REACTION OF 1,1-DISUBSTITUTED HYDRAZINES WITH BROMINE IN THE PRESENCE OF ARYL- AND HETEROARYLNITROSO COMPOUNDS IN ACID MEDIA: A GENERAL METHOD FOR THE SYNTHESIS OF 1-ARYL(HETEROARYL)-3,3-DISUBSTITUTED TRIAZENE 1-OXIDES

S. G. Zlotin, O. V. Prokshits, N. F. Karpenko, Yu. A. Strelenko, and O. A. Luk'yanov

UDC 541.91:547.234.2:547.491.8: 547.545

We have worked out a method for the synthesis of 1,3,3-trisubstituted triazene 1-oxides based upon reaction of 1,1-disubstituted hydrazines with bromine in the presence of aryl- and heteroarylnitroso compounds in acid media. Obtained are a broad range of triazene 1-oxides, among which hitherto unknown compounds of the series of pyrazole and 3,3-dialkyltriazene 1-oxides that contain functional groups at the alkyl part of the molecule. We propose a reaction scheme which includes in situ formation of diazenium cations and reaction of them with nitroso compounds that are present in the system. By means of PMR, ^{13}C, and ^{14}N NMR spectroscopy, and mass spectroscopy, it has been shown that in all the prepared compounds the oxidated nitrogen atom is at the N^1 position of the triazene N-oxide group.

Keywords: *1,1-disubstituted hydrazines, bromine, nitroso compounds, triazene 1-oxides, acid media, diazenium cations.*

Many compounds containing the triazene 1-oxide moiety have valuable pharmacological (antiinflammatory [1], immunodepressant [2], and other [3, 4]) properties. Traditional methods for the synthesis of triazene 1-oxides based upon reaction of nitrosoarenes with 1,1-disubstituted hydrazines in the presence of oxidants (HgO [1], $Pb(OAc)_4$ [5], dibromoisocyanurate [6]) or an excess of the nitroso compound [5, 7] in neutral organic solvents have limited application. In particular, they do not provide syntheses with preparative yields of known 1-aryl-3,3-dialkyltriazene 1-oxides that have high pharmacological activity [1] and they do not make it possible to prepare compounds of that series that contain functional substituents at the alkyl part of the molecule.

Recently we have shown that 1-aryl-3,3-dialkyltriazene 1-oxides that were not easily accessible earlier can be prepared by reacting nitrosoarenes with 1,1-dialkyldiazeneium salts, generated from the corresponding asymmetrical dialkylhydrazines under the influence of bromine in a strongly acidic (HBr) medium [8].

The aim of this study is the systematic investigation of the reaction of 1,1-disubstituted hydrazines with bromine in the presence of aromatic and heterocyclic nitroso compounds in acid media and to develop a general method for the synthesis of 1-aryl(heteroaryl)-3,3-disubstituted triazene 1-oxides of various structures based upon it.

The solution of the set problem was complicated by two factors: the low stability of triazene 1-oxides to strong acids [7] and the sharp lowering of the lifespan of diazenium salts when switching from strongly acidic to weakly acidic media [9]. To determine the optimal acidity of the medium for the synthesis of triazene 1-oxides we studied the reaction of 1-methyl-1-(β-cyanoethyl)hydrazine with bromine and nitrosobenzene in the presence of acids of different strength: HBr, CF_3COOH, HCOOH, and CH_3COOH.

N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow. Translated from Izvestiya Akademii Nauk, Seriya Khimicheskaya, No. 8, pp. 1804-1820, August, 1992. Original article submitted April 24, 1991; revision submitted March 18, 1992.

 1063-5211/92/4108-1400$12.50

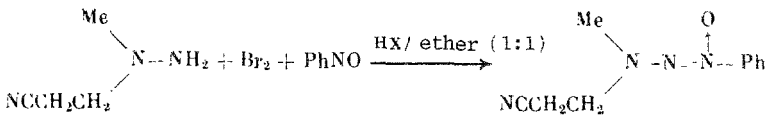
TABLE 1. Dependence of Maximum Yields of 1-Phenyl-3-methyl-3-(β-cyanoethyl)triazine 1-Oxide (**1**) on the Strength of Acid HX

X	pK_a*	Yield of 1, % †
CH_3COO	5.0	47
HCOO	3.7	72
CF_3COO	~0	63
Br‡	−9	63

*pK_a in water.

†When the reaction is carried out in ether without acid the yield of triazine 1-oxide **1** is 25%.

‡40% HBr was used.



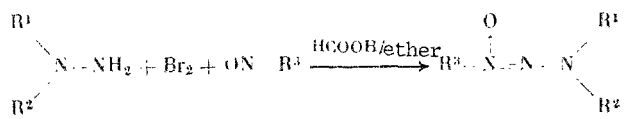
(1)

The reaction was carried out in the presence of an equal volume of an organic solvent (for example ether), the addition of which made it possible to lower the freezing point of the reaction mixture and, consequently, the reaction temperature to −20 to −25°C.* The course of the reaction was monitored with TLC. The time required to reach the maximum yield of product **1** was 2-4 h. Obtained data are listed in Table 1.

It can be seen from Table 1 that high yields of compound **1** are obtained when the reaction is carried out in a medium with an acid of which the pK_a is not greater than 3.7. Use of much weaker acids leads to considerable lowering of the efficiency of the process.

We used the solvent system formic acid−ether (1:1), which gives the highest yield of desired triazene 1-oxide **1**, for studying reactions of 1,1-disubstituted hydrazines of different structure with bromine and nitroso compounds in acidic media.

To determine the synthetic possibilities of the reaction we have carried it out with asymmetric dialkylhydrazines, 1-alkyl-1-arylhydrazines, and 3-amino-2-oxazolidinone. As nitroso compounds we used, in addition to nitrosobenzene, *p*-(dimethylamino)benzene and nitroso derivatives of pyrazole. In all cases we have isolated the corresponding triazene 1-oxides from the reaction. The conditions under which the reactions were carried out and the yields of products are listed in Table 2 (for comparison in a number of cases the yields of triazene 1-oxides in HBr and CF_3COOH are given).



It can be seen from Table 2 that the reaction is characterized by a broad range of applications. In contrast to known methods for the formation of the triazene 1-oxide group, in it react 1,1-disubstituted hydrazines of both linear and cyclic structure, among which compounds that contain other functional substituents.

