REACTION OF 1,3-THIAZOLIDINE-4-CARBOXYLIC AND 1,4-TETRAHYDRO-THIAZINE-3-CARBOXYLIC ACID ESTERS WITH ISOCYANATES AND ISOTHIOCYANATES AND STRUCTURES OF THE REACTION PRODUCTS

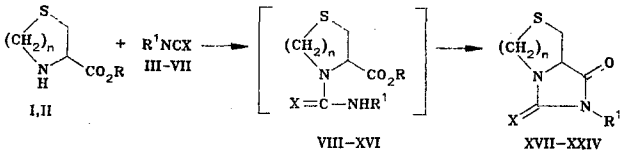
A. V. Eremeev, R. Nurdinov, F. D. Polyak,
R. M. Zolotoyabko, A. F. Mishnev,
M. F. Bundule, and Ya. Ya. Bleidelis

UDC 547.869.2:548.373:543.51

7-Thia-1,3-diazabicyclo[3.3.0]octane-2,4-diones and 7-thia-1,3-diazabicyclo[4.3.0]-nonane-2,4-diones, as well as their thio analogs, were obtained by the reaction of (S)-1,3-thiazolidine-4-carboxylic and 1,4-tetrahydrothiazine-3-carboxylic acid esters with isocyanates and isothiocyanates. Intermediate reaction products, viz., heterocyclic derivatives of urea, were isolated. The three-dimensional structures of the 3-methyl-4-oxo-7-thia-1,3-diazabicyclo[3.3.0]octane-2-thione and 3-methyl-4-oxo-7-thia-1,3-diazabicyclo[4.3.0]nonane-2-thione molecules were determined by x-ray diffraction analysis.

Bicyclic heterocycles that contain an imidazolidine ring are known as biologically active compounds with mainly fungicidal activity [1-3]. At the same time, they are of interest from the point of view of the stereochemistry of bicyclic heterocycles. By the reaction of 1,4-tetrahydrothiazine-3-carboxylic acid hydrazide with carbonyl compounds we have previously obtained a number of 7-thia-1,3-diazabicyclo[4.3.0]nonane derivatives, which are made up of a system of condensed 1,4-tetrahydrothiazine and imidazolidine rings [4]. It is known that 3-phenyl-1,3-diazabicyclo[3.2.0]heptane-2,4-dione and its thio analog could be obtained by refluxing the adduct of p-nitrophenyl azetidine-2-carboxylate with phenyl isocyanate and phenyl isothiocyanate [5], whereas the adduct of methyl aziridine-2-carboxylate with isocyanates could not be cyclized [6].

In continuing our research on the synthesis and structures of bicyclic heterocycles we investigated the reaction of (S)-1,3-thiazolidine-4-carboxylic (I) and 1,4-tetrahydrothiazine-3-carboxylic (II) acid esters with isocyanates and isothiocyanates.



VIII—XI R=Et, XII—XVI R=Me; VIII R^1=Me, X=O; IX R^1=Ph, X=O; X R^1=Me; X=S; XI R^1=Ph, X=S; XII R^1=Me, X=O; XIII R^1=Me, X=S; XIV R^1=Ph, X=O; XV R^1=Ph, X=S; XVI R^1=$SiMe_3$, X=O; XVII R^1=Me, X=S; XVIII R^1=Ph; X=O; XIX R^1=Ph, X=S; XX R^1=Me, X=O; XXI R^1=Me, X=S; XXII R^1=Ph, X=O; XXIII R^1=Ph, X=S; XXIV R^1=H, X=O; VIII—XI, XVII—XIX n=1, XII—XVI, XX—XXIV n=2

The reaction of esters I and II with isocyanates and isothiocyanates III-VII in acetonitrile in most cases led immediately to, respectively, N-substituted 7-thia-1,3-diazabicyclo-[3.3.0]octane-2,4-diones and 7-thia-1,2-diazabicyclo[4.3.0]nonane-2,4-diones, as well as their 2-thio analogs XVII-XXIV; unsubstituted bicyclic system XXIV was isolated when the products of the reaction of ester II with trimethylsilyl isocyanate (VII) was treated with ethanol. Compounds XVII-XXIV are formed in two steps, the occurrence of which depends on the structure of both the substrate (the size of the heteroring) and the isocyanate (R^1 and X). In a number of cases we were able to isolate reaction intermediates, viz., ureides VIII, XII, and XIV. Their structures were confirmed by the presence in the PMR spectra of signals of an ester group and the NH group of a urea fragment (Table 1), as well as by characteristic bands of

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1327-1332, October, 1985. Original article submitted February 9, 1985.

