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INTERACTION OF METHYL N-(3-OXOALKYL)CARBAMATES, S-METHYL -CARBAMATES, AND -DITHIOCARBAMATES WITH SODIUM BOROHYDRIDE. SYNTHESIS OF TETRAHYDRO-1,3-OXAZIN-2-ONES AND -THIONES

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The interaction of N-(3-oxoalkyl)carbamates, -thiocarbamates, and -dithiocarbamates with sodium borohydride has been studied. It was shown that reaction proceeds diastereoselectively, and reductive cyclization with the formation of tetrahydro-1,3-oxazin-2-ones and -thiones may occur. The tend to cyclization of the N-(3-hydroxyalkyl)carbamates, -thiocarbamates, and -dithiocarbamates formed as intermediates depends on the number of substituents in the alkyl chain.

Keywords: N-(3-oxoalkyl)carbamates, N-(3-oxoalkyl)thiocarbamates, N-(3-oxoalkyl)dithiocarbamates, tetrahydro-1,3-oxazines, diastereoselectivity, reductive cyclization.

The tetrahydro-1,3-oxazin-2-ones and -thiones are of interest as biologically active compounds [1], and are used for the synthesis of polymers [2,3] and liquid crystals [4]. Some of them are naturally occurring [5]. A series of reviews has been devoted to the methods of synthesis and properties of these compounds [6-9].

The N-(3-hydroxyalkyl)carbamates and their sulfur analogs **6** and **7** are converted by the action of bases or on heating into tetrahydro-1,3-oxazin-2-ones and -thiones [5,10-14]. At the same time it has been reported that N-(3-hydroxyalkyl)carbamates are formed on reducing the N-(3-oxoalkyl)carbamates [12,15] with complex metal hydrides in basic media. We obtained compounds **3-5** with the aim of studying the stereoselectivity of the borohydride reduction and the possibility of a one-stage conversion of N-3-oxoalkyl-substituted carbamates, thiocarbamates, and dithiocarbamates into tetrahydro-1,3-oxazin-2-ones and -thiones.

Carbamates **3a,c,e**, *syn*-**3b**, and *anti*-**3d** were synthesized by the reaction of the hydrochlorides of the corresponding 1,3-amino ketones **2a,c,e**, *syn*-2b, and *anti*-**2d** with methyl chloroformate in a two-phase system (water–ether) at reduced temperature. The *anti* isomer of the hydrochloride of amino ketone **2d** was obtained by the procedure of [16], and *syn*-**2b** by crystallization from acetone of a mixture of *syn* and *anti* isomers of **2b** formed on hydrolysis of 1,3-isothiocyanato ketone **1b** [17].

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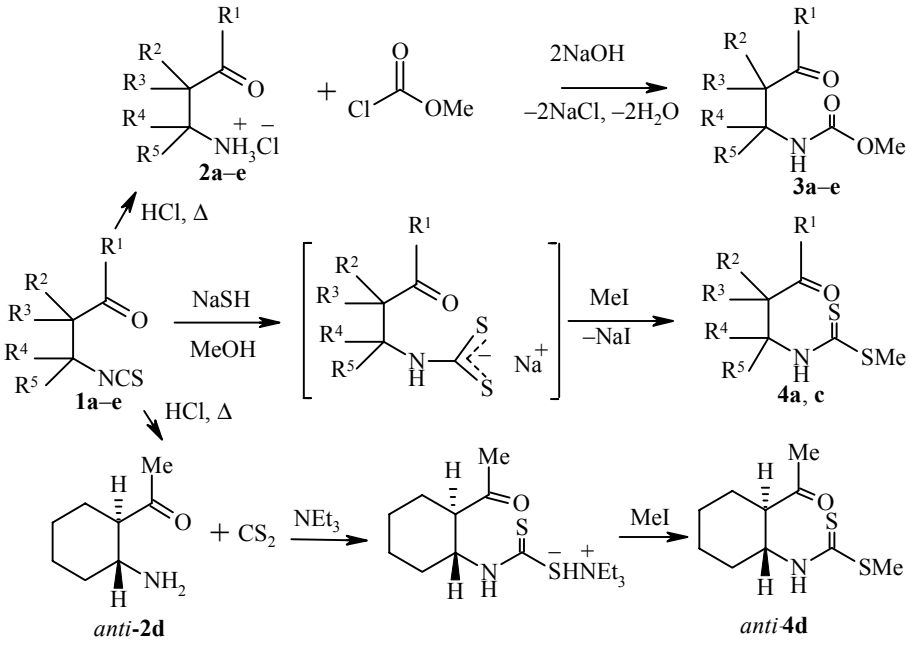
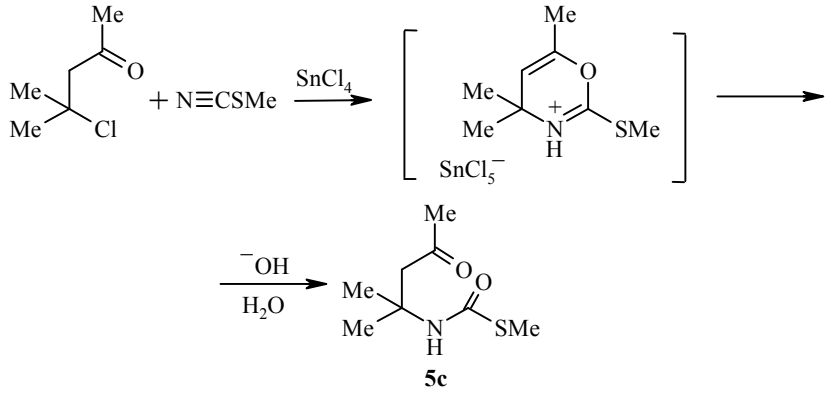
The dithiocarbamates **4a,c** and *anti*-**4d** were synthesized by the alkylation of salts of dithiocarbamic acids with methyl iodide. In the case of *anti*-**4d** the dithiocarbamic acid salt was obtained by the reaction of the *anti* isomer of amino ketone **2d** with carbon disulfide in the presence of triethylamine, and compounds **4b,c** by the interaction of 1,3-isothiocyanato ketones [18] and sodium hydrosulfide [19].



