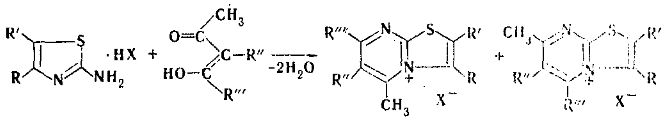
CONDENSATION OF 2-AMINOTHIAZOLE AND 2-AMINOBENZOTHIAZOLE SALTS WITH β-KETO ALDEHYDES AND UNSYMMETRICAL β-DIKETONES

S. I. Shul'ga and V. A. Chuiguk

UDC 547.789.6'859.3 : 542.953

2-Aminothiazole and 2-aminobenzothiazole salts react with benzoylacetone, propionylacetone, 1-ethoxyacetylacetone, and 2-formylcyclohexanone to form the corresponding thiazolo[3,2-*a*]pyrimidinium salts. Mixtures of isomers, the structures and ratios of which were established by means of the PMR spectra, are formed in most cases.

In one of our previous communications [1], we demonstrated that 2-aminothiazole salts react with unsymmetrical β-diketones to form thiazolo[3,2-*a*]pyrimidinium salts A and B.



A B

In the present paper, we have extended the investigation of this reaction to substituted 2-aminothiazoles and 2-aminobenzothiazoles.

As a rule, mixtures of isomeric compounds A and B are formed as a result of the reaction, although only one isomer was detected in the crude product in individual cases. A tendency for the formation of predominantly an isomer of the B type is observed for acetyl ketones in the condensation with 2-aminobenzothiazole salts, while the reverse ratio is generally observed in the reaction with 2-aminothiazole salts. The direction of the reaction is apparently determined by both steric factors and the basicity of the corresponding aminothiazole. The pure thiazolopyrimidinium salts (I and II) are presented in Table 1.

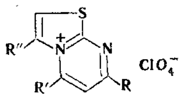
The structure of the reaction products was determined from their PMR spectra. Thus two signals of methyl groups at 2.56 and 1.72 ppm are observed in the PMR spectrum of the product of condensation of 2-amino-4-methylthiazole with benzoylacetone, and the signal of the phenyl group is unsplit. From a comparison with the PMR spectra of model compounds [1, 2], it can be concluded that the phenyl group is in the α position relative to the bridge nitrogen atom (it would give a split signal in the γ position [4]). In addition, it shields the thiazole methyl group, moving its chemical shift from ~2.70 to 1.72 ppm; the 2.56 ppm value is in the region of chemical shifts characteristic for a γ-methyl group. Thus the product is pure isomer I (Table 1).

The signal of the methyl group in the PMR spectra of the condensation products of 4-aryl-substituted 2-aminothiazole salts is observed at 2.0-2.1 ppm, which is characteristic for a methyl group in the pyrimidine ring in the α position relative to the bridge nitrogen atom, shielded by an aryl group bonded to the thiazole ring [2].

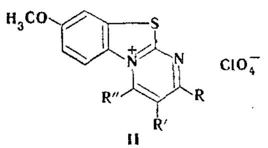
The structures of the condensation products in a number of benzothiazole derivatives were determined chiefly from the chemical shift of the methyl groups: δ_{CH_3} for the α position is found at 2.9-3.1

Kiev Technologic Institute of the Food Industry. T. G. Shevchenko Kiev State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 637-640, May, 1972. Original article submitted January 21, 1971.

TABLE 1.



