CONDENSATION OF 2-AMINOTHIAZOLES AND 2-AMINOBENZOTHIAZOLES AND THEIR SALTS WITH β-CHLOROVINYL KETONES

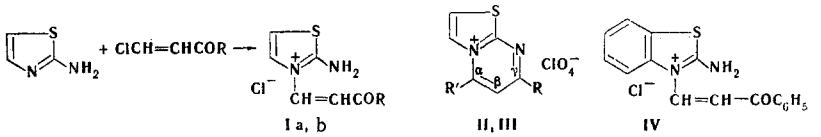
S. I. Shul'ga and V. A. Chuiguk

UDC 547.789.6'859.3:542.953

2-Aminothiazoles and 2-aminobenzothiazoles react with β-chlorovinyl ketones in the presence of acid in two directions to form isomeric thiazolo[3,2-*a*]pyrimidinium compounds. In the absence of acid, the aminothiazole is alkylated only at the cyclic nitrogen atom without closing of the pyrimidine ring. The PMR spectra were used to establish the structures of the reaction products and to determine the ratios of isomers formed.

It has been demonstrated [1] that 2-aminothiazoles, 2-aminobenzothiazoles, and 2-aminonaphtho[2,1-d]thiazole with methyl β-chlorovinyl ketone (XI) in the presence of perchloric acid form a mixture of isomeric thiazolo[3,2-*a*]pyrimidinium salts. This sort of reaction was first described in [2] for 2-aminopyridine and 2-aminopyrimidine, and only one isomer was isolated in each case.

The reaction was studied in greater detail in the present paper. It was established that the β-chlorovinyl ketone in alcohol solution in the absence of acid alkylates aminothiazole at the cyclic nitrogen atom; salt Ia is cyclized under the influence of acid to thiazolo[3,2-*a*]pyrimidinium salt II, which differs from the isomeric salt III previously isolated in [1].



Ia $R=CH_3$; Ib $R=C_6H_5$; II $R=CH_3$, $R'=H$; III $R=H$, $R'=CH_3$

The structure of I was confirmed by the IR spectrum, but the chief proof is cyclization to II. The magnitude of the chemical shift of the methyl group (2.55 ppm) and the spin–spin coupling constant of the pyrimidinium protons ($J_{H\alpha H\beta}=7$ Hz) [3] correspond to a methyl group in the γ position relative to the bridge nitrogen atom [1].

For III, $\delta_{CH_3}=2.76$ ppm, while the spin–spin coupling constant of the pyrimidinium protons is 5 Hz. In the thiazolo[3,2-*a*]pyrimidinium salt and other similar condensed pyrimidinium salts, $J_{H\alpha H\beta}$ and $J_{H\gamma H\beta}$ are always constant and are 7 and 5 Hz, respectively.

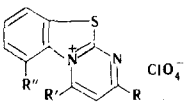
Salt IV was obtained from benzothiazole and phenyl β-chlorovinyl ketone (XII), but the reaction product obtained with methyl β-chlorovinyl ketone is a dye, the structure of which has not yet been established.

Thus β-chlorovinyl ketones initially alkylate aminothiazoles at the cyclic nitrogen atom, and cyclization to a pyrimidinium salt with a substituent in the γ position relative to the bridge nitrogen atom then occurs under the influence of acid.

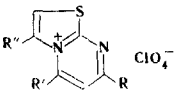
The scheme can also be taken for the reaction in acidic media, with the difference that alkylation will occur at both the cyclic and exocyclic nitrogen atoms, and the ensuing cyclization will lead to two iso-

Kiev Technologic Institute of the Food Industry. T. G. Shevchenko Kiev State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 632-636, May, 1972. Original article submitted January 21, 1971.

meric thiazolopyrimidinium salts. The direction of alkylation depends on the temperature, steric factors, and the nature of the β-chlorovinyl ketone. Thus 2-aminobenzothiazide reacts with XI in the presence of perchloric acid to give a mixture of pyrimido[2,1-b]benzothiazolium salts V and VI in a ratio of 1:2 in the cold and in a ratio of 2:1 on heating. The effect of steric factors is manifested in the reaction of 2-amino-4-methoxybenzothiazole with XI in acidic media: one pyrimido[2,1-b]benzothiazolium salt – VII, in which the methyl group is in the γ position relative to the bridge nitrogen atom – is formed.



