SOME TETRA-SUBSTITUTED AMMONIUM SALTS OF THE THIAZOLE SERIES

I. B. Lundina and I. Ya. Postovskii

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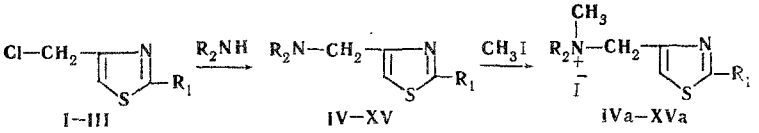
A series of monomethiodides of 2-amino(or 2-methyl- and 2-phenyl)-4-(N-cycloalkylamino)methylthiazoles are synthesized. It is shown that in these compounds the nitrogen atom of the cycloalkylamino group is quaternized.

The present paper describes thiazole derivatives containing a tetra-substituted ammonium group. Compounds of this kind are unknown, but are potentially interesting since the thiazole ring enters into the composition of some physiologically active compounds, and that compounds with ganglion blocking properties are to be numbered among tetra-substituted ammonium salts.

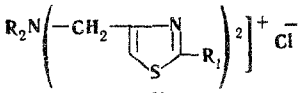
In the course of the work methiodides IVa–XVa were synthesized.



I–III IV–XV IVa–XVa

Compounds IVa–XVa were obtained by reacting bases IV–XV with methyl iodide in dry ethanol: they crystallized well, and were soluble in water.

Bases IV–XV were prepared by condensing 2-amino(methyl, phenyl)-4-chloromethylthiazoles (I–III) with cycloalkylamines (pyrrolidine, piperidine, hexamethylenimine, and morpholine). It is of interest to note that when preparing compounds IV and XII by condensation in this way, in addition to the basic reaction products, side reaction products, quaternary ammonium salts of type XVI, were obtained.



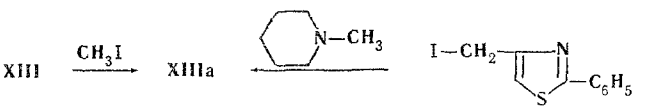
XVI

Confirmation of this structure is provided by the reaction of 2-phenyl-4-(N-pyrrolidino)methylthiazole (XIII) with 2-phenyl-4-chloromethylthiazole (III). The product is identical with the side reaction product formed by reaction of III with pyrrolidine.

When 2-amino(methyl, phenyl)-4-(N-cycloalkylamino)methylthiazoles (IV–XV) were treated with methyl iodide under the conditions used, only the monomethiodides IVa–XVa could be isolated. From this fact it could be reasoned that when compounds IV–XV react with methyl iodide it is the most basic nitrogen atom of the cycloalkylamino group which is quaternized. Experimental results confirm this view. Thermal decomposition of the quaternary base obtained by treating an aqueous solution of methiodide Va with silver oxide, led to the isolation of N-methylpiperidine, identified as its picrate.

The literature gives various melting points for N-methylpiperidine picrate, 220–222° [1–6] and 148–152° [7–10]. Our N-methylpiperdine picrate had melting point 223–224°. N-Methylpiperidine was prepared by treating piperidine with methyl iodide [11], and had boiling point 103–104° (744 mm) (105–107° [1,2]). Obviously the authors who gave the melting point of N-methylpiperidine picrate as 148–152° were dealing with piperidine picrate melting point 147–149° [1].

In the case of 2-phenyl-4-(N-piperidino)methylthiazole methiodide (XIIIa), its structure was proved by synthesis.



Treatment of 2-phenyl-4-(N-piperidino)methylthiazole (XIII) with methyl iodide, and reaction of N-methylpiperidine with 2-phenyl-4-iodomethylthiazole, gave the same quaternary ammonium salt XIIIa.

