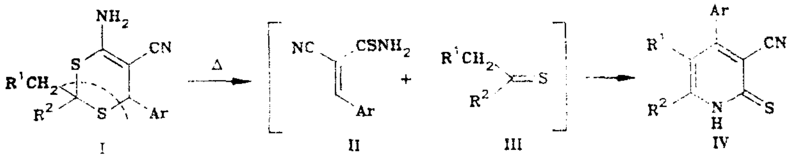
STEREOSELECTIVE TRANSFORMATION OF 1,3-DITHIA-4-CYCLOHEXENE ENAMINONITRILES INTO SUBSTITUTED 3,4-*trans*-1,2,3,4-TETRAHYDROPYRIDINE-6-THIOLATES WITH PYRIDINIUM YLIDES

A. M. Shestopalov, A. S. Demerkov,
Yu. A. Sharanin, and V. P. Litvinov

UDC 547.821.3:547.825

4-Amino-6-aryl-2,2-dialkyl-5-cyano-1,3-dithia-4-cyclohexenes react with pyridinium ylides in thermodynamically controlled conditions with the formation of 4-aryl-2-oxo-thioxo)-3-(1-pyridino)-5-cyano-3,4-trans-1,2,3,4-tetrahydropyridine-6-thiolates. Arylidenecyanothioacetamides act as intermediates of this recyclization, and the corresponding pyridine-6-thiolates were obtained from them by an independent method. The synthesized hydrogenated pyridine-6-thiolates are in the half-chair conformation with a trans-diaxial position of the 3-H and 4-H hydrogen atoms.

IR and NMR spectroscopy and x-ray structural analysis showed that a highly developed $p—\pi$ conjugation system in the NC—C=C—NH$_2$ enaminonitrile fragment exists in molecules of 4-amino-6-aryl-2,2-dialkyl-5-cyano-1,3-dithia-4-cyclohexenes (I) [1-3], and this results in the coplanarity of this fragment and the atoms bound with it. The S$_{(1)}$ and C$_{(2)}$ atoms go out into different planes relative to the planar S—C(NH$_2$)=C(CN)C fragment. The molecules of substituted 1,3-dithiacyclohexenes are sterically overloaded with bulky substituents which prevents free inversions at the axis of bonds joining the heterocyclic skeleton with the substituents [2-4]. These factors cause the relative conformational rigidity of the heterocyclic skeleton of 1,3-dithiacyclohexenes, for this reason, a decrease in the enthalpy in thermodynamically controlled conditions becomes impossible [5], and this causes the thermodynamic instability of 1,3-dithiacyclohexenes. When heated, these compounds undergo fragmentation at the weakest bonds, C$_{(2)}$—S$_{(3)}$ and S$_{(1)}$—C$_{(6)}$ (indicated by the broken line in the scheme), with the formation of arylidenecyanothioacetamides II and thioketones III [2, 3].



The formation of cyclohexanethione is confirmed by its separation from a mixture of products of pyrolysis of 4-amino-6-phenyl-5-cyano-2-cyclohexanespiro-1,3-dithia-4-cyclohexene [6], and the formation of arylmethylenecyanothioacetamide is confirmed by separation of 4-aryl-2-(2-aryl-1-cyanovinyl)thiazoles when phenacyl bromide added to the product of pyrolysis of (I) is used as a trap [1].

It has been hypothesized that the successive reaction of intermediates II and III causes the formation of products of recyclization — 2(1H)-pyridinethiones IV [3].

We investigated the reaction of 1,3-dithia-4-cyclohexenes Ia-c with pyridinium salts Va, b to study the mechanism of this transformation and extend its boundaries. The reaction takes place along the path of intermolecular elimination—inclusion on heating in ethanol under the effect of 4-methylmorpholine. Unsaturated thioamides IIa-c and thioketones IIa, b should be formed from compounds Ia-c in thermodynamically controlled conditions. Pyridinium ylides VIa, b are generated from pyridinium salts Va, b under the effect of 4-methylmorpholine. The rate of the reaction of pyridinium ylides VIa, b with arylidenecyanothioacetamides IIa-c is probably higher than the rate of their reaction with thioketones III, resulting in the formation of pyridine-6-thiolates VIIa-d (method A).