 0009-3122/85/2110-1086$09.50

TABLE 1. Parameters of the PMR Spectra of XVII-XXIV

Compound	Chemical shifts, ppm							
	5a-H	6a-H	6e-H	8a-H	8e-H	9a-H	9e-H	remaining protons
XVII	4,49	3,00	3,38	4,45	5,36	—	—	3,22 (NCH_3)
XVIII	4,67	3,15	3,41	4,50	5,44	—	—	7,1—7,7 (C_6H_5)
XIX	4,65	3,16	3,41	4,49	5,41	—	—	7,0—7,5 (C_6H_5)
XX	4,07	2,68	3,00	2,82	2,60	3,12	4,46	3,00 (NCH_3)
XXI	4,12	2,62	3,02	2,77	2,65	3,29	5,21	3,28 (NCH_3)
XXII	4,32	2,77	3,13	2,88	2,66	3,32	5,27	7,1—7,7 (C_6H_5)
XXIII	4,32	2,81	3,11	2,90	2,70	3,36	5,29	7,2—7,6 (C_6H_5)
XXIV	4,08	2,64	2,95	2,70	2,55	3,09	4,42	8,03 (NH)

SSCC, Hz									
$J_{5a,6a}$	$J_{5a,6e}$	$J_{6a,6e}$	$J_{8a,8e}$	$J_{8a,9e}$	$J_{8e,9e}$	$J_{9a,9e}$	$J_{8a,9a}$	$J_{8e,9a}$	$J_{8e,6e}$
8,4	7,6	11,0	9,8						
8,6	7,2	11,0	9,4						
8,8	7,2	10,8	9,4						
10,8	3,6	13,0	13,2	2,8	2,4	13,0	10,6	3,2	1,8
11,4	3,6	13,5	13,7	3,4	2,7	13,6	11,7	3,1	2,1
10,8	3,9	13,0	13,4	3,0	2,6	13,0	10,4	3,2	1,8
11,4	3,6	13,5	13,7	3,3	2,7	13,5	12,0	2,9	1,8
11,2	3,8	13,2	13,4	3,4	2,8	13,4	11,9	3,1	1,6

stretching vibrations of carbonyl groups of esters and thiocarbonyl groups of ureides in the IR spectra (Table 2). In particular, intermediates were isolated in the reaction of esters I and II with the least reactive methyl isocyanate, as well as in the reaction of ester II with phenyl isocyanate.

The rate of the second step, viz., cyclization of ureides VIII-XVI, depends chiefly on the structure of the isocyanates. Thus, in the reaction of esters I and II with isothiocyanates the cyclization proceeds so rapidly that intermediate ureides X, XI, XIII, and XV could not be isolated. However, refluxing in the presence of catalytic amounts of hydrochloric acid was required for the cyclization of the intermediates in the reaction of esters I and II with isocyanates. In addition, the structure of the heteroring affects the rate of the second step — cyclization p ceeds more readily for the urea derivative, viz., the 1,4-tetrahydrothiazine-3-carboxylic acid ester, than for the 1,3-thiazolidine-4-carboxylic acid ester. Thus the isolated intermediate VIII — a thiazolidine derivative of urea — could not be cyclized even upon refluxing in acetonitrile in the presence of an acid.