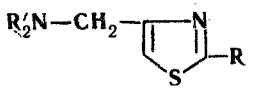
Among the compounds synthesized are the methiodides IVa–VIIa, containing besides the tetra-substituted ammonium group, an amino group at position 2 in the thiazole ring. These compounds can be acetylated at the amino group. Thus on heating the methiodide Va with acetic anhydride, the acetyl derivative XVIIa is formed. The same compound can be obtained in the reverse way, by reacting 2-actylamino-4-(N-piperidino)methylthiazole (XVII) with methyl iodide.

EXPERIMENTAL*

2-Amino-4-(N-cycloalkylamino)methylthiazoles (IV–VII). An ethanol solution of 0.1 mole 2-amino-4-chloromethylthiazole (I) hydrochloride [13] and 0.3 mole cycloalkylamine were refluxed together for 4 hr. The EtOH was vacuum-distilled off, water added to the residue, followed by hydrochloric acid until an acid reaction was obtained. After treating with active charcoal, the solution was neutralized with

*With the assistance of D. V. Kiryaeva

2-Amino(methyl,phenyl)-4-(N-cycloalkylamino)methylthiazoles (IV–XV) and their methiodies IVa–XVa)



R	R′₂N	Bases								Methiodides					
		Compound no.	Mp, °C, bp, °C (pressure, mm)	Formula	N, %		S, %		Yield, %	Compound no.	Mp, °C	Formula	S, %		Yield, %
					Found	Calculated	Found	Calculated					Found	Calculated	
NH_2	N-Pyrrolylidyl	IV	149—151	$C_8H_{13}N_3S$	22.68	22.93	17.12	17.49	42	IVa*	124—126	$C_8H_{13}N_3S \cdot CH_3I$	9.94	9.86	91
NH_2	N-Piperidyl	V	159—161 (ref. [13] 163)	$C_9H_{15}N_3S$	—	—	—	—	68	Va	196—197	$C_9H_{15}N_3S \cdot CH_3I$	9.53	9.44	83
NH_2	N-Homopiperidyl	VI	91—93	$C_{10}H_{17}N_3S$	19.30	19.88	15.00	15.17	50	VIa	144—146	$C_{10}H_{17}N_3S \cdot CH_3I$	8.88	9.07	86
NH_2	N-Morpholinyl	VII	172—173	$C_8H_{13}N_3OS$	20.89	21.09	15.89	16.09	74	VIIa	157—159	$C_8H_{13}N_3OS \cdot CH_3I$	8.99	9.38	97
CH_3	N-Pyrrolylidyl	VIII	132—135 (18)		—	—	—	—	70	VIIIa	114—117	$C_9H_{14}N_2S \cdot CH_3I$	10.28	9.89	90
		picrate	103—105	$C_9H_{14}N_2S \cdot C_6H_3N_3O_7$	17.43	17.02	8.25	7.79	—						
CH_3	N-Piperidyl	IX	140—143 (18)		—	—	—	—	67	IXa	120—122	$C_{10}H_{16}N_2S \cdot CH_3I$	9.59	9.47	80
		picrate	136—137	$C_{10}H_{16}N_2S \cdot C_6H_3N_3O_7$	15.98	16.46	7.95	7.54	—						
CH_3	N-Homopiperidyl	X	175—177 (38)		—	—	—	—	65	Xa**	117—119	$C_{11}H_{18}N_2S \cdot CH_3I$	9.31	9.09	84
		picrate	72—75	$C_{11}H_{18}N_2S \cdot C_6H_3N_3O_7$	16.07	15.93	7.45	7.28	—						
CH_3	N-Morpholinyl	XI	140—143 (12)		—	—	—	—	72	XIa	111—114	$C_9H_{14}N_2OS \cdot CH_3I$	9.52	9.41	79
		picrate	172—174	$C_9H_{14}N_2OS \cdot C_6H_3N_3O_7$	16.18	16.38	7.63	7.49	—						
C_6H_5	N-Pyrrolylidyl	XII	210—214 (26)		—	—	—	—	57	XIIa	179—181	$C_{14}H_{16}N_2S \cdot CH_3I$	8.36	8.29	87
		picrate	135—136 (ref. [17] 136)	$C_{14}H_{16}N_2S \cdot C_6H_3N_3O_7$	15.11	14.79	6.53	6.77	—						
C_6H_5	N-Piperidyl	XIII	223—226 (32)		—	—	—	—	65	XIIIa	145—148	$C_{15}H_{18}N_2S \cdot CH_3I$	7.81	8.01	85
		picrate	163—165	$C_{15}H_{18}N_2S \cdot C_6H_3N_3O_7$	13.91	14.37	6.85	6.58	—						
C_6H_5	N-Homopiperidyl	XIV	240—245 (30)		—	—	—	—	68	XIVa	124—126	$C_{16}H_{20}N_2S \cdot CH_3I$	7.95	7.74	75
		picrate	107—109	$C_{16}H_{20}N_2S \cdot C_6H_3N_3O_7$	14.36	13.97	6.88	6.39	—						
C_6H_5	N-Morpholinyl	XV	60—62	$C_{14}H_{16}N_2OS$	11.01	10.76	12.34	12.32	79	XVa***	185—186	$C_{14}H_{16}N_2OS \cdot CH_3I$	7.86	7.97	77
		picrate	169—171	$C_{14}H_{16}N_2OS \cdot C_6H_3N_3O_7$	14.72	14.31	6.59	6.55	—						