T. G. Shevchenko State Pedagogical Institute, Lugansk 348011. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1082-1086, August, 1991. Original article submitted June 27, 1989; revision submitted September 10, 1990.

TABLE 1. Characteristics of 4-Aryl-3-(1-pyridino)-2-thio-5-cyano-3,4-*trans*-1,2,3,4-tetrahydropyridine-6-thiolates (VIIa-g)

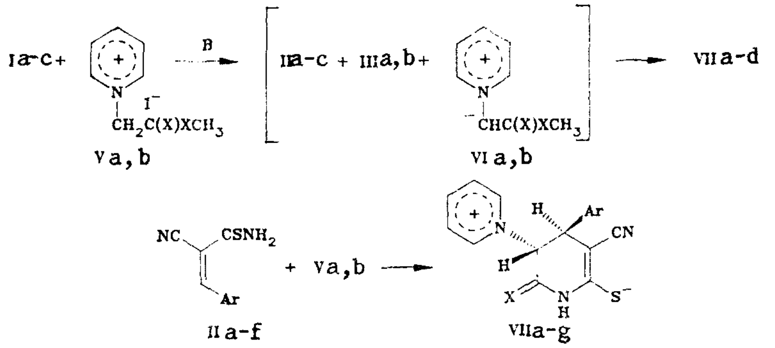
Compound	Empirical formula	T_m, °C (decomp.)	IR spectrum, ν, cm^{-1}				PMR spectrum, δ, ppm (J, Hz)								Yield, %	
			NH	C≡N	δ_{HCX}	C=S	pyridinium protons			NH, s	Ar, m	C_3H, d	C_4H, d	$^3J_{H_3H_4}$	A	B
							C_2H; C_6H, d	C_4H, t	C_3H; C_5H, t							
VII a	$C_{17}H_{12}FN_3O_2$	189 ... 193	3144, 3200	2193	1637, 1695		8,87	8,53	8,06	10,14	7,13	6,21	4,65	13,5	68	82
VII b	$C_{17}H_{12}FN_3S_2$	223 ... 224	3308, 3460	2172	1630	1200	8,92	8,53	8,03	11,87	7,00 ... 7,38	6,41	4,68	14,5	58	75
VII c	$C_{17}H_{12}ClN_3S_2$	228 ... 230	3284, 3440	2176	1630	1204	8,92	8,54	8,09	11,86	7,18 d; 7,32 d ($^3J = 5,8$)	6,42	4,72	13,7	48	71
VII d	$C_{17}H_{12}BrN_3S_2$	236 ... 237	3296, 3435	2178	1632	1202	8,95	8,55	8,09	11,86	7,18 d; 7,45 d ($^3J = 6,2$)	6,42	4,67	14,0	65	74
VII e	$C_{17}H_{13}N_3OS_2$	173 ... 174	3248	2168	1620	1200	8,88	8,51	8,08	11,73	6,97 d; 6,53 d* ($^3J = 7,8$)	6,25	4,49	13,8		68
VII f	$C_{18}H_{15}N_3OS_2$	193 ... 195	3295, 3427	2165	1632	1203	8,92	8,52	8,06	11,84	6,76 d; 7,12 d** ($^3J = 8,8$)	6,35	4,57	14,0		62
VII g	$C_{16}H_{12}N_4S_2$	224 ... 226	3308, 3424	2180	1628	1204	8,93***	8,52	8,08	11,93	7,31 q ($C_{(5)}H$; $^3J_{H_5H_4} = 7,9$; $^3J_{H_5H_6} = 4,9$); 7,47 d (C_4H); 8,38 d (C_6H); 9,90 s (C_2H)	6,49	4,74	13,4		54

---

*The signal from the OH group proton is manifested as the signal at 9.36 ppm.

