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EXHAUSTIVE N-*tert*-BUTYLATION OF TETRAZOLES IN THE *t*-BuOH-HBF_4 SYSTEM

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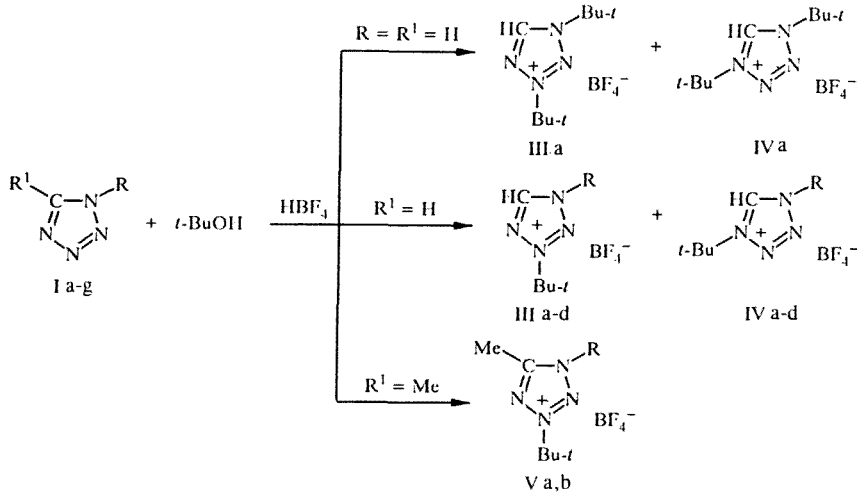
Tetrazole and its N-monosubstituted and C,N-disubstituted derivatives in a 48% HBF_4 medium react with tert-*butyl alcohol, forming the corresponding tetrazolium salts. In this case,* tert-*butylation of 2-monosubstituted and 2,5-disubstituted tetrazoles occurs at the $N_{(4)}$ atom, as in the case of other alkylating agents; the 1-substituted isomers, in contrast, are quaternized preferentially at the less basic atom $N_{(3)}$, while the 1,5-disubstituted isomers are quaternized exclusively at the $N_{(3)}$ atom.*

Exhaustive N-alkylation of tetrazoles is of interest both from the standpoint of determination of the possibilities for enhancing the reactivity of polynitrogen heterocycles [1-3], and also for synthesis of tetrazolium salts which are of practical importance [4, 5]. In this case, up to the present time various methylating [6-9] and ethylating [1, 9, 10] agents have been the best studied in quaternization processes, and only in isolated cases is N-quaternization by other compounds known (bromoacetone [11], phenacyl bromide [12], *tert*-butyl alcohol [7]). Moreover, the widespread use of various quaternizing agents makes it possible not only to expand the assortment of salts obtained and to regulate their properties (thermal stability, solubility, etc.), but also to arrive at a synthesis for other heterocyclic systems [13, 14].

In the case of tetrazoles, the major problems in quaternization are the regioselectivity of the process (connected with the ambident character of the tetrazole ring) and also the low basicity of the cyclic nitrogen atoms, which makes it necessary to search for the optimal reaction conditions.

In this paper, we have studied the quaternization of a large number of tetrazoles in the *t*-BuOH—HBF_4 system, capable of serving as a source of the *tert*-butyl carbocation.



We chose this quaternizing system for the above-indicated reasons and also because it is easy to isolate the tetrazolium tetrafluoroborates formed, and because facile elimination of the *tert*-butyl group from the tetrazole derivative is possible when needed [15].

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TABLE 1. Results of *tert*-Butylation of Tetrazole and Its 1-R-Substituted Derivatives

R	Products	Ratio III : IV*		PMR data for 5-H, δ, ppm			
		A, %	B, %	III	Δδ*2	IV	Δδ*2
H	IIIa, IVa	76 : 24	—	—	—	—	—
Me	IIIb, IVb	20 : 80	60 : 40	9,45	0,30	10,15	1,00
Ph	IIId IVd	37 : 63	67 : 33	9,72	0,42	10,48	1,18
t-Bu	IIIa, IVa	42 : 58	65 : 35	9,70	0,40	10,47	1,17

*A — from the results of preparative isolation; B — from PMR data when carrying out the reaction in the probe of the PMR instrument.

*2Downfield shift of the 5-H signal relative to the 5-H signal of the starting tetrazole.

