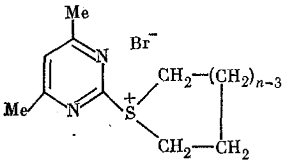
REACTION OF 2-(ω-BROMOALKYLTHIO)-4,6-DIMETHYLPYRIMIDINES WITH SOME NUCLEOPHILIC REAGENTS

A. S. Mikhailov, N. G. Pashkurov,
and V. S. Reznik

UDC 542.91: 547.854.83

In previous work [1], we have shown that the result of the conversions of 2-(ω-bromoalkylthio)-4,6-dimethylpyrimidines (I) upon heating depends on the number of methylene groups (n) in the bromoalkyl radical, and in the case of n = 4, the conversion of (I) proceeds significantly through an intermediate sulfonium salt (II, n = 4)

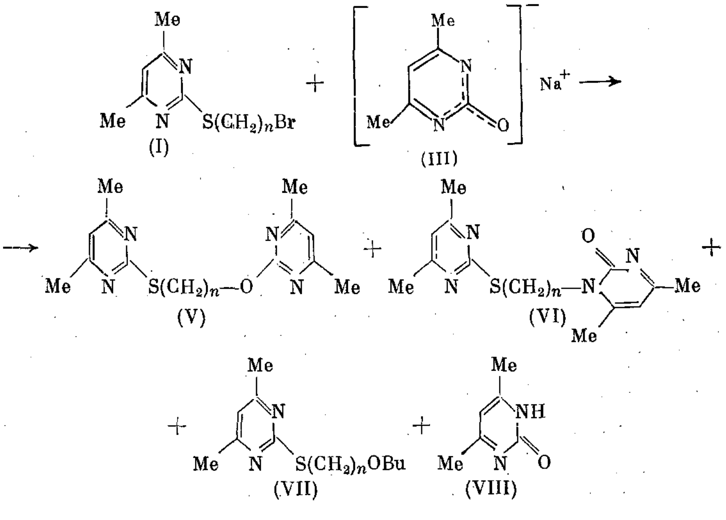


(II)

To determine the role of sulfonium salts (II) in the reactions of (I) with various types of nucleophilic reagents, we investigated the reaction of (I) with the sodium salt of 4,6-dimethyl-2-hydroxypyrimidine (III), the sodium salt of 6-methyl-2-thiouracil (IV), water, and 1-butanol.

The reactions of (I) with (III) were carried out in 1-butanol, which solvates anions, or in DMF, which does not solvate anions. The alkylation of (III) by (I) in 1-butanol yielded 2-[ω-4',6'-dimethylpyrimidinyl-2'-oxy)alkylthio]-4,6-dimethylpyrimidines (V), 2-[ω-(1',2'-dihydro-4',6'-dimethyl-2'-oxopyrimidinyl-N)alkylthio]-4,6-dimethylpyrimidines (VI), 2-(ω-butoxyalkylthio)-4,4-dimethylpyrimidines (VII), and 4,6-dimethyl-2-hydroxypyrimidine (VIII)

Scheme 1



The ratio of (V) and (VI) obtained in the different solvents (1-butanol and DMF) is in accord with literature data [2]. As expected, 1-butanol directly participates in the reaction. Thus, the reactions of (I) with (III) were carried out in 1-butanol in order to clarify the dependence of the ratio of the products on n in (I). The formation of (VII) may occur either through (II) by attack of a 1-butanol molecule on the α-carbon atom of the thia ring or as a result of nucleophilic substitution of the bromine in the bromoalkyl group by a BuO group [3].

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Branch of the Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 1, pp. 155-161, January, 1982. Original article submitted May 4, 1981.

TABLE 1

n in (I)	Reaction temp., °C	Solvent	Reaction time, h	Ratio of reaction products, %		
				(V)	(VI)	(VII)
4	117	1-Butanol	5	9.2	40,0	47,4
4	20	»	250	6,1	74,0	14.6
4	115	DMF	1	61,0	38,0	–
5	117	1-Butanol	12	19.7	54,3	17,4
6	117	»	16	37,1	50,8	4,8
7	117	»	25	34,4	58,0	–

TABLE 2

n in (I)	Time for the complete hydrolysis of (I), h (100°C, 0.24M)
4	6
5	40
6	100

