New Local Anaesthetics Part III. Synthesis of Some Di-5′,5″-acetylamino-2′,2″-arylamino-3′,3″-aryl-4′,4″-thiazolidonyl-1,4-piperazines

P. N. Bhargava and S. C. Sharma

Nine new di-5′,5″-acetylamino-2′,2″-arylamino-3′,3″-aryl-4′,4″-thiazolidonyl-1,4-piperazines and their hydrochlorides have been synthesised from aniline, *p*-chloroaniline, *o*-, *m*-, and *p*-toluidine, o-, and p-anisidine, o-and *p*-phenetidine respectively and their local anaesthetic activity has been tested. The hydrochlorides of di-5′,5″-acetylamino- 2′,2″-*p*-chlorophenylamino-3′,3″-*p*-chlorophenyl-, -2′,2″-*o*-tolylamino- 3′,3″-*o*-tolyl-, 2′,2″-*p*-anisylamino-3′,3″-*p*-anisyl-, 2′,2″-*p*-phenetylamino-3′,3″-*p*-phenetyl-4′,4″-thiazolidonyl-1,4-piperazines are potent local anaesthetics among the compounds reported.

In continuation of the previous work on thiazolidone derivatives as local anaesthetics[1] a series of di-5′,5″-acetylamino-2′,2″-arylamino-3′,3″-aryl-4′,4″-thiazolidonyl-1,4-piperazines has now been prepared from 5-amino-2-arylamino-3-aryl-4-thiazolidones on condensation with chloroacetyl chloride and subsequent treatment with piperazine. All these compounds have been converted into their hydrochlorides by the usual method.

The local anaesthetic activities of these hydrochlorides were tested by frog's sciatic plexus method[2]. The hydrochlorides of di-5′,5″-acetylamino-2′,2″-*p*-chlorophenylamino-3′,3″-*p*-chlorophenyl-, -2′,2″-*o*-tolylamino-3′,3″-*o*-tolyl-, -2′,2″-*p*-anisylamino-3′, 3″-*p*-anisyl-, 2′,2″-*p*-phenetylamino-3′, 3″-*p*-phenetyl-4′, 4″-thiazolidonyl-1, 4-piperazines were found to be the most effective local anaesthetics in this class of compounds.

EXPERIMENTAL

5-Phenylazo-, 5-amino-, and 5-chloroacetylamino derivatives of 2-arylamino-3-aryl-4-thiazolidones were prepared by the method of Bhargava and Singh[1].

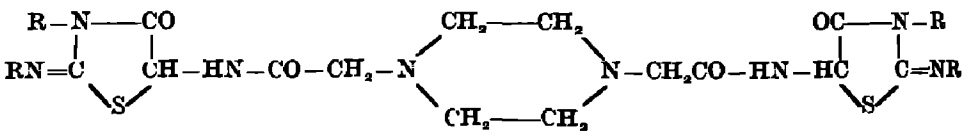
Di-5′,5″-acetylamino-2′,2″-phenylamino-3′,3″-phenyl-4′,4″-thiazolidonyl-1,4-piperazine.—To 5-chloroacetylamino-2-phenylamino-3-phenyl-4-thiazolidone (3.5 g.), dissolved in ethanol (40 ml), piperazine (1 g.) was added and the mixture was refluxed for 4 hours. Ethanol was recovered and the residue was washed with sodium bicarbonate solution to remove the acid impurities; it was finally washed with water to be free of excess of piperazine. The product was crystallised from 80% ethanol and recrystallised from benzene.

1. Bhargava and Singh, *J. Sci. Ind. Res.*, 1961, **20C**, 209.
2. Bulbring and Wajda, *J. Pharmacol. Exp. Therap.*, 1945, **85**, 78.

The hydrochloride of this base was prepared by the usual method and crystallised from absolute ethanol.

Similarly other di-5′,5″-acetylamino-2′,2″-arylamino-3′,3″-aryl-4′,4″-thiazolidonyl-1,4-piperazines and their hydrochlorides were prepared. Their properties and analytical data are reported in Table I.

TABLE I



R.	BASES M.P.	Formula	% Nitrogen Found.	Reqd.	HYDROCHLORIDES M. P.	% Nitrogen. Found.	Reqd.	Onset of anaesthesia (min.) with administration of anaesthetic in hydrochloric acid of strength. 0.05N.	0.1N	0.2N.
Phenyl-	164°	$C_{38}H_{36}O_4N_8S_2$	15.14	15.30	167°	13.73	13.91	13.0	14.0	14.5
p-Chlorophenyl-	134°	$C_{38}H_{32}O_4N_8Cl_4S_2$	12.61	12.87	166°	11.64	11.88	9.0	9.5	10.00
o-Tolyl-	147°	$C_{42}H_{44}O_4N_8S_2$	14.09	14.21	149°	12.89	13.00	9.0	10.0	10.5
m-Tolyl-	151°	$C_{42}H_{44}O_4N_8S_2$	14.13	14.21	150°	12.91	13.00	13.5	14.0	14.5
p-Tolyl-	120°	$C_{42}H_{44}O_4N_8S_2$	14.06	14.21	275°	12.86	13.00	12.0	12.5	13.0
o-Anisyl-	193°	$C_{42}H_{44}O_8N_8S_2$	13.01	13.15	184°	12.03	12.11	10.5	11.0	11.0
p-Anisyl-	112°	$C_{42}H_{44}O_8N_8S_2$	12.95	13.15	159°	11.98	12.11	9.0	9.5	10.0
o-Phenetyl-	111°	$C_{46}H_{52}O_8N_8S_2$	12.21	12.33	106°	11.37	11.42	10.5	11.0	12.0
p-Phenetyl-	100°	$C_{46}H_{52}O_8N_8S_2$	12.17	12.33	105°	11.25	11.42	9.5	10.5	11.0
Procainehydrochloride**								14.0	14.5	15.5

*Conc. of anaesthetic, 0.1%

**Procaine hydrochloride was used as such.

Pharmacological Tests: Plexus Anaesthesia in Frog.—The hydrochlorides of above bases were tested for local anaesthetic activities according to the method of Bulbring and Wajda[2]. The results are shown in Table I as above.

The results of this study indicate that the hydrochlorides of di-5′,5″-acetylamino-,2′,2″-*p*-chlorophenylamino-3′, 3″-*p*-chlorophenyl-,-2′,2″-*o*-tolylamino-3′,3″-*o*-tolyl-,2′,2″-*p*-anisylamino-3′,3″-*p*-anisyl-,-2′, 2″-*p*-phenetylamino-3-′, 3″-*p*-phenetyl-4′, 4″-thiazolidonyl 1,4-piperazines have the highest local anaesthetic activity among the present compounds. It is interesting that the hydrochlorides of all these compounds required less time for the onset of anaesthesia than the standard substance, procaine hydrochloride.

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Chemistry Department,
College of Science,
Banaras Hindu University
Varanasi.

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