# 1-ALKOXYAZIRIDINES

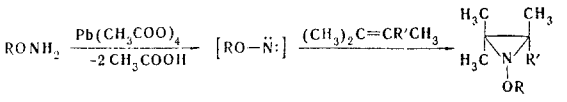
B. V. Ioffe and E. V. Koroleva

UDC 547.717+541.67'634

The corresponding 1-alkoxyaziridines were synthesized by oxidation of methoxy-, ethoxy-, and isopropoxyamines with lead tetraacetate in the presence of 2-methyl-2-butene and 2,3-dimethyl-2-butene. The PMR spectra of the oxidation products were investigated, and the high pyramidal stability of nitrogen in these compounds was confirmed. The individual invertomers of 1-alkoxy-2,2,3-trimethylaziridines were isolated by preparative gas-liquid chromatography.

The report concerning the preparation of 1-methoxy-2,2,3,3-tetramethylaziridine by oxidation of methoxyamine in the presence of tetramethylethylene [1] seems of interest, not only in connection with the investigation of the pyramidal stability of nitrogen but also as a new method for the synthesis of hard-to-obtain nitrogen heterocycles. It is assumed that the reaction proceeds through the intermediate formation of methoxynitrene ($CH_3O-\ddot{N}$), which, like carbene, reacts with the olefin. Recently performed quantum-chemical calculations of the electronic structure of the simplest hydroxynitrenes [2] confirm their analogy (with respect to their structures and reactivities) to carbenes. Since 1,1,-cycloaddition of carbene to olefins is presently hardly the most widely used method for the synthesis of cyclopropanes, it might be hoped that the preparative possibilities of the reactions of nitrenes with olefins are also great and that they are not exhausted by known examples of the synthesis of aziridines from C-nitrenes and N-nitrenes [3,4].

We undertook a systematic study of the possibility of the use of the addition of O-nitrenes to olefins as a method for the synthesis of 1-alkoxyaziridines:



I a-c II, III a-c

I–III a R = $CH_3$, b R = $C_2H_5$, c R = $i$-$C_3H_7$; II R' = $CH_3$; III R' = H

In all six of the investigated cases, the products of the oxidation of alkoxyamines Ia-c with lead tetraacetate in the presence of 2-methyl-2-butene or 2,3-dimethyl-2-butene proved to be the corresponding 1-alkoxyaziridines (IIa-c and IIIa-c). According to the results of gas-chromatographic analysis, the reaction mixtures contained 9-35% aziridines.* Since the experiments were carried out with relatively small amounts of the reagent (0.02-0.06 mole of alkoxyamine) and the 1-ethoxy-2,2,3,3-tetramethylaziridine obtained by distillation was not pure enough, we used preparative gas-liquid chromatography (GLC) to isolate the aziridines. Despite the low yield coefficient (which was 30-40%, but certainly may be improved), this method made it possible to obtain chromatographically pure aziridines (Table 1). The IR spectral data confirmed that the compounds obtained were 1-alkoxyaziridines: the spectra of all of the preparations contain bands of the pulsation vibrations of the aziridine ring at 1220-1260 $cm^{-1}$ and bands of the ring deformation vibrations at 885-920 $cm^{-1}$, the characteristic nature of which is affirmed in the literature.† The

*The percentage in the mixture corresponds to the yield of aziridine in percent of the theoretical yield.

† The summary of the characteristic frequencies of aziridines available in the literature [5] encompasses only 1-monosubstituted derivatives, so that the assignment of the bands of the ring vibrations should be considered to be a preliminary one. The splitting of the frequency of the symmetrical deformation

Leningrad State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1514-1519, November, 1972. Original article submitted April 11, 1972.