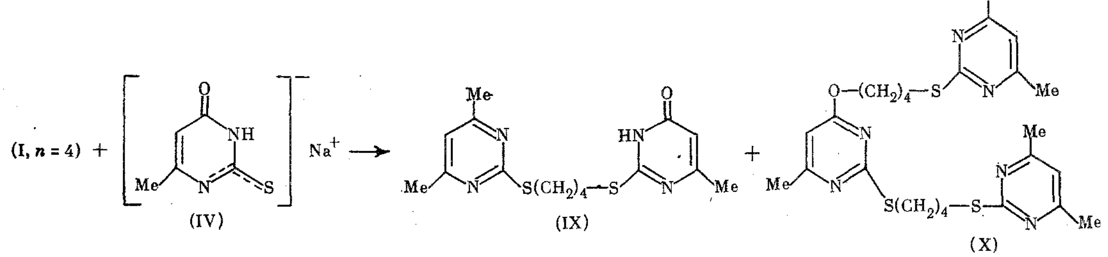
In the latter case, the yields of products (VII) should not depend on n in (I). However, Table 1 shows that such a dependence exists: the greatest yield of (VII) is obtained for n = 4, i.e., when the formation of (II) is most probable. In the case of n = 6, when a significant contribution of (II) would not be expected, the yield of (VII) is minimal, while (VII) is not formed when n = 7 [4]. These results indicate that the contribution of nucleophilic substitution of the bromine atom in the bromoalkyl group in (I) by a BuO group in the formation of (VII) is insignificant. In addition, in going from n = 4 to n = 7, the reaction time increases by a factor of 5; the reaction time is minimal for n = 4 when the formation of (II) is most probable. The latter finding is also indirect proof for the considerable role of intermediate sulfonium salts in the reaction. Carrying out the reaction of (I, n = 4) with (III) in 1-butanol at 20°C leads to a significant increase in the reaction time. In this case, the fraction of (VI, n = 4) rises to 74.0%, while the fraction of (VII, n = 4) drops to 14.6%, which apparently results from the lower probability for the formation of (II, n = 4) under these conditions. Thus, the dependence of the yield of (VII) on n indicates that sulfonium salts (II), whose participation is proven by products of their further transformation, play a significant role in the reaction of (I) with (III) in 1-butanol.

The IR spectra of (V) and (VII) have bands at 1100-1115 cm^{-1} (ν COC) [5], while the IR spectrum of (VI) has a band at 1650-1665 cm^{-1} ($\nu C{=}O$) [6].

Upon carrying out the reaction of (I, n = 4) with (III) in DMF, the solvent does not participate directly in the reaction and only (V, n = 4) and (VI, n = 4) (see Table 1) are formed; the ratio of these products is in accord with literature data [2].

The reaction of (I, n = 4) with (VI) in DMF, as expected [7], leads to the formation of 2-[ω-(3',4'-dihydro-6'-methyl-4'-oxopyrimidinyl-2'-thio)butylthio]-4,6-dimethylpyrimidine (IX) and a small amount of 2-[ω-4',6'-dimethylpyrimidinyl-2'-thio)butylthio]-4-[ω-4",6"-dimethylpyrimidinyl-2"-thio)butyloxy]-6]methylpyrimidine (X) as a result of the reaction of (I, n = 4) with the sodium salt of (IX). The latter is formed from (IX) and (IV) as a consequence of the slight difference in the acid ionization constants of (IX) and 6-methyl-2-thiouracil [7, p. 475]. The formation of (X) is in good accord with literature data on the alkylation of 4-hydroxypyridimines [8]

Scheme 2



(IV) (IX) (X)

The structures of these compounds were confirmed by elemental analysis and IR spectroscopy.

Heating (I) in water at reflux leads to the hydrobromide salt of (VIII), i.e., (XI) and the corresponding α,ω-monothioglycols (XII)

Scheme 3

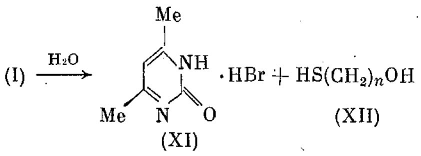
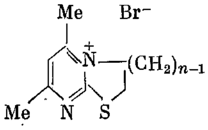


Table 2 shows that the time required for the complete hydrolysis of (I) also depends on n and it is least for n = 4 when the formation of (II, n = 4) is most probable [4]. At 20°C, even a threefold prolongation of the reaction time (relative to the reaction time at reflux) does not lead to the hydrolysis of (I, n = 4).