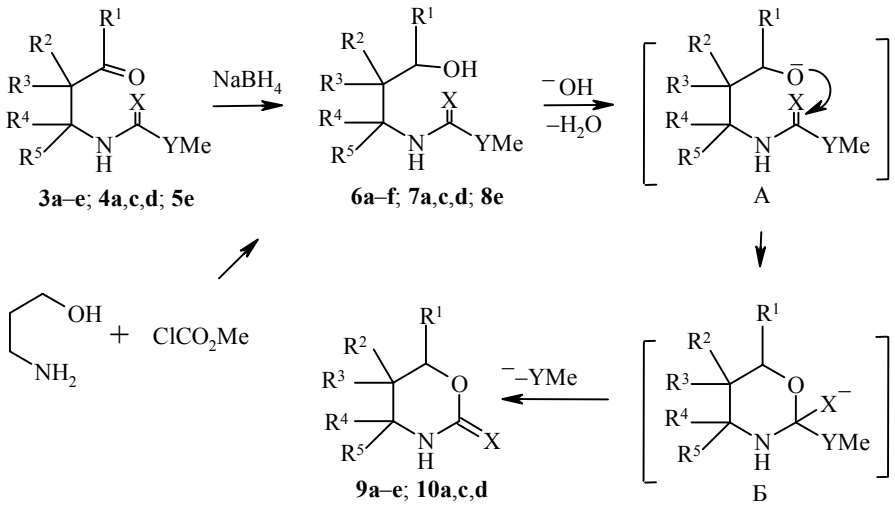
a $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$; **b** $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = H$;
c $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = H$; **d** $R^1 = Me$, $R^2 = R^5 = H$, $R^3 + R^4 = (CH_2)_4$;
e $R^1 + R^2 = (CH_2)_4$, $R^3 = H$, $R^4 + R^5 = (CH_2)_5$

It has been reported [20] that 1,3-chloro ketones undergo the Ritter reaction with methyl thiocyanate in the presence of Lewis acids to give 2-methylthio-4H-1,3-oxazines. We have shown that hydrolysis of 2-methylthio-4H-1,3-oxazines leads to an S-methyl N-(3-oxoalkyl)thiocarbamates. The S-methyl thiocarbamate **5c** was obtained in this way.



Study of the interaction of sodium borohydride with N-(3-oxoalkyl)carbamates **3a-e**, S-methyl thiocarbamate **5e**, and dithiocarbamates **4a,c** in alcohol showed that the initial reaction products N-(3-hydroxyalkyl)carbamates **6c,e**, thiocarbamate **8c**, and dithiocarbamate **7c** were not isolated since they are

unstable under the reaction conditions and are converted into tetrahydro-1,3-oxazin-2-ones **9c,e** and -thione **10c**. Compounds **6c** and **7c** were successfully obtained only in neutral medium which we maintained by the addition of phosphate buffer to the reaction mixture.



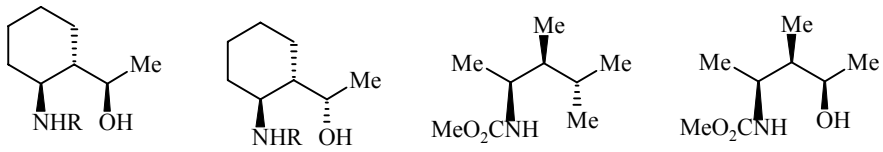
a $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$; **b** $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = H$;
c $R^1 = R^4 = R^5 = Me$, $R^2 = R^3 = H$, **d** $R^1 = Me$, $R^2 = R^5 = H$, $R^3 + R^2 = (CH_2)_4$;
e $R^1 = R^2 = (CH_2)_4$, $R^3 = H$, $R^4 + R^5 = (CH_2)_5$; **f** $R^1 = R^2 = R^3 = R^4 = R^5 = H$;
3, **6**, **9** X = Y = O; **5**, **8**, **10** X = O, Y = S; **4**, **7** X = Y = S

Several hours after adding sodium borohydride compounds **3c,e** and **4c** were practically completely converted into tetrahydro-1,3-oxazines **9c,e** and **10c**. Methyl N-(3-hydroxy-2-methylbutyl)carbamate (**6a**) and -dithiocarbamate (**7a**), with a lower number of substituents in the alkyl fragment, were less able to cyclization than compounds **6c,e** and **7c**, what enabled them to be obtained from substances **3a** and **4a** without buffer. Only an increase in the pH of the reaction mixture leads to conversion of compounds **6a** and **7a** into 1,3-oxazines **9a** and **10a**. Attempts to realise cyclization of unsubstituted methyl N-(3-hydroxypropyl)carbamate **6f** into a tetrahydro-1,3-oxazin-2-one under analogous conditions were unsuccessfull. The anomalous behavior of unsubstituted cyclic carbamates (instability on distillation, tendency to ring opening and polymerization) has been noted by many investigators [2,3,21]. At the same time the substituted tetrahydro-1,3-oxazin-2-ones are less capable to polymerization [2]. A thermodynamic concept based on a comparison of the enthalpy and entropy of the linear and cyclic structures has been proposed to explain the accelerated cyclization of polysubstituted bifunctional compounds [22]. It was shown that there were fewer sloped unbonded interactions in a series of substituted hexanes and cyclohexanes with alkyl substituents in the cycle than in compounds with open chains. This indicates that enthalpy factors favor to a large extent the cyclization of the methyl substituted chain as compared with the unsubstituted ones. Branchings restrict internal rotation, reduces the entropy of compounds with an open chain, but is unable to change significantly the entropy of cyclic compounds, having less freedom for internal rotation.

The mechanism of formation of tetrahydro-1,3-oxazinones **9**, **10** probably includes base catalyzed cyclization of N-(3-hydroxyalkyl)carbamates and their sulfur analogs into the 2-*gem*-substituted tetrahedral intermediate B stabilized by elimination of a methoxy or mercapto anion. An increase in the pH of the medium increases the reaction rate due to the increase in concentration of anion A.

Interaction of dithiocarbamate **4d** with $NaBH_4$ leads to a mixture of (4a,8a-*trans*-4a,4-*trans*)- and (4a,8a-*trans*-4a,4-*cis*)-4-methyloctahydro-2H-3,1-benzoxazine-2-thiones (**10d**) with a slight predominance of the latter (2/3), as a result of the cyclization of N-(3-hydroxyalkyl)dithiocarbamates with configurations *anti*,*anti*-**7d** and

anti,syn-**7d** formed as intermediates. The borohydride reduction of 2-aminoacetylcyclohexane **2d** in methanol [23] leads to the predominant formation of the *anti,anti* isomer of the 1,3-aminoalcohol **11d** (diastereomeric purity 30%), and proceeds probably through a cyclic transition state (control by chelation) characteristic for 1,3-amino ketones [15,16,23].