TABLE 1. Characteristics of the 1-Alkoxyaziridines

| Compound | R | R′ | Yield, * % | $n_D^{20}$ | Empirical formula | N, % found | N, % calc. | Relative retention time $t_{syn}$ / $t_{anti}$ | Relative retention time $t_{aziridine}$ / $t_{ether}$ | Ratio of stereoisomers in the reaction mixture acc. to GLC, anti/syn |
|---|---|---|---|---|---|---|---|---|---|---|
| IIa | $CH_3$ | $CH_3$ | 50 | — | $C_7H_{15}NO$ | — | 10,8 | — | 11,0 | — |
| IIb | $C_2H_5$ | $CH_3$ | 27 | 1,4225 | $C_8H_{17}NO$ | 9,9<br>9,9 | 9,8 | — | 22,5 | — |
| IIc | $i$-$C_3H_7$ | $CH_3$ | 15 | 1,4188 | $C_9H_{19}NO$ | 9,1<br>9,3 | 8,9 | — | 16,7 | — |
| IIIa | $CH_3$ | H | 31 | 1,4125 | $C_6H_{13}NO$ | 11,7<br>12,0 | 12,2 | 0,80 | 6,0 7,5 | 1,1 |
| IIIb (syn) | $C_2H_5$ | H | 20 | 1,4121 | $C_7H_{15}NO$ | 11,0<br>10,8 | 10,8 | 0,80 | 11,2 | 1,3 |
| IIIb (anti) | $C_2H_5$ | H | 20 | 1,4150 | $C_7H_{15}NO$ | 11,1<br>11,0 | 10,8 | 0,80 | 14,0 | 1,3 |
| IIIc | $i$-$C_3H_7$ | H | 8 | 1,4133 | $C_8H_{17}NO$ | 9,3<br>9,6 | 9,8 | 0,87 | 10,6 12,1 | 1,5 |

*With allowance for the yield coefficient. The yields from analysis of the reaction mixtures were in agreement with the preparative yields up to 1-3 absolute %.

shoulders at 3010 $cm^{-1}$ on the intense bands of the stretching vibrations of the methyl groups in the spectra of IIIa-c should be assigned to the stretching vibrations of the C–H bonds of the aziridine ring. Aziridines IIa and IIIa, obtained from methoxyamine, also have characteristic frequencies of symmetrical stretching vibrations of the methoxy group (2815 $cm^{-1}$).

The PMR spectra (Tables 2 and 3) provide complete and unambiguous proof of the structures of the synthesized alkoxyaziridines. The assumption that 1-alkoxyaziridines should display high pyramidal stability at room temperature [6] was previously confirmed [1] in the case of 1-methoxy-2,2,3,3-tetramethylaziridine. Aziridine IIa had a PMR spectrum identical to the spectrum of the previously described compound [1]. A peculiarity of the PMR spectra of all of the 1-alkoxy-2,2,3,3-tetramethylaziridines is nonequivalence of the geminal methyl groups; this is expressed in the appearance of two singlets with shifts differing by 0.02-0.06 ppm (Table 2).

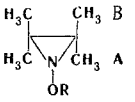
1-Alkoxy-2,2,3,3-trimethylaziridines IIIa-c were mixtures of two stereoisomers, from which 85-100% pure preparations of each of the stereoisomers, which have a nitrogen with a stable pyramidal structure, were isolated by GLC. The isolation of these two invertomers from a mixture was previously accomplished only in the case of 1-chloro-2-methylaziridine [7-9]. The trans configuration was assigned to the previously described 1-bromo-2-methyl- and 1-bromo-2-isopropylaziridines [8, 10, 11] and 1-amino-2-methylaziridine [12] on the basis of a priori assumptions regarding the steric hindrance to formation of cis isomers.

The absolute determination of the configuration of the invertomers seems of special interest in connection with the stereochemistry of the addition of hydroxynitrenes to a double bond. The configurations of each of the stereoisomeric forms of alkoxyaziridines obtained by us can be established by analysis of the PMR spectra on the basis of the following considerations.

1. Comparing the chemical shifts of the geminal methyl groups of the preparations synthesized by us with the literature data for the simplest aziridines (Table 4), we see that the signals of the relatively weakly shielded methyl protons at 1.2 ppm are present only for 2,2-dimethyl derivatives and one of the stereoisomeric forms of the trimethyl derivative. The conditions for the shielding of the methyl groups of 2,2-dimethylaziridine at 1.2 ppm are similar to the conditions for the shielding of the trans-oriented (relative to the substituent attached to the nitrogen) $CH_3$ groups of 1,2,2-trimethylaziridine and 1-methoxy-

vibrations for geminal methyl groups was distinctly displayed only for isopropoxyaziridines IIc and IIIc and apparently does not occur for the geminal methyl groups of the aziridine ring.