I



II

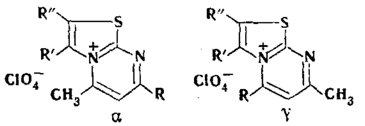
Compound	R	R′	R″	Mp, °C	Empirical formula	Found, %		Calc., %		PMR: pyrimidine δCH$_3$ ppm	Yield, %*
						S	N	S	N		
Ia	CH_3	C_6H_5	CH_3	225—226	$C_{14}H_{13}ClN_2O_4S$	9,31	7,89	9,40	8,21	2,56	35
Ib	C_6H_5	CH_3	p-BrC_6H_4	300	$C_{19}H_{14}BrClN_2O_4S$	6,71	—	6,65	—	2,12	16
Ic	C_2H_5	CH_3	C_6H_5	263	$C_{15}H_{15}JN_2S$†	8,52	7,35	8,41	7,32	2,04	17
Id	$CH_2OC_2H_5$	CH_3	p-$OCH_3C_6H_4$	185—186	$C_{17}H_{19}ClN_2O_6S$	7,88	—	7,71	—	2,13	14
IIa	CH_3	H	C_6H_5	251—252	$C_{18}H_{15}ClN_2O_5S$	7,83	—	7,88	—	2,59	57
IIb	CH_3	H	C_2H_5	256,5—257	$C_{14}H_{15}ClN_2O_5S$	9,66	7,48	8,93	7,77	2,52	14
IIc	C_2H_5	H	CH_3	289—290 (dec.)	$C_{14}H_{15}ClN_2O_5S$	9,13	7,52	8,93	7,77	2,92	2
IId	CH_3	H	$CH_2OC_2H_5$	235 (dec.)	$C_{15}H_{17}ClN_2O_6S$	8,36	—	8,24	—	2,57	36
IIe	H	H	$CH{=}C(CH_3)_2$	248—249 (dec.)	$C_{15}H_{15}ClN_2O_5S$	8,86	—	8,64	—	—	46
IIf	—$(CH_2)_4$—		H	239 (dec.)	$C_{15}H_{15}ClN_2O_5S$	8,69	7,69	8,64	7,55	—	70

---

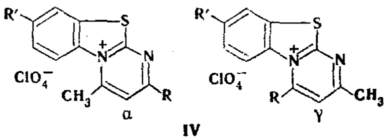
* Calculated on the basis of one isomer isolated as a result of fractional recrystallization.

† Iodide.

TABLE 2



III



IV

Mixture	R	R′	R″	Mp, °C*	Empirical formula	S, %		PMR, δ, ppm		Isomer ratio, α : γ	Yield, %
						found	calc.	α-CH$_3$	γ-CH$_3$		
IIIa	C_2H_5	CH_3	H	213	$C_{10}H_{13}ClN_2O_4S$	11,02	10,95	2,87	2,49	1 : 1,7	75
IIIb	C_2H_5	p-$OCH_3C_6H_4$	H	230	$C_{16}H_{17}ClN_2O_5S$	8,38	8,33	2,02	2,47	1 : 1	63
IIIc	C_2H_5	p-$CH_3C_6H_4$	H	253	$C_{16}H_{17}ClN_2O_4S$	8,67 8,70	8,69	2,04	2,52	1,4 : 1	61
IIId	C_2H_5	p-BrC_6H_4	H	300	$C_{15}H_{14}BrClN_2O_4S$	7,36	7,39	2,03	2,47	2 : 1	73
IIIe	$CH_2OC_2H_5$	C_6H_5	H	200,5—201	$C_{16}H_{17}ClN_2O_5S$	8,19	8,33	2,37	2,55	3 : 1	72
IIIf	$CH_2OC_2H_5$	CH_3	CH_3	188 (dec.)	$C_{12}H_{17}JN_2OS$ †	8,92	8,80	2,97	2,53	3 : 1	34
IVa	C_6H_5	Br	—	242—243	$C_{17}H_{12}BrClN_2O_4S$	7,02	7,03	3,07	2,58	1 : 2,5	47
IVb	C_2H_5	CH_3	—	238—239	$C_{14}H_{15}ClN_2O_4S$	9,88 9,70	9,35	3,03	2,55	1 : 4	50
IVc	C_2H_5	Br	—	273 (dec.)	$C_{13}H_{12}BrClN_2O_4S$	7,93 8,04	7,96	3,01	2,55	1 : 4	57

---

* The melting points of the isomer mixtures, which are not constants of the individual substances, nevertheless convey some information.

† Iodide.

ppm as compared with 2.5-2.6 ppm for the γ position. The mixture of isomeric salts formed in the reaction of 2-amino-6-methoxybenzothiazole perchlorate (V) with propionylacetone was separated into pure components; the chemical shift of the α-methyl group in one isomer (IIc) was 2.92 ppm, while that of the γ-methyl group in the other isomer (IIb) was 2.52 ppm. Compound V reacts with 2-formylcyclohexanone to give IIf. The selection of the structure was made on the basis of the PMR spectrum, in which the center of the signal of the least shielded methylene group is at 2.82 ppm; this signal should have been expected at 3.5 ppm [1] for the isomeric product.