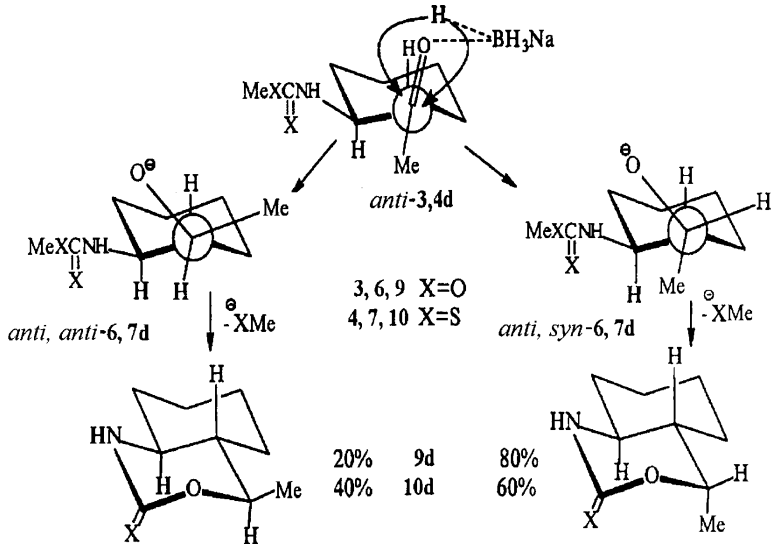


anti,anti -**6,7,11d** *anti,syn*-**6,7,11d** *syn,anti*-**6b** *syn,syn*-**6b**

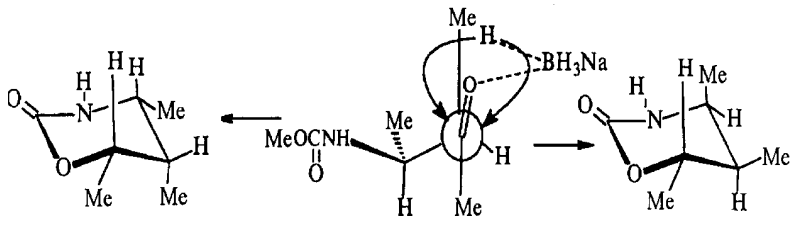
6 R = CO_2Me; **7** R = CS_2Me; **11** R = H

The slightly expressed stereoselectivity of the reduction of dithiocarbamate **4d** indicates the occurrence of nucleophilic attack of the carbon atom of the carbonyl group by hydride anion from both sides, but the change in the predominant direction of the attack corresponds to an open model of 1,2-asymmetric induction, which is effected from the less hindered side and not from the side of the amino group, as in the case of 1,3-aminoketones in [15,23]. The reductive cyclization of the carbamates *anti*-**3d** and *syn*-**3b** in alcohol occurs analogously, but with somewhat higher stereoselectivity. Reaction of compounds *anti*-**3d** and *syn*-**3b** with sodium borohydride gave a mixture of oxazines 4a,8a-*trans*-4,4a-*cis*-**9d** and 4a,8a-*trans*-4,4a-*trans*-**9d**, 4,5-*cis*-5,6-*trans*-**9b**, and 4,5-*cis*-5,6-*cis*-**9b** in ratios 4 : 1 with overall yields of 78 and 80%.

The differences in the stereoselectivity of the reduction of amino ketone **2d** and N-(3-oxoalkyl)carbamate **3d** enabled us to obtain the pure diastereomers 4a,4-*cis*-4a,8a-*trans*-**9d** and 4a,4-*trans*-4a,8a-*trans*-**10d**. We note that the known procedure for obtaining tetrahydro-1,3-oxazine-2-thiones, based on the interaction of 1,3-isothiocyanato ketones and sodium borohydride [24], for the synthesis of the individual isomers of **10d** is not useful, since the addition of thiocyanic acid to 1-acetyl-Δ^1-cyclohexene was not stereospecific [16] and did not permit the preparation of the individual *syn* and *anti* isomers of isothiocyanato ketone **1d**. Compound 4a,8a-*trans*-4a,4-*cis*-**9d** was isolated by crystallization of the products of reductive cyclization **3d**.

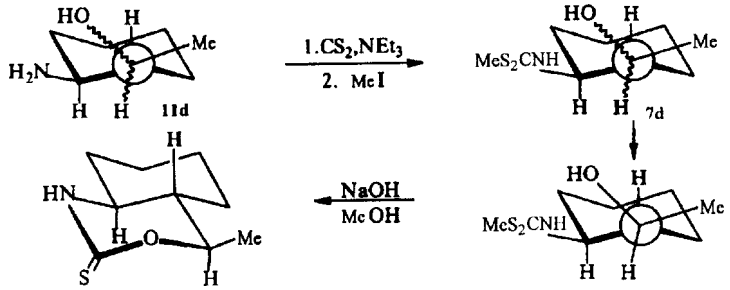


4a,8a-*trans*-4,4a-*trans*-**9,10d** 4a,8a-*trans*-4,4a-*cis*-**9,10d**



4,5-*cis*-5,6-*cis*-**9b** 20% | *syn*-**4b** | 4,5-*cis*-5,6-*trans*-**9b** 80%

By reacting the diastereomers of aminoalcohol **11d**, formed on borohydride reduction of amino ketone *anti*-**2d**, with carbon disulfide and methyl iodide [25] a mixture of the *anti* and *syn* isomers of methyl [*anti*-2-(1-hydroxyethyl)cyclohexyl]dithiocarbamate (**7d**) was obtained in an overall yield of 70%, from which a pure isomer with the configuration of *anti,anti*-**7d** was isolated. The dithiocarbamate *anti,anti*-**7d** was converted by the action of a solution of sodium hydroxide in methanol into (4a,8a-*trans*-4a,4-*trans*)-4-methyloctahydro-2H-3,1-benzoxazine-2-thione (**10d**).

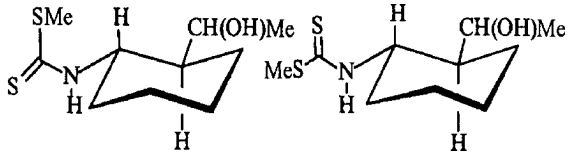


4a,8a-*trans*-4,4a-*trans*-**10d** | *anti,anti*-**7d**

Study of the products of reductive cyclization of carbamate **3b** and dithiocarbamate **4b** showed that the *cis* and *trans* isomers of oxazines **9b** and **10b** are formed in practically equal ratios. The oxazine *trans*-**10b** was isolated from this mixture of isomers by crystallization.