*Found: C 33.48; H 4.87; I 39.30%. Calculated for $C_8H_{13}N_3S \cdot CH_3$ I: C 33.24; H 4.96; I 39.02%.

**Found: C 41.21; H 6.36; I 36.10%. Calculated for $C_{11}H_{18}N_2S \cdot CH_3$ I: C 40.91; H 5.97; I 36.08%.

***Found: C 45.11; H 4.90; I 31.80%. Calculated for $C_{14}H_{16}NOS \cdot CH_3$ I: C 44.78; H 4.79; I 31.55%.

30% NaOH and made strongly alkaline. The precipitated product was filtered off, and recrystallized: IV ex acetone, V, VII ex EtOH, VI ex petrol ether.

In preparing 2-amino-4-(N-pyrrolidino)methylthiazole (IV), after IV had been filtered off, the mother liquors deposited on standing a by-product XVI (R_1=NH_2, R_2N=N-pyrrolidyl). Colorless prisms ex water, mp over 300°, yield 20%, based on the starting 2-amino-4-chloromethylthiazole (I) hydrochloride. Found: Cl 10.43; S 18.92%. Calculated for $C_{12}H_{18}ClN_5S_2$: Cl 10.71; S 19.31%.

2-Methyl-4-(N-cycloalkylamino)methylthiazoles (VIII–XI). Prepared as described for IV–VII, from 2-methyl-4-chloromethylthiazole (II) hydrochloride [14,15] and the cycloalkylamine. Products VIII–XI, which separated as oils, were extracted with ether. After drying over KOH the ether was distilled off, and bases VIII–IX were vacuum-distilled and analyzed as their picrates.

2-Phenyl-4-(N-cycloalkylamino)methylthiazoles (XII–XV). These were prepared as described for IV–XI, from 2-phenyl-4-chloromethylthiazole (III) [16] (0.1 mole) and the cycloalkylamine (0.2 mole).

N,N-Di(4-methylene-2-phenylthiazole)pyrrolidinium chloride (XVI, R_1=C_6H_5, R_2N=N-pyrrolidyl). a) When preparing 2-phenyl-4-(N-pyrrolidino)methylthiazoles (XII), making the acid solution alkaline gave, instead of basic product XII, a side-reaction product XVI (R_1=C_6H_5; R_2N=N-pyrrolidyl). After extracting XII with ether, the by-product was filtered off. Colorless plates (ex water), mp 105–108°; it crystallized with 1 molecule of water. Found: Cl 7.32; S 13.06%. Calculated for $C_{24}H_{24}ClN_3S_2 \cdot H_2O$: Cl 7.53; S 13.57%.

b) A solution of equimolecular amounts of XII and III in dry EtOH solution was refluxed for 1 hr 30 min., the EtOH completely distilled off, and the syrupy residue treated with dry ether. The product which crystallized was filtered off, mp 178–180°, yield 70%. Found: Cl 8.50; S 14.13% Calculated for $C_{24}H_{24}ClN_3S_2$: Cl 7.83; S 14.11. Recrystallization from water gave colorless plates of the hydrate mp 105–108°. Mixed up with the product prepared by method *a* undepressed.