Reactions that comprise the use of 1-alkyl-1-(2′,4′-dinitrophenyl)hydrazines as hydrazine component are characterized by the highest rate and effectiveness. Thus, by reacting 1-methyl-1-(2′,4′-dinitrophenyl)- and 1-(β-cyanoethyl)-1-(2′,4′-dinitrophenyl)hydrazines with bromine and nitrosobenzene for 30-40 min we have prepared the corresponding 1-phenyl-3-alkyl-3-(2′,4′-dinitrophenyl)triazene 1-oxides (**9**, **10**) in yields of 78-94%.

Generally, reactions with 1,1-dialkylhydrazines are characterized by a longer reaction time (1.5-15 h). The yields of desired 1-aryl(heteroaryl)-3,3-dialkyltriazene 1-oxides are in the range of 35-80%.

*Carrying out the reaction at much higher temperatures caused lowering of the yield of the desired product.

TABLE 2. Characteristics of 3,3-Disubstituted Aryl(pyrazolyl)-triazene 1-Oxides $R^1N(O)=N-NR^2R^3$ (**1-22**), Prepared by Reacting 1,1-Disubstituted Hydrazines with Bromine and Nitroso Compounds in the System HCOOH–Ether (1:1)

Compound	R^1	R^2	R^3	Reaction time, h	Yield, %	Mp, °C (crystallization solvent)	IR spectrum (ν, cm^{-1})	PMR spectrum (δ, ppm, J, Hz) (in $CDCl_3$, internal standard HMDS)	Found / Calculated, % C	H	N
1	Ph	Me	CH_2CH_2CN	2.5	72	Oil	1470 (N=NO),[a] 2240 (CN), 2820–3000 (CH)	2.69 t (2H, CH_2CN, [a] J=7), 3.14 s (3H, CH_3N), 3.54 t (2H, CH_2N, J=7), 7.23–7.47 m (3H, Ph), 7.82–8.09 m (2H, Ph)	58.98 / 58.82	5.71 / 5.88	27.29 / 27.45
2	Ph	Me	Me	1.5	24[b] (73)	Oil	1490 (N=NO),[c] 2800–2970 (CH)	3.15 s (6H, CH_3N), 7.30–7.60 m (3H, Ph), 7.90–8.20 m (2H, Ph)	58.42 / 58.18	6.74 / 6.67	25.68 / 25.45
3	Ph	CH_2CH_2CN	CH_2CH_2CN	0.3	45[d]	59–61 (hexane–ether, 1:1)	1470 (N=NO), 2250 (CN), 2890–2930 (CH)	2.73 t (4H, CH_2, J=7), 3.68 t (4H, CH_2N, J=7), 7.35–7.53 m (3H, Ph), 7.87–8.07 m (2H, Ph)	58.75 / 59.26	5.46 / 5.35	28.53 / 28.81
4	Ph	CH_2CH_2OH	CH_2CH_2OH	2.0	24	Oil	1460 (N=NO), 2920–3000 (CH), 3100–3500 (OH)	3.75 s (8H, CH_2), 4.24 s (2H, OH), 7.28–7.45 m (3H, Ph), 7.78–8.02 m (2H, Ph)	53.81 / 53.33	6.83 / 6.67	18.39 / 18.67
5	Ph	CH_2CH_2OH	CH_2CH_2OCHO	2.0	21[e]	Oil	1260 (C–O–C), 1475 (N=NO), 1710 (C=O), 2880–3000 (CH), 3200–3600 (OH)	3.76 s (4H, CH_2CH_2O(H)), 3.82 t (2H, CH_2N, J=7), 4.39 t (2H, CH_2O, J=7), 7.18–7.68 m (3H, Ph), 7.69–7.93 m (2H, Ph), 7.99 s (1H, CHO)	51.97 / 52.17	5.74 / 5.93	16.87 / 16.60
6	Ph	CH_2CH_2OCHO	CH_2CH_2OCHO	2.0	7[e]	Oil	1260 (C–O–C), 1480 (N=NO), 1725 (C=O), 2890–2980 (CH)	3.77 t (4H, CH_2N, J=7), 4.30 t (4H, CH_2O, J=7), 7.12–7.50 m (3H, Ph), 7.60–7.85 m (2H, Ph), 7.90 s (2H, CHO)	51.03 / 51.25	5.60 / 5.34	15.11 / 14.95
7	Ph	$-C(CH_3)_3$	CH_2CH_2CN	2.0	38	Oil	1480 (N=NO), 2255 (C≡N), 2880–2990 (CH)	1.22 s (9H, CH_3), 2.75 t (2H, CH_2, J=7), 4.03 t (2H, CH_2N, J=7), 7.30–7.50 m (3H, Ph), 7.85–8.03 m (2H, Ph),	63.73 / 63.41	7.51 / 7.32	22.49 / 22.76
8	Ph	CH_2CH_2Cl	CH_2CH_2Cl	2.0	56	Oil	760 (C–Cl), 1490 (N=NO), 2950–3040 (CH)	3.73–4.23 m (3H, CH_2CH_2), 7.37–7.67 m (3H, Ph), 7.78–8.10 m (2H, Ph)	–[f]	–	–

