics because it is more stable in solution and quick in onset. Kopacova *et al.*[4] have reported that 4-aryloxy- and 4-aralkoxy-2,6-dimethylanilides have greater local anaesthetic activity than procaine. 2-(*t*-Butylamino)-*N*-(2,6-dimethylphenyl)propionamide (**2**) has significantly long lasting local anaesthetic activity and low acute toxicity.[5] Johnson and co-workers[6] have prepared 2-aminopyrrole analogues (**3**) of lidocaine which showed significant local anaesthetic activity by the guinea pig wheal test and also showed antiarrhythmic activity against chloroform-induced ventricular arrhythmias in mice.

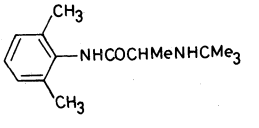
Keeping these facts in view and that 2-aminothiazole derivatives[1,7] exhibit marked



(1a) Y = O $(CH_2)_3 CH_3$, Z = NH_2
(1b) Y = H, Z = OC_2H_5



(3)



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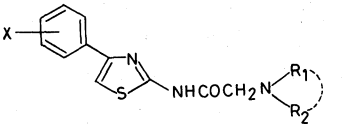

(4)

X = p-NO_2, m-NO_2 and 2′,5′-$(CH_3O)_2$

† Local Anaesthetics. Part III. See ref. 1.

TABLE I. CHARACTERISATION DATA OF 2-(*N*-SUBSTITUTED AND *N*, *N*-DISUBSTITUTED AMINOACETAMIDO)-4-ARYLTHIAZOLES (**4**)

S. No.	R_1	R_2	Yield (%)	mp (°C)	Colour of crystals	Molecular formula	Found[a]		Calcd.	
							%C	%H	%C	%H
					X=*p*-NO_2					
1	Et	H	80	257d	Red	$C_{13}H_{14}N_4O_3S$	51.36	4.68	50.98	4.57
2	iso-Pr	H	70	238	Dark red	$C_{14}H_{16}N_4O_3S$	52.10	5.28	52.50	5.00
3	iso-Bu	H	75	271	Red	$C_{15}H_{18}N_4O_3S$	53.56	5.52	53.91	5.39
4	*sec*-Bu	H	80	258	Light red	$C_{15}H_{18}N_4O_3S$	53.89	5.36	53.91	5.39
5	*t*-Bu	H	75	240	Red	$C_{15}H_{18}N_4O_3S$	53.98	5.45	53.91	5.39
6	Et	Et	60	255	Light red	$C_{15}H_{18}N_4O_3S$	54.28	5.26	53.91	5.39
7	Piperidino		65	227	Brick red	$C_{16}H_{18}N_4O_3S$	55.10	5.32	55.49	5.20
					X=*m*-NO_2					
8	Et	H	80	181	Dark yellow	$C_{13}H_{14}N_4O_3S$	50.62	4.48	50.98	4.57
9	iso-Pr	H	90	159	Light yellow	$C_{14}H_{16}N_4O_3S$	52.86	5.14	52.50	5.00
10	iso-Bu	H	90	151	Yellow	$C_{15}H_{18}N_4O_3S$	53.62	5.33	53.91	5.39
11	*sec*-Bu	H	80	146	Yellow	$C_{15}H_{18}N_4O_3S$	53.93	5.36	53.91	5.39
12	*t*-Bu	H	90	177	Dark yellow	$C_{15}H_{18}N_4O_3S$	54.38	5.12	53.91	5.39
					X=2′,5′-$(CH_3O)_2$					
13	Et	H	*b*							
14	iso-Pr	H	60	127	Yellow	$C_{16}H_{21}N_3O_3S$	57.02	6.15	56.69	6.27
15	iso-Bu	H	80	107	Yellow	$C_{17}H_{23}N_3O_3S$	58.30	6.60	58.45	6.59
16	*sec*-Bu	H	*b*							
17	Et	Et	*b*							
18	Piperidino		90	139	Yellow	$C_{18}H_{23}N_3O_3S$	60.13	6.32	59.84	6.37

[a] Satisfactory N and S analyses were also obtained.
[b] Compound numbers 13, 16 and 17 colud not be isolated in crystalline form, and were directly converted into their hydrochlorides.

local anaesthetic activity, the authors have synthesized a series of nitro and dimethoxy-substituted 4-phenyl-2-(*N*-substituted or *N,N*-disubstituted aminoacetamido)thiazoles having the general structure (**4**).

