INVESTIGATIONS ON ACYL ISOCYANATES AND THEIR DERIVATIVES

VII.* ACTION OF THIOUREA ON α-HALOGENOACYL CARBAMATES AND THE SYNTHESIS OF SOME 2-IMINOTHIAZOLIDIN-4-ONES

K. A. Nuridzhanyan and G. V. Kuznetsova

UDC 547.789.3

The reaction of thiourea with α-halogenoacyl carbamates has given the corresponding isothiouronium salts (stable in the case of the α-propionyl compound), which readily form 2-iminothiazolidin-4-one derivatives in the presence of moisture or alkalis.

In a search for new pesticides among acyl isocyanate derivatives, it appeared of interest to synthesize α-isothiouronium-containing acyl carbamates. For this purpose, in the present work we have studied the reaction of the α-halogenoacyl carbamates I-IV with the ureas V-VII and have shown that the nature of the final products of this reaction depends fundamentally on the nature of the α substituent (R = H or CH_3) in the initial I-IV and on the reaction conditions.

Unlike α-chloroacetamide [2] or chloromethylaryloxy carboxylic acids [3], with the thioureas V-VII in boiling 99.5% ethanol or in acetone (i.e., in the presence of even traces of water) at −4°C the chloroacetyl carbamates I and II (R = H, R" = CH_3, C_6H_4) give, instead of the expected isothiouronium salts, the corresponding 2-iminothiazolidinone salts VIII-X (Table 1), which are readily converted into the free bases in boiling water or in aqueous sodium acetate.

Conversely, the α-halogenopropionylcarbamates III and IV (R = R" = CH_3) do not undergo cyclization on being boiled in 99.5% ethanol with thiourea under similar conditions but form the corresponding isothiouronium salts XII and XIII (Table 2). These salts are stable in boiling water, but on treatment with sodium acetate are converted into 2-imino-5-methylthiazolidin-4-one (XI).

Isothiouronium salts could be obtained from the halogenoacetylcarbamates I and II only by carrying out the reaction in anhydrous acetone at room temperature. On heating in anhydrous acetone or at room temperature in perfectly anhydrous ethanol, only cyclization products are formed. Thus, under these conditions, compounds I and V gave 2-imino-4-methoxycarbonyliminothiazolidine (XVIII). On being heated in 99.5% ethanol, the isothiouronium derivatives of the halogenoacyl carbamates XIV-XVII (Table 2) form salts of the 2-iminothiazolidinones VIII-X (Table 1), and on being heated in water they form the free bases.

The results given permit the assumption that in the reaction of the thioureas V-VII with the α-halogenoacylcarbamates I-IV, as with α-halogeno ketones [4,5], in all cases the isothiouronium salts XII-XVII are formed first and then these undergo further conversion into XIX with an ease depending on whether there is a hydrogen atom or a CH_3 group in the α position. The extremely unstable compound XIX then splits out water (more readily in ethanol than in acetone) and is converted into the more stable XVIII which, however, hydrolyzes under the action of water to give VIII-X.

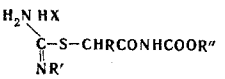
*For Communication VI, see [1].

All-Union Scientific-Research Institute for Chemical Plant Protecting Agents, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 6, No. 7, pp. 908-912, July, 1970. Original article submitted December 23, 1968.

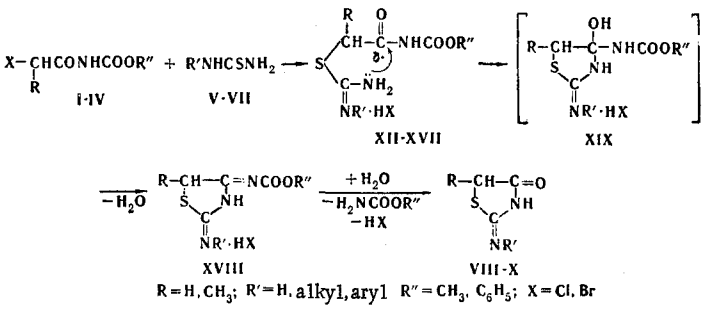
TABLE 1

Compound	Name	mp, °C	Empirical formula	Element	Found %	Calc. %	Yield, %
VIII	2-Iminothiazolidin-4-one hydrochloride	190—240 (decomp.)	$C_3H_4N_2OS \cdot HCl$	C	23,60 23,31	23,60	90
				H	3,21 3,47	3,28	
				Cl	23,13 22,98	23,26	
				N	18,47 18,70	18,36	
				S	20,50 20,30	20,95	
	Base	250[12]	—		—	—	95
IX	2-Phenyliminothiazolidin-4-one hydrochloride	200 (decomp.)	$C_9H_8N_2OS \cdot HCl$	S	13,92 13,96	14,00	65
	Base	175—176 (decomp., from water)	$C_9H_8N_2OS$	C	56,23 56,20	56,25	95
				H	3,90 4,25	4,17	
				S	16,66 16,82	16,72	
X	2-n-Octylaminothiazolidin-4-one hydrochloride	190 (decomp.)	$C_{11}H_{20}N_2OS \cdot HCl$	N	10,71 10,89	10,59	50
				S	12,38 12,24	12,09	
	Base	70—71 (from water)	$C_{11}H_{20}N_2OS$	C	57,75 57,81	57,72	90
				H	8,88 8,60	8,69	
XI	2-Imino-5-methylthiazolidin-4-one hydrochloride	205—206 (decomp., from water)	$C_4H_6N_2OS$	N	21,31 21,40	21,54	95