9	Ph	Me	$2,4(NO_2)_2C_6H_3$	0.2	94	95–97[g] (dec.)	1490 (N=NO), 1345, 1520 (NO_2), 1600 (Ar), 3050–3190 (CH)	3.64 s (3H, CH_3), [h] 7.35–7.75 m (3H, Ph), 7.83–8.05 m (2H, Ph), 8.26–8.74 m (3H, Ph),	48.89 49.21	3.43 3.47	24.89 25.24
10	Ph	CH_2CH_2CN	$2,4(NO_2)_2C_6H_3$	0.5	78	89–90[g] (dec.)	1480 (N=NO), 1350, 1520 (NO_2) 2255 (CN)	2.94 t (2H, CH_2C, J=7) [h] 4.15 t (2H, CH_2N, J=7), 7.10–9.07 m (8H, Ph, C_6H_3)	49.96 50.56	3.22 3.37	23.53 23.59
11	Ph	$-COOCH_2CH_2-$		1.0	29	101–102 (EtOH) Lit. data see [1]	1200 (C–O–C), [a] 1480 (N=NO), 1790 (C=O)	4.24–4.65m (4H, NCH_2CH_2O), [h] 7.47–7.67m (3H, Ph), 7.98–8.13 m (2H, Ph)	–	–	–
12	p-$Me_2NC_6H_4$	Me	Me	3.0	40	79–81 (hexane-ether, 1:1) cf. [1]	1500 (N=NO), 1600, 2800–2950 (CH)	2.91 s (6H, CH_3), 2.95s (6H, CH_3), 6.54[d] (2H, C_6H_4, J=9), 7.81[d] (2H, C_6H_4, J=9)	–	–	–
13	DMP[i]	Me	Me	2.0	68	64–66 (hexane-ether 2:1)	1490 (N=NO), 1600, 2900–3200 (CH, NH)	2.37 s (6H, CH_3C), 2.95 s (6H, CH_3N),	45.79 45.90	7.13 7.10	38.22 38.25
14[j]	DMP	Me	CH_2CH_2CN	2.5	70	43–45 (hexane-ether, 2:1)	1480 (N=NO), 1590, 2240 (C≡N), 2800–3600 (CH, H_2O, NH)	2.41 s (6H, CH_3C), 2.68t (2H, CH_2C, J=7), 3.05s (3H, CH_3N), 3.51[t] (2H, CH_2N, J=7)	45.31 45.00	6.39 6.67	35.28 35.00
15	DMP	CH_2CH_2CN	CH_2CH_2CN	4.0	35	84–86 (hexane-ether 2:1)	1480 (N=NO), 2250 (C≡N), 2900–3200 (CH, NH)	2.36 s (6H, CH_3), 2.69 t (4H, CH_2C, J=7), 3.63[t] (4H, CH_2N, J=7)	49.99 50.57	5.93 5.75	38.07 37.55
16	DMP	CH_2CH_2OH	CH_2CH_2OCHO	15.0	24[e]	Oil	1260 (C–O–C), 1480 (N=NO), 1590, 1710 (C=O), 2900–3600 (CH, OH, NH)	2.27 s (6H, CH_3) [h] 3.43–3.67 m (5H, CH_2CH_2OH), 3.74t (2H, CH_2N, J=7), 4.30[t] (2H, CH_2O, J=7), 8.05 s (1H, CHO)	44.75 44.28	6.53 6.27	25.39 25.83

TABLE 2 (continued)

Compound	R^1	R^2	R^3	Reaction time, h	Yield, %	Mp, °C (crystallization solvent)	IR spectrum (ν, cm^{-1})	PMR spectrum (δ, ppm, J, Hz) (in $CDCl_3$, internal standard HMDS)	Found / Calculated, % C	H	N
17	DMP	CH_2CH_2OCHO	CH_2CH_2OCHO	15.0	57[e]	Oil	1255 (C–O–C), 1480 (N=NO), 1590, 1710 (C=O), 2900–3600 (CH, NH)	2.23 s (6H, CH_3), 3.65 t (4H, CH_2N, J=7), 4.23 t (4H, CH_2O, J=7), 7.97 s (2H, CHO)	44.62 / 44.15	5.92 / 5.69	22.94 / 22.41
18	TMP[k]	Me	Me	2.5	69	25–26 (hexane–ether, 2:1)	1480 (N=NO), 1560, 2870–2970 (CH)	2.30s (3H, CH_3–C), 2.38s (3H, CH_3–C), 2.95s (6H, $N(CH_3)_2$), 3.67s (3H, $\diagdown NCH_3$)	48.38 / 48.73	7.49 / 7.61	34.97 / 35.53
19	TMP	Me	CH_2CH_2CN	2.5	80	53–54 (hexane–ether, 1:1)	1490 (N=NO), 1570, 2250 (C≡N), 2870–2970 (CH)	2.28s (3H, CH_3–C), 2.43s (3H, CH_3–C), 2.61t (2H, CH_2–C, J=7), 3.07s (3H, CH_3–N), 3.56t (2H, CH_2–N, J=7), 3.71s (3H, $\diagdown N$–CH_3)	50.98 / 50.85	7.01 / 6.78	36.02 / 35.59
20	TMP	CH_2CH_2CN	CH_2CH_2CN	3.0	45	74–75 (hexane–EtOH 1:1)	1480 (N=NO), 2250 (C≡N), 2870–2970 (CH)	2.32s (3H, CH_3–C), 2.42s (3H, CH_3–C), 2.68t (4H, CH_2C, J=7), 3.61t (4H, CH_2N, J=7), 3.66 s (3H, $\diagdown N$–CH_3)	52.50 / 52.36	6.23 / 6.18	35.71 / 35.64
21	TMP	CH_2CH_2OH	CH_2CH_2OCHO	4.5	15[e]	Oil	1240 (C–O–C), 1520 (N=NO), 1700 (C=O), 2870–2950 (CH), 3100–3600 (OH)	2.17 s (3H, CH_3–C),[h] 2.32s (3H, CH_3–C), 3.37s (5H, CH_2CH_2OH), 3.60 s (3H, $\diagdown N$–CH_3), 3.73t (2H, CH_2N, J=7), 4.31 t (2H, CH_2O, J=7), 8.07s (1H, OCHO),	46.77 / 46.32	6.74 / 6.67	24.29 / 24.56

22	IMP	CH_2CH_2OCHO	CH_2CH_2OCHO	4.5	39[e]	Oil	1240 (C–O–C), 1520 (N=NO), 1700 (C=O), 2870–2950 (CH)	2.22 s (3H, CH_3–C),[h] 2.35 s (3H, CH_3–C), 3.66 s (3H, $\diagdown N-CH_3$), 3.73 t (4H, CH_2N, $J=7$), 4.30 t (4H, CH_2O, $J=7$), 8.05 s (2H, OCHO)	45.83 / 46.01	6.22 / 6.07	22.04 / 22.36

[a]IR and PMR spectra identical with those of [6].

[b]Reaction carried out in 40% HBr–ether, time 10 h.

[c]IR and PMR spectra identical with those of [5].

[d]Reaction carried out in CF_3COOH.

[e]The hydrazine used in the reaction was 1,1-bis(β-hydroxyethyl)hydrazine.

[f]A satisfactory analysis could not be obtained — the product decomposed when chromatographed.

[g]Because of its low thermal stability the product could not be recrystallized. An analytically pure sample was prepared by washing the raw material with 50% aqueous ethanol.

[h]PMR spectrum recorded in acetone-d_6.

[i]3,5-Dimethylpyrazolyl-4.

[j]Product isolated as the monohydrate.

[k]1,3,5-Trimethylpyrazolyl-4.