The starting materials, 2-amino-4-arylthiazoles, were prepared by the condensation of *p*-nitroacetophenone or *m*-nitroacetophenone or 2,5-dimethoxyacetophenone with thiourea in the presence of iodine. The 2-amino-4-arylthiazoles were treated with chloroacetyl chloride in dry benzene to give the corresponding 2-chloroacetamido-4-arylthiazoles. Reaction of these compounds with different primary and secondary amines in the presence of potassium carbonate in absolute ethanol yielded 2-(*N*-substituted or *N,N*-disubstituted aminoacetamido)-4-arylthiazoles (Table I). These were converted into their hydrochlorides by the usual methods (Table II), and evaluated for conduction anaesthesia on frogs by the sciatic plexus method.[8]

EXPERIMENTAL

Materials and methods. Melting points were observed with a Gallenkamp apparatus and are uncorrected. Elemental analyses were carried out on a Coleman Analyser. The IR spectra were recorded on a Perkin-Elmer 720 grating spectrophotometer, with NMR on a Varian-A60D spectrometer at a probe temperature of 44.5° as $CDCl_3$ solutions using TMS as an internal standard. The purity of the compounds was checked by TLC using silica gel G (E. Merck).

2-Amino-4-(2′,5′-dimethoxy)phenylthiazole. This was prepared by the reaction between 2,5-dimethoxyacetophenone and thiourea in the presence of iodine.[1] The product was crystallized from EtOH as deep brown needles, mp 121°C. Found: N, 11.90. Calcd. for $C_{11}H_{12}N_2O_2S$: N, 11.87%. IR ν_{max}^{Nujol} cm^{-1}: 3450 m, 3330 m, 1620 m, 1520s, 1500s. NMR $\delta_{Me_4Si}^{CDCl_3}$: 3.85 and 3.90 (3H × 2, s, two methoxy groups), 5.30 (2H, broad, $-NH_2$) 6.85 ~ 7.75 (4H, m, aromatic).

TABLE II. CHARACTERISATION DATA OF 2-(*N*-SUBSTITUTED AND *N*,*N*-DISUBSTITUTED AMINOACETAMIDO)-4-ARYLTHIAZOLE HYDROCHLORIDES (**4**-HCl) AND THEIR LOCAL ANAESTHETIC ACTIVITIES

S. No.	R_1	R_2	Yield (%)	mp (°C)	Colour of crystals	Onset of anaesthesia (in minutes)[a]	
						0.05 N	0.1 N
					X=*p*-NO_2		
1	Et	H	60	108	Yellow	10.45	11.00
2	iso-Pr	H	65	115	Yellow	8.10	8.25
3	iso-Bu	H	60	117	Brownish yellow	11.25	11.35
4	*sec*-Bu	H	55	115	Dirty yellow	11.30	11.40
5	*t*-Bu	H	55	135	Light yellow	11.45	12.05
6	Et	Et	70	75	Dirty yellow	11.00	11.10
7	Piperidino		50	213	Light yellow	11.10	11.25
					X=*m*-NO_2		
8	Et	H	80	237	White	5.15	6.05
9	iso-Pr	H	75	227	White	4.55	5.50
10	iso-Bu	H	70	223	Pale yellow	4.55	5.40
11	*sec*-Bu	H	65	224	Pale yellow	4.25	5.00
12	*t*-Bu	H	60	225	Pink	8.45	9.40
					X=2′,5′-$(CH_3O)_2$		
13	Et	H	60	242	Brown	8.30	8.40
14	iso-Pr	H	80	231	Light brown	8.15	10.00
15	iso-Bu	H	75	226	Light brown	9.50	10.20
16	*sec*-Bu	H	65	238	Brown	10.50	11.30
17	Et	Et	65	122	Brown	7.20	7.30
18	Piperidino		75	187[b]	White	10.35	10.45
	Procaine hydrochloride[c]					10.00	10.15