In the IR spectra of liquid samples of compounds **6a,c,f** and **7a,c,** recorded in a thin film, a broad intense band was observed at 3200-3500 cm^{-1} assigned to H-bonded OH and NH groups. At the same time the spectrum of crystalline dithiocarbamate **7d** recorded in Nujol shows two absorption bands at 3320 and 3100 cm^{-1} of the OH and NH groups. The characteristic absorptions of 1,3-oxazin-2-ones **9** and -thiones **10** were in agreement with the known data [26]. In the IR spectra of tetrahydro-1,3-oxazin-2-ones **9** recorded in Nujol the lines observed at 1700 and 3255-3280 cm^{-1} resulted from intermolecular hydrogen bonding of NC=O and NH groups [26]. On dilution of these compounds in chloroform, the bands of NC=O and NH groups free from association appeared in the IR spectra at 1710-1720 and 3440-3460 cm^{-1} (Table 1).

The dithiocarbamates *anti*-**4d** and *anti,anti*-**7d** were in the form of *Z*- and *E*-isomers in a ratio of 4 : 1 in chloroform solution, the existence of which is caused by restricted rotation about the HN–CS_2Me bond. The signal of the proton on the carbon atom of the cyclohexane ring bound to the nitrogen of the *Z*-isomer is observed at lower field (4.43-4.92) than the signals of the *E*-isomer (3.67-4.18), which indicates restricted rotation about the C–$NHCS_2$Me bond [27].



E-anti,anti-7d | *Z-anti,anti*-**7d**

TABLE 1. Characteristics of Compounds **3-7, 9, 10**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (solvent), bp, °C/mm Hg	IR spectrum, ν, cm^{-1}			Yield, %
		C	H	(S)N		NC=X	NH	(C=O) OH	
1	2	3	4	5	6	7	8	9	10
3a*	$C_7H_{13}NO_3$	52.86 / 52.82	8.23 / 8.23	—	72-73/0.4	1710	3280	(1730)*[2]	69
3b	$C_8H_{15}NO_3$	55.49 / 55.47	8.67 / 8.73	—	76-77/0.6	1710	3280	(1725)*[2]	54
3c*	$C_8H_{15}NO_3$	—	—	—	73-75/0.6*[3]	1710	3280	(1725)*[2]	94
anti-**3d**	$C_{10}H_{17}NO_3$	60.32 / 60.28	8.64 / 8.60	7.32 / 7.03	95-96 (alcohol)	1690	3270	(1705)*[4]	97
3e	$C_{14}H_{23}NO_3$	66.33 / 66.37	9.13 / 9.15	5.52 / 5.53	91-92*[5] 30-50/1.0	1700	3320	(1715)*[4]	92
4a*	$C_7H_{13}NOS_2$	43.83 / 43.95	6.91 / 6.85	7.31 / 7.32	115-118/0.05	1510	3230	(1705)*[2]	77
4c	$C_8H_{15}NOS_2$	—	—	—	100-101 (acetone)*[6]	1550	3180	(1710)*[4]	84
anti-**4d**	$C_{10}H_{17}NOS_2$	51.87 / 51.91	7.33 / 7.41	—	91-92 (alcohol–water)	1530	3220	(1690)*[7]	37
5c	$C_8H_{15}NO_2S$	50.63 / 50.77	7.99 / 7.99	—	75-76 (hexane)	1670	3410	(1710)*[8]	71
6f*	$C_5H_{11}NO_3$	45.12 / 45.11	8.30 / 8.33	10.56 / 10.52	98-100/4	1710*[2]	3040-3500		60
6a*	$C_7H_{15}NO_3$	52.38 / 52.16	9.37 / 9.38	8.72 / 8.69	93-96/0.30	1695*[2]	3130-3500		86
6c*	$C_8H_{17}NO_3$	55.20 / 54.84	9.56 / 9.78	8.09 / 7.99	88-90/0.26	1695*[2]	3140-3480		92
7a*	$C_7H_{15}NOS_2$	43.52 / 43.49	7.69 / 7.82	(33.02) / (33.17)	93-95/0.09	1520*[2]	3040-3500		76
7c*	$C_8H_{17}NOS_2$	46.42 / 46.34	8.23 / 8.26	—	98-100/0.03-0.06	1530*[2]	3040-3500		85

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
anti, *anti*-**7d**	$C_{10}H_{19}NOS_2$	51.43 / 51.46	8.28 / 8.21	5.99 / 6.00	132-133 (alcohol)	1550*[4]	3100	3320	36 (68)*[9]
9a*[9]	$C_6H_{11}NO_2$	55.72 / 55.80	8.60 / 8.58	10.82 / 10.84	78-79 (acetone)	1700 1720*[10]	3280 3460	—	81
9c	$C_7H_{13}NO_2$	—	—	—	126-127 (acetone)*[11]	1700 1710*[10]	3255 3440	—	87 (80)*[12]
cis, *trans*-**9d**	$C_9H_{15}NO_2$	63.49 / 63.88	8.81 / 8.93	—	163-164 (acetone)	1680*[4]	3260	—	64*[13] (80)*[9]
9e*[9]	$C_{13}H_{21}NO_2$	69.92 / 69.92	9.54 / 9.48	—	212-213 (acetone)	1700*[8]	3275 3450	—	93
trans-**10a**	$C_6H_{11}NOS$	—	—	—	110-112 (alcohol)*[14]	1570*[4]	3120	—	47*[13] 93*[9]
10c	$C_7H_{13}NOS$	—	—	—	210-211 (alcohol)*[14]	1560*[4]	3165	—	99
trans, *trans*-**10d**	$C_9H_{15}NOS$	58.22 / 58.34	8.16 / 8.16	—	206-208 (alcohol)	1575*[4]	3140	—	93

* n_D^{20} **3a** 1.4505, **3c** 1.4483, **4a** 1.5680, **6a** 1.4605, **6c** 1.4500, **6d** 1.4564, **7a** 1.5630, **7c** 1.5395.

*[2] Thin film.

*[3] Lit. [30] bp 70°C/0.2 mm Hg.

*[4] In nujol.

*[5] Sublimation, 30-50°C/12 mm Hg.

*[6] Lit. [31] mp 101°C.

*[7] KBr pellet.