In addition to signals of the protons of substituents R, characteristic signals of ring protons of thiazolidine and tetrahydrothiazine rings are observed in the PMR spectra of VIII, XII, XIV, and XVII-XXIV (Table 1). The parameters of the PMR spectra of the tetrahydrothiazine rings of ureides XII and XIV and bicyclic systems XX-XXIV are similar, except that the signals of the 2-H and equatorial 6-H protons are shifted to stong and weak fields, respectively, on passing from ureides XXII and XIV to bicyclic systems XX and XXII. The spin—spin coupling constants (SSCC) of the ring protons in XX-XXIV are close to the analogous characteristics of the ring protons of the bicyclic systems obtained in [4]; this indicates the approximately identical chair conformation of the tetrahydrothiazine ring of both series of bicyclic systems. This was confirmed by comparison of the results of x-ray diffraction analysis of XXI and the data presented in [4]. Bicyclic system XVII was subjected to x-ray diffraction analysis for a comparison of the structural data for bicyclic systems that differ with respect to the presence of thiazolidine and tetrahydrothiazine rings.

The structure of the XVII molecule is presented in Fig. 1. The imidazolidine ring (A) is planar within the limits ±0.05 Å. The O and $C_{(6)}$ atoms lie in the plane of the A ring, whereas the $S_{(2)}$ atom deviates 1.172 Å from it. The O, $C_{(3)}$, $N_{(2)}$, $C_{(4)}$, $S_{(2)}$, and $N_{(1)}$ atoms form a conjugated π-electron system, and this leads to shortening of the C—N bonds in this fragment (1.36-1.40 Å) as compared with a single bond (1.47 Å) [7]; within the limits of the experimental error, their lengths correspond to the sums of the covalent radii of the corresponding atoms for a sesqui bond (1.38 Å) [8]. The remaining C—N bonds in the molecule $C_{(4)}$—$S_{(2)}$ double bond (1.63 Å) coincides precisely with the sum of the covalent radii of these atoms. The thiazolidine ring has a somewhat distorted envelope conformation, and the deviation of the $C_{(5)}$ atom from the middle of the plane of the remaining four atoms (the B plane)

TABLE 2. Physicochemical Characteristics of VIII, XII, XIV, and XVII-XXIV

Compound	mp, °C	IR spectrum, ν, cm⁻¹			M*	Found, %			Empirical formula	Calc., %			Yield, %
		C=O†	C=S	NH		C	H	N		C	H	N	
VIII	80,5—81,5	1632 (1755)	—	3295	218	44,1	6,5	12,9	$C_8H_{14}N_2O_3S$	44,0	6,4	12,8	94
XII	138—139	1637 (1742)	—	3378	218	43,9	6,4	12,9	$C_8H_{14}N_2O_3S$	44,0	6,4	12,8	96
XIV	122—124	1640 (1748)	—	3352	280	55,8	5,7	10,0	$C_{13}H_{16}N_2O_3S$	55,7	5,7	10,0	90
XVII	98—99	1745	1323	—	188	38,4	4,4	15,0	$C_6H_8N_2OS_2$	38,3	4,3	14,9	97
XVIII	145—146	1710	—	—	234	56,5	4,2	11,9	$C_{11}H_{10}N_2O_2$	56,4	4,3	12,0	82
XIX	194—195	1756	1308	—	250	52,8	4,1	11,1	$C_{11}H_{10}N_2OS_2$	52,8	4,0	11,2	98
XX	93—94	1638, 1700, 1757	—	—	186	45,1	5,4	15,0	$C_7H_{10}N_2O_2S$	45,2	5,4	15,1	93
XXI	97—97,5	1738	1332	—	202	41,6	4,9	13,8	$C_7H_{10}N_2OS_2$	41,6	5,0	13,9	98
XXII	195—197	1742	—	—	248	58,0	4,7	11,2	$C_{12}H_{12}N_2O_2S$	58,1	4,8	11,3	93
XXIII	205—207	1743	1310	—	264	54,6	4,5	10,7	$C_{12}H_{12}N_2OS_2$	54,5	4,5	10,6	96
XXIV	195—196	1702, 1731	—	—	172	41,8	4,6	16,4	$C_6H_8N_2O_2S$	41,9	4,7	16,3	84

*By mass spectrometry.
†The amide νCO values (and the ester νCO values in parentheses) are presented for VIII, XII, and XIV.

to the side opposite to the imidazolidine ring is 0.542 Å. The dihedral angles between the A, B, and C planes are as follows: A/B 57.1°, B/C 33.2°, and A/C 57.7°. The average value of the lengths of the C–S single bonds in the XVII molecule is 1.820 Å and corresponds to the standard value of 1.817 Å [7].