**The signal from the CH_3 group proton is manifested as a singlet at 3.65 ppm.

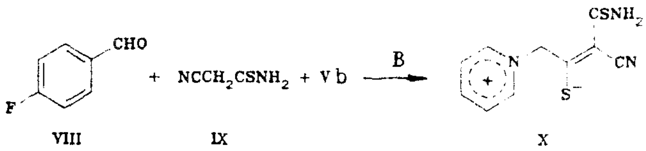
***Overlaps with the signal of the 3-Py $C_{(2)}H$ proton.



B = 4-methylmorpholine; I, III a $R^1-R^2 = (CH_2)_4$; b, c $R^1 = H$, $R^2 = CH_3$; II a Ar = 4-FC_6H_4, b Ar = 4-ClC_6H_4, c Ar = 4-BrC_6H_4; II d Ar = 4-HOC_6H_4, e Ar = 4-$CH_3OC_6H_4$, f Ar = 3-C_5H_4N; V, VI a X = O, b X = S; VII a, b Ar = 4-FC_6H_4, c Ar = 4-ClC_6H_4, d Ar = 4-BrC_6H_4, e Ar = 4-HOC_6H_4, f Ar = 4-$CH_3OC_6H_4$, g Ar = 3-C_5H_4N; a X = O, b – g X = S

It follows from these data that arylidenecyanothioacetamides II can act as intermediates in the reaction of compounds I and Va-f. However, the formation of compounds II from aromatic aldehydes and cyanothioacetamide is reversible. Arylmethylenecyanothioacetamides obtained by the reaction of aromatic aldehydes with cyanothioacetamide [7] are widely used in synthesis of substituted 3-cyanopyridine-2(1H)-thiones [7, 8].

We investigated the reactions of arylidenecyanothioacetamides IIa-f with pyridinium salts Va, b (method B) to more completely understand the mechanism of the recyclization [1-3]. Pyridine-6-thiolates VIIa-g are formed in the reaction of these compounds in the presence of 4-methylmorpholine in ethanol at 50-60°C. The yields of thiolates VIIa-d is higher with method B than with method A (see Table 1). Dipyridyl VIIg, difficult to obtain by other methods, is obtained by the reaction of compounds IIf and Vb. In addition, we investigated the possibility of formation of pyridine-6-thiolates from aromatic aldehydes, cyanothioacetamide, and pyridinium salt Vb and the participation of these components in recyclization of 1,3-dithiacyclohexenes I with pyridinium salts V. A different direction of the reaction occurs in the reaction of 4-fluorobenzaldehyde VIII, cyanothioacetamide IX, and pyridinium salt Vb. Betaine X, and not the anticipated pyridine-6-thiolate VIIa, was separated. It follows that the rate of the reaction of salt Vb with cyanothioacetamide IX is higher than the rate of formation of the corresponding arylmethylenecyanothioacetamide IIa.

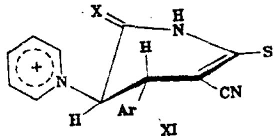


As a consequence, the participation of arylidenecyanothioacetamides II, and not the products of their further reversible transformation — aromatic aldehydes and cyanothioacetamide — in the recyclization process is most probable.

