Chemistry of Natural Compounds, Bioorganic, and Biomolecular Chemistry

Oxidation of diterpenoid alkaloids with dimethyldioxirane

E. G. Zinurova,[a] N. N. Kabal'nova,[a] V. V. Shereshovets,[a]† E. V. Ivanova,[a]
E. E. Shults,[b] G. A. Tolstikov,[b] and M. S. Yunusov[a]★

[a]*Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences,*
71 prosp. Oktyabrya, 450054 Ufa, Russian Federation.
Fax: +7 (347 2) 35 6066. E-mail: chemorg@anrb.ru
[b]*N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences,*
9 prosp. Akad. Lavrent'eva, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383 2) 34 4752. E-mail: osadchii@nioch.nsc.ru

Oxidation of diterpene alkaloids by dimethyldioxirane was studied with eldeline, talatizamine, aconitine, and zongorine as examples. Nitrones and 19-oxo derivatives of bases were obtained. The results of the oxidation allow one to draw an analogy with the oxidation by $KMnO_4$ and to suggest a mechanism of the reaction.

Key words: diterpenoid alkaloids; dimethyldioxirane; 19-oxoeldeline; 19-oxotalatizamine; nitrones; zongoramine.

One line of research in the chemistry of diterpene alkaloids is modification of their structures, mainly through oxidation. In this communication, we report the results of oxidation of diterpene alkaloids eldeline (**1**), talatizamine (**2**), aconitine (**3**), and zongorine (**4**) by dimethyldioxirane (DMDO).

The reaction of dioxiranes with amines is known to proceed rapidly under mild conditions. Primary amines react with dioxiranes giving rise to the corresponding nitro compounds.[1—5] The formation of hydroxylamines (for amine : DMDO ratio equal to 1 : 1),[6] nitrones,[7,8] and nitroxides[9] was observed in the oxidation of secondary amines. Tertiary amines are converted on treatment with dioxiranes into *N*-oxides,[5—12] which efficiently decompose dioxirane with liberation of oxygen and regeneration of the amine.

Oxidation of eldeline **1** gave an amide, 19-oxoeldeline (**5**), in 19% yield (Scheme 1). Oxidation of talatizamine **2** also yielded amide (**6**) (26%); however, the major product formed in this case was nitrone (**7**) (45%), which was converted into diacetate (**8**). A similar nitrone (**9**) was isolated as the major product (65%) in the oxidation of aconitine **3**. In the ^{13}C NMR spectra of compounds **7** and **9**, the signals corresponding to all of the C atoms present in the initial compounds are retained, except those for the eliminated *N*-ethyl groups. The structures of nitrones **7** and **9** are confirmed by the presence of characteristic signals at δ 137.2 and 135.7,

