*3-Aryl-2, 4-thiazolidindiones. New Local Anaesthetics. IV**

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In viw of close relationship between thiazolidones and thiazolidiones and reported uses of thiazolidone compounds as local anaesthetics*,[1,2], amoebacidal agents[3], and anticonvulsants[4], it was considered worthwhile to prepare 3-aryl-2, 4-thiazolidindiones under the conditions laid down by earlier workers[5-8]. The compounds having piperazino group connected to the heterocyclic nucleus as a lipophylic moiety confer greater activity and less toxicity than the benzene analogues[9-11].

3-Aryl-2, 4-thiazolidindiones have been obtained in good yields by interaction of *S*-diarylthiourea with monochloroacetic acid and glacial acetic acid. An amino group has been introduced at 5-position in the thiazolidindionyl nucleus at the reactive methylene group[12,13] through coupling[14] with benzenediazonium chloride and subsequent reduction[15,16] with sodium hydrosulfite. 5-Chloroacetyl-amino-3-aryl-2, 4-thiazolidindiones, prepared from the chloroacetyl chloride and respective 5-amino compounds, have been further condensed with piperazine to give the required piperazino-1, 4-bis(5-acetylamino-3-aryl-2, 4-thiazolidindiones). These bases have been converted into their hydrochlorides by the usual method.

These compounds have also been tested for the local anaesthetic activity by frog's sciatic plexus method[17] which has shown that the hydrochlorides of piperazino-1, 4-bis(5-chloroacetylamino-3-*p*-chlorophenyl-, -3-*m*-tolyl-, -3-*p*-tolyl-, -3-*p*-anisyl-, -3-*p*-phenetyl-2, 4-thiazolidindiones) have been found most effective local anaesthetics in this class of compounds.

Experimental

5-Phenylazo-3-phenyl-2, 4-thiazolidindione. — A solution of 5 g. of 3-phenyl-2, 4-thiazolidindione in 30 cc. of glacial acetic acid was slowly added to a solution of benzenediazonium chloride (prepared from 4 cc. of aniline), cooled with the freezing mixture at 0°C, with stirring and kept for an hour at 0~5°C. The precipitate formed was filtered, washed with water and dilute ethanol and crystallized from absolute ethanol, m. p. 122°C.

Similarly other thiazolidindiones were coupled with benzenediazonium chloride. Their properties and analytical data are recorded in Table I.

5-Amino-3-phenyl-2, 4-thiazolidindione. — A solution of 8 g. of sodium hydrosulfite in 20 cc. of water was added to the solution of 5 g. of azo compound dissolved in 20 cc. of ethanol. The product which separated, was filtered, washed with hot water and finally crystallized from absolute ethanol into a colorless form, m. p. 133°C.

Similarly, 5-amino derivatives of other 5-phenylazo-3-aryl-2, 4-thiazolidindiones were prepared. Their properties and analytical data are mentioned in Table II.

5-Chloroacetylamino-3-phenyl-2, 4-thiazolidindione.—Chloroacetyl chloride (0.5 cc.) and 5-amino compound (4 g.) were refluxed in 45 cc. of dry benzene for 2 hr. on a water bath at 70°C. Benzene and excess of chloroacetyl chloride were distilled off and the residue washed with the solution of sodium bicarbonate and water. The product was crystallized from absolute ethanol, m. p. 146°C.

Chloroacetylamino derivatives of other 5-amino-3-aryl-2, 4-thiazolidindiones were prepared similarly and their properties and analytical data are shown in Table III.

Piperazino-1, 4-bis(5-acetylamino-3-phenyl-2, 4-thiazolidindione).—A mixture of 5.6 g. of 5-chloroacetylamino-3-phenyl-2, 4-thiazolidindione and 0.84 g. of piperazine in 40 cc. of absolute ethanol was refluxed on a water bath at 60°C for 4 hr. Ethanol was recovered by distillation and the residue subsequently washed with sodium bicarbonate solution and water. The product was crystallized from ethanol and recrystallized from benzene, m. p. 304°C.

