New Local Anesthetics: Derivatives of 5-Diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones

P. N. BHARGAVA and M. R. CHAURASIA

Abstract □ A series of hydrochloride salts of 5-diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones was synthesized as potential local anesthetic agents. Pharmacological screening using the sciatic plexus of the frog showed that three of the hydrochloride salts were potent local anesthetics.

Keyphrases □ Anesthetics, local—synthesis □ 5-Diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones—synthesis □ Pharmacological screening—local anesthetics

Structural requirements for a local anesthetic are a lipophilic end containing an aromatic nucleus, a hydrophilic end containing a tertiary amino group, and an intermediate alkyl or substituted alkyl chain. Compounds having a dialkylamino group connected to an aromatic or a heterocyclic nucleus as the lipophilic moiety confer greater activity and less toxicity than the benzene analog (1–3).

Considering these facts a series of hydrochlorides of 5-diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones has been synthesized as local anesthetics. 2-Arylimino-3-aryl-4-thiazolidones (4) have been obtained in good yield by interaction of *N*-aryl-*N'*-*m*-tolylthiourea (4) with monochloroacetic acid and anhydrous sodium acetate. An amino group has been introduced at 5-position in the thiazolidonyl nucleus at the reactive methylene group (5, 6) through coupling (7) with benzenediazonium chloride and subsequent reduction (8, 9) with sodium hydrosulfite. These 5-aminothiazolidones on condensation with chloroacetyl chloride and subsequent treatment with diethylamine gave the required 5-diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones in good yield, and were converted into the respective hydrochlorides by the usual method (10).

Pharmacological screening of the compounds according to the procedure adopted by Bülbring and Wajda (11) has shown that of the seven compounds tested, the hydrochlorides of 5-diethylaminoacetamido-3-*m*-tolyl-2-*o*-chlorophenylimino-, 2-*o*-methoxyphenylimino-, and 2-*m*-methoxyphenylimino-4-thiazolidone were the most effective local anesthetics.

EXPERIMENTAL[1]

5-Phenylazo-2-o-chlorophenylimino-3-m-tolyl-4-thiazolidone—A solution of thiazolidone (3 g.) in glacial acetic acid was slowly added at 0° to a solution of benzenediazonium chloride (prepared from 2.5 g. of aniline) with stirring and kept for 1 hr. at 0–5°. The product which separated was filtered, washed with water and alcohol, and crystallized from absolute alcohol. Similarly 5-phenylazo derivatives of other thiazolidones were prepared as listed in Table I.

5-Amino-2-o-chlorophenylimino-3-m-tolyl-4-thiazolidone—The azo compound (3 g.) was dissolved in ethyl alcohol (50 ml.) by heating. To this, a solution of sodium hydrosulfite (10 g.) in water (25 ml.) was added when the 5-amino compound was obtained as a precipitate. It was filtered hot and washed with hot water and finally crystallized from absolute alcohol.

5-Amino derivatives of other 5-phenylazo-2-arylimino-3-aryl-4-thiazolidones, prepared similarly, are mentioned in Table II.

5-Chloroacetamido-3-m-tolyl-2-o-chlorophenylimino-4-thiazolidone—A mixture of chloroacetyl chloride (0.77 ml.) and 5-amino compund (2.5 g.) in dry benzene (25 ml.) was refluxed on a water bath at 70° for 2 hr. Benzene and an excess of chloroacetyl chloride were then distilled off and the residue washed with sodium bicarbonate solution and water. The product was crystallized from absolute ethanol.

[1] Melting points were determined on a Gallenkamp melting apparatus and are uncorrected.

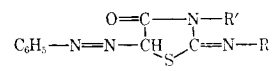
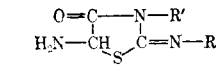


Table I—5-Phenylazo-2-arylimino-3-aryl-4-thiazolidones

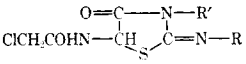
R	R'	Yield, %	M.p., °C.	Formula	Anal., % Calcd.	Found
o-Chlorophenyl	*m*-Tolyl	75	164	$C_{22}H_{17}ClN_4OS$	13.34 7.62	N, 13.24 S, 7.60
m-Chlorophenyl	*m*-Tolyl	50	141	$C_{22}H_{17}ClN_4OS$	13.34 7.62	N, 13.22 S, 7.66
o-Methoxyphenyl	*m*-Tolyl	48	145	$C_{23}H_{20}N_4O_2S$	13.46 7.69	N, 13.31 S, 7.70
m-Methoxyphenyl	*m*-Tolyl	40	157	$C_{23}H_{20}N_4O_2S$	13.46 7.69	N, 13.29 S, 7.68
o-Tolyl	*m*-Tolyl	65	144	$C_{23}H_{20}N_4OS$	14.00 8.00	N, 13.89 S, 8.09
m-Tolyl	*p*-Chlorophenyl	55	131	$C_{22}H_{17}ClN_4OS$	13.34 7.62	N, 13.20 S, 7.69
m-Tolyl	*p*-Methoxyphenyl	58	120	$C_{23}H_{20}N_4O_2S$	13.46 7.69	N, 13.30 S, 7.68
m-Tolyl	α-Naphthyl	60	151	$C_{26}H_{20}N_4OS$	12.84 7.34	N, 12.77 S, 7.40
m-Tolyl	β-Naphthyl	65	197	$C_{26}H_{20}N_4OS$	12.84 7.34	N, 12.71 S, 7.33