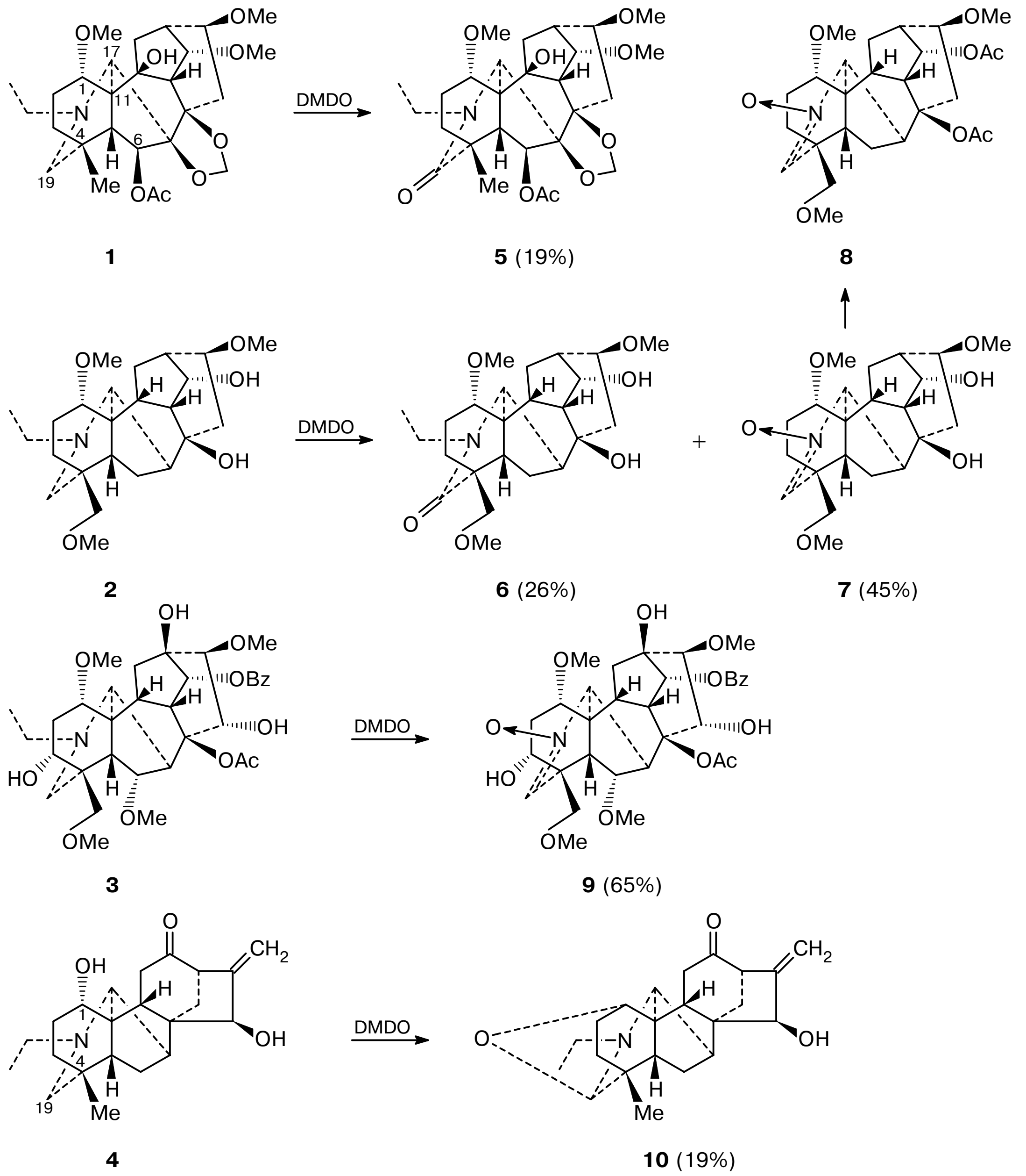
---

† Deceased.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 691—694, April, 2001.

1066-5285/01/5004-720 $25.00

Scheme 1



respectively, in the ^{13}C NMR spectra and of singlets at δ 6.70 and 6.78 due to C(19)H in the ^{1}H NMR spectra. The ^{13}C NMR signals for C(4) and C(17) are also markedly shifted. Oxidation of zongorine **4** gave rise to zongoramine (**10**) in 19% yield; this product was identified by comparison with an authentic sample.