A crystal of XXI is constructed from two crystallographically nonequivalent enantiomer molecules linked by a center of supersymmetry. Three-dimensional models of enantiomer molecules XXI are given in Fig. 2. Within the limits of the experimental error, the imidazolidine rings in the two molecules are planar. The O and $C_{(10)}$ atoms lie in the plane of the imidazolidine ring, and the $S_{(2)}$ atom deviates, on the average, 0.61(2) Å from it. The tetrahydrothiazine ring has a chair conformation. The average (for both enantiomers) deviations of the $S_{(7)}$ and $N_{(1)}$ atoms from the plane of the remaining four ring atoms are 0.87 and 0.65 Å, respectively, and the dihedral angles between the I-IV planes (see Fig. 2) in the molecules of the two enantiomers are as follows: I/II 44° and 55°, I/III 9° and 1°, II/III 53° and 55°, and (I + II + III)/IV 36° and 35°. Packing of the molecules in both crystals is realized at distances that are no less than the sums of the van der Waals radii of the contacting atoms [9].

EXPERIMENTAL

The NMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Bruker WH-90 and WM-360 spectrometers (90 and 360 MHz) with tetramethylsilane (TMS) as the internal standard. The IR spectra of mineral oil suspensions were recorded with a UR-20 spectrometer. The mass spectra were obtained with an MS-50 AEI spectrometer at an electron-ionization energy of 70 eV; the samples were admitted into the source through a direct-introduction system, and the temperature of the ionization chamber was 150°C. The elementary compositions of the ions were determined at a resolution of 50,000. X-ray diffraction analysis was carried out with a Syntex-$P2_1$ diffractometer. The melting points were determined with a Fisher-M350 apparatus. The course of the reaction was monitored by thin-layer chromatography (TLC) on Silufol-254 plates in ethyl acetate–hexane (2:1) (A) and chloroform–ethanol (4:1) (B) systems with detection in UV light at 254 nm and development of the spots in iodine vapors.

X-Ray Diffraction Analysis. Orthorhombic XVII ($C_6H_8N_2OS_2$) crystals were grown from ethyl acetate and had the following parameters: a = 7.359(1), b = 8.049(1), c = 13.792(2) Å, V = 816.8(2) Å^3, M 188.28, d_{calc} = 1.53 g/cm^3, μ(Cu K_α) = 52.4 cm^{-1}, z = 4, and space group $P2_12_12_1$. Orthorhombic XXI ($C_7H_{10}N_2OS_2$) crystals were grown from alcohol and had the following parameters: a = 16.539(4), b = 5.692(2), c = 19.850(4) Å, V = 1868.8(8) Å^3, M 202.31, d_{calc} = 1.44 g/cm^3, μ(Cu K_α) = 46.2 cm^{-1}, z = 8, and space group $Pca2_1$. The intensities of 696 (for XVII) and 1122 (for XXI) independent nonzero reflections were measured with a Syntex-$P2_1$ diffractometer by the method of θ/2θ scanning (Cu K_α emission, graphite monochromator) up

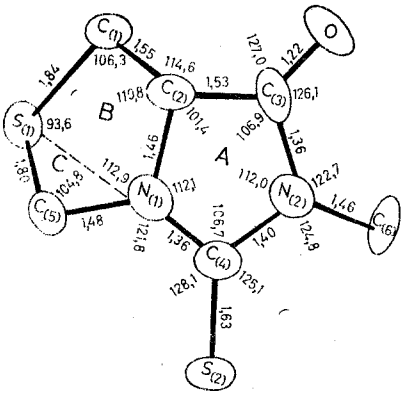


Fig. 1. Geometry of the XVII molecule.

to $2\theta_{max} = 150°$. Models of the molecules were found by the direct method by means of the Multran program of the XTL system. The structure of XVII was refined by the method of least squares, anisotropically for the nonhydrogen atoms and isotropically for the hydrogen atoms, up to R = 0.047. In the structure of XXI only the nonhydrogen atoms were refined anisotropically. The final R factor was 0.102. The standard deviations of the bond lengths and bond angles did not exceed 0.01 Å and 0.7° in XVII and 0.02 Å and 2° in XXI. The coordinates of the nonhydrogen atoms of the XVII and XXI molecules are given in Table 3.

