DIPOLE STABILIZED CARBANIONS IN SERIES OF CYCLIC ALDONITRONES. PART I (1). ALDONITRONES METALLATION AND DIMERIZATION IN LDA AND *n*-BuLi SOLUTIONS.

Maxim A. Voinov*, Igor A. Grigor'ev and Leonid B. Volodarsky
Novosibirsk Institute of Organic Chemistry, Ave. akad. Lavrent'eva 9, 630090 Novosibirsk, Russia.
Fax: 007-3832-354752. E-mail: maxx@nioch.nsc.ru

Abstract: Cyclic aldonitrones 1 **(Figure 1)** of pyrroline, 3-imidazoline and 2*H*-imidazole series was shown to be lithiated in LDA and *n*-BuLi ether solutions yielding dipole-stabilized carbanions **2**. In the absence of an "external" electrophile the latter ones react with aldonitrone group of a non-metallated molecule to give dimer products with the structure depending on the initial nitrone structure. Nitrones with non-conjugated aldonitrone group **4a,b** yield dinitrones **8a,b** **(Scheme 2)**, whereas conjugated nitrones **5a,b** yield iminonitrones **10a,b** **(Scheme 3)**. Acyclic aldonitrone **7** (PBN) does not undergo lithiation under the same conditions, which is likely to be due to its *Z*-configuration.

Introduction: Possibilities of aldonitrone group chemical transformations are related as a rule to nucleophilic addition (2) and 1,3-dipolar cycloaddition (3) reactions. Aldonitrone group deprotonation can yield carbanion **2**, stabilized with *N*-oxide group inductive effect [cf. (4)]. Previously the necessary conditions providing the existence of carbanions of general formula **3** **(Figure 1)** are stated (5): group Y must possess a rather strong acidifying effect; be free of hydrogen atoms, which might compete with CH-protons for a base; be a poor leaving group to prevent β-elimination in the resulting anion; the molecule must not involve groups, which are electrophilic towards deprotonating reagent or towards the anion formed.

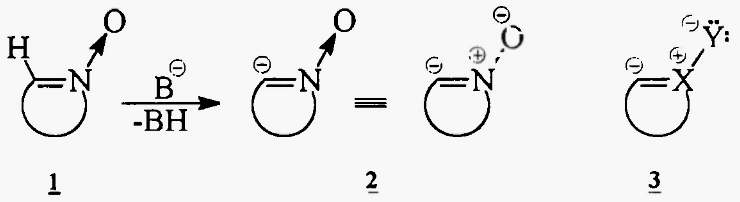
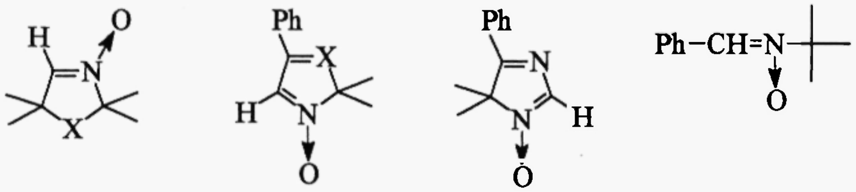


Figure 1

The first three conditions are fulfilled in a full measure in the case of aldonitrones. As for aldonitrone group electrophilicity, its effect could be minimized by means of a non-nucleophilic base using, by aldonitrone group exhaustive metallation, using an excess of the "external" electrophile to trap the resulting anion, as well as by selecting a favorable order of reagents mixing. Carbanions of such type are likely to be useful intermediates in organic synthesis and allow the use of electrophilic reagents of different structure in the reactions with aldonitrones. However, there are no data on aldonitrones reactions of such type in literature, although particles similar 2 **(Figure 1)** have been postulated as intermediates to rationalize the base-catalyzed hydrogen-deuterium exchange of the olefinic hydrogen of the nitronyl-nitroxide radical (6) and the dimerization of 2,2-dimethyl-pyrroline-*N*-oxide in the soda amide liquid ammonia solution (7).

The aim of our work is a systematical study of possible synthetic use of dipole-stabilized carbanions of aldonitrones series. In this paper we have studied metallation of aldonitrones of different structure in the absence of an "external" electrophile. We have chose cyclic nitrones **(Figure 2)** with non-conjugated (**4**) and conjugated (**5**,**6**) aldonitrone group as well as a well-known acyclic *N*-*tert*-butyl-α-phenylnitrone (PBN) 7 as objects of investigation. Lithium diisopropilamide (LDA) and *n*-butyl lithium (*n*-BuLi) were taken as bases.



