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4- AND 5-HYDROXYLAMINOTHIAZOLIDINE-2-THIONES. REARRANGEMENT OF THE CARBAMOYL DERIVATIVES TO 4- AND 5-UREIDOTHIAZOLIDIN-2-ONES

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UDC 547.789.1.04:541.124

The carbamoylation of 4- and 5-hydroxyaminothiazolidine-2-thiones by methyl and 3,4-dichlorophenyl isocyanates leads to the corresponding hydroxyureas, which rearrange to 4- and 5-ureidothiazolidin-2-ones on heating in the presence of a base. Under these conditions, the hydroxyurea based on 5-hydroxylaminothiazolidin-2-one is converted to 5-ureidooxazolidin-2-one.

In the continuation of work on the study of the properties of 4- and 5-hydroxylaminothiazolidine-2-thiones [1, 2], we investigated their reaction with isocyanates, as well as some conversions of the carbamoyl derivatives obtained.

The treatment of the hydroxylamines (Ia, c) and (IIa-c) with methyl and 3,4-dichlorophenyl isocyanates is accompanied by the formation of the corresponding N-monocarbamoyl derivatives — the hydroxyureas (III) and (IV). The structure of the hydroxyureas (III) and (IV) is confirmed by the presence of the band of the carbonyl absorption in the region of 1640-1695 cm^{-1} and the amide-II band at 1500-1545 cm^{-1} in the IR spectra (KBr), and by the appearance of the signals of the protons of the NH group in the region of 7.0-9.5 ppm and the OH group in the region of 9.0-10.0 ppm in the PMR spectra. Moreover, the presence of the hydroxyurea fragment in the compounds (III) and (IV) is confirmed by the positive reaction with an alcoholic solution of ferric chloride. In the carbamoylation of the sterically hindered hydroxylamine (Ib) ($R^1 = R^2 = CH_3$), the corresponding carbamoyl derivatives are not successfully isolated.

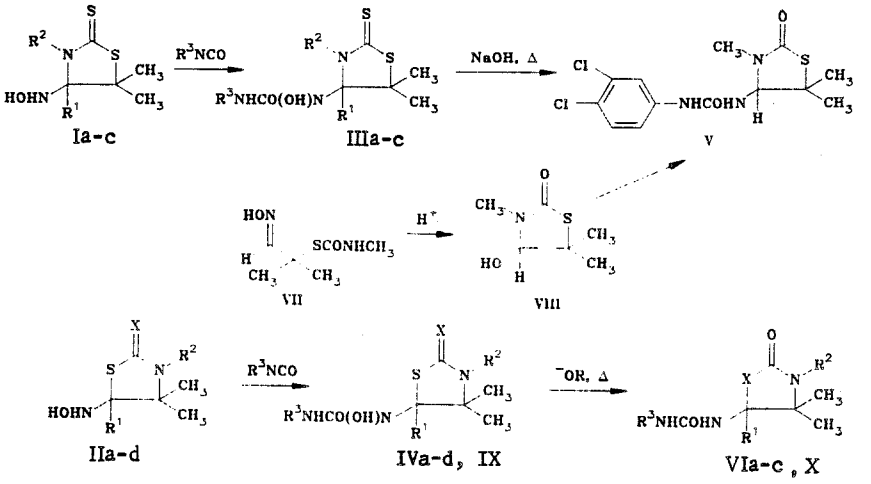
The hydroxyureas (III) and (IV) are stable to the action of acids. The heating of the hydroxyurea (IIIa) and (IVa-c) in the presence of sodium ethoxide or NaOH leads to the formation of the compounds (V) and (VI), which contain one sulfur atom less than the initial hydroxyureas according to the data of the elemental analysis. The IR spectra of the compounds (V) and (VI) are characterized by the presence of the absorption bands of two carbonyl groups in the regions of 1625-1670 and 1700-1752 cm^{-1}; this indicates the substitution of the thione group by the carbonyl group in the compounds (III) and (IV).