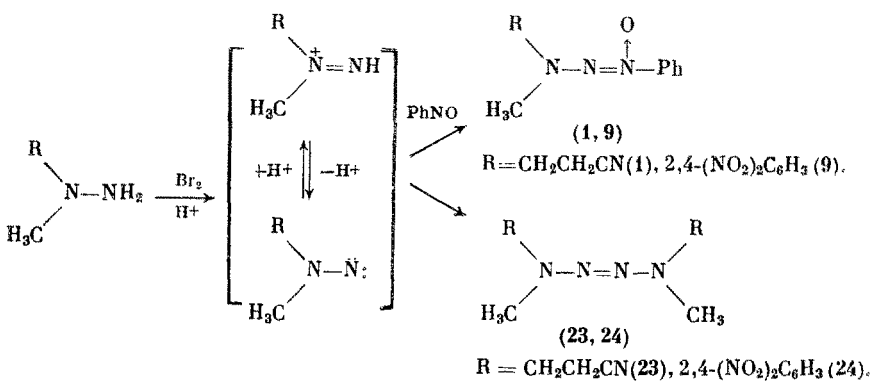
Reaction of 3-aminooxazolidone-2 with nitrosobenzene and bromine in both HCOOH–ether and in CF_3COOH leads to 3-(O,N,N-phenylazoxy)oxazolidone-2 **11** in only moderate yield (29%). Functional groups contained in the hydrazine component may enter into chemical conversions under the reaction conditions. Thus, in processes in which 1,1-bis(β-hydroxyethyl)hydrazine participates, a noticeable role is played by formylation of the hydroxyl groups by HCOOH. As a result, in addition to the expected 3,3-bis(β-hydroxyethyl)triazene 1-oxides, we have isolated from the reaction mixture their mono- and diformylated derivatives (**5, 6, 16, 17, 21, 22**).* The total yield of alcohols and formates is 52-81% in this case.

In addition to compounds containing a triazene 1-oxide group, in reactions of asymmetrical dimethyl- and bis(β-hydroxyethyl)hydrazines with bromine and nitrosobenzene in HCOOH we have detected formation of noticeable amounts (18-40%) of 4,4′-dibromoazoxybenzene, which probably is the product of supplementary oxidation–reduction processes that proceed under the influence of bromine under the reaction conditions. However, formation of unwanted by-products can successfully be avoided by carrying out the reaction in HBr.

The most important merit of the proposed method is the possibility of preparing with it triazene 1-oxides containing heterocyclic fragments. Thus, by reacting nitroso derivatives of pyrazole with 1,1-disubstituted hydrazines and bromine in HCOOH–ether we have prepared in good yields the corresponding 1-pyrazolyltriazene 1-oxides (**13-22**). It should be noted that nitroso compounds of the heterocyclic series were earlier not involved in the reaction with hydrazine derivatives and prepared triazene N-oxides **13-22** are the first members of compounds that contain heterocyclic substituents at the oxidated nitrogen atom of the triazene 1-oxide group.

Thus, the method that we have developed for the synthesis of 1,3,3-trisubstituted triazene 1-oxides based upon the reaction of hydrazine derivatives with bromine and nitroso compounds in acidic media is of a general nature. It makes it possible to synthesize a broad range of triazene 1-oxides of different structures, among them earlier-unknown compounds of the heterocyclic series and 3,3-dialkyltriazene 1-oxides containing functional groups at the alkyl part of the molecule.

Probably, the reaction of 1,1-disubstitued hydrazines with bromine and nitroso compounds in a medium of relatively weak organic acids, as with conversions of similar compounds in strongly acidic media [8], may include the stage of formation of a protonated form of nitrenes (diazenium salts) that react further with nitroso compounds present in the system with repulsion of the proton and formation of desired triazene 1-oxides.



The important role of acid–base conversions of diazenium intermediates in the reaction is confirmed by the considerable lowering of the yield of 1-phenyl-3-methyl-3-(β-cyanoethyl)triazene 1-oxide **1** when the acidity of the medium is lower to under a certain value (Table 1) and the synthesis of tetrazenes **23** and **24**, which are characteristic dimerization products of diazenium salts in neutral and weakly acidic media [9], when the reaction of corresponding 1,1-disubstituted hydrazines with bromine is carried out without nitroso compounds. In contrast to triazene oxide **1**, the yield of compound **23** increases with the increase in pK_a of the used acid (17% CF_3COOH, 82% HCOOH–ether), which corresponds with literature data on the influence of the acidity of the medium on the dimerization of diazenium salts [9] and is in agreement with the assumption of participation of the latter in the studied reaction.

The wide variety of derivatives of triazene N-oxides that can be prepared by the proposed method is significantly enlarged as a result of the capability of the prepared compounds to enter into chemical conversions in which the functional groups that they contain react. We have demonstrated the possibility of chemical transformations of the substituents in 1-aryl(heteroaryl)-3,3-disubstituted triazene 1-oxides with the examples of esterification and saponification reactions of 1-aryl(heteroaryl)-3,3-bis(β-hydroxyethyl)triazene 1-oxides and their esters, respectively, and the decyanoethylation reaction of 1-phenyl-3-(2′,4′-dinitrophenyl)-3-(β-cyanoethyl)triazine 1-oxide (**10**).

*In the case of triazene N-oxides of the pyrazole series, mono- and diformates (**16, 17, 21, 22**) are the only reaction products.

TABLE 3. Chemical Shifts of ^{13}C NMR Signals of Triazene 1-Oxides R–N(O)=N–N(Me)R′ (ppm)

Compound	CH_3	CH_2N	CH_2CN	CN	Signals of R
1	40.78	53.12	17.04	119.55	146.52 (C^i), 121.78 (C^o), 129.75 (C^m), 131.30 (C^p)
2	43.51	–	–	–	146.77 (C^i), 121.66 (C^o), 129.76 (C^m), 131.06 (C^p)
19*	40.70	52.90	16.79	119.54	127.52 (C^1), 135.62 (C^2), 141.44 (C^3), 13.80 (C^4), 10.88 (C^5), 36.61 (C^6)

*$^3J_{(H^6\text{-}C^2)}$ = 2.3 Hz; $^2J_{(H^4\text{-}C^3)}$ = 4.9 Hz; $^3J_{(H^4\text{-}C^1)}$ = 2.0 Hz.