TABLE 2. Results of Methylation of 1-R-Tetrazoles (Ic,d,h) in Probe of PMR Instrument*

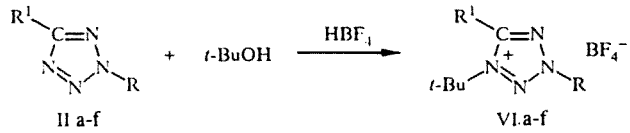
R	Reaction conditions		Isomer ratio of reaction products	
	temperature, °C	time, min	fraction of 1,3-isomer, %	fraction of 1,4-isomer, %
Et	19	500	18	82
Et	34	120	21	79
Et	48	30	22	78
Ph	19	1800	13	87
Ph*2	Room	>2880	10	90
CH=CH$_2$*3	55	300	16	84

*The reaction was carried out without a solvent in an excess of dimethylsulfate.

*2Data from [9].

*3Data from [6].

We showed that the tetrazole (Ia) and its derivatives (Ib-g, IIa-f) react with *tert*-butanol in a 48% HBF_4 medium, forming the corresponding tetrazolium salts (IIIa-d, IVa-d, Va,b, VIa-f):



II a-f VI a-f

I a R = R^1 = H; b-e, III b-d, IV b-d, R^1 = H, b R = Me, c R = CH = CH_2, d R = Ph, e R = *t*-Bu; If, Va R = R^1 = Me; Ig, Vb R = CH = CH_2, R^1 = Me; II a-c, VI a-c, R^1 = H, a R = Me, b R = Et, c R = Allyl; II d-e, VI d-e, R^1 = CH = CH_2, d R = Me, e R = *t*-Bu; IIf, VIf R = Et, R^1 = Mf

We propose the following reaction mechanism:

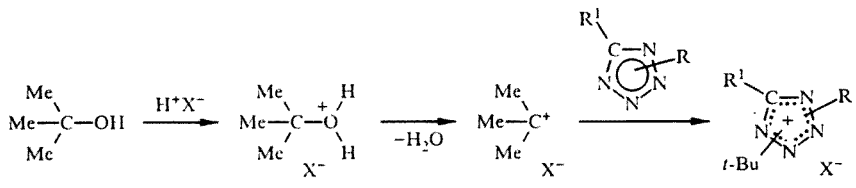


TABLE 3. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	PMR spectrum			Yield, %
			solvent	proton signals, ppm		
				t-Bu	5-H, and other substituents	
Mixture of IIIa*, IVa (from Ia)	$C_9H_{19}N_4BF_4$	—	$DMSO-D_6$	1,73–1,83 (36H, m)	10,48 (1H, s, 5-H, III), 11,03 (1H, s, 5-H, IV)	26
Mixture of IIIa*, IVa (from Ie)	$C_9H_{19}N_4BF_4$	—	CD_3CN	1,73–1,84 (36H, m)	9,60 (1H, s, 5-H, III), 10,06 (1H, s, 5-H, IV)	73
Mixture of IIIb*, IVb	$C_6H_{13}N_4BF_4$	—	CD_3CN	1,79 (9H, s, III), 1,74 (9H, s, IV)	4,34 (3H, s, Me, III), 4,29 (3H, s, Me, IV), 9,52 (1H, s, 5-H, III), 10,25 (1H, s, 5-H, IV)	63
IVc	$C_7H_{13}N_4BF_4$	193–194	CD_3CN	1,78 (9H, s)	5,78–6,42 (2H, m, $\underline{CH_2}$=CH), 7,45 (1H, q, CH_2=$\underline{CH}$), 10,38 (1H, s, 5-H)	19
Mixture of IIIc*2, IVc	$C_7H_{13}N_4BF_4$	—	CD_3CN	1,82 (9H, s, III), 1,78 (9H, s, IV)	5,77–6,44 (4H, m, 2$\underline{CH_2}$=CH, III, IV), 7,31–7,62 (2H, m, 2CH_2=$\underline{CH}$, III, IV), 9,70 (1H, s, 5-H, III), 10,38 (1H, s, 5-H, IV)	41
IIId	$C_{11}H_{15}N_4BF_4$	120–122	CD_3CN	1,88 (9H, s)	7,80–8,00 (5H, m, Ph), 10,30 (1H, s, 5-H)	26
IVd	$C_{11}H_{15}N_4BF_4$	183–185	CD_3CN	1,85 (9H, s)	7,80–8,00 (5H, m, Ph), 10,40 (1H, s, 5-H)	45
Va	$C_7H_{15}N_4BF_4$	151–152*3	CD_3CN	1,76 (9H, s)	2,70 (3H, s, 5-Me), 4,17 (3H, s, 1-Me)	40
Vb	$C_8H_{15}N_4BF_4$	Decomp. without melting > 50°	CD_3CN	1,79 (9H, s)	2,75 (3H, s, Me), 5,84–6,34 (2H, m, $\underline{CH_2}$=CH), 7,30 (1H, q, CH_2=$\underline{CH}$)	40
VIa	$C_6H_{13}N_4BF_4$	155–156	CD_3CN	1,79 (9H, s)	4,59 (3H, s, Me), 9,61 (1H, s, 5-H)	56
VIb	$C_7H_{15}N_4BF_4$	136–137	CD_3CN	1,75 (9H, s)	1,65 (3H, t, CH_2–$\underline{CH_3}$), 4,95 (2H, q, $\underline{CH_2}$–CH_3), 9,50 (1H, s, 5-H)	72
VIc	$C_8H_{15}N_4BF_4$	105–107	CD_3CN	1,82 (9H, s)	5,50–5,73 (4H, m, $\underline{CH_2}$=CH–$\underline{CH_2}$), 6,23 (1H, m, CH_2=$\underline{CH}$–CH_2), 10,22 (1H, s, 5-H)	62
VId	$C_8H_{15}N_4BF_4$	Decomp. without melting > 50°	CD_3CN	1,76 (9H, s)	4,48 (3H, s, Me), 6,15–6,62 (2H, m, $\underline{CH_2}$=CH), 7,10 (1H, q, CH_2=$\underline{CH}$)	45
VIe	$C_{11}H_{21}N_4BF_4$	138–140 (decomp.)	CD_3CD	1,76 (9H, s), 1,78 (9H, s)	6.13-6.62 (2H, m, $\underline{CH_2}$=CH), 7,10 (1H, q, CH_2=$\underline{CH}$)	50
VIf	$C_8H_{17}N_4BF_4$	130–132	$DMSO-D_6$	1,75 (9H, s)	1,59 (3H, t, $\underline{CH_3}$–CH_2), 2,90 (3H, s, Me), 4,86 (2H, q, CH_3–$\underline{CH_2}$)	33
VII	$C_7H_{16}N_4SO_4$	113–115	CD_3CN	1,76 (9H, s)	3,49 (3H, s, CH_3SO_4), 4,33 (3H, s, Me), 10,89 (1H, s, 5-H)	55
VIII	$C_7H_{15}N_4ClO_4$	140–141	$DMSO-D_6$	1,74 (9H, s)	2,74 (3H, s, 5-Me), 4,23 (3H, s, 1-Me)	46

*Isomer ratio indicated in table.

*2Isomer ratio indicated in Experimental section.

*3According to data in [7], 149-150°C.

The process occurs easily at room temperature, and in the case of monosubstituted derivatives, according to PMR spectroscopy the reaction goes to completion within 48 h for 1-R-tetrazoles (Ib-e) and 72 h for 2-R-tetrazoles (IIa-c). The overall yields of tetrazolium salts are 55-80%.

In *tert*-butylation of compounds Ia-e, which do not have a substituent in the 5 position of the ring (R^1 = H), a mixture of isomeric 1,3- and 1,4-disubstituted salts is formed, separation of which is generally a rather complicated problem. We could not judge their actual ratio in the mixture from the results of preparative isolation (Table 1) due to substantial losses of 1,3-isomers (IIIa-d), since the latter are much more soluble than the 1,4 salts (IVa-d) in the solvents used to treat the reaction mixture in isolation of the products.

Accordingly, we carried out *tert*-butylation of tetrazoles Ib,d,e in the probe of the NMR instrument. The results obtained (Table 1) suggest preferential quaternization in the 3 position of the ring, which substantially distinguishes them from data available in the literature and obtained by us on methylation of compounds Ic,d,h (h: R = Et, R^1 = H) by dimethylsulfate (Table 2), which mainly occurs in the direction of formation of the 1,4-disubstituted salts. Such differences in the orientation of alkylation (in the case of *tert*-butylation) are primarily due to the use of a protic solvent, which by reacting with the more nucleophilic center of the tetrazole derivative (the $N_{(4)}$) atom blocks that center and facilitates quaternization at the less nucleophilic atom. Similar behavior was also observed for other ambident molecules in S_N2 reactions when going from aprotic solvents to protic solvents [16].