[a] Onset of anaesthesia in minutes after administration of the anaesthetic, detected by using HCl of given normality.
[b] Shrinks at 165°C and melts at 187°C.
[c] Procaine hydrochloride (at 0.1% concentration) was used as the standard.

2-Amino-4-m-nitrophenylthiazole. This was obtained from *m*-nitroacetophenone as above, mp 185°C (lit.[9] mp 188~190°C). IR ν_{max}^{KBr} cm^{-1}: 3470 m, 3320 w, 3150 m, 1640 s, 1550 s, 1520 s, 1360 s, 730 m.

2-Amino-4-p-nitrophenylthiazole. This was prepared as above in a 90% yield from *p*-nitroacetophenone, mp 282°C (from DMF) (lit.[9] mp 285~286°C). IR ν_{max}^{Nujol} cm^{-1}: 3440 w, 3350 w, 3200 w, 1640 s, 1600 s, 1530 m, 1500 s.

2-Chloroacetamido-4-(2′,5′-dimethoxy)phenylthiazole. To a solution of 2-amino-4-(2′,5′-dimethoxy)phenylthiazole (9.7 g) in dry benzene (40 ml) was added dropwise a cooled solution of chloroacetyl chloride (4.0 ml) in dry benzene (15 ml). The reaction mixture was refluxed on a steam bath at 80°C for 3 hr. Benzene and excess chloroacetyl chloride were removed by distillation. The residue was washed with aqueous sodium bicarbonate followed by cold water. The crude product was dried and crystallized from ethanol, yield 65%, mp 142°C. Found: N, 9.10; S, 10.15. Calcd. for $C_{13}H_{13}ClN_2O_3S$: N, 8.95; S, 10.24%. IR ν_{max}^{Nujol} cm^{-1}: 3250 m, 1665 s, 1560 s, 1500 s, 1220 s.

2-Chloroacetamido-4-m-nitrophenylthiazole. This was prepared likewise, crystallized from ethanol, yield 80%, mp 216°C (lit.[10] mp 203°C). IR ν_{max}^{Nujol} cm^{-1}: 3250 w, 1710 w, 1640 s, 1570 s, 1530 s.

2-Chloroacetamido-4-p-nitrophenylthiazole. This was prepared as above. The crude product was crystallized from benzene–ethanol (3:1), yield 60%, mp 175°C. Found: N, 13.76; S, 11.10. Calcd. for $C_{11}H_8ClN_3O_3S$: N, 14.11; S, 10.75%. IR ν_{max}^{Nujol} cm^{-1}: 3400 w, 1700 w, 1660 m, 1600 m, 1520 s.

2-(N-Isobutylaminoacetamido)-4-(2′,5′-dimethoxy)-phenylthiazole. A mixture of 2-chloroacetamido-4-(2′,5′-dimethoxy)phenylthiazole (5.0 g), isobutylamine (2.2 ml, 1.60 g), absolute ethanol (40 ml) and anhydrous potassium carbonate (2.0 g) was heated under reflux on a steam bath for 12 hr. The excess amine and