4
a) X=N-CH$_3$
b) X=CH$_2$

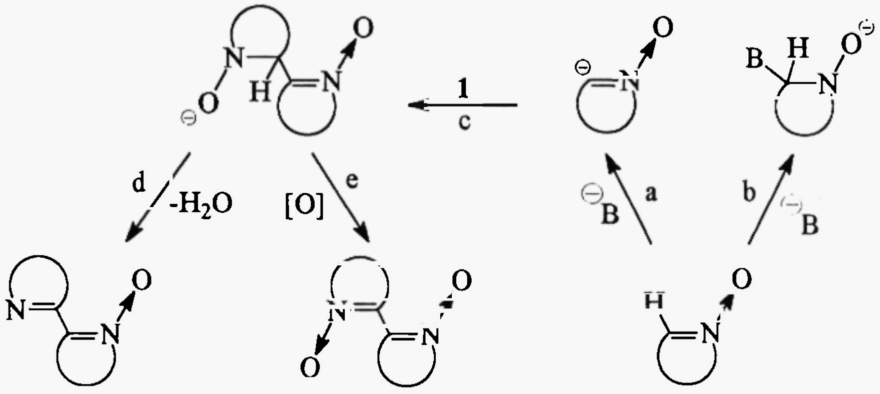
5
a) X=N
b) X=N→O

6

7

Figure 2

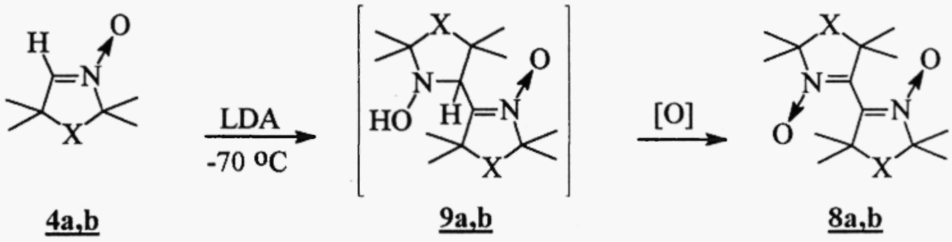
Several pathways of aldonitrone transformations in a base containing medium could be envisioned **(Scheme 1)**.



Scheme 1

Either a base used [according to (b)] or the resulting carbanion [according to (c)] can react with the aldonitrone group of non-metallated molecule. The use of non-nucleophilic or poorly nucleophilic bases allows pathway (b) to be excluded. The pathways (e) and (d) represent possible scenarious of the addition product further transformations. The isolation of the products derived from aldonitrones "self addition" [pathways (c), (d) and (e) of **Scheme 1**] will demonstrate the synthetic utility of aldonitrones metallation.

Results and Discussion: To find out which possible pathway is realized in the case of each aldonitrone, we have treated them with LDA and *n*-BuLi ether solutions at -70 °C and have quenched the resulting mixtures with H_2O. Thus, in LDA ether solution nitrone **4a** was converted with a good yield into a compound which IR-spectrum has no C=N→O group vibration band at 1600 cm^{-1} and shows vibration band at 1500 cm^{-1}, assigned to valent vibrations of group O←N=C-C=N→O [cf. (7)]. Three signals are found in ^{1}H-NMR spectrum at δ=1.42, 1.46 and 2.31 with the integral intensities ratio 2:2:1, which are assigned to geminal methyl groups protons at imidazoline ring 2- and 5-positions and to the protons of the group $N-CH_3$. The ^{13}C-NMR spectrum contains only the signals of methyl groups carbons at 1-, 2- and 5-positions of imidazoline ring, the signals of C-2 and C-5 atoms of imidazoline ring and the signal of conjugated nitrone group carbon atom (see **Table 2**). UV-spectrum of the obtained compound showed two absorption maximums of equal extinction at 232 and 317 nm, which were assigned to conjugated dinitrone group absorption [cf. (7,8)]. The determination of the obtained compound molecular weight gave a value close to the doubled initial nitrone molecular weight. Basing on the above data a structure of conjugated dimer nitrone *1,1',2,2,2',2',5,5,5',5'-decamethyl-4,4'-bi(3-imidazoline)-3,3'-dioxide* **8a** (**Scheme 2**) was assigned to the compound. Intermediate hydroxylamine **9a** is oxidized by air oxygen upon the reaction mixture work-up (9).

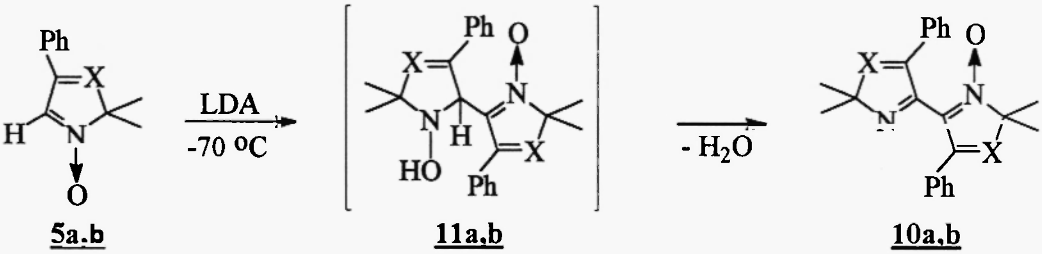


Scheme 2

Under these conditions aldonitrone **4b** undergoes similar transformation to give conjugated dinitrone *3,3,3',3',5,5,5',5'-octamethyl-2,2'-bi(1-pyrroline)-1,1'-dioxide* **8b**.