* Part III of this series: P. N. Bhargava and S. C. Sharma, *J. Ind. Chem. Soc.*, **39**, 319 (1962).

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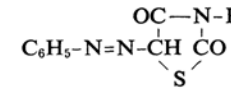
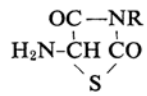
TABLE I. 5-PHENYLAZO-3-ARYL-2,4-THIAZOLIDINDIONES



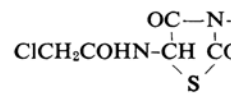
R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
Phenyl-	60	122	$C_{15}H_{11}N_3O_2S$	14.03	14.14	10.82	10.77
p-Chlorophenyl-	53	137	$C_{15}H_{10}N_3O_2SCl$	15.56	12.67	9.69	9.65
o-Tolyl-	45	150	$C_{16}H_{13}N_3O_2S$	13.35	13.50	10.08	10.29
m-Tolyl-	50	89	$C_{16}H_{13}N_3O_2S$	13.31	13.50	10.21	10.29
p-Tolyl-	59	148	$C_{16}H_{13}N_3O_2S$	13.40	13.50	10.17	10.29
o-Anisyl-	41	107	$C_{16}H_{13}N_3O_3S$	12.69	12.84	9.74	9.79
p-Anisyl-	39	111	$C_{16}H_{13}N_3O_3S$	12.72	12.84	9.78	9.79
p-Phenetyl-	57	98	$C_{17}H_{15}N_3O_3S$	12.17	12.32	9.42	9.38

TABLE II. 5-AMINO-3-ARYL-2,4-THIAZOLIDINDIONES



R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
Phenyl-	40	133	$C_9H_8N_2O_2S$	13.29	13.46	15.41	15.38
p-Chlorophenyl-	49	131	$C_9H_7N_2O_2SCl$	11.47	11.55	13.12	13.19
o-Tolyl-	39	156	$C_{10}H_{10}N_2O_2S$	12.53	12.61	14.29	14.41
m-Tolyl-	32	91	$C_{10}H_{10}N_2O_2S$	12.45	12.61	14.33	14.41
p-Tolyl-	50	157	$C_{10}H_{10}N_2O_2S$	12.42	12.61	14.44	14.41
o-Anisyl-	43	90	$C_{10}H_{10}N_2O_3S$	11.64	11.76	13.51	13.45
p-Anisyl-	55	117	$C_{10}H_{10}N_2O_3S$	11.61	11.76	13.38	13.45
p-Phenetyl-	40	102	$C_{11}H_{12}N_2O_3S$	11.08	11.11	12.47	12.50

TABLE III. 5-CHLOROACETYLAMINO-3-ARYL-2,4-THIAZOLIDINDIONES



R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
Phenyl-	75	146	$C_{11}H_9N_2O_3SCl$	9.66	9.84	11.32	11.29
p-Chlorophenyl-	62	148	$C_{11}H_8N_2O_3SCl_2$	8.71	8.78	10.11	10.06
o-Tolyl-	59	158	$C_{12}H_{11}N_2O_3SCl$	9.27	9.38	10.74	10.76
m-Tolyl-	78	157	$C_{12}H_{11}N_2O_3SCl$	9.25	9.38	10.85	10.76
p-Tolyl-	51	160	$C_{12}H_{11}N_2O_3SCl$	9.28	9.38	10.81	10.76
o-Anisyl-	76	103	$C_{12}H_{11}N_2O_4SCl$	8.82	8.90	10.09	10.21
p-Anisyl-	53	113	$C_{12}H_{11}N_2O_4SCl$	8.79	8.90	10.16	10.21
p-Phenetyl-	49	101	$C_{13}H_{13}N_2O_4SCl$	8.41	8.52	9.73	9.77

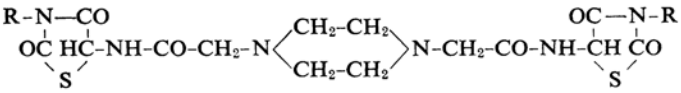
The hydrochloride of the base was prepared by dissolving in dry ether and passing into it dry hydrochloric acid gas. The mass was crystallized from absolute ethanol, m. p. 305°C.