V–VII



VIII–X

V R=R″=H, R′=CH$_3$; VI R=CH$_3$, R′=R″=H, VII R=CH$_3$, R′=H, R″=OCH$_3$;

VIII R=H, R′=CH$_3$, R″=C$_6$H$_5$, IX R=CH$_3$, R′=H, R″=C$_6$H$_5$; X R=H, R′=C$_6$H$_5$, R″=CH$_3$

As a rule, XI reacts with 2-aminothiazoles in acidic media to give primarily α-methyl-substituted salts, and the isomer ratio is reversed in the benzothiazole series; the yield of condensation products (in the form of a mixture of isomers) is 45–98%.

α-Phenyl-substituted pyrimidinium salts are obtained in both series in 20–70% yields with XII.

In some cases, the mixtures of isomeric salts were separated by fractional recrystallization; in others only one isomer (generally the α-substituted compound) was isolated in pure form. Several products were obtained only as mixtures. The pure thiazolo[3,2-*a*]pyrimidinium and pyrimido[2,1-b]benzothiazolium salts are presented in Table 1.

The chief method of proof of the structures of the products was PMR spectroscopy. Other characteristics of the PMR spectra in addition to the characteristic magnitude of the chemical shift and the spin–spin coupling constant of the pyrimidine protons were used. Thus the shielding of the methyl group by the phenyl group was utilized; for example, in VIII, in contrast to IX, the methyl group is shielded by a phenyl group, and its chemical shift is 2.12 ppm (instead of 2.7–2.9 ppm when the phenyl group is absent [1]). In IX, δ_{CH_3} has the value characteristic for the γ position (2.60 ppm). Similar shielding is observed in X, the isomer of VIII: δ_{CH_3} is 1.78 ppm instead of the usual 2.70–2.75 ppm.

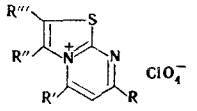
We also used the character of the signal of the protons of the phenyl group bonded to the pyrimidine ring. It is known [4] that a phenyl group in the α position relative to a tertiary disubstituted nitrogen atom appears in the PMR spectrum as two groups of peaks with an intensity ratio of two (at weak field) to three (at strong field). In our case, the phenyl group in the α position relative to the bridge nitrogen atom should give one unsplit peak, while a phenyl group in the γ position should give two groups of peaks with an intensity ratio of 2:3. As we have already stated, only α-phenyl-substituted compounds were isolated from the reaction with phenyl β-chlorovinyl ketone, and the phenyl group always appears as an unsplit peak in the PMR spectra of these products.

The factors of the PMR spectra enumerated above often act jointly, and this provides a complete guarantee of the correctness of the selected structure. Thus the methyl group in the PMR spectrum of X is shielded by the phenyl group, as demonstrated above; the phenyl protons give one unsplit peak, and the spin–spin coupling constant of the pyrimidine protons is 5 Hz. All of the data make it possible to accurately determine the position of the phenyl group as being the α position relative to the bridge nitrogen atom.

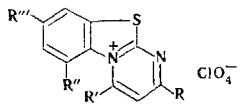
The ratio of the isomers in the crude products of the condensation with XI was determined from the integral intensities of the methyl groups in the α and γ positions of the pyrimidine ring. Neither the starting salt nor any side products give signals in the region of the absorption of these methyl groups; the composition of an artificial mixture of the isomers, which was determined from the PMR spectrum, was in agreement with their weight ratio.

The products of the condensation with XI – quaternary salts with methyl groups in the α and γ positions relative to the bridge nitrogen atom – give polymethine dyes in the usual manner; this test serves as a qualitative indication of the occurrence of the condensation reaction.

TABLE 1. Thiazolo[3,2-*a*]pyrimidinium (A) and Pyrimido[2,1-b]benzothiazolium (B) Salts