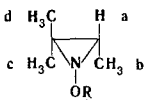
TABLE 2. Parameters of the PMR Spectra of 1-Alkoxy-2,2,3,3-tetramethylaziridines*



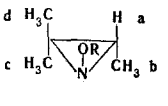
| R | Chemical shift, δ, ppm (J, Hz) | | |
|---|---|---|---|
| | A | Б | R |
| $CH_3$ | 1,05 s | 1,09 s | 3,40 s |
| $C_2H_5$ | 1,06 s | 1,12 s | 1,06 t (7); 3,64 q (7) |
| $i$-$C_3H_7$ | 1,03 s | 1,06 s | 1,05 d (6); 3,8 sep (6) |

*The following abbreviations were used here and elsewhere: s is singlet, d is doublet, t is triplet, q is quartet, and sep is septet.

TABLE 3. Parameters of the PMR Spectra of 1-Alkoxy-2,2,3-trimethylaziridines



syn form



anti form

| R | Configuration | Chemical shifts, δ, ppm (J, Hz) | | | | |
|---|---|---|---|---|---|---|
| | | R | a q (6) | b d (6) | c s | d s |
| $CH_3$ | syn | 3,42 s | 1,76 | 1,05 | 1,02 | 1,26 |
| $CH_3$ | anti | 3,44 s | 1,69 | 1,10 | 1,04 | 1,09 |
| $C_2H_5$ | syn | 3,64; 3,65 two quartets (7) 1,06 t (7) | 1,71 | 1,01 | 0,98 | 1,24 |
| $C_2H_5$ | anti | 3,65 q (7), 1,06 t (7) | 1,66 | 1,08 | 1,01 | 1,05 |
| $i$-$C_3H_7$ | syn | 3,84 sep (6), 1,05 d (6) | 1,65 | 1,02 | 0,96 | 1,20 |
| $i$-$C_3H_7$ | anti | 3,84 sep (6), 1,05 d (6) | 1,65 | † | 1,00 | 1,02 |

*From the diastereotopic protons of the $CH_2$ group.
† Apparently covered by the adjacent R signals.

TABLE 4. Chemical Shifts of the Geminal Methyl Groups in the Simplest Aziridines

| Aziridines | δ, ppm |
|---|---|
| 2,2-Dimethylaziridine [13] | 1,2 |
| 1,2,2-Trimethylaziridine [14] | 1,05 ; 1,16 |
| 1-Methoxy-2,2-dimethylaziridine | 1,01 ; 1,26 |
| 1-Methoxy-2,2,3-trimethylaziridine (two stereoisom.) | 1,02 ; 1,26 |
| | 1,04 ; 1,09 |
| 1-Methoxy-2,2,3,3-tetramethylaziridine | 1,05 ; 1,09 |

2,2-dimethylaziridine, as well as the d groups in the syn forms* of 1-alkoxy-2,2,3-trimethylaziridines (Table 3). On this basis, the signals with δ values close to 1.2 (i.e., signals with δ from 1.16 to 1.26 ppm) can be assigned to the methyl groups that are cis-oriented relative to the proton of the aziridine ring and the unshared pair of electrons of nitrogen, and the isomers of 1-alkoxy-2,2,3-trimethylaziridines, which also have such signals, can be acknowledged as the syn forms. In this case, the signals of these forms at 0.96-1.05 ppm should be assigned to the cis-oriented (relative to the substituents attached to nitrogen) geminal methyl (c). It hence follows that the alkoxy groups (and methyl groups) attached to the nitrogen shield the adjacent (cis-oriented) methyl groups more markedly than the unshared pairs of the nitrogen atom.

*The terms syn and anti were used in analogy with the designations of the stereoisomeric cyclopropanes [15].

2. Since the difference in the chemical shifts of the doublets of the methyl groups (b) of the stereoisomeric trimethyl derivatives IIIa-c (0.05-0.07 ppm) is caused by the different shielding by the alkoxy group and the unshared pair of electrons of the nitrogen atom (Table 3), the isomer with the lower $\delta$ value of the doublets should be considered to be the syn form; this confirms the assignment made from the signals of the geminal methyl groups.

3. The difference (0.02-0.06 ppm) in the chemical shift of the geminal methyl groups of the tetramethyl derivatives (Table 2) is also caused by the different shielding by the alkoxy group and the unshared pair of electrons and, on the same basis, the signals with lower values (1.03-1.06 ppm) can be assigned to the cis-oriented methyl groups. The closeness of the chemical shifts of these groups, on the one hand, and of group c in the syn forms of the trimethyl derivatives, on the other, can be considered to be additional confirmation of the configuration assignment made above.