3-(N-Methylcarbamoyl)-4-ethoxycarbonyl-1,3-thiazolidine (VIII). A solution of 0.57 g (0.01 mmole) of methyl isocyanate in 5 ml of acetonitrile was added to a solution of 1.61 g (0.01 mmole) of ethyl (S)-thiazolidine-4-carboxylate (I) in 10 ml of acetonitrile, and the mixture was stirred at room temperature for 1 h. After ester I had vanished (according to TLC in system A), the solvent was removed at reduced pressure, and the residual mass was triturated with dry ether. The precipitate was removed by filtration and washed with dry ether to give a product with $[\alpha]_D^{20}$ −136.9° (c 2.6 in ethanol). PMR spectrum ($CDCl_3$): 1.29 (3H, t, OCH_2CH_3, J = 7.0 Hz), 2.83 (3H, d, N−CH_3, J = 4.7 Hz), 3.25 (2H, dd, 5-CH_2, $J_{4,5}$ = 4.7 Hz), 4.23 (2H, q, OCH_2CH_3, J = 7.0 Hz), 4.48 (2H, dd, 2-CH_2, J_{2a2e} = 7.2 Hz), 4.75 (1H, m, NH, J_{NHCH} = 4.8 Hz), and 5.01 ppm (1H, t, 4-H_a, J_{45} = 4.8 Hz).

3-Methoxycarbonyl-4-(N-methylcarbamyl)-1,4-tetrahydrothiazine (XII) and 3-Methoxycarbonyl-4-(N-phenylcarbamoyl)-1,4-tetrahydrothiazine (XIV). These compounds were similarly obtained from 1.61 g (0.01 mole) of methyl 1,4-tetrahydrothiazine-3-carboxylate and 0.57 g (0.01 mole) of methyl isocyanate or 1.19 g (0.01 mole) of phenyl isocyanate. PMR spectrum of XII: 2.43 (1H, dd, 6e-H, J_{6e6a} = 13.4 Hz, J_{6e5a} = 3.6 Hz, J_{6a5e} = 2,6 Hz, J_{6e2e} = 1.6 Hz), 2.75 (1H, m, 6a-H, J_{6a6e} = 13.4 Hz, J_{6a5a} = 11.2 Hz, J_{6a5e} = 3.6 Hz), 2.80 (3H, d, N−CH_3, J_{CH_3NH} = 5.0 Hz), 2.96 (1H, dd, 2-H_a, J_{2a2e} = 13.0 Hz, J_{2a2e} = 3.8 Hz), 3.11 (1H, q, 2-H_e, J_{2e2a} = 13.0 Hz, J_{2e3e} = 3.2 Hz, J_{2e2a} = 1.6 Hz), 3.42 (1H, m, 5a-H, J_{5a5e} = 13.2 Hz, J_{5a6a} = 3.4 Hz, J_{5a6e} = 3.6 Hz), 3.75 (3H, s, OCH_3), 3.76 (1H, m, 5-H_e, J_{5e5a} = 13.2 Hz, J_{5e6a} = 11.2 Hz, J_{5e6e} = 2.6 Hz), 4.71 (1H, broad s, NH), and 5.38 ppm (1H, t, 3-H_e, J_{3e2a} = 3.8 Hz, J_{3e2e} = 3.2 Hz). PMR spectrum of XIV: 2.51 (1H° dd, 6e-H, J_{6a6e} = 1.6 Hz, J_{6e5a} = 3.2 Hz, J_{6e6a} = 13.4 Hz), 2.82 (1H, m, 6a-H, J_{6a6e} = 13.4 Hz, J_{6a5e} = 11.2 Hz, J_{6a5e} = 3.4 Hz), 2.94 (1H, dd, 2a-H, J_{2a2e} = 13.0 Hz, J_{2a3e} = 3.8 Hz), 3.18 (1H, q, 2e-H, J_{2e2a} = 13.0 Hz, J_{2e6e} = 1.6 Hz, J_{2e3e} = 3.0 Hz), 3.68 (1H, m, 5a-H, J_{5a5e} = 2.6 Hz, J_{5a6a} = 11.2 Hz, J_{5a6e} = 2.6 Hz), 3.79 (3H, s, OCH_3), 4.00 (1H, m, 5e-H, J_{5e5a} = 13.0 Hz, J_{5e6e} = 2.6 Hz), J_{5a6e} = 3.2 Hz), 5.44 (1H, t, 3e-H, J_{3e2a} = 3.2 Hz, J_{3e2e} = 3.0 Hz), 6.44 (1H, broad s, NH), and 6.9-7.3 ppm (5H, m, C_6H_5).