*[8] In chloroform.

*[9] Mixture of isomers.

*[10] Solution (2%) in $CHCl_3$.

*[11] Lit. [32] 125-126°C.

*[12] Obtained from **6a**.

*[13] According to data of NMR spectrum.

*[14] Lit. [24] **10a** 111-112°C, **10c** 212-213°C (alcohol).

TABLE 2. ^{1}H NMR Spectra of Compounds **3**-**7**, **9**, and **10**

Compound	Chemical shifts of protons, δ, ppm and CC, $^{2,3}J$, Hz							
	C_6-H(^{3}J) C<u>H</u>-OH	R^1 (^{3}J)	R^2 ($^{2,3}J$)	R^3 ($^{2,3}J$)	R^4($^{2,3}J$)	R^5($^{2,3}J$)	NH (^{3}J)	YMe (OH)
1	2	3	4	5	6	7	8	9
3a	—	2.10	1.08 d (6.5)	2.74 m (6.5, 6.5, 6.5)	3.25-3.12 m		5.38 br. s	3.37 s
syn-**3b**	—	2.13	1.11	2.61 m (6.8, 6.8)	2.06 d (7.2)	4.06-3.88 m	4.88 br. d (8.0)	3.58 s
3s	—	2.03	2.76		1.29		5.18 br. s	3.48 s
anti-**3d**	—	2.14	2.34 (4.0, 11.5, 11.5)	2.12-1.10 m		3.68 m	5.97 br. d (9.0)	3.56 s
3e	—	2.12-1.10 m		3.03 dd (5.0, 13.0)	2.12-1.10 m		4.97 br. s	3.58 s
4a	—	2.15	1.13 d (7.5)	3.05 m	3.90-3.57 m		8.00 br. s	2.52 s
4s	—	2.01	3.36		1.53		7.37 br. s	2.47 s
Z-anti-**4d**	—	2.20 s	2.51 m * (11.5, 11.5, 3.3)	2.20-1.60* m	4.92 m (11.5, 11.5, 7.3, 4.0)		7.69 d (7.3)	2.59 s
E-anti-**4d**	—	2.19	2.66-2.55*	2.20-1.60* m	4.18 m (11.5, 11.5, 8.6, 3.3)		8.37 d (8.6)	2.67 s
5s	—	2.06	2.81		1.33		5.79 br. s	2.21 s.
syn-**6a**	3.79 m (6.5, 3.0)	1.05 d (6.5)	0.76 d (7.0)	1.68-1.35 m *	3.50-2.87 m		5.62 br. s	3.58 s *
anti-**6a**	3.52-3.64* m	1.10 d (6.5)	0.80 d (7.0)	1.68-1.35 m *	3.50-2.87 m		5.62 br. s	3.58 s *
6s	3.97 m (9.0, 6.0, 2.5)	1.05 d (6.0)	1.63 dd (14.5, 9.0)	1.33 dd (14.5, 2.5)	1.28 s	1.25 s	6.48 br. s	3.43 s (3.83 br. s)
6f	3.56 m		3.14 m		3.52 m		5.86 br. s	3.52 s (4.00 br. s)
7s	4.18 m (9.5, 6.5, 2.0)	1.25 d (6.5)	1.92 dd (9.5, 15.0)	1.59 dd (2.0, 15.0)	1.69 s	1.65 s	8.90 br. s	2.49 s (2.56 br. s)
Z-anti,*anti*-**7d**	3.90 m (6.5, 5.0)	1.20 d (6.5)		2.30-1.05 m		4.43 m (10.8, 10.8, 8.2, 4.0)	7.52 d (8.2)	2.62 s

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9
E-anti-,anti-**7d**	3.99 m (6.5, 5.0)	1.17 d (6.5)		2.30-1.05 m		3.67 m (10.5, 10.5, 8.2, 5.0)	8.14 d (8.2)	2.68 s
trans-**9a**	4.00 m (10.0, 6.5)	1.32 d (6.5)	0.97 d (6.5)	1.76 m	3.45-2.85 m*		6.80 br. s	—
cis-**9a**	4.42 m (3.5, 6.5)	1.26 d (6.5)	0.92 d (6.5)	2.06 m	3.45-2.85 m*		6.74 br. s	—
trans,cis-**9b**	4.28 m (6.4, 8.0)	1.40 d (6.4)	1.00 d (7.1)	1.93 m (5.3, 7.1, 8.0)	1.19 d (6.7)	3.63 (3.0, 6.7, 5.3)	6.99 br. s	—
cis,cis-**9b**	4.56 m (2.0, 6.5)	1.38 d (6.5)	0.95 d (7.1)	1.80 m	1.23 d (6.6)	3.79 m (4.0, 6.6)	6.70 br. s	—
9s	4.38 (12.0, 7.0, 3.5)	1.26 d (7.0)	1.50 dd (12.0, 3.5)	1.38 dd (12.0, 12.0)	1.23 s	1.23 s	7.31 br. s	—
trans,cis-**9d**	4.44 m (4.6, 6.6)	1.28 d (6.6)	1.97-2.12 m	1.90-0.96 m		3.15 m (4.0, 10.4, 10.4)	7.13 br. s	—
trans,trans-**9d**	3.78 m (6.6, 10.6)	1.32 d (6.6)	1.97-2.12 m	1.90-0.96 m		2.89 m (3.8, 10.5, 10.5)	7.13 br. s	—
trans-**9e**	3.98 m			2.33-0.90 m			6.23 br. s	—
cis-**9e**	4.55 m			2.33-0.90 m			6.23 br. s	—
trans-**10a**	4.15 m (9.6, 6.3)	1.41 d (6.3)	1.04 d (7.0)	1.91 m	3.38 m (12.8, 5.2, 5.0)	2.96 m (12.8, 10.5)	8.99 br. s	—
cis-**10a**	4.57 m (3.0, 6.6)	1.38 d (6.6)	1.02 d (6.6)	2.21 m	3.46 m (12.8, 5.2, 1.9)	3.12 m (12.8, 5.2, 3.2)	8.91 br. s	—
10s	4.47 m (11.4, 6.0, 2.5)	1.44 d (6.0)	1.85 dd (13.4, 2.5)	1.63 dd (13.4, 11.4)	1.36 s	1.33 s	8.61 br. s	—
trans,cis-**10d**	4.60 m (4.7, 6.7)	1.34 d (6.7)	2.18-2.00 m	1.91-0.96 m		3.19 m (4.2, 10.5, 10.5)	8.85 br. s	—
trans, *trans*-**10d**	4.22 m (6.4, 10.4)	1.41 d (6.4)	2.18-2.00 m	1.91-0.96 m		3.08 (4.2, 10.5, 10.5)	8.85 br. s	—

* Signals overlap.