As noted previously [1, 9], the formation of bicyclic ammonium salts such as (XIII) with greater than a six-membered side-chain was not detected in the reaction of salts of 2-mercaptopyrimidines with α,ω-dihaloalkanes

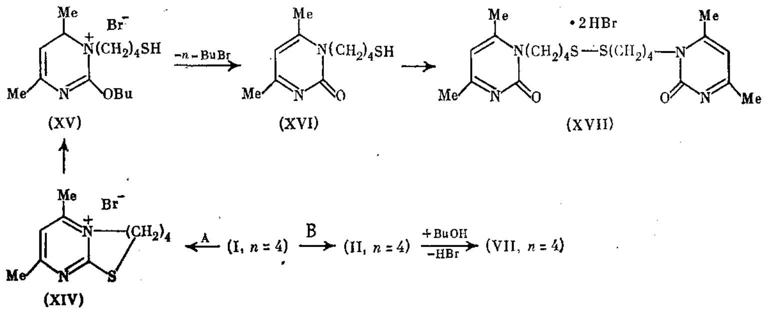


(XIII)

In the present work, we obtained results which indicate the participation of such a structure with a seven-membered side-chain as a reaction intermediate.

Heating (I, n = 4) in 1-butanol led to the isolation of the dihydrobromide salt of bis(1,2-dihydro-4,6-dimethyl-2-oxopyrimidinyl-N-butyl) disulfide (XVII) and (VII, n = 4)

Scheme 4



The formation of (XVII) may be attributed to pathway A through a bicyclic ammonium salt (XIV), which, upon attack by a 1-butanol molecule at the C^2 atom of the pyrimidine ring, opens to give (XV). Similar to the second step of the Hilbert–Johnson reaction (XV) splits off butyl bromide (XVIII) and yields (XVI), which is converted to (XVII) under the reaction conditions. The proof of the structure of (XVII) is based on the elemental analysis and the IR spectrum: 1730 cm^{-1} (C =O) [11] and 2720 cm^{-1} ($\overset{+}{N}H$) [12]. Treatment of (XVII) with a solution of sodium alcoholate yields bis(1,2-dihydro-4,6-dimethyl-2-oxypyrimidinyl-N-butyl) disulfide (XIX) in quantitive yield. The IR spectrum of (XIX) in $CHCl_3$ lacks the band at 2550-2600 cm^{-1} (ν SH) [5, p. 497]. These results, as well as the molecular mass of (XIX) determined by the ebullioscopic method, support structures (XVII) and XIX). Product (VII, n = 4) is formed by the attack of a 1-butanol molecule on the α-carbon atom of the thia ring (II, n = 4) (pathway B). The yields and some physical constants of (XVII) and (XIX) are given in Table 3. The structures of the known (VIII), (XII), and (XVIII) were established by IR spectroscopy, elemental analysis, and comparison of physical constants with literature values.

EXPERIMENTAL

A sample of (I) was obtained according to a previously described procedure [9], and (III) was obtained according to Kosolapoff [13]. The IR spectra were taken on a UR-10 spectrophotometer. The solids were taken