The chemical shifts of the geminal methyl groups in the anti forms differ only slightly (by 0.02-0.05 ppm), and the reliable assignment of them is not yet possible. The singlet, which is closer to signal c of the syn form, apparently should also be assigned to the c group, while the second signal should be assigned to the less shielded d group.

The difference in the shifts of the geminal methyl groups in both forms does not fit into the additive scheme of the effects of shielding ($\Delta\delta^{syn}_{gem} - \Delta\delta^{anti}_{gem} = 2\Delta\delta^{tetra}_{gem}$); this can apparently be considered to be an indication of the difference in the conformations of the alkoxy groups in the invertomers.

All of the isomers to which the syn configuration was thus assigned had lower relative retention times. The ratio of the anti to syn isomers in the reaction mixtures on passing from methoxy- to isopropoxyaziridine (IIIa-c) increases from 1.1 to 1.5 (Table 1); this can be considered to be a consequence of the greater steric hindrance caused by the isopropyl group. This also confirms the correctness of the determinations of the configuration of the invertomers made from the PMR spectra, since there is no basis to suppose that the fraction of sterically more hindered syn isomer will increase as the bulk of the substituent attached to the sextent hydroxynitrene atom increases.

Without dwelling here in detail on a discussion of the stereoselectivity of O-nitrenes in addition reactions, we note only that, judging from the composition of the stereoisomeric mixtures of aziridines formed, the alkoxy group is an anti-orienting substituent in the presence of a sextet nitrogen atom.

## EXPERIMENTAL

Alkoxyamine. Methoxyamine (Ia) was obtained via the method in [16]. Ethoxyamine (Ib) and isopropoxyamine (Ic) were obtained by hydrolysis of the corresponding O-alkyl ethers of acetone oxime by refluxing in 17% hydrochloric acid (400 ml per mole of ether) for 4-6 h; the yields were 40% ($C_2H_5ONH_2 \cdot HCl$) and 32% (iso-$C_3H_7ONH_2 \cdot HCl$). After drying with KOH and distillation, the bases had the following physical constants: methoxyamine had bp 49.0-49.7° (783 mm), $n_D^{20}$ 1.3843, and $d_4^{20}$ 0.9088 (bp 46.5-47.5° (764 mm), $n_D^{20}$ 1.3837, and $d_4^{20}$ 0.9069 [16]); ethoxyamine had bp 68-69° (783 mm), $n_D^{20}$ 1.3929, and $d_4^{20}$ 0.8719 (bp 68-69° [17]); isopropoxyamine had bp 80.0-80.7° (770 mm), $n_D^{20}$ 1.3959, and $d_4^{20}$ 0.8486 (bp 79-80° [18]).

Acetoxime O-Ethyl Ether. This compound was obtained in 60% yield by alkylation of acetoxime with ethyl bromide via the method in [17]. The product had bp 94.0-94.5° (760 mm); $n_D^{20}$ 1.4052.

Acetoxime O-Isopropyl Ether. A 50-g (0.7 mole) sample of acetoxime was placed in a solution of 40 g (1.0 mole) of NaOH in 160 ml of water, and 93 g (0.8 mole) of isopropyl bromide was added at 54-56° in the course of 2 h. The temperature of the mixture was gradually raised to 85° in the course of 3 h, after which it was cooled, and the upper layer was separated, dried with calcium chloride, and distilled to give a fraction (40%) with bp 105.0-105.8° (755 mm), $n_D^{20}$ 1.4067, $d_4^{20}$ 0.8217, and $MR_D$ 30.28 (calculated value 30.05).

2-Methyl-2-butene and 2,3-Dimethyl-2-butene. These compounds (90-99% pure according to GLC) were obtained in 35-40% yield by dehydration of dimethylethylcarbinol and dimethylisopropylcarbinol with 5 wt.% 85% phosphoric acid.

1-Alkoxyaziridine. A 0.042-mole sample of lead tetraacetate and 25 ml of dry methylene chloride were added with vigorous stirring in the course of 10-15 min to a cooled (to −45°) mixture of 0.04 mole of

alkoxyamine, 0.2 mole of olefin,* and 10 ml of dry methylene chloride. The reaction mixture was then stirred at −45° for 30 min, the cooling bath was removed, and the temperature of the mixture was brought up to room temperature. Water (70 ml) and 100 ml of ether were added, and the ether layer was separated, washed twice with water, dried with magnesium sulfate, and vacuum evaporated with a water aspirator at room temperature.