TABLE 3. ^{13}C NMR Spectra of Compounds **3, 4, 6, 7, 9**, and **10**

Compound	Chemical shifts of carbon atoms, δ, ppm ($CHCl_3$)				
	C–O (C=O)	NC=O (NC=S)	OCH_3 (SCH_3)	C–N	signals of other carbon atoms
3a*	(208.8)	156.3	51.2	46.8	42.8, 27.8, 13.8
3c*	(205.1)	154.8	51.3	51.3	50.7, 31.1, 27.3, 27.3
anti-**3d**	(210.1)	155.7	56.9	51.2	50.8, 32.4, 28.1, 26.0, 24.3, 24.1
3e	(211.8)	155.0	56.4	55.8	50.9, 43.6, 31.1, 30.2, 28.9, 28.0, 25.4, 25.2, 21.0, 21.0
4a	(210.3)	198.1	17.0	47.2	44.7, 27.4, 13.4
4c	(206.5)	196.7	17.7	57.2	49.8, 30.7, 26.7, 26.7
6c	64.3	155.5	50.6	51.8	49.5, 27.9, 25.2, 24.7
6f	58.5	156.8	50.7	37.1	31.4
7c	64.2	(195.3)	(17.5)	58.8	49.4, 26.4, 24.6, 22.6
cis-**9a**	75.5	154.2	—	44.4	28.5, 15.8, 10.9
trans-**9a**	78.3	154.5	—	45.3	31.6, 18.4, 13.5
9c	70.1	154.5	—	49.8	41.5, 30.2, 28.9, 20.5
cis-**9e**	71.4	153.2	—	54.2	46.7, 38.3, 36.9, 35.0, 34.1, 32.3, 32.1, 30.1
trans-**9e**	74.7	154.3	—	54.4	25.0, 24.9, 24.6, 24.6, 24.3, 23.6, 21.6, 21.3, 20.2, 20.2, 19.9, 18.9
cis,trans-**9d**	76.1	153.5	—	49.4	40.9, 32.2, 25.6, 25.1, 23.4, 15.2
cis-**10a**	77.7	(185.8)	—	45.7	27.6, 15.8, 11.2
trans-**10a**	80.6	(186.1)	—	46.1	30.5, 18.0, 13.8
10c	73.5	(186.4)	—	53.1	41.6, 30.3, 29.4, 21.1

* Solvent CCl_4.

The chemical shifts and the values of coupling constants (CC) of the *cis*- and *trans*-isomers of oxazines **9** and **10** were in agreement with known data for these heterocyclic systems [11,15,28]. The values of the coupling constants for compounds *trans,cis*-**9d** and **10d** at $^3J_{4a\text{-}H,8a\text{-}H} = 10.5$ and $^3J_{4a\text{-}H,4\text{-}H} = 4.5$ indicate the transoid linking of the rings in 4-methyloctahydro-2H-3,1-benzoxazines and the axial orientation of the 4-CH_3 methyl group. On the other hand oxazines *cis*-**9,10a** and *cis,cis*-**9b** have the axial methyl group at $C_{(5)}$ ($^3J_{6\text{-}Ha,5\text{-}He} = 2.0\text{-}3.5$ and $^3J_{4\text{-}Ha,5\text{-}He} = 4.0\text{-}5.2$), and *trans,cis*-**9b** ($^3J_{6\text{-}Ha,5\text{-}Ha} = 8.0$ and $^3J_{4\text{-}He,5\text{-}Ha} = 5.3$) at $C_{(4)}$. The coupling constant $^3J_{4\text{-}Ha,NH} = 3.0$ Hz characteristic for equatorially oriented 4-H proton also proves the above orientation of compound *trans,trans*-**9b**.

Consequently we have studied the behavior of N-(3-oxoalkyl)carbamates and -dithiocarbamates under borohydride reduction and have shown that, depending on the pH of the medium and the structure of the reactant, this may lead to the formation of N-(3-hydroxyalkyl)carbamates and -dithiocarbamates or tetrahydro-1,3-oxazin-2-ones or -thiones. The results obtained enabled us to develop a one-step method of obtaining tetrahydro-1,3-oxazin-2-ones from N-(3-oxoalkyl)carbamates [29]. Taking into account the availability of N-(3-oxoalkyl)carbamate esters, the stereoselectivity of borohydride reduction, and the simplicity of carrying out reductive cyclization, the present method is of preparative interest for obtaining tetrahydro-1,3-oxazin-2-ones. The pH-controlled borohydride reduction of N-(3-oxoalkyl)carbamates and -dithiocarbamates may be used for obtaining the corresponding hydroxy derivatives and competes successfully with known methods.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker WM 250 (250.2 MHz) and Tesla BS 467 (60 MHz) spectrometers in $CDCl_3$ solution with HMDS as internal standard, and the ^{13}C NMR spectra on a Bruker WP 80 (20.13 MHz) spectrometer. The IR spectra were recorded on Specord IR 75 and UR 10 instruments. The

1,3-amino ketone hydrochlorides were obtained by the procedures of [16,17], and methyl N-(3-oxoalkyl)dithiocarbamates **4a,c** by the procedure of [19].

Methyl N-(3-Oxoalkyl)carbamates (3a-e). The 1,3-amino ketone hydrochloride (0.145 mol), water (10.3 ml), and ether (36.6 ml) were placed in a four-necked flask fitted with a mechanical stirrer and two dropping funnels. The mixture was cooled to -5 to -20°C, and a solution of sodium hydroxide (5.8 g, 0.145 mol) in water (9 ml) was added with vigorous stirring, then methyl chloroformate (0.075 mol) was added dropwise. Thereafter NaOH (5.9 g, 0.145 mol) in H_2O (9 ml) and methyl chloroformate (0.075 mol) were added simultaneously from the two dropping funnels, maintaining the same temperature. The mixture was stirred at room temperature for 30 min. The precipitated NaCl was dissolved in H_2O (10 ml), the organic layer was separated, and the aqueous layer extracted with chloroform (3 × 25 ml). The combined extract was dried over $MgSO_4$, and the solvent was distilled off. The residue was purified by distillation in vacuum or by crystallization.