TABLE 3

Compound	n	Yield, % of theoretical	mp., °C (solvent)	d_4^{20}	n_D^{20}	Found/calculated,%			Chemical formula
						C	H	N	
(V)	4	9,2	81–82 (ether)	–	–	60,37 60,38	6,77 6,91	17,81 17,59	$C_{16}H_{22}N_4SO$
(V)	5	19,7	Oil	1,1814	1,5540	61,66 61,45	7,31 7,22	16,80 16,85	$C_{17}H_{24}N_4SO$
(V)	6	37,1	»	1,1884	1,5450	62,24 62,43	7,38 7,50	16,09 16,17	$C_{18}H_{26}N_4SO$
(V)	7	26,1	50–51 (ether)	–	–	63,41 63,34	7,75 7,77	15,53 15,54	$C_{19}H_{28}N_4SO$
(VI)	4	40,0	95–96 (benzene–petrol. ether)	–	–	60.44 60,38	6,81 6,91	17,64 17,59	$C_{16}H_{22}N_4SO$
(VI)	5	54,3	130–131 (benzene–petrol. ether)	–	–	61.60 61,45	7,29 7,22	16,73 16,85	$C_{17}H_{24}N_4SO$
(VI)	6	50,8	180–181 (benzene–petrol. ether)	–	–	62,76 62,43	7,46 7,50	16,21 16,17	$C_{18}H_{26}N_4SO$
(VI)	7	45,6	Oil	–	1,5620	63,50 63,34	7,49 7,77	15.61 15,54	$C_{19}H_{28}N_4SO$
(VII)	4	47,4	Liquid	0,9873	1,4891	62,50 62,69	8,80 8,95	10,45 10,44	$C_{14}H_{24}N_2SO$
(VII)	5	17,4	»	0,9950	1,4955	63,98 63,86	9,11 9,21	9,98 9,92	$C_{15}H_{26}N_2SO$
(VII)	6	4,8	»	1,0635	1,4670	64,82 64,87	9,67 9,45	9,54 9,45	$C_{16}H_{28}N_2SO$
(IX)		79,4	131–132 (benzene)	–	–	53.56 53,57	5,80 5,95	16,75 16,66	$C_{15}H_{20}N_4S_2O$
(X)		16,6	Oil	1,9344	1,5913	56,78 56,60	6,47 6,41	15,79 15,83	$C_{25}H_{34}N_6S_3O$
(XVII) *		39,6	209–210 (dec.) (1-propanol–petrol. ether)	–	–	40,83 40,96	5,82 5,79	9,51 9,55	$C_{20}H_{34}N_4S_2O_2Br_2$
(XIX)			Glassy mass	—	–	56,71 56,60	7,60 7,55	13,21 13,21	$C_{20}H_{32}N_4S_2O_2$

* Found: S 10.81, Br 27.38%. Calculated: S 10.93; Br 27.28%.

as suspensions in Vaseline oil, and the liquids were taken as a thin layer between KBr plates. The column chromatography was carried out on neutral alumina (act. II).

Reaction of (I, n = 4) with (III). a) A sample of 0.47 g sodium was dissolved in 150 ml abs. 1-butanol, 2.54 g (VIII) was added, and the mixture was heated at reflux for 10 h. Then, 5.63 g (I, n = 4) was added, and the mixture was heated at reflux for an additional 5 h. After cooling, 1.5 g (71.4%) sodium bromide was filtered off, the filtrate was evaporated in vacuum to 50 ml, and an additional 0.4 g (19%) sodium bromide was filtered off. The filtrate was evaporated entirely, the residue was treated with 200 ml ether, and 1 g (39.3%) (VIII) was filtered off with mp 200-202°C [14]. The ethereal mother liquor was evaporated, and the residue was subjected to chromatography on an alumina column to yield 2.6 g (VII, n = 4) as a colorless, mobile liquid using 3 : 1 petroleum ether–ether eluent, 0.6 g (V, n = 4) as white crystals using ether eluent, and 2.6 g (VI, n = 4) as white crystals using 1-propanol eluent.

b) A sample of 0.29 g sodium was dissolved in 150 ml 1-butanol, 1.57 g (VIII) was added, and the mixture was heated at reflux for 10 h. Then, 3.5 g (I, n = 4) was added and the mixture was stirred for 250 h at 20°C. The 1-butanol solvent was evaporated in vacuum, and the residue was subjected to chromatography on an alumina column to yield 0.5 g (14.6%) (VII, n = 4) using 1 : 3 ether–petroleum ether eluent, 0.25 g (6.1%) (V, n = 4) using ether eluent, and 3 g (74%) (VI, n = 4) using 1-propanol eluent.

c) A sample of 0.3 g sodium was dissolved in 100 ml 1-butanol, 1.66 g (VIII) was added, and the mixture was heated at reflux for 10 h. The mixture was then evaporated to dryness, and a solution of 3.7 g (I, n = 4) in 150 ml abs. DMF was introduced, and the mixture was heated for 1 h at 115°C. The DMF was evaporated in vacuum, and the residue was subjected to chromatography on alumina to yield 2.6 g (61%) (V, n = 4) using ether eluent and 1.62 g (38%) (VI, n = 4) using 1-propanol eluent.