TABLE 2



Compound	R	R′	R″	X	mp, °C	Empirical formula	Element	Found, %	Calc., %	Yield, %
XII	CH_3	H	CH_3	Br	194—195 (from ethanol)	$C_6H_{11}N_3O_3S \cdot HBr$	C	25,36 25,33	25,17	68
							H	4,19 4,50	4,19	
							N	14,98 14,97	14,68	
XIII	CH_3	H	CH_3	Cl	195—196 (decomp., from ethanol)	$C_6H_{11}N_3O_3S \cdot HCl$	N	17,69 17,70	17,39	54
XIV	H	H	CH_3	Cl	170 (decomp.)	$C_5H_9N_3O_3S \cdot HCl$	N	18,74 18,80	18,46	97
							S	13,72 13,83	14,07	
XV	H	n-C_8H_{17}	CH_3	Cl	129—131 (decomp.)	$C_{13}H_{25}N_3O_3S \cdot HCl$	S	9,59 9,40	9,43	70
XVI	H	C_6H_5	CH_3	Cl	145 (decomp.)	$C_{11}H_{13}N_3O_3S \cdot HCl$	N	13,67 13,78	13,84	92
XVII	H	C_6H_5	C_6H_5	Cl	137—138 (decomp.)	$C_{16}H_{15}N_3O_3S \cdot HCl$	N	11,50 11,66	11,49	60
							S	8,58 8,47	8,75	



The reason for the higher stability of the isothiouronium salts XII and XIII containing a propionyl residue is apparently (by analogy with [6, 7]) that in the first case the α-methyl group sterically inhibits the intramolecular nucleophilic attack of the nitrogen atom on the carbon atom of the carbonyl group. Consequently, the salts XII and XIII prove to be fairly stable compounds which do not decompose even on being boiled in water and cyclize only when they are neutralized, i.e., when the nucleophilicity of the nitrogen atoms is substantially raised. In the case of compounds XIV-XVII, where the screening action of an α-methyl group is absent, their cyclization into XIX takes place far more readily even on boiling in anhydrous acetone or in the presence of such polar solvents as ethanol and, particularly, water.

EXPERIMENTAL

Methyl and phenyl N-chloroacetylcarbamates (I and II, respectively) and methyl N-α-chloro- and N-α-bromopropionylcarbamates (III and IV, respectively) were obtained by the action of the appropriate α-halogenoacyl isocyanates on methanol or phenol [8] or by the acylation of methyl or phenyl carbamates [9]. Phenyl- and octylureas were obtained by published methods [10, 11].

2-Iminothiazolidin-4-one (VIII). A. Solutions of 1.52 g (0.01 mole) of I and 0.76 g (0.01 mole) of thiourea (V) in 20 ml of ethanol each were mixed at room temperature and boiled with stirring for 1 h 30 min in the water bath. Then the reaction mixture was cooled and the yellow precipitate was filtered off to give 1.37 g of the hydrochloride of VIII. In boiling water or under the action of aqueous sodium acetate solution this formed the free base VIII (Table 1). The IR spectra of these and the other 2-iminothiazolidinones that we obtained exhibit bands in the 1650, 1700, and 1750 cm^{-1} regions which, according to the literature [13-17] apparently means, in the first place, that the reaction products are obtained in the form of tautomeric mixtures and, in the second place, that the imino form predominates in these mixtures if the substituent is aryl and the amino form if the substituent is alkyl. The melting points of compound VIII and its hydrochloride coincide with those of samples obtained by independent synthesis from ethyl chloroacetate and thiourea [12].

B. A suspension of 1 g (0.0066 mole) of I in 15 ml of acetone was treated over 30 min at −4° to 0°C with 0.5 g (0.0066 mole) of V in 30 ml of acetone, and the mixture was stirred at this temperature for 5 h. The precipitate that deposited was filtered off at 0°C and washed with acetone, giving 0.30 g (85%) of ammonium chloride. The filtrate was evaporated in vacuum at 0°C, and the residual oil, consisting of VIII containing XIV as an impurity (identified by thin-layer chromatography), was recrystallized from water or ethanol, giving 0.69 g (90%) of VIII.

C. A mixture of 1 g of XVIII and 10 ml of ethanol was boiled for 2 h and cooled, and 0.62 g (85%) of the hydrochloride of VIII was filtered off.

D. A mixture of 1 g of XVIII and 10 ml of water was boiled for 30 min and cooled, and 0.51 g (92%) of the free base XVIII, identified by a comparison of IR spectra, as in the case of all the substances obtained, was filtered off.