S-Methyl N-(*anti*-2-Acetylcyclohexyl)dithiocarbamate (4d). A solution of sodium methylate, prepared from sodium (0.078 g, 3.37 mmol) in methanol (2 ml), was added with stirring to a solution of the *anti* isomer of amino ketone hydrochloride **2d** (0.603 g, 3.38 mmol) in methyl alcohol (6 ml) at 0-5°C. Then carbon disulfide (0.257 g, 3.38 mmol) in methanol (1.5 ml) and triethylamine (0.341 g, 3.37 mmol) in methanol (1 ml) were added simultaneously from two dropping funnels. The reaction mixture was stirred for 30 min at the same temperature, methyl iodide (0.480 g; 3.38 mmol) was added, and the mixture was left for 4 h. The solvent was distilled off, and water (5 ml) and chloroform (5 ml) were added to the residue. The organic layer was separated, and the aqueous one extracted with chloroform (2 × 5 ml). The combined chloroform extract was washed with water (3 × 5 ml), and dried with sodium sulfate. The solvent was distilled off. Dithiocarbamate **4d** (0.293 g) was obtained by recrystallization from aqueous alcohol.

S-Methyl N-(1,1-Dimethyl-3-oxobutyl)thiocarbamate (5c). A sample of $SnCl_4$ (4.7 g, 0.04 mol) was added dropwise with stirring to a solution of 4-chloro-4-methylpentan-2-one (5.4 g, 0.04 mol) and methyl thiocyanate (2.7 ml, 0.04 mol) in absolute chloroform (25 ml) at 0°C. The reaction mixture was stirred for 15 min at 0°C, then left overnight at room temperature. The mixture was neutralized with saturated aqueous sodium carbonate solution and left for 20 h. The organic layer was then separated, and the aqueous one extracted with ether (2 × 25 ml). The combined organic layer was dried with anhydrous magnesium sulfate, the solvent was removed, and the residue was recrystallized from hexane. Compound **5c** (5.4 g) was obtained.

Methyl N-(3-Hydroxypropyl)carbamate (6f). 3-Aminopropanol (21.7 g, 0.289 mol), water (20 ml), and ether (70 ml) were mixed in a flask fitted with a stirrer and two dropping funnels. The mixture was cooled to -10°C and methyl chloroformate (11 ml, 0.144 mol) was added with vigorous stirring. A solution of sodium hydroxide (11.4 g, 0.295 mol) in water (18 ml) and methyl chloroformate (11.4 ml, 0.149 mol) were added from the two dropping funnels. The mixture was stirred for 30 min at room temperature, the organic layer was separated off, the aqueous layer was saturated with potassium carbonate, and then extracted with chloroform (4 × 50 ml). The combined extract was dried with sodium sulfate, the solvent was distilled off, and the residue was distilled in vacuum. Compound **6f** (23.2 g) was obtained.

S-Methyl N-[*anti*-2-(*anti*-1-Hydroxyethyl)cyclohexyl]dithiocarbamate (7d). Triethylamine (3.86 ml, 27.8 mmol) and carbon disulfide (1.67 ml, 27.8 mmol) were added simultaneously from two dropping funnels during 30 min to a solution of a mixture of isomers of 1-(*anti*-2-aminocyclohexyl)ethanol [16] (3.97 g, 27.8 mmol) containing 65% *anti* and 35% *syn* isomers in pyridine (4.7 ml) at 0°C. The reaction mixture was stirred for 1 h at 0°C, then methyl iodide (1.73 ml, 27.8 mmol) was added dropwise, and the mixture was left at 0-5°C overnight. The reaction mixture was poured into 1 M sulfuric acid solution (100 ml), and extracted with chloroform (3 × 100 ml). The combined chloroform extract was washed with 1 M sulfuric acid solution (until the disappearance of pyridine according to TLC), with 5% sodium bicarbonate solution, with water, and then dried with sodium sulfate. The solvent was evaporated and a mixture (4.41 g, 68.1%) of the *anti,syn* and *anti,anti* isomers of **7d** was obtained. The compound was crystallized twice from aqueous alcohol. S-Methyl N-[*anti*-2-(*anti*-1-hydroxyethyl)cyclohexyl]dithiocarbamate (2.31 g, 35.6%) was isolated.

Methyl N-(3-Hydroxyalkyl)carbamate (6c) and -Dithiocarbamate (7c). Sodium borohydride (22 mmol) in water (8 ml) was added dropwise with stirring to a mixture containing sodium dihydrophosphate (10.42 g), sodium hydrophosphate (23.82 g), and carbamate **3c** (22 mmol) or dithiocarbamate **4c** (22 mmol) in methanol (150 ml). After 1 h the reaction mixture was diluted with water (150 ml) and ether (100 ml). The organic layer was separated, and the aqueous layer extracted with ether (3 × 70 ml). The combined ether extract was washed with water (2 × 100 ml), dried with magnesium sulfate, the ether was distilled off, and the residue was distilled in vacuum.

Methyl N-(3-Hydroxyalkyl)carbamate (6a) and -Dithiocarbamate (7a). Compounds **3a** and **4a** were reduced analogously to compounds **3c** and **4c** in the absence of the buffer mixture. The reaction mixture was acidified to about pH 7 with conc. HCl 1 h after adding the sodium borohydride, and the methanol was removed in vacuum. Water (5-10 ml) was added to the residue, and the solution was extracted with ether (3 × 30 ml). The combined ether extract was washed with water, with saturated NaCl solution, dried with magnesium sulfate, the ether was distilled off, and the residue was distilled in vacuum.

Tetrahydro-1,3-oxazin-2-ones (9a-e) and -thiones (10a,c). Sodium borohydride (24.5 mmol) was added portionwise into a solution of carbamate **6a-e** (24.5 mmol) or dithiocarbamate **7a,c** (24.5 mmol) in alcohol (40 ml). The mixture was stirred for 1 h, 5 M sodium hydroxide solution (20 ml) in alcohol was added, and the mixture was left overnight. The solvent was distilled off, water (20 ml) was added to the residue, and the solution was extracted with chloroform (3 × 30 ml). The combined chloroform extract was washed with water, with saturated NaCl solution, then dried with calcium chloride, and the solvent was distilled off. Compounds **9c** and **10c** were obtained analogously from **3c**, **4c**, and **5c**, without adding sodium hydroxide solution. Pure (4a,8a-*trans*-4a,4-*cis*)-4-methyloctahydro-2H-3,1-benzoxazin-2-one **9d** and *trans*-5,6-dimethyltetrahydro-1,3-oxazine-2-thione **10a** were isolated from the mixture of isomers after 2-3 recrystallizations from alcohol or acetone.