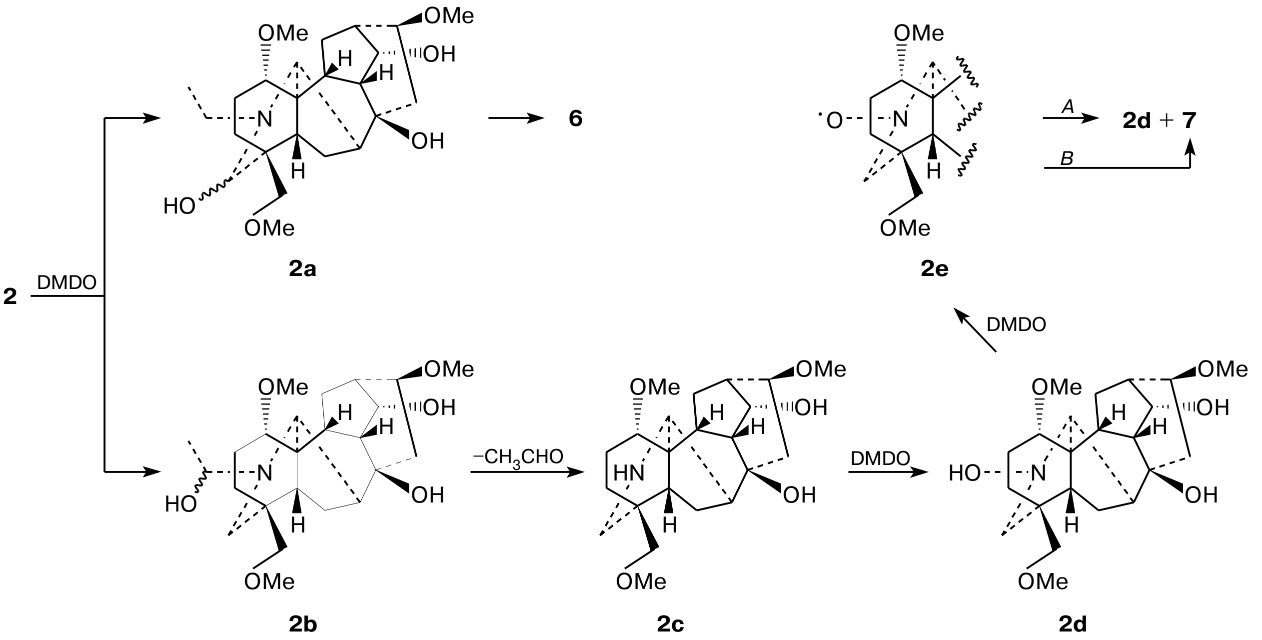
The results of oxidation of diterpene alkaloids by dimethyldioxirane point to an analogy with the oxidative process involving $KMnO_4$. In the latter case, in the presence or in the absence of a β-methoxy group at C(6), the reaction affords C(19)-oxo- or C(1)—C(19)-epoxy derivatives, while in the presence of an α-methoxy group, *N*-dealkylation takes place.[13]

The difference between the oxidation by dimethyldioxirane and by potassium permanganate showed itself in the oxidation of talatizamine **2**; in this case, the use of $KMnO_4$ furnished 19-oxo derivative **6** as the major product.

Our results together with the data on the oxidation of diterpene alkaloids by potassium permanganate allow one to propose the mechanism of the oxidation process in question (Scheme 2).

The first step is oxidation involving the C(19) atom (alcohol **2a**) or the methylene group of the *N*-ethyl substituent (alcohol **2b**). The former pathway yields epoxide in the presence of a $C(1)OH_\alpha$ group, as ob-

Scheme 2



served for zongorine. In the absence of C(1)OH$_\alpha$, oxidation goes further to give the 19-oxo product. In the latter case, amino alcohol decomposes to give acetaldehyde and secondary amine **2c**. Secondary amine is further oxidized by dimethyldioxirane to give hydroxylamine **2d** and then nitrone **7**. On treatment with DMDO, hydroxylamine **2d** might be converted into nitroxide **2e**, which can disproportionate to nitrone **7** and hydroxylamine **2d** (Scheme 2, pathway *A*).[14] This product is again converted into niroxide, *etc*. An alternative pathway, namely, oxidation of nitroxide **2e** by dimethyldioxirane to nitrone **7** (Scheme 2, pathway *B*), is also possible. No products assoiciated with the oxidation of the hydroxy groups in alkaloid molecules were detected.

In a previous study, no amides were found upon the oxidation of tertiary amine by dimethyldioxirane.[15] In the series of diterpene alkaloids, nitrones were prepared by pyrolysis of aconitine *N*-oxide[16] and by oxidation of lappaconitine, elatine, and elatidine *N*-desethyl-*N*-hydroxy derivatives by manganese dioxide or potassium ferricyanide.[17]

Experimental

IR spectra were recorded on a Specord M-80 spectrometer. The ^{1}H and ^{13}C NMR spectra were run on a Bruker AM-300 instrument in $CDCl_3$. The melting points were determined on a Koffler stage. Dimethyldioxirane was prepared by a standard procedure[18] using high-purity grade acetone purified by distillation.