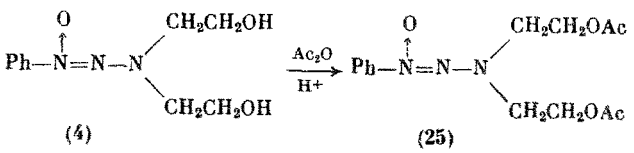
TABLE 4. Chemical Shifts (ppm) and Width (Hz) of ^{14}N NMR Signals of Triazene 1-Oxides R–N^1(O)=N^2–N^3(Me)R′ (**1, 2 19**)

Compound	N^1		N^2		N^3		CN		N of pyrazole ring	
	δ	$\Delta\nu_{1/2}$	δ	$\Delta\nu_{1/2}$	δ	$\Delta\nu_{1/2}$	δ	$\Delta\nu_{1/2}$	δ	$\Delta\nu_{1/2}$
1	–77.5	170	–20.7	900	–275.9	1400	–135.0	700	–	–
2	–79.3	52	–15.1	520	–270.7	800	–	–	–	–
19	–77.1	119	*	*	*	*	–134.9	600	–189.9†	600†

*Not found.

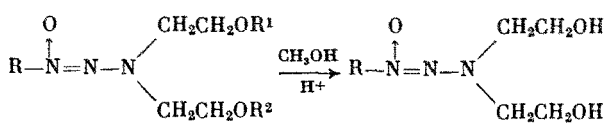
†Only one signal was found.

As has been mentioned above, the reaction of partial formylation of 3,3-bis(β-hydroxyethyl)triazene 1-oxides already proceeds under the conditions of the synthesis of these compounds from nitrosoarenes (nitrosoazoles), 1,1-bis(β-hydroxyethyl)hydrazine, and bromine in HCOOH. Also the initially obtained triazene 1-oxides containing hydroxyl groups enter easily in the esterification reaction. Thus, reaction of compound **4** with acetic anhydride in the presence of a catalytic amount of H_2SO_4 leads to formation of 1-phenyl-3,3-bis(β-acetoxyethyl)triazene 1-oxide (**25**) in a yield of 60%.



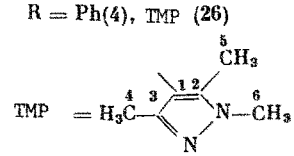
(4) (25)

The esterification reaction is reversible: addition of a catalytic amount of H_2SO_4 to a methanolic solution of esters **5, 6, 21, 22,** and **25** makes it possible to prepare the corresponding 1-aryl(heteroaryl)-3,3-bis(β-hydroxyethyl)triazene 1-oxides, among them compound **26**, which is inaccessible by direct oxidative condensation reaction of 1,1-bis(β-hydroxyethyl)hydrazine with 1,3,5-trimethyl-4-nitrosopyrazole in the presence of a halogenating agent.



(5, 6, 21, 22, 25) (4, 26)

R = Ph(4), TMP (**26**)

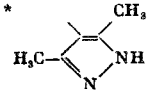


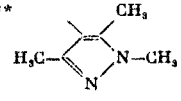
Compound	R	R^1	R^2
5	Ph	H	CHO
6	Ph	CHO	CHO
21	TMP	H	CHO
22	TMP	CHO	CHO
25	Ph	Ac	Ac

TABLE 5. Molecular and Fragmental Ions in the Mass Spectra of 1-Aryl(heteroaryl)-3,3-disubstituted Triazene 1-Oxides $R^1N(O)=N-NR^2R^3$

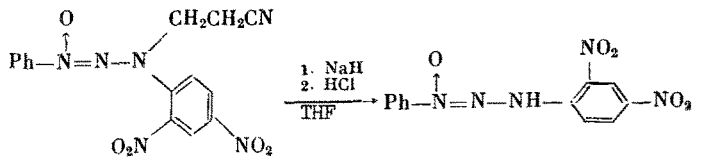
Compound	R^1	R^2	R^3	Molecular and fragmental ions, m/z (I_{rel}, %)					
				M^+	R^1-NO^{+}	$(H)N-N^{R^2}_{R^3}$	$R^1N_2^+$	$(H)N^{R^2}_{R^3}$	Other fragmental ions
1	Ph	Me	CH_2CH_2CN	204 (43)	107 (67)	97 (62)	105 (40)		93 (38) $PhNH_2^+$, 78 (69) $C_6H_6^+$, 68 (100) $NCH_2CH_2CN^+$, 54 (48) $CH_2CH_2CN^+$
2	Ph	Me	Me	165 (16)	107 (11)	58 (83)	105 (17)		77 (100) $C_6H_5^+$
3	Ph	CH_2CH_2CN	CH_2CH_2CN	243 (100)	107 (80)	136 (40)	105 (70)	122 (15) or PhN (O) NH^+	77 (100) $C_6H_5^+$, 54 (60) $CH_2CH_2CN^+$
5	Ph	CH_2CH_2OH	CH_2CH_2OCHO	253 (37)	107 (27)	146 (37)	105 (33)		77 (100) $C_6H_5^+$, 73 (90) $CH_2CH_2OCH^+$, 45 (80) $CH_2CH_2OH^+$
6	Ph	CH_2CH_2OCHO	CH_2CH_2OCHO	281 (75)	107 (100)	174 (50)	105 (90)	161 (10)	77 (90) $C_6H_5^+$, 73 (100) $CH_2CH_2OCHO^+$, 45 (59) $CH_2CH_2OH^+$
7	Ph	*t*-Bu	CH_2CH_2CN	246 (1)	107 (11)		105 (2)		77 (18) $C_6H_5^+$, 57 (100) $C(CH_3)_3^+$, 54 (5) $CH_2CH_2CN^+$
8	Ph	CH_2CH_2Cl	CH_2CH_2Cl	261 263 265	107		105		77 $C_6H_5^+$, 78 $C_6H_6^+$, 63,65 $CH_2CH_2Cl^+$
9	Ph	Me	2,4-$(NO_2)_2C_6H_3$	317 (1)	107 (16)		105 (36)		195 (8) 2,4-$(NO_2)_2C_6H_3N_2^+$, 183 (8) 2,4-$(NO_2)_2C_6H_3NH_2^+$, 77 (100) $C_6H_5^+$