3-Phenyl-7-thia-1,3-diazabicyclo[3.3.0]octane-2,4-dione (XVIII). A 1.19-g (0.01 mmole) sample of phenyl isocyanate was added with stirring to a solution of 1.61 g (0.01 mmole) of ester I in 10 ml of dry acetonitrile, and the mixture was maintained at room temperature for 1 h. After starting ester I had vanished (according to TLC in system B), the solvent was evaporated at reduced pressure, and the residual viscous mass was treated with 10 ml of petroleum ether until crystals formed. The crystals were removed by filtration and washed with dry ether to give a product with $[\alpha]_D^{20}$ −60.0° (c 0.25 in EtOH).

3-Methyl-4-oxo-7-thia-1,3-diazabicyclo[3.3.0]octane-2-thione (XVII). This compound was obtained from 1.61 g (0.01 mole) of ester I and 0.73 g (0.01 mole) of methyl isocyanate in dry tetrahydrofuran (THF) by a method similar to that used to prepare XVIII. The product had $[\alpha]_D^{20}$ −67.8° (c 1.4 in chloroform).

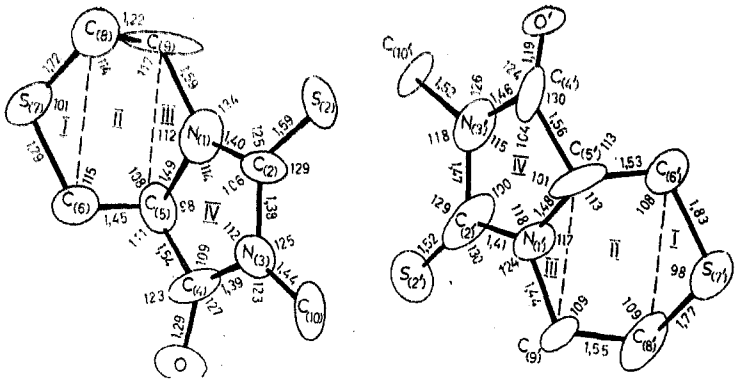


Fig. 2. Geometries of the enanthiomers of XXI.

TABLE 3. Coordinates of the Nonhydrogen Atoms ($\cdot 10^4$)