19-Oxoeldeline (5). Eldeline **1** (220 mg) was dissolved in 50 mL of acetone, and a solution of DMDO (4 equiv.) in 21.7 mL of acetone was added in small portions with continuous stirring. The reaction was carried out at ~20 °C until DMDO was completely consumed (monitoring by a color test with an iodide—starch paper strip). Then acetone was evaporated *in vacuo*, the residue was dissolved in 50 mL of 2% H_2SO_4, and the acidic solution was extracted with benzene (3×50 mL). The extract was concentrated and the residue was triturated with acetone to give 41 mg (19%) of 19-oxoeldeline **5**, m.p. 254—255 °C (from acetone). $C_{27}H_{39}NO_9$. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 521 $[M]^+$ (100), 506 (16), 490 (50), 462 (64). ^{13}C NMR ($CDCl_3$), δ: 80.6 (C(1)); 26.9 (C(2)); 43.0 (C(3)); 34.1 (C(4)); 49.6 (C(5)); 75.6 (C(6)); 90.1 (C(7)); 83.4 (C(8)); 53.9 (C(9)); 81.3 (C(10)); 54.9 (C(11)); 37.8 (C(12)); 39.2 (C(13)); 81.1 (C(14)); 34.8 (C(15)); 81.1 (C(16)); 62.5 (C(17)); 22.0 (C(18)); 183.0 (C(19)); 45.1 (N—$\underline{C}H_2$—CH_3); 12.4 (N—CH_2—$\underline{C}H_3$); 54.9 (C(1)—O$\underline{Me}$); 57.9 (C(14)—O$\underline{Me}$); 56.4 (C(16)—O$\underline{Me}$); 94.1 (OCH_2O); 21.6 (OCO$\underline{C}H_3$); 169.6 (O$\underline{C}$OCH$_3$). ^{1}H NMR ($CDCl_3$), δ: 1.09 (t, 3 H, N—CH_2—C$\underline{H}_3$, *J* = 7.0 Hz); 1.15 (s, 3 H, C(18)H$_3$); 2.00 (s, 3 H, $CO_2C\underline{H}_3$); 3.15, 3.25, 3.48 (all s, 3 H each, OCH_3); 4.10 (t, 1 H, C(14)H, *J* = 4.8 Hz); 4.85, 4.88 (both br.s, 1 H each, CH_2O_2); 5.32 (br.s, 1 H, C(6)H$_\alpha$). IR (KBr), ν/cm^{-1}: 1620 (HNCO). The spectroscopic data and the melting points were identical to those of 19-oxoeldeline prepared by oxidation of eldeline by potassium permanganate using a previously reported procedure.[13]

19-Oxotalatizamine (6) and nitrone (7). Oxidation of talatizamine **2** (200 mg) was performed in a way similar to that for the oxidation of alkaloid **1** to give 52 mg (26%) of 19-oxotalatizamine **6**, m.p. 185—186 °C (from acetone). $C_{24}H_{37}NO_6$. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 435 $[M]^+$ (22), 420 (100), 404 (11). ^{13}C NMR ($CDCl_3$), δ: 84.0 (C(1)); 26.1 (C(2)); 31.0 (C(3)); 41.4 (C(4)); 37.1 (C(5)); 26.4 (C(6)); 45.9 (C(7)); 71.6 (C(8)); 52.7 (C(9)); 45.8 (C(10)); 50.7 (C(11)); 26.9 (C(12)); 43.4 (C(13)); 75.2 (C(14)); 36.8 (C(15)); 82.0 (C(16)); 61.8 (C(17)); 74.9 (C(18)); 171.6 (C(19)); 47.2 (N—$\underline{C}H_2$—CH_3); 13.1 (N—CH_2—$\underline{C}H_3$); 55.8 (C(1)—O$\underline{Me}$); 56.7 (C(16)—O$\underline{Me}$); 59.4 (C(18)—O$\underline{Me}$). ^{1}H NMR ($CDCl_3$), δ: 1.18 (t, 3 H, N—CH_2—C$\underline{H}_3$, *J* = 7.0 Hz); 3.23, 3.32, 3.38 (all s, 3 H each, OCH_3); 3.48, 3.52 (both d, 1 H each, C(18)H$_2$, *J* = 3.2 Hz); 4.15 (t, 1 H, C(14)H, *J* = 5.1 Hz). IR (KBr), ν/cm^{-1}: 1620

(HNCO). The spectroscopic data and the melting points coincide with those for 19-oxotalatizamine prepared by oxidation of talatizamine by potassium permanganate by a previously reported procedure.[13]