When a methyl substituent is present in the 5 position of 1-R-tetrazoles (see If,g), the orientation of *tert*-butylation is completely shifted toward formation of the corresponding 1,3,5-trisubstituted salts (Va,b), which is probably due to steric factors. In this case, the yield of end products markedly decreases.

We should note that along with HB_4, for *tert*-butylation of substituted tetrazoles we can also use $HClO_4$ (concentration > 59%) and H_2SO_4 (50-80%). However, in these cases, the tetrazolium salts formed are explosion hazards ($HClO_4$) or difficult to isolate (H_2SO_4).

Earlier, unsuccessful attempts to quaternize various 5-R^1-*tert*-butyltetrazoles (R^1 = CH_3, Cl, SCH_3) by dimethylsulfate were reported, due to the cleavage of the substrates occurring in this case [7, 8]. Only the use of more powerful methylating agents (the methyl ester of fluorosulfonic acid, trimethyloxonium tetrafluoroborate) made it possible to obtain the corresponding methyl-*tert*-butyl-substituted salts. We have shown that in the case of 1-*tert*-butyltetrazole (Ie) (unsubstituted at the 5 position), quaternization by dimethylsulfate occurs at room temperature and 1-*tert*-butyl-4-methyltetrazolium methylsulfate is formed in 55% yield (VII).

The tetrazoles IIa-c substituted in the 2 position and the 2,5-disubstituted tetrazoles IId-f are *tert*-butylated exclusively at the $N_{(4)}$ atom; and in the case of the 2,5-derivatives, the yields of end products are significantly lower. Since the basicity of the 2,5-disubstituted isomers is somewhat higher than the basicity of 2-substituted tetrazoles [17], the decrease in the yield of quaternization products is probably connected (as in the case of the 1,5-derivatives) with steric hindrances to *tert*-butylation in the 4 position.

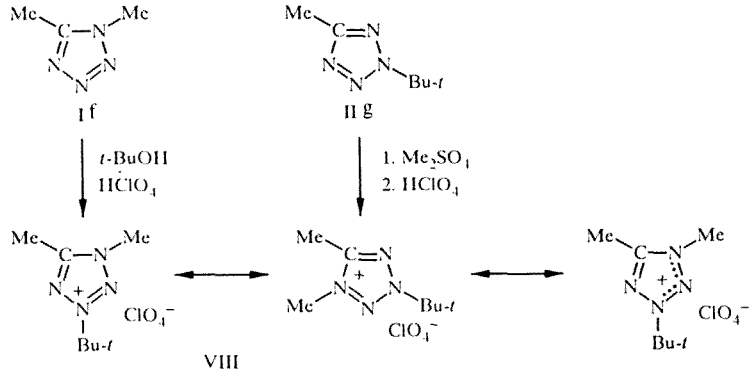
From the data obtained and literature data [6-10], it follows that tetrazoles which have a substituent in the 2 position or are 2,5-disubstituted, in contrast to their 1- and 1,5-isomers, are quaternized selectively at the $N_{(4)}$ atom with formation of 1,3-disubstituted and 1,3,5-trisubstituted salts respectively. The reference to the possibility of quaternization of 2,5-diphenyltetrazole in the 3 position in [18] is incorrect. Tetrazoles with a substituted nitrogen atom, due to their low nucleophilicity, probably cannot be quaternized in the position α to the nitrogen atom. The fact that tetrazoles substituted in the 1 or 1,5 positions are quaternized at the $N_{(4)}$ and $N_{(3)}$ atoms while their 2- and 2,5-isomers are quaternized only at the $N_{(4)}$ atom is consistent with this hypothesis, and agrees well with quantum chemical calculations of the interaction energies for reaction of isomeric tetrazoles with the simplest electrophile (the proton) [19].

We know that in exhaustive alkylation of unsaturated heterocyclic compounds, the quaternization centers do not always coincide with subsequent localization of the positive charge. In a number of salts of isomeric tetrazoles, delocalization of the positive charge has been demonstrated for several examples [6, 10]. We can also include our data on the fact that from 1,5-dimethyltetrazole (If) and 2-*tert*-butyl-5-methyltetrazole (IIg) we obtained salts identical in spectral and physicochemical properties to 1,5-dimethyl-3-*tert*-butyltetrazolium perchlorate (VIII) (see scheme on next page).

The characteristics of the compounds obtained are presented in Table 3.