Table II—5-Amino-2-arylimino-3-aryl-4-thiazolidones



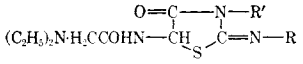
R	R′	Yield, %	M.p., °C.	Formula	Anal., % Calcd.	Found
o-Chlorophenyl	*m*-Tolyl	75	160	$C_{16}H_{14}ClN_3OS$	12.67	N, 12.55
					9.65	S, 9.64
m-Chlorophenyl	*m*-Tolyl	70	145	$C_{16}H_{14}ClN_3OS$	12.67	N, 12.50
					9.65	S, 9.69
o-Methoxyphenyl	*m*-Tolyl	65	134	$C_{17}H_{17}N_3O_2S$	12.84	N, 12.77
					9.79	S, 9.77
m-Methoxyphenyl	*m*-Tolyl	55	156	$C_{17}H_{17}N_3O_2S$	12.84	N, 12.72
					9.79	S, 9.80
o-Tolyl	*m*-Tolyl	65	151	$C_{17}H_{17}N_3OS$	13.82	N, 13.69
					10.29	S, 10.30
m-Tolyl	*p*-Methoxyphenyl	50	119	$C_{17}H_{17}N_3O_2S$	12.84	N, 12.70
					9.79	S, 9.82
m-Tolyl	α-Naphthyl	67	147	$C_{20}H_{17}N_3OS$	12.11	N, 12.00
					9.22	S, 9.21
m-Tolyl	β-Naphthyl	56	194	$C_{20}H_{17}N_3OS$	12.11	N, 12.01
					9.22	S, 9.26

Table III—5-Chloroacetamido-2-arylimino-3-aryl-4-thiazolidones



R	R′	Yield, %	M.p., °C.	Formula	Anal., % Calcd.	Found
o-Chlorophenyl	*m*-Tolyl	70	146	$C_{18}H_{15}Cl_2N_3O_2S$	10.29	N, 10.12
					17.40	Cl, 17.41
m-Chlorophenyl	*m*-Tolyl	68	141	$C_{18}H_{15}Cl_2N_3O_2S$	10.29	N, 10.16
					17.40	Cl, 17.40
o-Methoxyphenyl	*m*-Tolyl	65	154	$C_{19}H_{18}ClN_3O_3S$	10.41	N, 10.30
					9.75	Cl, 9.77
m-Methoxyphenyl	*m*-Tolyl	75	160	$C_{19}H_{18}ClN_3O_3S$	10.41	N, 10.36
					9.75	Cl, 9.80
o-Tolyl	*m*-Tolyl	65	112	$C_{19}H_{18}ClN_3O_2S$	10.83	N, 10.77
					9.16	Cl, 9.09
m-Tolyl	α-Naphthyl	70	138	$C_{22}H_{18}ClN_3O_2S$	9.92	N, 9.89
					8.38	Cl, 8.33
m-Tolyl	β-Naphthyl	60	178	$C_{22}H_{18}ClN_3O_2S$	9.92	N, 9.87
					8.38	Cl, 8.40

Table IV—5-Diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones



R	R′	Yield, %	M.p., °C.	Formula	Anal., % Calcd.	Found
o-Chlorophenyl	*m*-Tolyl	65	156	$C_{22}H_{25}ClN_4O_2S$	12.60	N, 12.55
					7.20	S, 7.21
m-Chlorophenyl	*m*-Tolyl	55	144	$C_{22}H_{25}ClN_4O_2S$	12.60	N, 12.49
					7.20	S, 7.25
o-Methoxyphenyl	*m*-Tolyl	68	142	$C_{23}H_{28}N_4O_3S$	12.73	N, 12.66
					7.27	S, 7.30
m-Methoxyphenyl	*m*-Tolyl	70	154	$C_{23}H_{28}N_4O_3S$	12.73	N, 12.60
					7.27	S, 7.31
o-Tolyl	*m*-Tolyl	50	135	$C_{23}H_{28}N_4O_2S$	13.20	N, 13.09
					7.55	S, 7.58
m-Tolyl	α-Naphthyl	60	149	$C_{26}H_{28}N_4O_2S$	12.17	N, 12.01
					6.95	S, 6.99
m-Tolyl	β-Naphthyl	55	175	$C_{26}H_{28}N_4O_2S$	12.17	N, 12.00
					6.95	S, 7.00

Similarly, chloroacetyl derivatives of other 5-amino-3-aryl-2-arylimino-4-thiazolidones were prepared and are listed in Table III.