The acidic solution (after extraction of 19-oxotalatizamine **6** into benzene) was additionally extracted three times with equal volumes of chloroform, the extract was concentrated, the residue was triturated with hexane to isolate 90 mg (45%) of amorphous compound **7**. $C_{22}H_{33}NO_6$. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 407 $[M]^+$ (100), 392 (85), 377 (80), 360 (78). ^{13}C ($CDCl_3$), δ: 82.2 (C(1)); 24.3 (C(2)); 29.1 (C(3)); 45.0 (C(4)); 37.5 (C(5)); 26.9 (C(6)); 45.7 (C(7)); 71.8 (C(8)); 52.8 (C(9)); 44.8 (C(10)); 48.95 (C(11)); 25.5 (C(12)); 41.4 (C(13)); 76.1 (C(14)); 37.7 (C(15)); 81.4 (C(16)); 75.0 (C(17)); 74.9 (C(18)); 137.2 (C(19)); 56.2 (C(1)—O$\underline{Me}$); 56.6 (C(16)—O$\underline{Me}$); 59.4 (C(18)—O$\underline{Me}$). ^1H NMR ($CDCl_3$), δ: 3.25, 3.35, 3.37 (all s, 3 H each, OCH_3); 4.20 (t, 1 H, C(14)H, *J* = 5.3 Hz); 3.45, 3.50 (both br.s, 1 H each, $C(18)H_2$); 6.70 (s, 1 H, C(19)H).

Nitrone diacetate (8). Acetyl chloride (2 mL) was added to nitrone **7** (90 mg) and the mixture was left for 48 h and concentrated, and the residue was dissolved in dilute HCl. The acidic solution was extracted with an equal volume of benzene and then three times with chloroform. The chloroform extract was concentrated to give 39 mg (43%) of amorphous compound **8**. $C_{26}H_{37}NO_8$. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 491 $[M]^+$ (27), 475 (5), 474 (3), 461 (29), 460 (7), 431 (6), 415 (10), 414 (12), 43 (100). ^{13}C NMR ($CDCl_3$), δ: 81.56 (C(1)); 21.9 (C(2)); 28.8 (C(3)); 43.6 (C(4)); 38.4 (C(5)); 27.1 (C(6)); 42.4 (C(7)); 84.8 (C(8)); 40.3 (C(9)); 39.3 (C(10)); 50.3 (C(11)); 24.0 (C(12)); 50.1 (C(13)); 74.6 (C(14)); 36.8 (C(15)); 80.4 (C(16)); 74.4 (C(17)); 74.8 (C(18)); 137.6 (C(19)); 56.4 (C(1)—O$\underline{Me}$); 56.6 (C(16)—O$\underline{Me}$); 59.4 (C(18)—O$\underline{Me}$); 21.2, 22.1 ($OCO\underline{C}H_3$); 168.8, 170.7 ($O\underline{C}OCH_3$). ^1H NMR ($CDCl_3$), δ: 1.90, 2.00 (both s, 3 H each, $CO_2C\underline{H}_3$); 3.15, 3.25, 3.25 (all s, 3 H each, OCH_3); 4.48 (t, 1 H, C(14)H, *J* = 5.5 Hz).

Nitrone (9). Oxidation of aconitine **3** (92 mg) was carried out as described above for oxidation of eldeline **1**. Compound **9** was extracted from the acidic solution with chloroform, chloroform was evaporated, and the residue was triturated with acetone to give 60 mg (65%) of crystalline compound **9**, m.p. 182—183 °C (from acetone). $C_{32}H_{41}NO_{12}$. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 555 (35), 554 (49), 553 (49), 540 (45), 256 (100). ^{13}C NMR ($CDCl_3$), δ: 82.1(C(1)); 29.8 (C(2)); 72.9 (C(3)); 47.2 (C(4)); 47.2 (C(5)); 80.6 (C(6)); 41.7 (C(7)); 88.9 (C(8)); 43.9 (C(9)); 37.2 (C(10)); 52.1 (C(11)); 36.8 (C(12)); 73.9 (C(13)); 78.9 (C(14)); 78.9 (C(15)); 89.3 (C(16)); 73.1 (C(17)); 75.6 (C(18)); 135.7 (C(19)); 57.2 (C(1)—O$\underline{Me}$); 57.6 (C(6)—O$\underline{Me}$); 61.3 (C(16)—O$\underline{Me}$); 59.1 (C(18)—O$\underline{Me}$); 21.3 ($OCO\underline{C}H_3$); 171.9 ($O\underline{C}OCH_3$); 165.9 ($O\underline{C}OPh$); 129.4, 128.9, 129.7, 133.7 (OCOPh). ^1H NMR ($CDCl_3$), δ: 1.30 (s, 3 H, Ac); 3.00, 3.25, 3.30, 3.75 (all s, 3 H each, OCH_3); 3.65, 3.83 (both d, 1 H each, $C(18)H_2$, *J* = 8.0 Hz); 4.05 (d, 1 H, $C(6)H_\beta$, *J* = 6.5 Hz); 4.82 (t, 1 H, $H(14)_\beta$, *J* = 4.8 Hz); 6.78 (s, 1 H, C(19)H).