Moreover, the compounds (V) and (VI) do not give a qualitative reaction with ferric chloride solution; their PMR spectra lack the signal of the N-OH group which is characteristic of the initial hydroxyureas. In the case of compounds (VIb, c), the broad singlet of the proton of one more NH group appears in the region of 5.9-7.2 ppm. In the case of the compounds (V) and (VIa), two doublets are observed in the regions of 5.3-5.5 and 6.7-7.3 ppm ($J = 10$ Hz); these pertain to the protons of the CHNH group. On the basis of these data,

All-Union Scientific-Research Institute of Chemical Plant Protection Agents, Moscow 109088. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1678-1682, December, 1987. Original article submitted June 27, 1986.

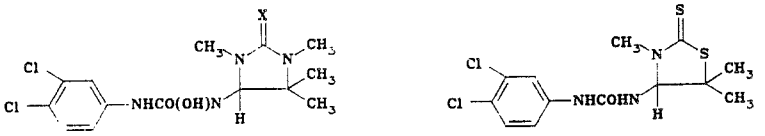
 0009-3122/87/2312-1352$12.50

the structure of the 4- and 5-ureidothiazolidin-2-ones is assigned to the compounds (V) and (VI) correspondingly. The direct synthesis of the ureido derivatives (V) by the reaction of 3,4-dichlorophenylurea with the 4-hydroxythiazolidin-2-one (VIII) [the latter is obtained by the treatment of the thiolcarbamate (VII) with HCl] serves as a chemical confirmation of the structure of the compounds (V) and (VI).



Ia,IIa,d,IIIa, IVa, IX $R^1=H$, $R^2=CH_3$; Ib IIb IVb,c $R^1=R^2=CH_3$; Ic IIc IIIb,c IVd $R^1=CH_3$, $R^2=H$; VIa X $R^1=H$; VIb,c $R^1=CH_3$; IIIa,b IVa,b,d VIa,b IX, X $R^3=$ $=3,4\text{-}Cl_2C_6H_3$; IIIc IVc VIc $R^3=CH_3$; IIa-c IVa-d, VIa-c, X=S; IId,IX, X X=O; R=H, C_2H_5; *tert*-C_4H_9

It should be noted that, in the conditions characteristic for the rearrangement of the hydroxyureas (IIIa) and (IVa-c), the hydroxyureas based on imidazolidin-2-one (XI) and imidazolidine-2-thione (XII) (the sulfur atom in the ring is absent) remain unchanged, and the 4-ureidothiazolidine-2-thione (XIII) (without the hydroxyurea fragment) is not desulfurized. The heating of the ureido derivative (XIII) in the presence of 3,4-dichlorophenylhydroxyurea or the hydroxyurea (XI) (the hydroxyurea fragment and the cyclic sulfur atom occur in the different molecules) is not accompanied by the exchange of the sulfur atom in compound (XIII) and the loss of the OH group in the hydroxyureas (XI).