Reaction of (I, n = 5) with (III). A sample of 0.42 g sodium was dissolved in 150 ml abs. 1-butanol, 2.27 g (VIII) was added, and the mixture was heated at reflux for 10 h. Then, 5.29 g (I, n = 5) was added, and the mixture was heated at reflux for 12 h. After cooling, 1.1 g (61.1%) NaBr was filtered off. The filtrate was evaporated in vacuum to 50 ml, and an additional 0.6 g (33.3%) NaBr was filtered off. The filtrate was completely evaporated, and the residue was treated with 200 ml ether, and 0.3 g (13.2%) (VIII) was filtered off. The ethereal mother liquor was evaporated, and the residue was subjected to chromatography on an alumina column to yield 0.9 g (VII, n = 5) as a colorless, mobile liquid using 3 : 1 petroleum ether–ether eluent, 1.2 g (V, n = 5) as a colorless, viscous oil using ether eluent, and 3.3 g (VI, n = 5) as pale-pink crystals using 1-propanol eluent.

Reaction of (I, n = 6) with (III). A sample of 0.48 g sodium was dissolved in 150 ml abs. 1-butanol, 2.61 g (VIII) was added, and the mixture was heated at reflux for 10 h. Then, 6.37 g (I, n = 6) was added, and the mixture was heated at reflux for 16 h. After cooling, 1.6 g (76%) NaBr was removed by filtration. The filtrate was evaporated in vacuum to 50 ml, and an additional 0.4 g (19.0%) NaBr was filtered off. The filtrate was completely evaporated, the residue was treated with 250 ml ether, and 0.1 g (3.8%)(VIII) was filtered off. The ethereal mother liquor was evaporated, and the residue was subjected to chromatography on an alumina column to yield 0.3 g (VII, n = 6) as a colorless, mobile liquid using 3: 1 petroleum ether–ether eluent, 2.7 g (V, n = 6) as a colorless, viscous oil using ether eluent, and 3.7 g (VI, n = 6) as pale-pink crystals using 1-propanol eluent.

Reaction of (I, n = 7) with (III). A sample of 0.30 g sodium was dissolved in 120 ml abs. 1-butanol, 1.62 g (VIII) was added, and the mixture was heated at reflux for 10 h. Then, 4.1 g (I, n = 7) was added, and the mixture was heated at reflux for 25 h. After cooling, 0.9 g (67%) NaBr was filtered off. The solvent was completely evaporated, the residue was treated with 50 ml 2 : 1 ether–chloroform, and 0.5 g (III) was filtered off. The mother liquor was evaporated, and the residue was subjected to chromatography on an alumina column to yield 1.0 g (24.3%) (I, n = 7) using 4: 1 petroleum ether–ether eluent, 1.2 g (26.1%) (V, n = 7) as white crystals using ether eluent, and 2.1 g (45.6%) (VI, n = 7) as a light-red viscous oil using chloroform eluent.

Reaction of (I, n = 4) with (IV). A sample of 1.4 g (I, n = 4) was added to a solution of 0.83 g (IV) in 100 ml abs. DMF, and the mixture was heated for 3 h at 50°C. The DMF was evaporated in vacuum, the residue was treated with 150 ml benzene, and 0.5 g (96%) NaBr was filtered off. The filtrate was evaporated in vacuum to 50 ml, 30 ml ether was added, and 1.3 g white crystalline (IX) was filtered off. IR spectrum: 1660 cm^{-1} (C =O). The mother liquor was completely evaporated to yield 0.2 g (X) as a colorless, viscous oil using ether eluent. IR spectrum: 1170 cm^{-1} (COC); bands are lacking from 1600 to 1700 cm^{-1} (C =O).

Reaction of (I) with Water. a) A sample of 10.2 g (I, n = 4) was heated at reflux in 150 ml water for 6 h, cooled, and extracted with five 150-ml portions of ether. The extract was dried over magnesium sulfate and evaporated in vacuum to yield 3.5 g (89%) 4-mercaptobutan-1-ol (XII, n = 4) with bp 69-71°C (5 mm) [15]. The water was evaporated in vacuum to yield 7.5 g (98.6%) (XI). IR spectrum: 1730 cm^{-1} (C =O), 2500-2800 cm^{-1} ($\overset{+}{N}$H). Found: C 35.25; H 4.48; N 13.76%. Calculated for $C_6H_9N_2OBr$: C 35.15; H 4.39; N 13.65%. A sample of 4.0 g (XI) was treated with a solution of 0.78 g NaOH in 100 ml water and evaporated to dryness. Fractional crystallization from acetonitrile yielded 2.1 g (87%) (VIII).