A



B

Formula	Compound	R	R′	R″	R‴	Mp, °C	Empirical formula	Found, %		Calc., %		Yield, %*
								S	N	S	N	
A	II	CH_3	H	H	H	177—178	$C_7H_7ClN_2O_4S$	12,75	—	12,78	—	6
	III	H	CH_3	H	H	213	$C_7H_7ClN_2O_4S$†	12,47	11,16	12,78	11,17	36
	XIX	H	CH_3	CH_3	H	248—249	$C_8H_9ClN_2O_4S$	11,99	10,56	12,11	10,58	90
	IX	CH_3	H	C_6H_5	H	232—233	$C_{13}H_{11}ClN_2O_4S$	9,54	8,71	9,81	8,54	9
	VIII	H	CH_3	C_6H_5	H	246—247	$C_{13}H_{11}ClN_2O_4S$†	10,06	8,45	9,81	8,54	44
A	XX	H	CH_3	p-$CH_3C_6H_4$	H	256	$C_{14}H_{13}ClN_2O_4S$	9,33	8,00	9,41	8,22	12
	XIII	CH_3	H	p-$CH_3C_6H_4$	H	238—240	$C_{14}H_{13}ClN_2O_4S$‡	—	—	—	—	16
	XIV	H	CH_3	CH_3	CH_3	243—244	$C_9H_{11}ClN_2O_4S$	11,18	9,92	11,50	10,05	13
	XV	H	C_6H_5	H	H	166	$C_{12}H_9ClN_2O_4S$	10,15 10,19	8,99 9,00	10,25	8,96	74
	X	H	C_6H_5	CH_3	H	212—213	$C_{13}H_{11}ClN_2O_4S$	9,99	8,03	9,81	8,54	18
B	VII	CH_3	H	OCH_3	H	225—226	$C_{12}H_{11}ClN_2O_4S$	9,59	—	9,69	—	45
	XVI	H	C_6H_5	H	H	278—279	$C_{16}H_{11}ClN_2O_4S$	8,94	—	8,83	—	17
	XVII	H	C_6H_5	H	OCH_3	273—274	$C_{17}H_{13}ClN_2O_4S$	8,09	7,17	8,16	7,13	17
	XVIII	H	C_6H_5	H	NO_2	305	$C_{16}H_{10}ClN_3O_6S$	7,88	10,42	7,86	10,31	19

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

† The synthesis was described in [1].

‡ The purity and individuality were determined from the PMR spectrum.

EXPERIMENTAL

The IR spectra of KBr pellets were recorded with a UR-10 spectrometer. The PMR spectra of trifluoroacetic acid solutions were determined with a Varian A-60A spectrometer. The chemical shifts are presented on the δ scale with respect to hexamethyldisiloxane (HMDS).

2-Amino-3-(1-buten-3-on-1-yl)thiazolium Chloride (Ia). A mixture of 2 g (0.02 mole) of 2-aminothiazole, 3 ml (0.029 mole) of XI, and 3 ml of methanol was allowed to stand at room temperature. After 30-40 min, the reaction product was isolated. The precipitate was separated and washed with alcohol and ether to give 2.15 g (52%) of a product with mp 183.5° (methanol). IR spectrum, cm^{-1}: ν_{NH_2} 3300; $\nu^{+}_{NH_2}$ 2500-3180; $\nu_{C=O\ conj.}$ 1700; $\nu_{C=O}$ and $\nu_{C=N}$ 1640-1670; $\nu_{-CH=CH-trans}$ 960. Found: N 13.78; S 15.67%. $C_7H_9ClN_2OS$. Calculated: N 13.68; S 15.66%.

2-Amino-3-(3-phenyl-1-propen-3-on-1-yl)thiazolium Chloride (Ib). This compound was similarly obtained in 79% yield and had mp 197.5° (methanol). IR spectrum, cm^{-1}: ν_{NH_2} 3275; $\nu^{+}_{NH_2}$ 2350-3200; $\nu_{C=O}$ 1680; $\nu_{-CH-trans}$ 948. Found: N 10.53; S 11.75%. $C_{12}H_{11}ClN_2OS$. Calculated: N 10.50; S 12.02%.

2-Amino-3-(3-phenyl-1-propen-3-on-1-yl)benzothiazolium Chloride (IV). This compound was similarly obtained in 25% yield and had mp 251°. IR spectrum, cm^{-1}: ν_{NH_2} 2750-3100; $\nu_{C=O}$ 1679; $\nu_{-CH=CH-trans}$ 965. Found: S 10.02%. $C_{16}H_{13}ClN_2OS$. Calculated: S 10.01%.