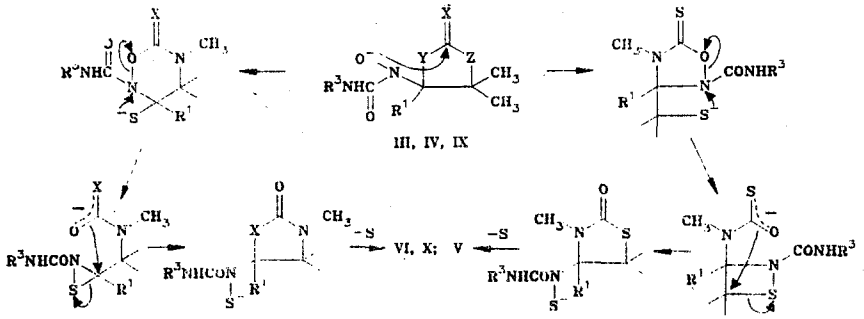
XI X=O; XII X=S

XIII

Therefore, the formation of the ureido derivatives (V) and (VI) evidently proceeds as a result of an accomodated intramolecular process requiring the simultaneous presence of the hydroxyurea fragment and of the heterocyclic sulfur atom in the molecule. However, it remains unclear as to which of the two sulfur atoms of the thiazolidinethione ring is eliminated from the molecule of the initial hydroxyurea. This problem can be solved by the consideration of the rearrangement of the hydroxyurea based on the thiazolidin-2-one (IX). When it is heated in the presence of potassium tert-butoxide, the compound (X) is formed. According to the data of the elemental analysis and the mass spectrometry (m/e 332), (X) does not contain an atom of sulfur, and has the empirical formula $C_{13}H_{15}Cl_2N_3O_3$. These data, as well as the IR and PMR spectral data, permit the assignment of the structure of a 5-ureidooxazolidin-2-one to the compound (X); its formation testifies in favor of the elimination of the cyclic sulfur atom in the course of the reaction.

The data obtained for the rearrangement of hydroxyureas to ureido derivatives permit the proposition of a general scheme (see next page) of conversions starting from the stage of the attack of the hydroxamate anion at the dithio(or thiol)carbamate $C_{(2)}$ carbon atom.

It should be noted that the corresponding ureido derivatives could not be obtained from the hydroxyureas (IIIb, c) and (IVd) (R^2 = H). The presence of an available hydrogen atom in the heterocycle evidently leads to the formation of the thiol form of the initial compounds in the alkaline conditions and, consequently, to a decrease in the electrophilicity of the $C_{(2)}$ atom. The prolonged heating of the hydroxyureas (IIIb, c) and (IVd) in the presence of a base causes their decomposition.



III X=Z=S, Y=N; IV X=Y=S, Z=N; IX X=O, Y=S, Z=N

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 457 instrument using KBr tablets and the solutions in dioxane and DMSO. The PMR spectra were taken on the Varian FT-80A (80 MHz) and Bruker HX-90E (90 MHz) instruments with TMS as the internal standard. The monitoring of the course of the reaction was accomplished on Silufol UV-254 plates in the 3:1 system of benzene-acetone and the 1:1 system of THF-hexane.

The physicochemical data and spectral characteristics are presented in Tables 1 and 2.

Carbamoylation of the Hydroxylamines (I) and (II). To the solution of the compounds (Ia, c) or (II) in acetone is added the equimolar amount of 3,4-dichlorophenyl or methyl isocyanate (the latter in the presence of catalytic amounts of triethylamine). At the end of the reaction (monitoring by TLC), the acetone is evaporated, and the residue is crystallized from ether. The compounds (III), (IV), and (IX) are obtained.

Compounds (XI) and (XII) are obtained analogously from 1,5,5-trimethyl-3-phenyl-4-hydroxylaminoimidazolidin-2-one [3] or -2-thione.

4- and 5-[3,4-Dichlorophenyl(or methyl)ureido]thiazolidin-2-ones (V) and (VI). A. The solution of 1.3 mmole of the hydroxyurea (IIIa) or (IVa, b) in 15 ml of alcohol is boiled in the presence of 3 ml of a 4 N solution of NaOH. At the end of the reaction (monitoring by TLC), the reaction mass is neutralized with HCl to the pH ∿ 7 (release of H_2S). The brown residue is filtered off and recrystallized from acetone. The compounds (V) and (VIa, b) are obtained.