Gas-Liquid Chromatography. A steel column (4 m × 10 mm) filled with diaphorite (0.5-1.0 mm) containing 10% Span 80 was used for preparative isolation of the aziridine with a Khrom-31 ZK chromatograph. The column temperature under isothermal conditions ranged from 65 to 90°, the vaporizer temperature was 100-120°, the carrier gas was nitrogen (30 ml/min), the flow partition at the outlet of the column was 1:100, and the detector was a flame ionization device (the hydrogen flow rate was 55 ml/min, and the air flow rate was 900 ml/min). The exiting components were condensed at −10 to −15°. The sample dose was 1 ml, and the time required for a separation cycle was 60-90 min. The analysis of the reaction mixtures and monitoring of the purity of the fractions were accomplished with the same device. The column was 2 m × 6 mm and was filled with Gellite C-22 (0.25-0.50 mm) modified with 1% polyethylene polyamine containing 10% Span 80. The column temperature was 50°, the vaporizer temperature was 90°, the carrier gas was nitrogen (40 ml/min), and the detector was a flame ionization unit. The percentage of the components in the mixtures analyzed was calculated by the internal standard method (decane) with allowance for the experimentally determined relative detector sensitivity coefficients. The chromatograms, which were recorded in the integral form of recording of the detector signal, were subjected to quantitative interpretation.

The IR spectra (in a thin layer or in $CCl_4$ solution) were recorded with a UR-20 spectrophotometer. The PMR spectra of 10% solutions in $CH_2Cl_2$ were obtained with a Varian-HA 100-D spectrometer at 30-35° with hexamethyldisiloxane as the internal standard.

The authors thank A. A. Potekhin, I. N. Somin, R. R. Kostikov, M. I. Komendantov, and M. A. Kuznetsov for their useful discussions.

## LITERATURE CITED

1. S. J. Brois, J. Am. Chem. Soc., 92, 1079 (1970).
2. V. Ya. Bespalov, L. A. Kartsova, V. I. Baranovskii, and B. V. Ioffe, Dokl. Akad. Nauk SSSR, 200, 99 (1971).
3. W. Lwowski (editor), Nitrenes, Interscience, New York (1970), p. 209.
4. O. C. Dermer and G. E. Ham, Ethylenimine and Other Aziridines, Academic Press, New York (1969).
5. H. L. Spell, Anal. Chem., 39, 185 (1967).
6. S. J. Brois, Trans. New York Acad. Science, 31, 931 (1969).
7. S. J. Brois, J. Am. Chem. Soc., 90, 508 (1968).
8. R. G. Kostyanovskii and Z. E. Samoilova, Izv. Akad. Nauk SSR, Ser. Khim., 727 (1969).
9. R. G. Kostyanovskii, Z. E. Samoilova, and I. I. Chervin, Tetrahedron Lett., 719 (1969).
10. R. G. Kostyanovskii, I. I. Chervin, and O. A. Pan'shin, Izv. Akad. Nauk SSSR, Ser. Khim., 1423 (1968).
11. R. G. Kostyanovskii, Z. E. Samoilova, and I. I. Chervin, Izv. Akad. Nauk SSSR, Ser. Khim., 2845 (1968).
12. S. A. Giller, A. V. Eremeev, M. Yu. Lidak, V. A. Pestunovich, É. É. Liepin'sh, and I. Ya. Kalvin'sh, Khim. Geterotsikl. Soedin., 45 (1971).
13. G. Lamaty, A. Delbord, and W. Werner, Lieb. Ann., 726, 77 (1969).
14. M. Jautelat and J. D. Roberts, J. Am. Chem. Soc., 91, 642 (1969).
15. G. L. Closs, in: Topics in Stereochemistry, Vol. 3, Interscience, New York (1968), p. 193.
16. B. V. Ioffe and K. N. Zelenin, Izv. Vuzov., Ser. Khim., 78 (1963).
17. M. Torigoe, Chem. Pharm. Bull. (Tokyo), 9, 613 (1961).
18. W. Theilacker and K. Ebka, Angew. Chem., 68, 303 (1954).

*An increase in the excess amount of olefin did not increase the yield of aziridine.