2-Amino(methyl, phenyl)-4-(N-cycloalkylamino) methylthiazole methiodides (IVa–XVa). A dry EtOH solution of equimolecular amounts of 2-amino(methyl, phenyl)-4-(N-cycloalkylamino)methylthiazole (IV–XV) and methyl iodide was refluxed for 1–2 hr. If the methiodide did not separate on cooling, the EtOH was completely distilled off, and the residue treated with dry ether. The precipitate formed was filtered off, and recrystallized: methiodides IVa–VIIa and XIIa–XVa ex dry EtOH; VIIIA, IXa, and XIa ex dry EtOH + dry ether; Xa ex BuOH.

Reaction of 2-phenyl-4-iodomethylthiazole with N-methylpiperidine. A solution of 0.5 g 2-phenyl-4-iodomethylthiazole [18] and 0.18 g N-methylpiperidine in 3 m*l* dry EtOH was refluxed for 3 hr. The reaction product which separated on cooling was filtered off, colorless prisms mp 145–147°, yield 0.5 g (76%), undepressed mixed mp with XIIIa prepared by treating base XIII with methyl iodide.

Reaction of 2-amino-4-(N-piperidino)methylthiazole methiodide (Va) with silver oxide, and pyrolysis of the resultant quaternary bases. An aqueous solution of 1 g methiodide Va was stirred and moist Ag_2O (ex 1 g $AgNO_3$) added. After standing for 1/2 hr the solid was filtered off, and the solution heated to boiling and distilled. Addition of picric acid solution to the aqueous distillate gave a picrate, plates (ex EtOH), mp 223–224° (222° [1–6]), yield 25%. Found: N 17.30%. Calculated for $C_6H_{13}N \cdot C_6H_3N_3O_7$: N 17.07%. Undepressed mixed mp with N-methylpiperidine picrate: N-methylpiperidine prepared from equimolecular amounts of piperidine and methyl iodide [11].

2-Acetylamino-4-(N-piperidino)methylthiazole (XVII). 1 g 2-amino-4-(N-piperidino)methylthiazole (V) and 2 m*l* Ac_2O were heated together for 1 hr on a water bath, the products cooled, 6 m*l* water added, and then they were neutralized with a saturated Na_2CO_3 solution. The precipitate was filtered off, colorless needles (ex water), mp 118–120°, yield 0.8 g (66%). Found: N 17.49%; S 13.08%. Calculated for $C_{11}H_{17}N_3OS$: N 17.57; S 13.39%.

2-Acetylamino-4-(N-piperidino)methylthiazole methiodide (XVIIa). a) 0.6 g 2-acetylamino-4-(N-piperidino)methylthiazole (XVII), 0.2 m*l* MeI, and 2 m*l* dry EtOH were refluxed together for 2 hr. The solid reaction product which separated on cooling was filtered off, colorless prisms (ex dry EtOH), mp 220–222°, yield 0.77 g (80%). Found: S 8.53%. Calculated for $C_{11}H_{17}N_3OS \cdot CH_3I$: S 8.40%.

b) 0.5 g 2-amino-4-(N-piperidino)methylthiazole methiodide (va) and 1 m*l* Ac_2O were heated together on a water bath for 1 hr. The product which separated on cooling was filtered off, colorless prisms (ex dry EtOH), mp 218–220°, yield 0.33 g (59%). Found S 8.49%. Calculated for $C_{11}H_{17}N_3OS \cdot CH_3I$: S 8.40%. The compounds prepared by the two methods *a* and b were shown to be spectroscopically identical.

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Kirov Urals Polytechnic Institute, Sverdlovsk