TABLE 1. Physicochemical Data on the Compounds (III)-(XIII)

Compound	T_{mp}, °C	IR spectrum, cm^{-1} (KBr)		Found, %			Empirical formula	Calculated, %			Yield, %
		C=O	amide II	C	H	N		C	H	N	
IIIa	196—198	1695	1520	41.0	4.3	11.2	$C_{13}H_{15}Cl_2N_3O_2S_2$	41.1	4.0	11.0	81
IIIb	80—83	1670	1510	41.0	4.2	11.3	$C_{13}H_{15}Cl_2N_3O_2S_2$	41.1	4.0	11.0	64
IIIc	148—149	1640	1535	38.7	6.3	17.1	$C_8H_{15}N_3O_2S_2$	38.5	6.1	16.9	50
IVa	179—181	1670	1510	41.3	4.2	10.9	$C_{13}H_{15}Cl_2N_3O_2S_2$	41.1	4.0	11.0	87
IVb	107	1655	1520	42.7	4.3	10.5	$C_{14}H_{17}Cl_2N_3O_2S_2$	42.6	4.3	10.7	80
IVc	157—158	1655	1545	41.1	6.7	16.1	$C_9H_{17}N_3O_2S_2$	41.0	6.5	16.0	76
IVd	104—105	1675	1500	41.3	3.8	11.0	$C_{13}H_{15}Cl_2N_3O_2S_2$	41.1	4.0	11.0	70
V	169—170	1635, 1710	1535	45.0	4.5	12.2	$C_{13}H_{15}Cl_2N_3O_2S$	44.8	4.3	12.1	40
VIa	250	1665, 1700*	1525	45.1	4.4	12.1	$C_{13}H_{15}Cl_2N_3O_2S$	44.8	4.3	12.1	55
VIb	198—200	1625, 1725	1530	46.0	5.0	12.0	$C_{14}H_{17}Cl_2N_3O_2S$	46.4	4.7	11.6	30
VIc	178—180	1670, 1710**	1560	47.0	7.5	18.5	$C_9H_{17}N_3O_2S$	46.7	7.4	18.2	60
VII	120—122	1660	1545	41.1	6.5	16.1	$C_6H_{12}N_2O_2S$	40.9	6.7	15.9	55
VIII	65—66	1640	—	44.5	7.1	8.9	$C_6H_{11}NO_2S$	44.7	6.9	8.7	61
IX	195—197	1660***	1520	42.9	4.2	11.5	$C_{13}H_{15}Cl_2N_3O_3S$	42.8	4.1	11.1	73
X	150—152	1675, 1745	1540	46.5	4.5	12.1	$C_{13}H_{15}Cl_2N_3O_3$	47.0	4.6	12.6	30
XI	181—183	1670***	1500	54.1	5.0	13.0	$C_{19}H_{20}Cl_2N_4O_3$	53.9	4.8	13.2	95
XII	113—115	1675	1505	52.0	4.7	12.9	$C_{19}H_{20}Cl_2N_4O_2S$	51.9	4.6	12.8	50
XIII	215—217	1710	1530	42.7	4.3	11.6	$C_{13}H_{15}Cl_2N_3OS_2$	42.9	4.2	11.5	56

*In DMSO.

**In dioxane.

***Broad band.

TABLE 2. PMR Spectra of the Compounds (III)-(X) (in DMSO-D_6)*

Compound	Chemical shifts, ppm (J, Hz)					
	$C(CH_3)_2$	CCH_3 or CH	NCH_3	Ar or CH_3	NH	OH** (broad s)
IIIa	1,50; 1,65	6,09	3,22	7,30—8,10	9,22	9,34
IVa	1,35; 1,46	6,0	3,18	7,43—7,99	9,53	9,94
IVb	1,43; 1,54	1,61	3,19	2,7 d (J=4,5)	7,09	9,60
V	1,47; 1,67	5,38 d (J=10)	2,91	7,40—8,04	6,78 d (J=10)	8,40
VIa	1,32; 1,35	5,49 d (J=10)	2,80	7,20—7,80	7,24 d (J=10)	8,73
VIb	1,28; 1,35	1,80	2,78	7,12—7,95	7,05	8,89
VIc	1,31; 1,35	1,84	2,78	2,61 d (J=5)	5,96	6,53
VII	1,46	7,58 (CH=N)	2,55 d (J=4,5)	—	7,88	10,6
VIII	1,31; 1,41	4,59 d (J=7,5)	2,72	—	—	6,38 d (J=7,5)
IX	1,28; 1,35	5,85	2,68	7,35—8,01	9,49	9,86
X	1,20; 1,27	5,7 d (J=11)	2,67	7,18—7,93	7,4 d (J=11)	9,02

*The spectra of compounds (IIIa) and (V) were recorded in $(CD_3)_2CO$; the spectrum of compound (IVc) was recorded in DMSO-D_6 + $(CD_3)_2CO$.
**For the compounds (V) and (VIa-c), δ_{NH} are presented.