14	DMP*	Me	CH_2CH_2CN	222 (18)	125 (97)	98 (100)			54 (59) $CH_2CH_2CN^+$
15	DMP*	CH_2CH_2CN	CH_2CH_2CN	261 (1)	125 (100)	137 (14)	123 (3)	122 (2)	54 (70) $CH_2CH_2CN^+$
18	TMP**	Me	Me	197 (42)	139 (87)	58 (62)	137 (27)		154 (100)
19	TMP**	Me	CH_2CH_2CN	236 (2)	139 (36)	97 (40)	137 (9)	83 (36)	54 (100) $CH_2CH_2CN^+$
20	TMP**	CH_2CH_2CN	CH_2CH_2CN	275 (4)	139 (100)	137 (3)	137 (3)		54 (20) $CH_2CH_2CN^+$
21	TMP**	CH_2CH_2OH	CH_2CH_2OCHO		139 (100)				73 (20) $CH_2CH_2OCHO^+$ 45 (66) $CH_2CH_2OH^+$
22	TMP**	CH_2CH_2OCHO	CH_2CH_2OCHO	313 (13)	139 (100)		137 (15)		73 (97) $CH_2CH_2OCHO^+$
25	Ph	$CH_2CH_2OCOCH_3$	$CH_2CH_2OCOCH_3$	309	107		105	188	87 $CH_2CH_2OCOCH_3^+$, 77 $C_6H_5^+$
27	Ph	H	$2,4\text{-}(NO_2)_2C_6H_3$	303 (11)	107 (15)		105 (6)		108 (100) $PhNOH^+$, 78 (56) $C_6H_6^{+\cdot}$, 77 (54) $C_6H_5^+$

* 

** 

The decyanoethylation reaction of triazene 1-oxides that we have discovered opens up considerable synthetic possibilities. Thus, treatment of 1-phenyl-3-(2′,4′-dinitrophenyl)-3-(β-cyanoethyl)triazene 1-oxide (**10**) with NaH in tetrahydrofuran gives splitting off of the cyanoethyl substituent and leads to formation of 1-phenyl-3-(2′,4′-dinitrophenyl)triazene 1-oxide (**27**) in a yield of 48%.



(10) (27)

That reaction is likely to be the first example of the conversion of trisubstituted triazene N-oxides to disubstituted ones and may serve as a convenient method for the synthesis of compounds of that series, among which compounds that contain strong electron-accepting substituents.

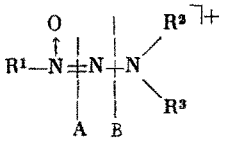
The compounds that have been synthesized by the reaction of nitroso compounds with 1,1-disubstituted hydrazines and bromine in acidic media are oily or crystalline substances characterized by moderate thermal and chemical stability. They can be stored at room temperature without decomposition and are stable under TLC conditions, but they decompose when heated in organic solvents. The lowest stability is displayed by 1-phenyl-3,3-bis(β-chloroethyl)triazene 1-oxide (**8**), which already at room temperature is rapidly converted to a complex mixture of unidentified compounds.

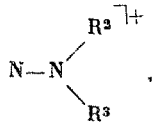
The structure of the prepared triazene 1-oxides was determined by IR, PMR, ^{13}C, and ^{14}N NMR spectra, mass spectra, and elemental analyses. Physicochemical and spectral data of the products are listed in Tables 2-5.

The IR spectra of the prepared compounds contain absorption bands characteristic of the azoxy group in the region 1450-1520 cm^{-1}, and also bands that correspond with other functional groups that are present in the molecule (NH, OH, CN, C=O, etc.) (Table 2). The PMR spectra unambiguously demonstrate the structure of the hydrocarbon fragments of molecules **1-28** (Table 2).

Important structural information is provided by ^{13}C and ^{14}N NMR spectra of compounds **1, 2,** and **19** (Tables 3 and 4). Assignment of the signals of ^{13}C and ^{14}N atoms of compounds **1, 2,** and **19** was carried out on the basis of analysis of the values of their chemical shifts (δ) and (in the case of ^{14}N) the half-width ($\Delta\nu_{1/2}$) [10]. Assignment of the ^{13}C signals in triazene oxide **19** was proven by means of selective suppression of the spin–spin interaction and experiments on the selective transfer of $^{1}H \rightarrow C^{13}$ polarization. The obtained data make it possible to determine the position of oxidated nitrogen atoms in compounds **1, 2,** and **19**. Thus, the signals of the ipso carbon atoms of the aromatic ring in molecules **1** and **2** and the C^1 atom of the pyrazole ring in triazene oxide **19** are broadened because of the spin–spin interaction $^{1}J^{13}C^{1}-{}^{14}N$ with the neighboring N^1 atom, which gives a narrow signal in the ^{14}N NMR spectrum. The presence of the mentioned interaction is shown by considerable narrowing of the C^i and C^1 signals in the case of their suppression, which is evidence of the localization of the $N \rightarrow O$ bond at the N^1 atom of the triazene oxide moiety in compounds **1, 2,** and **19**. That conclusion is confirmed by the identity of spectral characteristics of triazene oxide **2** and the well-known 1-phenyl-3,3-dimethyltriazene 1-oxide, prepared according to [5], and by the clear difference of the characteristics of 1-phenyl-3,3-dimethyltriazene 2-oxide in which the ^{14}N signal of the N-oxygen atom is by 31.1 ppm upfield in comparison with compound **2** [11].

The structure of the triazene oxide group in the prepared compounds is further confirmed by mass spectral data of products **1-3, 5-9, 14, 15, 18, 22, 25,** and **27**. It can be seen in Table 5 that most of the studied compounds give molecular ion peaks that are generally of low intensity. Fragmentation of the molecular ions proceeds, according to mass-spectral data, by different ways, among them rupture of bonds by routes A and B.

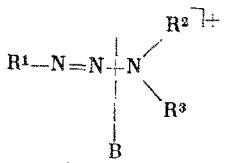


Disintegration by route A with localization of the charge at the oxidated part of the molecule leads to formation of intensive fragmental ions $R^1-NO^{\rceil+}$. Alternative localization of the charge at the second separating fragment goes with appearance of ions  , peaks of which are found in a number of compounds.

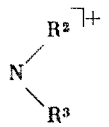
The presence of peaks $R^1-NO^{\rceil+}$ in the mass spectra of the prepared triazene N-oxides is, in our opinion, sufficiently conclusive evidence of the fact that the N-oxide oxygen in them is at the N^1 atom of the triazene N-oxide moiety. In favor of this statement is also the absence of the fragmental ion $R^1-NO^{\rceil+}$ in the mass spectrum of the isomeric 1-phenyl-3,3-dimethyltriazine 2-oxide, in which the oxidated nitrogen atom is at position N^2 of the triazene chain [11].

Rupture of the bonds by route B has less significance and is only realized in the case of compounds **1-3**, in the mass spectra of which a peak of low intensity of the fragmental ion $R^1-N-NH^{\rceil+}$ is found.