The properties and analytical data of the piperazino derivatives and hydrochlorides of the bases prepared similarly from other 5-chloroacetylamino compounds are reported in Tables IV and V respectively.

Pharmacological Screening.—Adopting the procedure of Bülbring and Wajda[17], the local anaesthetic activity of these hydrochlorides was tested on frogs and the time of onset of anaesthesia i. e. the time for which a given concentration (0.1%) of the local anaesthetic failed to provoke withdrawal of feet is also recorded in Table V.

Pharmacological screening of these compounds

TABLE IV. PIPERAZINO-1,4-BIS(5-ACETYLAMINO-3-ARYL-2,4-THIAZOLIDINDIONES)



R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
Phenyl-	57	304	$C_{26}H_{26}N_6O_6S_2$	14.32	14.43	11.07	10.99
p-Chlorophenyl-	69	311	$C_{26}H_{24}N_6O_6S_2Cl_2$	12.81	12.90	9.94	9.83
o-Tolyl-	54	135	$C_{28}H_{30}N_6O_6S_2$	13.63	13.77	10.53	10.49
m-Tolyl-	62	174	$C_{28}H_{30}N_6O_6S_2$	13.68	13.77	10.46	10.49
p-Tolyl-	59	273	$C_{28}H_{30}N_6O_6S_2$	13.71	13.77	10.51	10.49
o-Anisyl-	71	168	$C_{28}H_{30}N_6O_8S_2$	13.00	13.08	9.86	9.97
p-Anisyl-	70	99	$C_{28}H_{30}N_6O_8S_2$	12.94	13.08	9.92	9.97
p-Rhenetyl-	58	95	$C_{30}H_{34}N_6O_8S_2$	12.45	12.54	9.63	9.55

TABIE V. HYDROCHLORIDES OF PIPERAZINO-1,4-BIS(5-ACETYLAMINO-3-ARYL-2,4-THIAZOLIDINDIONES) AND THEIR LOCAL ANAESTHETIC ACTIVITY

R	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	Onset of anaesthesis (min.) with administration of anaesthetic* in hydrochloric acid of strength 0.05 N	0.1 N	0.2 N
Phenyl-	305	$C_{26}H_{26}N_6O_6S_2 \cdot 2HCl$	12.72	12.82	22.0	23.0	23.5
p-Chlorophenyl-	313	$C_{26}H_{24}N_6O_6S_2Cl_2 \cdot 2HCl$	11.41	11.60	14.5	15.0	16.0
o-Tolyl-	145	$C_{28}H_{30}N_6O_6S_2 \cdot 2HCl$	12.17	12.30	15.0	16.5	17.5
m-Tolyl-	183	$C_{28}H_{30}N_6O_6S_2 \cdot 2HCl$	12.23	12.30	8.5	9.5	10.0
p-Tolyl-	278	$C_{28}H_{30}N_6O_6S_2 \cdot 2HCl$	12.19	12.30	11.0	12.0	12.5
o-Anisyl-	185	$C_{28}H_{30}N_6O_8S_2 \cdot 2HCl$	11.61	11.75	13.5	15.5	17.0
p-Anisyl-	168	$C_{28}H_{30}N_6O_8S_2 \cdot 2HCl$	11.68	11.75	10.5	11.5	12.0
p-Phenetyl-	162	$C_{30}H_{34}N_6O_8S_2 \cdot 2HCl$	11.22	11.31	11.5	12.0	13.0
Procaine hydrochloride**					16.0	17.0	17.5

* Concn. of anaesthetic, 0.1%

** Procaine hydrochloride was used as such.

has shown that the hydrochlorides of piperazino-1,4-bis(5-acetylamino-3-*p*-chlorophenyl-, -3-*m*-tolyl-, -3-*p*-tolyl-, -3-*p*-anisyl-, -3-*p*-phenetyl-2,4-thiazolidindiones) were the most potent local anaesthetics amongst the compounds reported, as they required less time for the onset of anaesthesia than the standard substance, procaine hydrochloride, at 0.1% concentration in 0.7% of saline solution.

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