B. Metallic sodium (0.2 g) is dissolved in 10 ml of alcohol prior to the addition of 2.2 mmole of compound (IVc); the mixture is boiled until the completion of the reaction (monitoring by TLC). The reaction mass is neutralized with HCl and concentrated to dryness. The residue is recrystallized from acetone; compound (VIc) is obtained.

3,4,4-Trimethyl-5-(3,4-dichlorophenylureido)oxazolidin-2-one (X). To the solution of 1.5 mmole of the hydroxyurea (IX) in 50 ml of alcohol is added the equimolar amount of potassium tert-butoxide; the mixture is boiled for 1 h. The reaction mass is neutralized and filtered. The mother liquor is concentrated. The residue is treated with ether, and the residue obtained is filtered off. Compound (X) is isolated from it by the method of TLC (Silufol, with the 3:1 mixture of benzene-acetone as the eluent).

N-Methyl-S-(2-methyl-2-hydroximinoprop-2-yl)thiocarbamate (VII). This is obtained from the dimeric isobutylene nitrosochloride and sodium N-methylthiocarbamate according to the method of [1].

3,5,5-Trimethyl-4-hydroxythiazolidin-2-one (VIII). Moist HCl gas is passed through the solution of 1 mmole of the thiocarbamate (VII) in 50 ml of benzene. At the end of the reaction (monitoring by TLC), the inorganic residue is filtered off; the benzene is evaporated. The residue is crystallized from hexane; compound (VIII) is obtained. The IR spectrum (CCl_4) is characterized at 3570 cm^{-1} (OH).

Condensation of Compound (VIII) with 3,4-Dichlorophenylurea. The solution of equimolar amounts of compound (VIII) and 3,4-dichlorophenylurea in benzene is boiled using a Dean—Stark attachment in the presence of catalytic amounts of p-toluenesulfonic acid. At the end of the reaction (monitoring by TLC), the reaction mass is filtered; the benzene is evaporated. The residue is treated with ether. Compound (V) is obtained.

The Ureido Derivative (XII). This is obtained analogously from 3,5,5-trimethyl-4-hydroxythiazolidine-2-thione [1].

1,5,5-Trimethyl-3-phenyl-4-hydroxylaminoimidazolidine-2-thione. To the solution of 5 mmole of 2-methyl-2-methylaminopropionaldoxime in 50 ml of THF are added 5 mmole of phenyl isothiocyanate; the mixture is held at 20°C for ∿2 h. The solvent is evaporated, and the residue is crystallized with ether. The yield is 40%. The product has the mp 126-128°C. The IR spectrum (CCl_4) is as follows: 3580 (OH) and 3400 cm^{-1} (NH). Found: C 57.0; H 7.1; and N 16.5%. $C_{12}H_{17}N_3OS$. Calculated: C 57.3; H 6.8; and N 16.3%.