7-Methylthiazolo[3,2-*a*]pyrimidinium Perchlorate (II). A mixture of 2 g (9.6 mmole) of Ia and 4 ml of trifluoroacetic acid was refluxed on a water bath for 1 h. The mixture was allowed to stand for 2 days, and the cyclization product was precipitated by the addition of ether to give 1.65 g (91%) of the chloride. The chloride was converted to the perchlorate (mp 177-178°) by means of $NaClO_4$. This product did not depress the melting point of II isolated from the mixture of isomers [1] but did depress the melting point of III.

Condensation of 2-aminothiazoles and 2-Aminobenzothiazoles with Methyl and Phenyl β-Chlorovinyl Ketones. The condensation was carried out by the method in [2] with the introduction of several changes. A mixture of an alcohol solution of 0.02 mole of the appropriate 2-aminothiazole or 2-aminobenzothiazole, 0.035 mole of XI or XII, and 4 ml of 57% perchloric acid was warmed slightly on a water bath until spontaneous heating of the mixture commenced. The precipitated reaction product was separated after 1.5-2 h, washed with alcohol and ether, and recrystallized from methanol.

Reaction of 2-Amino-4-(p-methoxyphenyl)thiazole with Methyl β-Chlorovinyl Ketone. This reaction was carried out similarly with 1.01 g (0.005 mole) of 2-amino-4-(p-methoxyphenyl)thiazole and 2 ml (0.019 mole) of XI to give 1.3 g (73%) of product. One recrystallization from methanol gave a mixture of isomers A ($R=R'''=H$, $R'=CH_3$, $R''=p\text{-}OCH_3C_6H_4$) and A ($R=CH_3$, $R'=R'''=H$, $R''=p\text{-}OCH_3C_6H_4$) in a ratio of 1:5 (from the intensity of the methyl groups at 2.57 and 2.13 ppm) with mp 246-247°. Found: N 8.02; S 8.82%. $C_{14}H_{13}ClN_2O_5S$. Calculated: N 7.82; S 8.98%.

Reaction of 2-Amino-6-methoxybenzothiazole with Methyl β-Chlorovinyl Ketone. The reaction was carried out similarly with 1.8 g (0.01 mole) of 2-amino-6-methoxybenzothiazole and 2.5 ml (0.024 mole) of XI to give 0.7 g (21%) of product. Three recrystallizations from methanol gave a mixture of isomers B ($R=R''=H$, $R'=CH_3$, $R'''=OCH_3$) and B ($R=CH_3$, $R'=R''=H$, $R'''=OCH_3$) in a ratio of 1:2 (from the intensity of the methyl groups at 2.60 and 3.08 ppm) with mp 210-212°. Found: S 9.75%. $C_{12}H_{11}ClN_2O_5S$. Calculated: S 9.69%.

Reaction of 2-Amino-6-methylbenzothiazole with Methyl β-Chlorovinyl Ketone. The reaction was carried out similarly with 1.6 g (0.01 mole) of 2-amino-6-methylbenzothiazole and 2.5 ml (0.024 mole) of XI to give 1.6 g (51%) of product. One recrystallization from methanol gave a mixture of isomers B ($R=R''=H$, $R'=R'''=CH_3$) and B ($R=R'''=CH_3$, $R'=R''=H$) in a ratio of 4:1 (from the intensity of the methyl groups at 2.62 and 3.12 ppm) with mp 234-236°. Found: S 10.10%. $C_{12}H_{11}ClN_2O_4S$. Calculated: S 10.18%.

Reaction of 2-Amino-6-nitrobenzothiazole with Methyl β-Chlorovinyl Ketone. The reaction was carried out similarly with 1.9 g (0.01 mole) of 2-amino-6-nitrobenzothiazole and 2.5 ml (0.024 mole) of XI to give 1.3 g (38%) of product. Two recrystallization from methanol gave a mixture of isomers B ($R'=R''=H$, $R=CH_3$, $R'''=NO_2$) and B ($R=R''=H$, $R'=CH_3$, $R'''=NO_2$) in a ratio of 3.7:1 (from the intensity of the methyl groups at 2.67 and 3.18 ppm) with mp 212-213°. Found: S 9.33%. $C_{11}H_8ClN_3O_6S$. Calculated: S 9.27%.

LITERATURE CITED

1. S. I. Shul'ga and V. A. Chuiguk, Ukr. Khim. Zh., 37, 257 (1971).
2. A. I. Nesmeyanov and M. I. Rybinskaya, Dokl. Akad. Nauk SSSR, 118, 297 (1958).
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).