The enol of formylmesityl oxide reacts with V to give IIe, the structure of which was established on the basis of the PMR spectrum, in which the spin–spin coupling constant of the pyrimidinium protons is 5 Hz, which is characteristic for $J_{H\gamma H\beta}$ in analogous pyrimidinium compounds, in contrast to $J_{H\alpha H\beta}$, which is 7 Hz [2, 3].

The product of the condensation of 2-amino-4,5,6,7-tetrahydrobenzothiazole with propionylacetone is a mixture of isomers (after one recrystallization) of the A and B types [R'' = H, R''' = C_2H_5, R' — R = $(CH_2)_4$—] in a ratio of 4:1. The isomer of the A type was isolated in pure form by fractional recrystallization.

By recording the spectrum of the reaction product, which is a mixture of two isomers, one can readily establish the isomer ratio in the mixture using the integral intensities of the α- and γ-methyl groups.

The mixtures of isomeric salts that were isolated in analytically pure form (after one recrystallization from methanol) are presented in Table 2.

EXPERIMENTAL

The PMR spectra of trifluoroacetic acid solutions were recorded with a Varian A-60A spectrometer. The chemical shifts are presented on the δ scale with respect to hexamethyldisiloxane (HMDS).

Condensation of 2-Aminothiazole and 2-Aminobenzothiazole Salts with Unsymmetrical β-Diketones. The appropriate β-diketone (10-20% excess) was added to a hot alcohol solution of 0.015 mole of the perchlorate of the corresponding 2-aminothiazole or 2-aminobenzothiazole, and the resulting solution was refluxed for 2-4 h and cooled. The precipitate was separated, washed with alcohol and ether, and recrystallized from methanol.

2-Methyl-4-ethoxymethylpyrimido[2,1-b]benzothiazolium Perchlorate. This compound was obtained from 2.5 g (0.01 mole) of 2-aminobenzothiazole perchlorate and 3 ml (0.023 mole) of 1-ethoxyacetylacetone. The yield of the mixture of isomers [α-IVd ($R=CH_2OC_2H_5$, R'=H) and γ-IVe ($R=CH_2OC_2H_5$, R'=H)] was 2.57 g (72%) in a ratio of 1:16 (after one recrystallization). Fractional recrystallization gave 0.2 g (5.5%) of IVe with mp 218-219°. PMR spectrum: $\delta_{CH_3}=2.6$ ppm. Found: N 7.79; S 8.94%. $C_{14}H_{15}ClN_2O_5S$. Calculated: N 7.81; S 8.93%.

4-Methyl-2-ethyl-6,7,8,9-tetrahydropyrimido[2,1-b]benzothiazolium Perchlorate. This compound was obtained from 1.5 g (0.01 mole) of 2-amino-4,5,6,7-tetrahydrobenzothiazole perchlorate and 2 ml (0.015 mole) of propionylacetone. The yield of the mixture of isomers [α-IIIg ($R=C_2H_5$, $R'-R''=-(CH_2)_4-$) and γ-IIIh ($R=C_2H_5$, $R'-R''=-(CH_2)_4-$] was 1.93 g (58%) in a ratio of 4:1. Fractional recrystallization gave 0.1 g (3%) of IIIg with mp 239-240°. PMR spectrum: $\delta_{CH_3}=2.82$ ppm. Found: N 8.35; S 9.64%. $C_{13}H_{17}ClN_2O_4S$. Calculated: N 8.41; S 9.63%.

LITERATURE CITED

1. S. I. Shul'ga and V. A. Chuiguk, Ukr. Khim. Zh., 37, 350 (1971).
2. S. I. Shul'ga and V. A. Chuiguk, Khim. Geterotsikl. Soedin., 632 (1972).
3. L. W. Werbel, A. Curry, E. F. Elslager, C. A. Hess, M. P. Hutt, and C. Gongstron, J. Heterocycl. Chem., 6, 787 (1969).
4. A. Le Berre and C. Renault, Bull. Soc. Chim. France, 3139 (1969).