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FRIES REACTION AND DAKIN REARRANGEMENT IN BENZO-2,1,3-THIADIAZOLES

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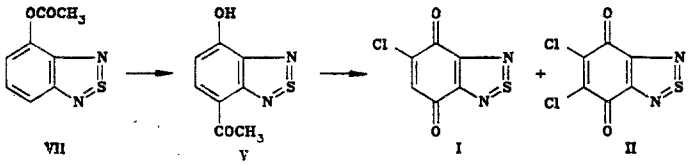
UDC 547.567.3'572.1'655.6'794.3

The Fries rearrangement of 4- and 5-acetoxybenzo-2,1,3-thiadiazoles has given 4-hydroxy-7-acetyl- and 5-hydroxy-4-acetylbenzo-2,1,3-thiadiazoles, which on oxidation afford mixtures of 5-chloro-4,7-dioxo- and 5,6-dichloro-4,7-dioxobenzo-2,1,3-thiadiazole and of 6-chloro-4,5-dioxo- and 6,7-dichloro-4,5-dioxobenzo-2,1,3-thiadiazole. Reaction of 6,7-dichloro-4,5-dioxobenzo-2,1,3-thiadizole with ortho-phenylenediamine gives 4,5-dichloro-2,1,3-thiadiazolo[4,5-a]phenazine.

5-Chloro-4,7-dioxo- and 5,6-dichloro-4,7-dioxobenzo-2,1,3-thiadiazole (I, II) are known to possess high antiviral activity in ovo [1]. It is noteworthy that 4-hydroxy- and 4-aminobenzo-2,1,3-thiadiazole (III, IV), which give the quinone (I) on oxidation in the presence of HCl [2, 3], also exhibit antiviral activity [1, 4]. It might be expected that other benzo-2,1,3-thiadiazoles, which undergo oxidation under these conditions to give the chloro-compounds, would be viral inhibitors. To test this theory, 4-hydroxy-7-acetyl- and 5-hydroxy-4-acetylbenzo-2,1,3-thiadiazoles (V, VI) were selected.

The hydroxyketones (V) and (VI) were obtained by the Fries rearrangement of 4- and 5-acetoxybenzo-2,1,3-thiadiazole (VII, VIII). The acetoxy-compounds (VII, VIII) were obtained by reacting 4- and 5-hydroxybenzo-2,1,3-thiadiazole (III, IX) with acetic anhydride.



Oxidation of (V) and (VI) with hydrogen peroxide in alkaline media (the Dakin reaction) as for the oxidation of p-hydroxyacetophenone [5] failed to give the dihydroxy-compounds. Only when the alkali was replaced by concentrated hydrochloric acid and the reaction was carried out in acetonitrile were mixtures of quinones obtained, these being in the first case 5-chloro,4-7-dioxo- and 5,6-dichloro-4,7-dioxobenzo- (I, II), and in the second case 6-chloro-4,5-dioxo- and 6,7-dichloro-4,5-dioxobenzo-2,1,3-thiadiazole (X, XI). Treatment of a mixture of (I) and (II) with chlorine in acetic acid in the presence of iodine gave the quinone (II), identical with that described in [2]. Prolonged chlorination of the mixture of quinones (X) and (XI) failed to give the pure dichloro-compound (XI), but its concentration in the mixture was increased to such an extent that it was possible to separate (XI) from (X).

Oxidation of the hydroxy-compound (IX) and 5-aminobenzo-2,1,3-thiadiazole (XII) under conditions similar to those used to oxidize ketone (VI) likewise gave a mixture of quinones (X) and (XI).

The structure of quinone (XI) was confirmed by its IR spectrum, elemental analysis (Table 1), the formation therefrom with o-phenylenediamine of 4,5-dichloro-2,1,3-thiadiazolo[4,5-a]-phenazine (XIII), and the presence of (XI) amongst the chlorination products of 4,5-dioxobenzo-2,1,3-thiadiazole (XIV) [6].

The quinone (X) and 7-chloro-4,5-dioxobenzo-2,1,3-thiadiazole (XV) could not be obtained analytically pure. The position of the chlorine in quinones (X) and (XV) was established from the TLC data for the phenazine (XIII), 4-chloro-2,1,3-thiadiazolo[4,5-a]phenazine (XVI) (obtained as in [7]), a mixture of the phenazine (XIII) and 5-chloro-2,1,3-thiadiazolo[4,5-a]-

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 0009-3122/87/2312-1356$12.50