The data from the IR and PMR spectra and the data in [2, 9-11] from x-ray structural analysis of related hydrogenated pyridinethiolates indicate that the formation of pyridine-6-thiolates from compounds I or II and pyridinium salts V is highly regio- and stereoselective. Compounds VIIa-g are yellow-orange crystalline powders. In the solid state and in solutions, they are in the form of betaines with delocalization of the positive and negative charges in the Py+ and $S\underline{\cdots}C\underline{\cdots}C\underline{\cdots}C\underline{\cdots}N^-$ fragments, respectively. Delocalization of the negative charge in the indicated fragment of the molecules of compounds VIIa-g decreases the frequency of vibrations of the $C \equiv N$ group to 2165-2180 cm^{-1} with a simultaneous increase in its intensity similar to piperidine or morpholinium salts of 4-aryl-3-cyano-1,4-dihydropyridine-2-thiolates [9, 10]. The strong conjugation in the $S\underline{\cdots}C\underline{\cdots}C\underline{\cdots}C\underline{\cdots}N^-$ fragment causes the coplanarity of this fragment and the $N_{(1)}$ and $C_{(4)}$ atoms bound with it. In addition, absorption bands of NH and C=S groups are present in the IR spectra of compounds VIIa-f (see Table 1). The absorption band of the C=S group at 1200-1204 cm^{-1} indicates the existence of compounds VIIb-g in the solid state in the thione, but not the thiol tautomeric forms. Compound VIIa exists in the form of pyridone; a number of absorption bands of NH and CONH groups in the regions of 3144, 3200, and 1637, 1695 cm^{-1}, respectively is observed in its spectrum.

The PMR spectra also confirm the high regio- and stereoselectivity of reactions of formation of pyridine-6-thiolates VIIa-g. The signals of the $C_{(3)}H$ and $C_{(4)}H$ protons are in the form of two doublets in the 6.21-6.42 and 4.49-4.74 ppm regions, respectively, with SSCC of ^3J = 13.4-14.5 Hz (see Table 1). The high value of the SSCC suggests a *trans*-diaxial position of the 3-H and 4-H atoms, similar to the previously studied salts of hydrogenated

3-cyanopyridine-2-thiolates [9, 11]. After comparing the IR and PMR spectral characteristics of compounds VIIa-g with the data for hydrogenated 3-cyanopyridine-2-thiolates [9, 11], we can hypothesize that pyridine-6-thiolates are in half-chair conformation XI. The $C_{(2)}$ and $C_{(3)}$ atoms go out of the plane of the $N—C_{(6)}=C_{(5)}—C_{(4)}$ fragment on different sides, as the indicated value of $^3J_{H_3H_3}$ indicates.



XI

The signal of the $C_{(3)}H$ proton is shifted to weak fields in comparison to the $C_{(4)}H$ proton by $\Delta\delta \approx 1.5$-1.3 ppm, probably due to its polarization by the electron-deficient pyridinium cation and emergence from the shielding effect of the equatorial aryl substituent into the axial position. In addition, the PMR spectra of compounds VIIa-g contain signals of protons from Ar, Py^+, and NH groups (see Table 1). The signals of the protons of the pyridinium substituent are shifted to weak fields in comparison to the signals of the nonquaternized pyridine protons [12]. This also supports a betaine structure of VII with separated charges. The position of the NH group proton signal at 11.73-11.93 ppm and the data from conformational analysis confirm the existence of compounds VIIa-g in the form of pyridone and thiones.

It follows from the data obtained that pyridinium ylides are convenient reagents for "catching" intermediates of cycloelimination. The study of the mechanism of recyclization and the detection of the intermediates of these reactions will allow proposing simpler approaches to the preparation of substituted 3-cyanopyridine-2(1H)-thiones used in different areas of precision organic synthesis [13].

EXPERIMENTAL

The IR spectra were made on a Perkin—Elmer 577 in KBr pellets. The PMR spectra were made on a Bruker WM-250 (250 MHz) in DMSO-D_6 relative to TMS. Substituted 1,3-dithia-4-cyclohexenes Ia-c were prepared by the reaction of geminal dithiols with arylidenemalononitriles according to [1-3, 6].

4-Aryl-3-(1-pyridino)-2-oxo(thio-5-cyano-3,4-*trans*-1,2,3,4-tetrahydropyridine-6-thiolates (VIIa-g).* A. A mixture of 10 mmole of 1,3-dithia-4-cyclohexene Ia-c, 10 mmole of pyridinium salt Va, b, and 10 mmole of 4-methylmorpholine was boiled for 2-3 h in ethanol while stirring. A sediment gradually formed. The reaction mixture was cooled, the sediment was filtered off, washed with ethanol and hexane, and compounds VIIa-d were obtained.