ethanol were removed by distillation and the residue was treated with 5% sodium bicarbonate solution to remove the acid impurities, filtered under suction, washed with water and dried. It was crystallized from 80% ethanol to give yellow plates, yield 80%, mp 107°C. Found: C, 58.30; H, 6.60; N, 12.10; S, 9.20. Calcd. for $C_{17}H_{23}N_3O_3S$: C, 58.45; H, 6.59; N, 12.03; S, 9.15%. IR ν_{max}^{Nujol} cm^{-1}: 3320 w, 3170 w, 1740 w, 1700 s, 1590 s, 1570 s, 1500 s. NMR $\delta_{Me_4Si}^{CDCl_3}$: 0.96 (6H, d, J=7 Hz, –CH ($\underline{CH_3}$)$_2$), 1.55~2.06 (1H, m, –CH_2–$\underline{CH}$ (CH_3)$_2$), 2.51 (2H, d, J=6 Hz, –$\underline{CH_2}$·CH·(CH_3)$_2$), 3.50 (2H, s, –CO·$\underline{CH_2}$–), 3.85 and 3.93 (3H × 2, s, two methoxy groups at the separation of 5 Hz), 5.03~6.38 (2H, broad, –$\underline{NH}COCH_2\underline{NH}$–), 6.86~7.85 (4H, m, aromatic).

Similarly, other 2-(*N*-substituted or *N,N*-disubstituted aminoacetamido)-4-*p*-nitrophenyl, 4-*m*-nitrophenyl and 4-(2′,5′-dimethoxy)phenylthiazoles were prepared by the reaction of different primary and secondary acyclic and cyclic amines with 2-chloroacetamido-4-arylthiazoles separately. These were crystallized from ethanol. Their characterization data are given in Table I. The IR and NMR spectral data of the compounds were typical of the structures assigned to them.

Hydrochloride of 2-(N-isobutylaminoacetamido)-4-(2′,5′-dimethoxy)phenylthiazole. A solution of 2-(*N*-isobutylaminoacetamido)-4-(2′,5′-dimethoxy)phenylthiazole (2.0 g) in anhydrous benzene was saturated with dry hydrogen chloride gas. A solid mass was formed which was filtered and washed with dry ether. The crude product was crystallized from ethanol to give light brown crystals, mp 226°C. Found: C, 53.16; H, 6.16; N, 10.66; Cl, 9.32. Calcd. for $C_{17}H_{24}ClN_3O_3S$: C, 52.90; H, 6.22; N, 10.64; Cl, 9.23%.

Following the above procedure, hydrochlorides of the other 2-(*N*-substituted or *N,N*-disubstituted aminoacetamido)-4-arylthiazoles were prepared. Their yields and melting points are recorded in Table II. Satisfactory C, H, N and Cl analyses of the hydrochlorides were obtained.

Pharmacological screening for plexus anaesthesia on frogs. The base hydrochlorides reported in Table II were screened for their local anaesthetic activity on frogs at 0.1% concentration of the compounds in 0.7% saline adopting the procedure of Bulbring and Wajda.[8] Three frogs were tested for each of the compounds and the average time for the onset of anaesthesia was recorded. The results (Table II) are compared with that of procaine hydrochloride taken as the standard.

RESULTS AND DISCUSSION

From the screening results it is concluded that all the hydrochlorides of 2-(*N*-substituted aminoacetamido)-4-*m*-nitrophenylthiazoles are relatively better in producing the onset of anaesthesia in frogs in comparison with the standard substance procaine hydrochloride. Of these, 2-(*N-sec*-butylaminoacetamido)-4-*m*-nitrophenylthiazole is the most potent local anaesthetic. The hydrochlorides of 2-(*N*-substituted and *N,N*-disubstituted aminoacetamido)-4-*p*-nitrophenyl and 4-(2′,5′-dimethoxy)phenylthiazoles require a more or less similar length of time in producing the onset of anaesthesia as the standard chosen.

It is also apparent that the significantly greater local anaesthetic activity of compound numbers 8~12 in comparison with that of others is due to the presence of the 4-*m*-nitrophenyl substituent. However, the *m*-nitrophenyl substituent does not confer the same degree of potency as the *p*-fluorophenyl substituent reported in our earlier communication.[1]

Acknowledgments. We wish to thank Professors B. M. Shukla and R. C. Aggarwal, Heads of the Department of Chemistry, Banaras Hindu University, for providing the necessary facilities. Thanks are also due to CSIR, New Delhi for the award of a Junior Research Fellowship to one of us (O.P.S.).

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