In the PMR spectra of the synthesized 5-unsubstituted tetrazolium salts (IIIa-e, IVa-e), we observe a substantial downfield shift of the 5-H signal (relative to the signal from the same proton in the starting compounds Ia-e), which is 0.3-0.5 ppm for the 1,3-isomers III and 0.9-1.5 ppm for the 1,4-isomers IV (also see Table 1). The magnitude of the shift, significantly

depending on the solvent used and the concentration of the solution (also see [20]), suggests a substantial increase in mobility of the proton at the carbon atom during quaternization and formation of hydrogen bonds with solvent molecules.



Such values of the chemical shifts for the proton on the cyclic carbon in protonation [21, 22] and quaternization [11, 21] have been previously obtained for the example of a few 1- and 2-substituted tetrazoles. The spin—spin coupling constants $^{13}J_{C-H}$ in this case vary from 211-216 to 233-238 Hz. Using the familiar relationship between the $^{13}J_{C-H}$ and pK_{α} values [23], we can conclude that in quaternization the CH-acidity of N-substituted tetrazoles increases by 5-6 pK_{α} units, which makes the corresponding salts (like other 1,3-azolium salts) considerably more active in deuterium-exchange reactions and other electrophilic processes [3, 24, 25] occurring (as shown repeatedly [1-3, 25, 26]) with intermediate formation of azolium ylides.

The structure of all the compounds was proven with the aid of elemental analysis and PMR spectroscopy data. The products obtained were categorized as 1, 4 (1,4,5)- or 1, 3 (1,3,5)-isomers, as in [7, 9, 21], on the basis of PMR spectroscopy data, which does not cause any difficulties when two isomers are present. The only isomer formed in the case of *tert*-butylation of disubstituted tetrazoles was identified as the 1,3,5-isomer on the basis of comparison of the PMR data with the spectra of the above-indicated mixtures of isomers; the validity of the assignment is also supported by the fact that the properties of compound Va are identical to the properties of the corresponding 1,3,5-isomer described in the literature [7].

EXPERIMENTAL

The starting tetrazoles were synthesized according to the familiar techniques in [27-29]. The PMR spectra were taken on Bruker-360 and Tesla-100 spectrometers.

General Technique for *tert*-Butylation of Substituted Tetrazoles Ia-g and IIa-f. Synthesis of Substituted Tetrazolium Tetrafluoroborates IIIa-d, IVa-d, Va,b, VIa-f. A mixture of 0.01 moles substituted tetrazole Ib-g, IIa-f, 1.48 g (0.02 moles) *tert*-butanol, and 3.7 ml (0.02 moles) 48% HBF_4 was stirred at room temperature for 48 h (in the case of 1-R-tetrazoles I) or 72 h (in the case of 2-R-tetrazoles II). Then the reaction mixture (the starting Ia,b,e-g, IIa-f) was diluted two-fold with water and cooled down to −30 to −50°C. The precipitate was filtered off, washed with cold isopropanol and ether, and dried under vacuum. The products IVc,d were crystallized from the reaction mixture. They were filtered off and the filtrates were diluted with water. A mixture (37:63) of IIIc and IVc precipitated from the dilute filtrate from IVc. From the diluted filtrate from IVd, the salt IIId was crystallized. When carrying out the reaction with tetrazole Ia, the amount of *tert*-butanol and HBF_4 was increased up to 0.05 moles.

When we carried out the reaction according to the technique described above but in $HClO_4$, from If we synthesized 1,5-dimethyl-3-*tert*-butyltetrazolium perchlorate VIII.

1-*tert*-Butyl-4-methyltetrazolium Methylsulfate VII. 1.26 g (0.01 moles) 1-*tert*-butyltetrazole Ie was dissolved in 6.3 g (0.05 moles) dimethylsulfate and held at 20°C for 72 h. Then 15-20 ml ether was added to the reaction mixture. The precipitating crystals were filtered off and washed with cold isopropanol. Obtained: 1.4 g product VII.

1,5-Dimethyl-3-*tert*-butyltetrazolium Perchlorate VIII. A solution of 1.4 g (0.01 moles) tetrazole IIg in 3.78 g (0.03 moles) dimethylsulfate was held for 3 h at 75°C. Then the reaction mixture was cooled, the excess dimethylsulfate was extracted with ether (4 × 5 ml); the residue was dried under vacuum. The 1,5-dimethyl-3-*tert*-butyltetrazolium methylsulfate

obtained (colorless, viscous oil) was dissolved in 2 ml water and 3 ml conc. $HClO_4$ was added. This was cooled, and the precipitating crystals were filtered off and washed on the filter with ice water. Obtained: 2.0 g perchlorate VIII, identical to the product of *tert*-butylation of If in $HClO_4$ described above (T_{mp}, PMR spectrum).