The Thiazolidinones IX-XI. A. Compounds IX and X (Table 1) were obtained in a similar manner to method A described previously.

B. One gram of the hydrochloride XVII was boiled in 99.5% ethanol for 1 h, the solution was cooled, and 0.59 g (94%) of the light yellow crystalline hydrochloride of IX was filtered off. The filtrate was evaporated, giving 0.35 g (93%) of phenyl carbamate, mp 141°C (from water; according to [18], mp 141°C).

C. Compound XI (Table 1) was formed when XII and XIII were heated in aqueous sodium acetate solution.

S-[α-(Methoxycarbonylcarbamoyl)ethyl]isothiourea Hydrobromide (XII). A solution of 0.61 g (0.008 mole) of V in 30 ml of ethanol was added to a solution of 1.6 g (0.0076 mole) of IV in 40 ml of ethanol. The reaction mixture was boiled for 4 h, cooled, and treated with ether, and 1.5 g of colorless crystalline XII was filtered off. Compound XIII (Table 2) was obtained similarly.

S-(Methoxycarbonylcarbamoylmethyl)isothiourea Hydrochloride (XIV). Suspensions of 1.52 g (0.01 mole) of I and 0.76 g (0.01 mole) of V, each in 20 ml of anhydrous acetone, were mixed at room temperature. The clear solution that formed after 5 min was then stirred at 20°C for 3 h, and the greasy crystalline precipitate was separated off and subjected to prolonged drying in vacuum, giving 2.2 g of XIV. Compounds XV-XVII (Table 2) were synthesized similarly.

2-Imino-4-methoxycarbonyliminothiazolidine Hydrochloride (XVIII). A. A mixture of 1.52 g (0.01 mole) of I and 0.76 g (0.01 mole) of V in 40 ml of anhydrous acetone was boiled for 5 h 30 min, and the precipitate was filtered off and washed with acetone to give 2 g (95%) of XVIII, mp 175°C (decomp.). Found %: N 20.30, 19.90; S 15.02, 15.22. $C_5H_7N_3O_2S \cdot HCl$. Calculated %: N 20.05; S 15.27. Gas-liquid chromatography of the mother solution showed that water was liberated during the reaction. The IR spectra of XVIII contain bands at 1630 cm^{-1}, 1720 cm^{-1} (m), and 1780 cm^{-1} (s).

B. A mixture of 1.52 g (0.01 mole) of I and 0.76 g (0.01 mole) of V in 40 ml of anhydrous ethanol was stirred at room temperature for 10 h, and the precipitate was filtered off to give 1.5 g (71%) of XVIII, mp 175°C (decomp.). The elementary analyses and IR spectra of the samples of XVIII obtained in acetone and in ethanol were identical.

LITERATURE CITED

1. K. A. Nuridzhanyan, N. P. Bulanova, and G. A. Pivovarov, ZhOrKh (in press).
2. E. B. Knott and U. Morgan, US Patent No. 2,461,987 (1949); C. A., 43, 4156 (1949).
3. N. M. Mel'nikov, K. A. Nuridzhanyan, G. V. Kuznetsova, and N. P. Bulanova, ZhOrKh, 4, 1186 (1968).
4. K. M. Murav'eva and M. N. Shchukina, ZhOKh, 30, 2327 (1960).
5. K. M. Murav'eva, M. N. Shchukina, and N. V. Arkhangel'skaya, Chemistry of Heterocyclic Compounds, 3, 1036 (1967).
6. E. Berliner, J. Am. Chem. Soc., 66, 533 (1964).
7. K. A. Nuridzhanyan, L. M. Nesterova, A. F. Vasil'ev, N. L. Aryutkina, and V. V. Negrebetskii, ZhOrKh, 5, 874 (1969).
8. K. A. Nuridzhanyan, G. V. Kuznetsova, N. P. Bulanova, and L. M. Nesterova, ZhOrKh, Collection: Biologically Active Compounds [in Russian] (1968), p. 290.
9. S. Basterfield and M. E. Greig, Canad. J. Res., 8, 453 (1933).
10. Org. Synth. Coll. III (1955), p. 735.
11. T. Meda, S. Kato, and S. Toyoshima, Japanese Patent No. 13,624 (1964); C. A., 56, 12,749 (1962).
12. Org. Synth. Coll. III (1955), p. 751.
13. N. N. Khovratovich and I. N. Chizhevskaya, Chemistry of Heterocyclic Compounds, 3, 637 (1967).
14. Yu. V. Svetkin, E. N. Minlibaeva, and S. A. Vasil'eva, ZhOKh, 37, 116 (1968).
15. A. E. Dixon and I. Taylor, J. Chem. Soc., 101, 558 (1912).
16. E. Akerblot, Acta Chem. Scand., 21, 843 (1967).
17. E. Akerblot, Acta Chem. Scand., 21, 1437 (1967).
18. R. Scholl and F. Kacer, Ber., 33, 4 (1900).