b) A sample of 3.1 g (94.5%) 5-mercaptopentan-1-ol (XII, n = 5) with bp 100-103°(17 mm) [16] and 5.5 g (98.2%) (XI) were obtained analogously from 7.9 g (I, n = 5) by heating in 110 ml water for 40 h.

c) A sample of 2.1 g (95.4%) 6-mercaptohexan-1-ol (XII, n = 6) with bp 120-122°C (17 mm) [16] and 3.2 g (94.6%) (XI) were obtained analogously from 5.0 g (I, n = 6) by heating in 65 ml water for 100 h.

Reaction of (I, n = 4) with 1-Butanol. A sample of 9.5 g (I, n = 4) was heated at reflux in 200 ml 1-butanol for 15 h, cooled, and 5.0 g of an initial fraction was distilled over at 100-105°C. 1-Butanol was evaporated in vacuum, the residue was treated with 200 ml ether, and 4.0 g yellow crystalline (XVII) was filtered off. A sample of 2.0 g (XVII) was treated with a solution of 0.16 g sodium in 100 ml isopropyl alcohol and evaporated. The residue was subjected to chromatography on an alumina column to yield 1.3 g (92.8%) (XIX) as a red glassy mass. Molecular mass: 435 (found), 424 (calculated). IR spectrum: 1680 cm^{-1} (C =O). The initial fraction was redistilled at 101-102°C to yield 2.1 g (44.6%) (XVIII) [17]. After the removal of (XVII) the ethereal filtrate was evaporated, and the residue was distilled to yield 4.0 g (43.4%) (VII, n = 4) with bp 122-125°C (2 mm Hg).

CONCLUSIONS

1. The reaction of 2-(ω-bromoalkylthio)-4,6-dimethylpyrimidines with several nucleophilic reagents was studied under various conditions.

2. Cyclic sulfonium or ammonium salts play a significant role in these transformations in the case of four methylene groups in the bromoalkyl group. The participation of these salts was supported by finding the products of their subsequent conversions.

LITERATURE CITED

1. A. S. Mikhailov, N. G. Pashkurov, and V. S. Reznik, Izv. Akad. Nauk SSSR, Ser. Khim., 2767 (1981).
2. G. C. Hopkins, J. P. Jonak, H. Tieckelmann, and H. J. Minnemeyer, J. Org. Chem., 31, 3969 (1966).
3. Laboratory Textbook in Organic Chemistry [Russian translation], Vol. 1, Mir, Moscow (1979), p. 262.
4. E. E. Reid, Organic Chemistry of Bivalent Sulfur, Vol. 3, Chemical Publ. Co., New York (1960), p. 35.
5. L. J. Bellamy, Infrared Spectra of Complex Molecules, Wiley (1958).
6. A. Albert and E. Spinner, J. Chem. Soc., 1221 (1960).
7. D. J. Brown and S. F. Mason, The Pyrimidines, Wiley-Interscience, New York–London (1962), p. 282.
8. J. P. Jonak, G. C. Hopkins, H. J. Minnemeyer, and H. Tieckelmann, J. Org. Chem., 35, 2512 (1970).
9. N. G. Pashkurov and V. S. Reznik, Dokl. Akad. Nauk SSSR, 171, 874 (1966).
10. G. E. Hilbert and T. B. Johnson, J. Am. Chem. Soc., 52, 2001 (1930).
11. E. Spinner, J. Chem. Soc., 1226 (1960).
12. K. Nakanishi, Infrared Absorption Spectroscopy, Holden-Day (1962).
13. G. M. Kosolapoff, and C. H. Roy, J. Org. Chem., 26, 1896 (1961).
14. A. R. Katritzky, M. Kingsland, and O. S. Tee, J. Chem. Soc., B, 1484 (1968).
15. Yu. K. Yur'ev, Kh. M. Minachev, and K. A. Samurskaya, Zh. Obshch. Khim., 9, 1710 (1939).
16. E. J. Goethals and M. Verzele, Bull. Soc. Chim. Belg., 74, 21 (1965).
17. B. P. Nikol'skii (editor), Chemist's Handbook [in Russian], Vol. 2, Goskhimizdat, Moscow–Leningrad (1963), p. 556.