In the mass spectra of most of the compounds (Table 5) ion peaks $R^1-N^{2\rceil+}$ are present. Formation of these ions may occur via intermediate formation of ions **29**, obtained from molecular ions by means of splitting off of the N-oxide oxygen and are not found in the mass spectra, probably because of their low intensity



(29)

Rupture of the bonds in ion **29** by route B with localization of the charge at the R^1-N^2 fragment leads to fragmental ions $R^1N_2^{\rceil+}$ that were found. Localization of the charge at the second part of the molecule, found for compounds **3**, **6**, **15**, and **19**, leads to ions 

The presence of substituents of different nature at the atoms N^1 and N^3 of the triazene oxide group leads to noticeable difference in the details of the mass spectra of compounds **1-28**. Ions of which the origin is connected with the specific structure of each individual compound are listed in the tenth column of Table 5.

Thus, the combination of spectral characteristics of the prepared compounds does not leave doubt about the fact that all prepared compounds are pure regioisomers in which the oxidated nitrogen atom is at position N^1 of the triazene oxide moiety. The obtained data demonstrate regiospecificity of the proposed method for the synthesis of the compounds mentioned, based upon reaction of 1,1-disubstituted hydrazines with bromine in the presence of nitroso compounds in acid media, which makes it possible to use that method for the directed synthesis of 1,3,3-trisubstituted triazene 1-oxides of various structures.

EXPERIMENTAL

The IR spectra were taken on a Specord 75 IR spectrometer. PMR spectra were recorded on a Tesla BS-467 spectrometer operating at 60 MHz, with HMDS as internal standard. ^{13}C and ^{14}N NMR spectra were recorded on a Bruker AM-300 spectrometer at frequencies of 75.47 and 21.69 MHz. Chemical shifts of ^{13}C signals were measured relative to the solvent, acetone-d_6 (30.0 ppm), and of ^{14}N signals relative to the external standard CH_3NO_2 (0.0 ppm), without considering correction for diamagnetic susceptibility. Mass spectra were taken on a Varian MAT CH-6 mass spectrometer with direct introduction of the sample in the ion source at an electron ionization energy of 70 eV, accelerating voltage 1.75 kV, and emission current 100 μA. TLC was carried out on Silpearl UV 250.

Starting compounds were prepared by known methods: 1-methyl-1-cyanoethylhydrazine [12], 1,1-bis(cyanoethyl)hydrazine [13], 1,1-bis(hydroxyethyl)hydrazine [14], 1,1-bis(β-chloroethyl)hydrazine hydrochloride [15], 1-methyl-1-(2′,4′-dinitrophenyl)hydrazine [16], 3-amino-1,3-oxazolidone-2 [17], 3,5-dimethyl-4-nitrosopyrazole [18], and 1,3,5-trimethyl-4-nitrosopyrazole [19].

1-*tert*-Butyl-1-cyanoethylhydrazine was prepared in much the same way as 1-methyl-1-cyanoethylhydrazine [12]. Yield 56%, oil, bp 77-79°C (2 mm). Hydrochloride, mp 159-161°C (ethanol). IR spectrum (ν, cm^{-1}): 2260 (C≡N). PMR spectrum

(CD_3OD, δ, ppm, J, Hz): 1.33 s (9H, *t*-Bu), 3.13 t (2H, CH_2CN, J = 6.0), 3.31 t (2H, $N-CH_2$, J = 6.0), 4.82-5.10 br.s (3H, $NH_2 \cdot HCl$).

1-(2′,4′-Dinitrophenyl)-1-cyanoethylhydrazine was prepared in much the same way as 1-methyl-1-(2′,4′-dinitrophenyl)hydrazine [16]. Yield 77%, mp 155-157°C (ethanol). IR spectrum (ν, cm^{-1}): 2230 ($C \equiv N$), 1490 (NO_2), 1300 (NO_2).

General Method for the Preparation of 1-Aryl(pyrazolyl)-3,3-disubstituted Triazene 1-Oxides (1-22). To a mixture of 1,1-disubstituted hydrazine or its hydrochloride (15 mmoles), acid (10 ml), and ether (10 ml) is added dropwise with stirring at −25°C bromine (15 mmoles) and then in one portion the nitroso compound (15 mmoles). The reaction mixture is allowed to stand for 0.2-15.0 h (Table 2) while the temperature is gradually increased to −10 to +10°C, and poured out in a mixture of ice (100 g), $NaHCO_3$ (an amount necessary for neutralization of the acid), and ether (100 ml). The ether layer is separated off, the water layer is extracted with ether or ethyl acetate (5 × 100 ml), and the combined extracts are dried over $MgSO_4$. Compounds **1-22** are isolated by means of TLC. Yields, IR and PMR spectra, and elemental analyses of the products are listed in Table 2.

1,4-Dimethyl-1,4-bis(β-cyanoethyl)tetrazene-2 (23). To a mixture of 1-methyl-1-(β-cyanoethyl)hydrazine (0.5 g, 5 mmoles), 90% HCOOH (10 ml), and ether (10 ml) is added dropwise with stirring at −25°C bromine (0.8 g, 5 mmoles). The reaction mixture is allowed to stand for 2 h while gradually increasing the temperature to 0°C, and poured out in a mixture of ice (100 g), $NaHCO_3$, and ether (100 ml). The product is isolated in the same way as in the preceding synthesis. Yield 0.4 g (82%) of **23**, oil. Found, %: C 49.11; H 6.88; N 42.91. $C_8H_{14}N_6$. Calculated, %: C 49.48; H 7.22; N 43.30. IR spectrum (ν, cm^{-1}): 2260 ($C \equiv N$). PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 2.58 t (4H, $C-CH_2$, J = 7), 2.82 s (6H, $N-CH_3$), 3.47 t (4H, $N-CH_2$, J = 7.0). Mass spectrum, *m/z*: M^+ 194.97.

1,4-Dimethyl-1,4-bis(2′,4′-dinitrophenyl)tetrazene-2 (24). Prepared in much the same way as tetrazene **23**. Yield 92%, mp 208-210°C (dec.) (after washing with ether−hexane, 1:1). IR spectrum (ν, cm^{-1}): 1500, 1300 (NO_2). PMR spectrum (DMSO-d_6, δ, ppm): 3.62 s (6H, $N-CH_3$), 8.04-8.88 m (6H, C_6H_3). Mass spectrum, *m/z* (*I*, %): M^+ 420 (10), 212 (2), 196 (9), 182 (100), 168 (18).