Atom	x	y	z	Atom	x	y	z
	XVII molecule			$S_{(7')}$	3657 (4)	4128 (14)	2549 (11)
$N_{(1)}$	−0037 (13)	8216 (36)	−0459 (0)	$C_{(8')}$	3894 (14)	6428 (46)	1983 (19)
$C_{(2)}$	0479 (12)	6410 (47)	−020 (15)	$C_{(9')}$	3367 (12)	6170 (68)	1342 (16)
$N_{(3)}$	1200 (10)	6780 (47)	−585 (13)	$C_{(10')}$	0579 (14)	9529 (46)	1499 (18)
$C_{(4)}$	1172 (12)	8744 (46)	−0999 (17)	$S_{(2')}$	2245 (5)	10252 (11)	0757 (12)
$C_{(5)}$	0345 (18)	9943 (40)	−0929 (22)	O'	0765 (11)	5206 (26)	2354 (15)
$C_{(6)}$	−0099 (17)	9903 (36)	−1516 (21)		XXI molecule		
$S_{(7)}$	−1160 (4)	10500 (13)	−1484 (11)				
$C_{(8)}$	−1514 (14)	8604 (56)	−0843 (17)	$S_{(1)}$	5742 (3)	2748 (3)	2188 (2)
$C_{(9)}$	−0975 (17)	8757 (75)	−0350 (19)	$S_{(2)}$	4680 (3)	4869 (3)	5124 (1)
$C_{(10)}$	1907 (21)	5309 (57)	−0522 (22)	O	−0361 (8)	3708 (8)	2847 (5)
$S_{(2)}$	0282 (5)	4592 (11)	0336 (12)	$N_{(1)}$	3860 (9)	2536 (9)	3794 (4)
O	1748 (11)	9571 (29)	−1368 (15)	$N_{(2)}$	1674 (9)	4375 (9)	4048 (5)
$N_{(1')}$	2531 (11)	6514 (35)	1519 (9)	$C_{(1)}$	331 (1)	223 (1)	2034 (6)
$C_{(2')}$	2047 (11)	8348 (39)	1267 (15)	$C_{(2)}$	249 (1)	216 (1)	3065 (6)
$N_{(3')}$	1291 (9)	7917 (32)	1640 (12)	$C_{(3)}$	106 (1)	349 (1)	3276 (6)
$C_{(4')}$	1273 (14)	5758 (57)	2036 (16)	$C_{(4)}$	344 (1)	392 (1)	4311 (6)
$C_{(5')}$	2166 (13)	4840 (38)	2005 (20)	$C_{(5)}$	574 (1)	220 (1)	3456 (7)
$C_{(6')}$	2588 (21)	4844 (44)	2688 (21)	$C_{(6)}$	068 (2)	579 (1)	4444 (8)

3-Phenyl-4-oxo-7-thia-1,3-diazabicyclo[3.3.0]octane-2-thione (XIX). This compound was obtained from 1.61 g (0.01 mole) of ester I and 1.35 g (0.01 mole) of phenyl isothiocyanate by a method similar to that used to prepare XVIII. The product had $[\alpha]_D^{20}$ −87.3° (c 2.7 in acetonitrile).

3-Methyl-7-thia-1,3-diazabicyclo[4.3.0]nonane-2,4-dione (XX). Several drops of concentrated HCl were added to a solution of 1.0 g of 3-methoxycarbonyl-N-methylcarbamoyl-1,4-tetrahydrothiazine (IX) in 20 ml of acetonitrile, and the mixture was refluxed for 3 h. The course of the reaction was monitored by TLC (system B). After ureide IX had vanished, the solvent was removed at reduced pressure, and the residue was recrystallized from dry ether.

3-Phenyl-7-thia-1,3-diazabicyclo[4.3.0]nonane-2,4-dione (XXII). A solution of 1.61 g (0.01 mole) of methyl 1,4-tetrahydrothiazine-3-carboxylate (II) and 1.19 g (0.01 mole) of phenyl isocyanate in 10 ml of dry THF was stirred at room temperature for 1 h. The course of the reaction was monitored by TLC (system B). After ester II had vanished, the solvent was removed at reduced pressure, and the residue was recrystallized from dry ether.

3-Methyl-4-oxo-7-thia-1,3-diazabicyclo[4.3.0]nonane-2-thione (XXI). This compound was obtained from 1.61 g (0.01 mole) of ester II and 0.73 g (0.01 mole) of methyl isocyanate by a method similar to that used to prepare XXII. The product was recrystallized from ethyl acetate.

3-Phenyl-4-oxo-7-thia-1,3-diazabicyclo[4.3.0]nonane-2-thione (XXIII). This compound was obtained from 1.61 g (0.01 mole) of ester II and 1.35 g (0.01 mole) of phenyl isothiocyanate by a method similar to that used to prepare XXII.

7-Thia-1,3-diazabicyclo[4.3.0]nonane-2,4-dione (XXIV). A 1.18-g (0.01 mole) sample of trimethyl isocyanate in 5 ml of acetonitrile was added slowly with stirring at 0°C to a solution of 1.61 g (0.01 mole) of ester II in 10 ml of acetonitrile, after which the temperature of the reaction mixture was raised to room temperature and maintained at this temperature for

0.5 h. The resulting colorless precipitate was dissolved by the addition of 10 ml of absolute ethanol, the solvent was removed at reduced pressure, and the precipitate was recrystallized from hexane–ethanol (1:1).