Zongoramines (10). Zongorine **4** (100 mg) was dissolved in 50 mL of *tert*-butyl alcohol, and a solution of DMDO (4 equiv.) in 14.0 mL of acetone was added in small portions with continuous stirring. The reaction was carried out at ~20 °C until DMDO was completely consumed (monitoring by an iodide—starch paper strip). Then the solvent was evaporated, the residue was dissolved in 50 mL of 2% H_2SO_4, and the solution was washed with chloroform. The acidic solution was alkalified by a 2% solution of KOH to pH 10 and extracted with chloroform. The chloroform extract was concentrated, and the residue was triturated with acetone to isolate 19 mg (19%) of crystalline zongoramine **10**, m.p. 211—212 °C (from acetone). The melting point and the spectroscopic data coincide with those of the authentic sample.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 99-03-33509).

References

1. R. W. Murray, *Chem. Rev.*, 1989, **89**, 1187.
2. R. W. Murray, R. Jearand, and L. Mohan, *Tetrahedron Lett.*, 1986, **27**, 2335.
3. R. W. Murray, S. N. Rajadhyaksha, and L. Mohan, *J. Org. Chem.*, 1989, **54**, 5783.
4. J. K. Grandall and T. Reix, *J. Org. Chem.*, 1992, **57**, 6759.
5. W. Adam and L. Hadjiarapoglou, in *Topics Current Chemistry*, Ed. W. A. Herrman, Springer Verlag, Berlin—Heidelberg, 1993, **164**, 45.
6. R. W. Murray and M. Singh, *Synth. Commun.*, 1989, **19**, 3509.
7. R. W. Murray and M. Singh, *Magnetic resonance in chemistry*, 1991, **29**, 962.
8. R. W. Murray and M. Singh, *J. Org. Chem.*, 1990, **55**, 2954.
9. R. W. Murray and M. Singh, *Tetrahedron Lett.*, 1988, **29**, 4677.
10. W. Adam, K. Briviba, F. Duscher, D. Golsch, W. Kiefer, and H. Sies, *J. Chem. Soc., Chem. Commun.*, 1995, 1831.
11. M. Ferrer, F. Sanchez-Baeza, A. Messeguer, A. Diez, and M. Rubiralta, *J. Chem. Soc., Chem. Commun.*, 1995, 293.
12. P. C. Buxton, J. N. Ennis, B. A. Marples, V. L. Waddington, and T. R. Boehlou, *J. Chem. Soc., Perkin Trans. 2*, 1998, 265.
13. O. Achmatowiez Jr., Y. Tsuba, and Leo Marion, *Can. J. Chem.*, 1965, **43**, 2336.
14. V. E. Zubarev, V. N. Belevskii, and L. T. Bugaenko, *Usp. Khim.*, 1979, **48**, 1361 [*Russ. Chem. Rev.*, 1979, **48** (Engl. Transl.)].
15. *Khimiya i khemilyuminestsentsiya dioksiranov* [*Chemistry and Chemiluminescence of Dioxiranes*], Ed. Yu. N. Bubnov, Nauka, Moscow, 1999, 93 (in Russian).
16. K. Wiesner, M. Gotz, D. L. Simmons, and L. R. Fowler, *Tetrahedron Lett.*, 1959, 15.
17. S. A. Osadchii, N. A. Pankrushina, M. M. Shakirov, E. E. Shul′ts, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, **49**, 552 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 557].
18. C. F. Grabovskii, N. N. Kabal′nova, S. L. Khursan, and V. V. Shereshovets, *Izv. Akad. Nauk, Ser. Khim.*, 1998, **47**, 1321 [*Russ. Chem. Bull.*, 1998, **47**, 1284 (Engl. Transl.)].

Received May 29, 2000;
in revised form January 24, 2001