1-Phenyl-3,3-bis(β-acetoxyethyl)triazene 1-Oxide (25). To a solution of 1-phenyl-3,3-bis(β-hydroxyethyl)triazene 1-oxide (**4**) (1.12 g, 5 mmoles) in acetic anhydride (10 ml, 90 mmoles) is added at 0°C with stirring 1 drop of conc. H_2SO_4. The temperature is increased to ~20°C in 1.5 h. The reaction mixture is poured out in a mixture of ice (100 g) and $NaHCO_3$. The product is isolated in much the same way as compounds **1-22**. Yield 0.93 g (60%) of triazene 1-oxide **25**, oil. Found, %: C 54.02; H 6.98; N 43.31. $C_{14}H_{19}N_3O_5$. Calculated, %: C 54.37; H 6.15; N 13.59. IR spectrum (ν, cm^{-1}): 1740 (C=O), 1485 [N(O)=N], 1240 (C−O−C). PMR spectrum ($CDCl_3$, δ, ppm, J, Hz): 1.95 s (6H, $C-CH_3$), 3.81 t (4H, $N-CH_2$, J = 7.0), 4.25 t (4H, CH_2-O, J = 7.0), 7.22-7.50 m (3H, C_6H_5), 7.68-8.15 m (2H, C_6H_5). Mass spectrum, *m/z*: M^+ 309, 188, $PhNO^{]+}$ 107, $PhN_2^{]+}$ 105, 87, 77.

1-(1′,3′,5′-Trimethylpyrazolyl-4′)-3,3-bis(β-hydroxyethyl)triazene 1-Oxide (26). To a solution of compound **21** or **22** (5 mmoles) in absolute MeOH (70 ml) is added with stirring at 20°C 1 drop of conc. H_2SO_4. After 1 h MeOH is evaporated under vacuum, the residue is dissolved in ethyl acetate (70 ml), the solution is extracted with water (3 × 5 ml), and dried over $MgSO_4$. The product is isolated by means of TLC. Yield 1.21 g (94%) of compound **26**, oil. Found, %: C 46.54; H 7.63; N 27.07. $C_{10}H_{19}N_5O_3$. Calculated, %: C 46.69; H 7.39; N 27.24. IR spectrum (ν, cm^{-1}): 3600-3100 br (OH), 1510 [N(O)=N]. PMR spectrum (CD_3OD, δ, ppm): 2.22 s (3H, $C-CH_3$ in Pyr),* 2.36 s (3H, $C-CH_3$ in Pyr), 3.66 s ($N-CH_3$ in Pyr and CH_2-CH_2).

1-Phenyl-3,3-bis(β-hydroxyethyl)triazene 1-Oxide (4). Prepared in much the same way as compound **26** from esters **5, 6,** or **25**. Yield ~100%. Spectral data correspond with those given in Table 2.

1-Phenyl-3-(2,4-dinitrophenyl)triazene 1-Oxide (27). To a suspension of NaH (0.035 g, 1.46 mmoles) in absolute THF (10 ml), which is kept under an argon atmosphere, is added with stirring at 0°C 1-phenyl-3-(2′,4′-dinitrophenyl)-3-(β-cyanoethyl)triazene 1-oxide (**10**) (0.50 g, 1.40 mmoles). The reaction mixture is kept at 0°C for 40 min, aqueous HCl (1.50 mmoles) is added, the precipitate is filtered off, washed with water, and dried in a steam of air. A further amount of the product is obtained by evaporation of the filtrate. Total yield of compound **27** 0.21 g (50%), mp 205-207°C (dec.) (ethanol). Found, %: C 47.22; H 3.08; N 22.87. $C_{12}H_9N_5O_5$. Calculated, %: C 47.52; H 2.97; N 23.10. IR spectrum (ν, cm^{-1}): 1490 [N=N(O)], 1325, 1510 (NO_2). The mass spectrum of triazene 1-oxide is **27** given in Table 5.

*Pyr = pyrazole ring.

REFERENCES

1. J. Miesel, US Patent No. 3,989,680, cl. 260-140 R (C07c 107/04) (1976); *Ref. Zh., Khim.*, 17047P (1977).
2. F. K. Hess, P. A. Stewart, G. Possanza, and K. Freter, Ger. Offen. 2,208,368, cl. C07c A 61k (1973); *Chem. Abstr.*, **79**, 146271s (1973).
3. A. Kumar, S. K. Mukerjee, and S. K. Bhattacharya, *Pharmazie*, **38**, No. 1, 66 (1983).
4. A. Kumar, S. K. Mukerjee, and S. K. Bhattacharya, *Pharm. Res.*, No. 1, 49 (1985); *Chem. Abstr.*, **102**, 125417x (1985).
5. L. Hoesch and B. Köppel, *Helv. Chim. Acta*, **64**, No. 3, 864 (1981).
6. S. G. Zlotin, O. V. Prokshits, N. F. Karpenko, and O. A. Luk'yanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 7, 1679 (1990).
7. E. Bamberger, *Helv. Chim. Acta*, **14**, 242 (1931).
8. S. G. Zlotin, O. V. Prokshits, and O. A. Luk'yanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 11, 2668 (1990).
9. M. A. Kuznetsov, *Usp. Khim.*, **48**, No. 6, 1054 (1979).
10. E. Breitmaier and W. Voelter, *Carbon-13 NMR Spectroscopy*, VCH Verlagsgesellschaft, Weinheim (1987).
11. É. T. Anasov, A. V. Kalinin, B. A. Dzhetigenov, and V. A. Tartakovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 6, 1450 (1991).
12. H. Dorn, A. Lubek, and G. Hilgetag, *Chem. Ber.*, **98**, 3377 (1965).
13. M. Mungo and M. Bornengo, *Gazz. Chim. Ital.*, **86**, 451 (1956); Houben-Weyl, *Methoden der Organischen Chemie*, Vol. 10/2 (1967), p. 21.
14. G. Gever and C. J. Keefe, US Patent No. 2,660,607 (1951); Houben-Weyl, *Methoden der Organischen Chemie*, Vol. 10/2 (1967), p. 15.
15. S. Zakhariev, S. Stoev, and E. Golovinskii, *Dokl. Bolg. Akad. Nayk*, **35**, No. 5, 631-634 (1979); *Chem. Abstr.*, **92**, 41236z (1980).
16. Z. Rappoport and T. Sheradsky, *J. Chem. Soc. (B)*, No. 3, 277 (1968).
17. R. F. Evans and J. I. Jones, *J. Chem. Soc.*, No. 7, 3523 (1963).
18. S. F. Torf, N. I. Kudryashov, N. V. Khromov-Borisov, and T. A. Mikhailova, *Zh. Obshch. Khim.*, **32**, 1740 (1962).
19. US Patent No. 2,827,415 (1958); *Chem. Abstr.*, **52**, 14957g (1958).