5 - Diethylaminoacetamido - 2 - o - chlorophenylimino - 3 - m-tolyl-4-thiazolidone—To the chloroacetylamino compound (2 g.) dissolved in absolute ethanol (20 ml.), diethylamine (0.4 g.) was added and the mixture was refluxed on a water bath at 70° for 4 hr. An excess of alcohol and diethylamine was distilled off and the residue washed first with sodium bicarbonate solution and finally with water. The product was crystallized from ethanol in pale yellow needles.

Other 5-diethylaminoacetamido-3-aryl-2-arylimino-4-thiazolidones obtained similarly are listed in Table IV.

The hydrochlorides were prepared as usual (10) and crystallized from absolute ethanol (see Table V).

Table V—Hydrochlorides of 5-Diethylaminoacetamido-2-arylimino-3-aryl-4-thiazolidones and Their Local Anesthetic Activity

R	R′	Yield, %	M.p., °C.	Formula	N, % Calcd.	N, % Found	Onset of Anesthesia (min.) with Administration of Anesthetic[a] in Hydrochloric Acid of Strength 0.05 *N*	0.1 *N*	0.2 *N*
o-Chlorophenyl	*m*-Tolyl	70	164	$C_{22}H_{25}ClN_4O_2S.HCl$	11.64	11.54	15.45	21.30	22.00
m-Chlorophenyl	*m*-Tolyl	65	150	$C_{22}H_{25}ClN_4O_2S.HCl$	11.64	11.50	36.30	38.00	38.30
o-Methoxyphenyl	*m*-Tolyl	50	146	$C_{23}H_{28}N_4O_3S.HCl$	11.75	11.66	26.10	26.40	26.40
m-Methoxyphenyl	*m*-Tolyl	60	162	$C_{23}H_{28}N_4O_3S.HCl$	11.75	11.63	27.00	27.20	27.20
o-Tolyl	*m*-Tolyl	61	138	$C_{23}H_{28}N_4O_2S.HCl$	12.16	12.01	34.00	34.55	36.00
m-Tolyl	α-Naphthyl	65	157	$C_{26}H_{28}N_4O_2S.HCl$	11.28	11.17	35.40	38.20	39.30
m-Tolyl	β-Naphthyl	55	201	$C_{26}H_{28}N_4O_2S.HCl$	11.28	11.11	34.50	36.20	39.00
Procaine hydrochloride[b]		—	—	—	—	—	33.00	34.20	34.20

[a] Concentration of anesthetic, 0.1%. [b] Procaine hydrochloride was used as such.

Pharmacological Screening—Adopting the frog sciaticplexus method (11), the local anesthetic activity of these hydrochlorides was tested on frogs and the time of onset of anesthesia, *i.e.*, the time for which a given concentration (0.1%) of the local anesthetic failed to provoke withdrawal of feet is also reported in Table V.

Pharmacological screening of these compounds has shown that the hydrochlorides of 5-diethylaminoacetamido-3-*m*-tolyl-2-*o*-chlorophenylimino-, *o*-methoxyphenylimino-, and *m*-methoxyphenylimino-4-thiazolidone were the most potent local anesthetics among the compounds reported, as they required less time for the onset of anesthesia than the standard substance, procaine hydrochloride, at 0.1% concentration in 0.7% of saline solution.

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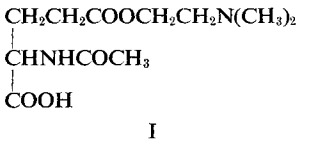
Synthesis of *N*-Acetyl-DL-glutamic Acid 5-Dimethylaminoethyl Ester

G. F. TAMAGNONE and F. De MARCHI

Abstract □ *N*-Acetyl-L-glutamic acid reacted with dimethylaminoethanol in the presence of dicyclohexylcarbodiimide to give *N*-acetyl-DL-glutamic acid 5-dimethylaminoethyl ester (I), which furnished N^2-acetylglutamine by ammonolysis. Compound I could not be obtained by transesterification of *N*-acetyl-L-glutamic acid 5-methyl ester with dimethylaminoethanol, whereas L-pyroglutamic acid salt (III) was obtained from L-glutamic acid 5-methyl ester and dimethylaminoethanol.

Keyphrases □ *N*-Acetyl-DL-glutamic acid 5-dimethylaminoethyl ester—synthesis □ TLC—identity □ IR spectrophotometry—identity, structure

Various dimethylaminoethanol salts have been reported for their CNS-stimulant properties (1–3); particularly, the salt with acetyl-L-glutamic acid which has been recently introduced in Europe as a psychoenergizer (4). Therefore it seemed interesting to synthesize *N*-acetylglutamic acid 5-dimethylaminoethyl ester (I) for pharmacological evaluation.



I

SYNTHESIS

The following attempts were made to synthesize Compound I:

(1) From L-Glutamic Acid 5-Dimethylaminoethyl Ester (II)—The synthesis of II through transesterification of L-glutamic acid 5-methyl ester with dimethylaminoethanol was claimed by Fabre