Interaction of S-Methyl N-(*anti*-2-Acetylcyclohexyl)dithiocarbamate (4d) with Sodium Borohydride. Sodium borohydride (16 mg, 0.42 mmol) in methanol (0.6 ml) was added to a solution of compound **4d** (100 mg, 0.43 mmol) in alcohol (0.5 ml). The reaction mixture was stirred for 4 h and left for a day. The alcohol was then distilled off, water (2 ml) was added to the residue, and the mixture was extracted with chloroform (3 × 10 ml). The chloroform extract was washed with water, then with saturated NaCl solution, and dried with sodium sulfate. The solvent was distilled off, the residue was washed with ether to obtain a mixture of isomers (70 mg, 87.9%) containing according to the data of ^{1}H NMR spectroscopy 60% (4a,8a-*trans*-4a,4-*cis*)- and 40% (4a,8a-*trans*-4a,4-*trans*)-4-methyloctahydro-2H-3,1-benzoxazine-2-thione (**10d**); mp 143-144°C.

(4a,8a-*trans*-4a,4-*trans*)-4-Methyloctahydro-2H-3,1-benzoxazine-2-thione (10d). The N-[*anti*-2-(*anti*-1-hydroxyethyl)cyclohexyl]dithiocarbamate **7d** (0.207 g, 0.89 mmol) was dissolved in 2 M sodium hydroxide solution in methanol (2.0 ml), the mixture was kept at room temperature for 3 h, the solvent was distilled off, the residue was dissolved in water (2 ml), and the mixture was extracted with chloroform (3 × 10 ml). The combined chloroform extract was washed with water, with saturated NaCl solution, dried with magnesium sulfate, and the solvent was distilled off to give 4a,8a-*trans*-4a,4-*trans*-**10d** (0.152 g).

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REFERENCES

1. A. S. Ali, J. S. Wilke, and K. N. Winzenberg, *Aust. J. Chem.*, **49**, 927 (1996).
2. S. Neffgen, H. Keul, and H. Hoecker, *Macromol. Rapid Commun.*, **17**, 373 (1996).
3. B. V. Lebedev, N. N. Smirnova, and E. G. Kiparisova, *Macromol. Chem. Phys.*, **198**, 41 (1997).

4. T. Takiguchi, T. Iwaki, T. Tokano, Y. Kosaka, and S. Nakamura, Jpn. Patent 09151179; *Chem. Abstr.*, **127**, 42427 (1996).
5. A. I. Meyers and C. C. Shaw, *Tetrahedron Lett.*, 717 (1974).
6. V. E. Zakhs, I. P. Yakovlev, and B. A. Ivin, *Khim. Geterotsikl. Soedin.*, 1443 (1987).
7. Z. Eckstein and T. Urbanski, *Adv. Heterocycl. Chem.*, **2**, 311 (1963).
8. Z. Eckstein and T. Urbanski, *Adv. Heterocycl. Chem.*, **23**, 1 (1978).
9. T. Kato, N. Katagiri, and Y. Yamamoto, *Heterocycles*, **14**, 1333 (1980).
10. H. Hioki, T. Izawa, M. Yoshizuka, R. Kunitake, and S. Ito, *Tetrahedron Lett.*, **36**, 2289 (1995).
11. G. Stajer, E. A. Szabo, F. Fulop, G. Bernath, A. Kalman, G. Argay, and P. Sohar, *Tetrahedron*, **39**, 1829 (1983).
12. T. Shono, N. Kise, F. Sanda, S. Ohi, and K. Yoshioka, *Tetrahedron Lett.*, **30**, 1253 (1989).
13. S. J. Kemp, J. Bao, and S. F. Pedersen, *J. Org. Chem.*, **61**, 7162 (1996).
14. C. Singh, H. K. Parwana, and G. Singh, *Indian J. Pharm. Sci.*, **57**, 198 (1995).
15. J. Barluenga, B. Olano, and S. Fustero, *J. Org. Chem.*, **50**, 4052 (1985).
16. I. P. Boiko, Yu. F. Malina, Yu. Yu. Samitov, and B. V. Unkovskii, *Zh. Org. Khim.*, **11**, 605 (1975).
17. L. A. Ignatova, Yu. E. Kazantsev, and B. V. Unkovskii, *Zh. Org. Khim.*, **5**, 1792 (1969).
18. A. V. Peretokin, A. D. Shutalev, V. V. Chupin, A. M. Mergenova, L. A. Ignatova, Yu. F. Malina, and B. V. Unkovskii, *Zh. Org. Khim.*, **21**, 1004 (1985).
19. A. S. Fisyuk and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 416 (1991).
20. R. R. Schmidt, *Chem. Rev.*, **98**, 334 (1965).
21. B. Lebedev, N. Smirnova, and V. Telnoy, *Macromol. Chem. Phys.*, **197**, 3807 (1996).
22. N. Allinger and V. Zalkov, *J. Org. Chem.*, **25**, 701 (1960).
23. M. J. Lyapova and B. J. Kurtev, *Chem. Ber.*, **102**, 3739 (1969).
24. A. B. Khasirdzhev, N. F. Korolenok, and B. V. Unkovskii, USSR Authors Certificate 423796; *Byull. Izobret.*, No. 14, 82 (1974).
25. J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, **257**, 3094 (1952).
26. T. Urbanski and A. Schmidt-Szalowska, *Bull. Pol. Acad. Sci.*, **24**, 447 (1976).
27. H. Paulsen, K. Todt, and H. Ripperger, *Chem. Ber.*, **101**, 3365 (1968).
28. Yu. Yu. Samitov, O. I. Zhuk, I. P. Boiko, B. V. Unkovskii, and Yu. F. Malina, *Zh. Org. Khim.*, **10**, 1283 (1974).
29. A. S. Fisyuk, B. V. Unkovskii, V. P. Zaitsev, A. A. Kondratova, and Yu. F. Malina, USSR Authors Certificate 1203092; *Byull. Izobret.*, No. 123 (1986).
30. R. Lantsch and D. Arlt, *Synthesis*, 756 (1977).
31. J. C. Jochims and A. Abu-Taha, *Chem. Ber.*, **109**, 139 (1976).
32. M. Kahan, *Monatsh. Chem.*, **26**, 942 (1905).