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REFERENCES

1. A. C. Rochat and R. A. Olofson, Tetrahedron Lett., No. 39, 3377 (1969).
2. M. A. Schroeder and R. C. Makino, Tetrahedron, **29**, 3469 (1973).
3. S. Araki, Y. Wanibe, F. Uno, A. Morikawa, K. Yamamoto, K. Chiba, and Y. Butsugan, Chem. Ber., **126**, No. 5, 1149 (1993).
4. Jpn. Pat. 0,527,368; Chem. Abstr., **119**, 59638 (1993).
5. A. B. Zhivich, G. I. Koldobskii, and V. A. Ostrovskii, Khim. Geterotsikl. Soedin., No. 12, 1587 (1990).
6. P. N. Gaponik, O. A. Ivashkevich, V. N. Naumenko, T. B. Kovalyova, T. N. Andreeva, and A. O. Koren, Spectrochim. Acta, Pt. A, **49**, 135 (1993).
7. H. Quast, L. Bieber, and G. Meichsner, Lieb. Ann. Chem., 469 (1987).
8. H. Quast and L. Bieber, Chem. Ber., **114**, 3253 (1981).
9. A. Konneke and E. Lippmann, Z. Chem., **17**, No. 7, 261 (1977).
10. L. A. Lee and J. W. Wheeler, J. Org. Chem., **37**, 348 (1972).
11. V. V. Semenov, V. S. Bogdanov, B. S. Él'yanov, L. G. Mel'nikova, S. A. Shevelev, V. M. Zhulin, and L. Fainzil'berg, Khim. Geterotsikl. Soedin., No. 8, 1118 (1982).
12. D. Moderhack and A. Lembcke, J. Chem. Soc., Perkin Trans. I, 1157 (1986).
13. D. Moderhack, D. O. Bode, and D. Schomburg, Chem. Ber., **126**, 129 (1993).
14. H. Quast and T. Hergenrother, Lieb. Ann. Chem., 581 (1992).
15. R. A. Henry, J. Heterocycl. Chem., **13**, 391 (1976).
16. J. E. Gordon, The Organic Chemistry of Electrolyte Solutions [Russian translation], Mir, Moscow (1979), p. 431.
17. V. N. Naumenko, P. N. Gaponik, A. O. Koren', and M. M. Degtyarik, Vestsi Akad. Nauk Belarusi., Ser. Khim. Navuk, No. 1, 64 (1993).
18. R. M. Claramunt, D. Sanz, G. Boyer, J. Catalan, J. L. G. Paz, and J. Elquero, Magn. Res. Chem., **31**, 791 (1993).
19. O. A. Ivashkevich, P. N. Gaponik, A. O. Koren, O. N. Bubel, and E. V. Fronchek, Int. J. Quant. Chem., **43**, 813 (1992).
20. A. Konneke, S. Behrendt, and E. Lippmann, J. Prakt. Chem., **319**, 408 (1977).
21. A. Konneke, E. Lippmann, and E. Kleinpeter, Tetrahedron, **33**, 1399 (1977).
22. G. I. Koldobskii, V. A. Ostrovskii, and V. S. Poplavskii, Khim. Geterotsikl. Soedin., No. 10, 1299 (1981).
23. O. A. Reutov, I. P. Beletskaya, and K. P. Butin, CH-Acids [in Russian], Nauka, Moscow (1980).
24. P. N. Gaponik, V. N. Naumenko, Yu. V. Grigor'ev, and T. A. Madzievskaya, Vestnik Belorussk. Univ., Ser. 2, No. 1, 9 (1955).
25. L. I. Belen'kii, Khim. Geterotsikl. Soedin., No. 6, 749 (1986).
26. R. H. Lowack and R. Weiss, J. Am. Chem. Soc., **112**, 333 (1990).
27. P. N. Gaponik, V. P. Karavai, and Yu. V. Grigor'ev, Khim. Geterotsikl. Soedin., No. 11, 1521 (1985).
28. P. N. Gaponik, O. A. Ivashkevich, and M. M. Degtyarik, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., **25**, No. 11, 43 (1985).
29. J. H. Markgraf, W. T. Bachmann, and D. P. Hollis, J. Org. Chem., **30**, No. 10, 3472 (1965).