B. A mixture of 10 mmole of arylidenecyanothioacetamide IIa-f, 10 mmole of pyridinium salt Va, b, and 10 mmole of 4-methylmorpholine in 25 ml of ethanol was rapidly brought to boiling and filtered through a folded filter. The reaction mixture was held for 10-12 h at 25°C, the sediment was filtered off, washed with ethanol and hexane, and thiolates VIIe-g were obtained. Compounds VIIa-d, prepared by methods A and B, had identical IR spectra and did not cause depression of the melting point when mixed.

3-(1-Pyridino)-1-thioamido-1-cyanopropyl-1-ene-2-thiolate (X, $C_{10}H_9N_3S_2$). A mixture of 3.1 g (10 mmole) of salt Vb, 1 g (10 mmole) of cyanothioacetamide IX, and 0.9 g (10 mmole) of 4-methylmorpholine in 20 ml of ethanol was brought to boiling and rapidly filtered through a folded filter. The reaction mixture was held for 5 h at 25°C, the sediment was filtered off, washed with ethanol and hexane, and 1.67 g (71%) of compound X was obtained, T_m 187-189°C. IR spectrum: 1634 (δ_{CSNH_2}); 2194 ($C\equiv N$); 3170, 3242 cm^{-1} (NH_2). PMR spectrum: 5.78 (s, 2H, CH_2); 8.11 (t, 2H, $C_{(3)}H$ and $C_{(5)}H$-pyridino); 8.61 (t, 1H, $C_{(4)}H$-pyridino); 8.88 (d, 2H, $C_{(2)}H$- and $C_{(6)}H$-pyridino); 9.17 (br. s, 1H, NH); 10.05 ppm (br. s, 1H, NH).

LITERATURE CITED

1. Yu. A. Sharanin, A. M. Shestopalov, V. K. Promonenkov, and L. A. Rodinovskaya, Zh. Org. Khim., **20**, 1539 (1984).
2. Yu. A. Sharanin, V. P. Litvinov, A. M. Shestopalov, V. N. Nesterov, Yu. T. Struchkov, V. E. Shklover, V. K. Promonenkov, and V. Yu. Mortikov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1768 (1985).
3. V. P. Litvinov, Yu. A. Sharanin, and A. M. Shestopalov, Sulfur Lett., **3**, 99 (1985).
4. V. N. Nesterov, V. E. Shklover, Yu. T. Struchkov, Yu. A. Sharanin, A. M. Shestopalov, and V. P. Litvinov, Proceedings of the V All-Union Conference on Organic Crystal Chemistry [in Russian], Chernogolovka (1987), p. 146.
5. V. M. Potapov, Stereochemistry [in Russian], Khimiya, Moscow (1988).

6. J. Morgenstern and R. Mayer, J. Prakt. Chem., No. 1, 116 (1986).
7. B. Y. Ried, A. M. Negm, S. E. Abdou, and H. A. Daboun, Heterocycles, No. 1, 205 (1987).
8. A. M. El-Torgoman, S. M. El-Kousy, and K. Z. El-Shahat, Z. Naturforsch., No. 1, 107 (1987).
9. A. A. Krauze, E. E. Liepin'sh, Yu. E. Pelcher, Z. A. Kalme, and G. Ya. Dubur, Khim. Geterosikl. Soedin., No. 1, 75 (1987).
10. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, L. A. Rodinovskaya, A. M. Shestopalov, V. Yu. Mortikov, and V. S. Bogdanov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 9, 2101 (1985).
11. M. I. Rubio, C. Seoane, J. L. Soto, and A. Susaeta, Liebigs Ann. Chem., No. 2, 210 (1986).
12. H. Günther, Introductory Course in NMR Spectroscopy [Russian translation], Mir, Moscow (1984).
13. V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin, and A. M. Shestopalov, Itogi Nauki Tekh., Ser. Org. Khim., **17**, 72 (1989).