LITERATURE CITED

1. Japanese Patent No. 8161384; Chem. Abstr., 95, 115576 (1981).
2. Japanese Patent No. 8161390; Chem. Abstr., 95, 115553 (1981).
3. European Patent No. 70389; Chem. Abstr., 99, 5630 (1983).
4. R. Nurdinov and F. D. Polyak, in: Summaries of Papers Presented at the 8th Conference of Young Scientists on the Synthesis and Investigation of Biologically Active Compounds [in Russian], Riga (1984), p. 49.
5. H. T. Nagasawa, P. S. Fraser, and I. A. Elberling, J. Org. Chem., 37, 516 (1977).
6. P. T. Trapentsier, I. Ya. Kalvin'sh, É. É. Liepin'sh, É. Ya. Lukevits, and V. Ya. Kauss, Khim. Geterotsikl. Soedin., No. 8, 1070 (1985).
7. Tables of Interatomic Distances and Configrations in Molecules and Ions, The Chemical Society, London (1965).
8. G. V. Bokii, Crystal Chemistry [in Russian], Nauka, Moscow (1971), p. 355.
9. Yu. V. Zefirov and P. M. Zorkii, Zh. Struk. Khim., 17, 994 (1976).

ACYLATION AND BROMINATION OF SOME 2-MERCAPTOTHIENO[2,3-d]PYRIMIDINONES AND SYNTHESIS OF THEIR 2-AMINO DERIVATIVES

S. M. Khripak, V. I. Yakubets, and A. A. Dobosh

UDC 547.735'854.1:542.951'944'958.3

The acylation of 2-thio-3-R-4-oxo-3,4-dihydrothieno[2,3-d]-pyrimidines by means of benzoyl chloride was studied. Depending on the reaction conditions, it may take place with the formation of S-substituted and N-substituted derivatives. The bromination of the sodium salts of thienopyrimidines and their S- and N-substituted derivatives is accompanied by the formation of disulfides, which do not react with electrophilic reagents but react with amines to give 2-amino derivatives of thienopyrimidines.

It is known [1, 2] that compounds with amido and thioamido groups, having dual reactivities, can undergo reactions with migration of the reaction center. It has been shown [3, 4] that the acylation of triazolo-3-thiones with a thioamido grouping in their compositions by means of acid halides leads to the formation of S- and N-substituted derivatives.

We have studied the acylation of 3-phenyl- (Ia) [5] and 3-allyl-2-thio-4-oxo-3,4,5,6,7,8-hexahydrobenzo[b]thieno[2,3-b]pyrimidine (Ib) [6], as well as sodium salts IIa, b, which were obtained from them by treatment with sodium hydroxide solution. The thioamido grouping in Ia, b and IIa, b is included in the pyrimidine ring. The acylation of Ia, b and IIa, b was carried out by means of benzoyl chloride in benzene.

Compounds Ia, b are not acylated even in the case of prolonged heating. Sodium salts IIa, b are acylated at room temperature to give S-substituted derivatives IIIa, b, and refluxing benzene solutions of the latter for 2 h leads to N-substituted derivatives IVa, b.

The simultaneous formation of S- and N-substituted derivatives IIIa and IVa in approximately equal amounts (38.8 and 41.8%) is observed when IIa is refluxed with benzoyl chloride. The reaction of IIb with benzoyl chloride under similar conditions leads only to N-substituted derivative IVb; this is evidently explained by the effect of different radicals in the 3 position of the pyrimidine ring on the electron density distribution in the thioureide fragment of the starting compounds.

The hydrolysis of S- and N-substituted derivatives IIIa, b and IVa, b by a 2 N aqueous alcohol solution of alkali proceeds at room temperature and gives sodium salts IIa, b, the acidification of which with hydrochloric acid gives starting thienopyrimidines Ia, b.

The bromination of S- and N-substituted derivatives IIIa, b and IVa, b gave benzoyl bromide (identified in the form of benzamide – after separation of the precipitate, the reaction

Uzhgorod State University, Uzhgorod 294000.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1333-1336, October, 1985. Original article submitted July 10, 1984; revision submitted November 6, 1984.