It should be noted, that in spite of dimers **8a** and **8b** structural similarity they differ greatly in spectral characteristics. In contrast to biimidazoline **8a** pyrroline dimer **8b** shows considerably lower intensity of long wave absorption maximum in UV-spectrum (see **Table 1**). Moreover, dimer nitrone **8b** shows two bands of correspondingly asymmetric (1500 cm^{-1}) and symmetric (1512 cm^{-1}) vibrations in the region of conjugated nitrone group valent vibrations in IR-spectrum, while symmetric vibrations of dimer **8a** nitrone group (1517 cm^{-1}) are active only in Raman spectrum (10), which is characteristic for conjugated azomethines having *s-trans* molecule conformation [cf. (8)]. These data testify that nitrone groups in pyrroline dimer **8b** are disturbed from conjugation to a large extent due to the molecule geometry.

Under the above conditions 2*H*-imidazole-1-oxide **5a** is converted into a compound which IR-spectrum displays valent vibration bands of phenyl ring and C=N bonds in the region of 1500-1600 cm^{-1}, which is characteristic for 2*H*-imidazoles (11) and which contains, according to the element analysis, only one oxygen atom. The obtained compound was assigned the structure of *2,2,2',2'-tetramethyl-4,4'-diphenyl-5,5'-bi(2H-imidazole)-1-oxide* **10a** dimer (**Scheme 3**). Non-symmetric nature of this compound is supported by ^{13}C-NMR spectra (see **Table 2**). Intermediate hydroxylamine **11**, unlike its non-conjugated analogue **9**, undergoes dehydration under the reaction conditions, that is likely to be due to the methine hydrogen larger acidity as well as by the molecule quest to keep maximum conjugated π-system. Similarly, 2*H*-imidazole-1,3-dioxide **5b** yields *2,2,2',2'-tetramethyl-4,4'-diphenyl-5,5'-bi(2H-imidazole)-1,3,3'-trioxide* **10b** under these conditions.



Scheme 3

The derivative of 4*H*-imidazole serie **6** under the above mentioned conditions does not yield a stable metallated derivative. Our attempts to isolate any products of aldonitrone **6** transformations have failed.

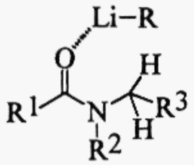
When the more strong base *n*-BuLi was applied, nitrone **4a** afforded to dimer **8a** also. In the case of nitrone **5a** under the same conditions the reaction mixture decomposition by water results in regeneration of up to 40% of the initial nitrone along with dimer **10a**. which can be attributed to higher metallation rate of conjugated aldonitrone as compared with the isolated one.

Thus, pathway (e) of **Scheme 1** is realized for cyclic nitrones with non-conjugated aldonitrone group and pathway (d) is realized for conjugated ones.

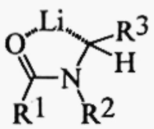
Acyclic nitrone **7** (PBN) in LDA solution does not give dimer and the initial compound is completely regenerated after the reaction mixture treatment. The reaction mixture decomposition with D_2O does not lead to substitution of aldonitrone group hydrogen atom with deuterium.

Electron factors could be hardly responsible for such low CH-acidity of *N*-*tert*-butyl-α-phenylnitrone, especially as the kinetics of aldonitrone group hydrogen isotope exchange in other *N*-alkyl-α-arylnitrones was studied before (12). In the ^{1}H-NMR experiment on hydrogen-deuterium exchange in the conditions, described in paper (12), the integral intensity of aldonitrone hydrogen in PBN did not change within two months, while the corresponding hydrogens signals in imidazoline **4a** and 2*H*-imidazole **5a** disappeared within several hours.

Such difference in cyclic aldonitrones and acyclic PBN ability to be metallated is likely to be related to the difference in their aldonitrone groups configurations. The results of the work (13) testify that PBN exist in solution exceptionally as a stable *Z*-isomer (with *anti*-alignment of *N*-oxide fragment and aldonitrone group α-hydrogen). Nitrones, studied in (12), are found to be exist in solutions as an equilibrium mixture of *E*- and *Z*-isomers [cf. (13)], while cyclic nitrones exist only as *E*-isomers (with *syn*-alignment of *N*-oxide fragment and aldonitrone group α-hydrogen). Therefore, we observe here the case of the regioselective aldonitrone metallation, and exactly the *syn*-metallation. The literature data show, that our suggestion concerning the aldonitrones configuration influence on their ability to metallation is not out of sense. Thus, the lithiation of methyl group in amides was shown to go only in *syn*-position to carbonyl group (14); *syn*-substitution for hydrogen atom upon *N*-alkylamides metallation is assigned to the association of organolithium compound with carbonyl group oxygen (15), spectral methods provided the direct observation of the complex **12** between the tertiary amide carbonyl group oxygen and *s*-BuLi formation and the rate constant of this complex transformation into *syn*-metallated amide was measured (16); initial formation of the complex **12** of an organolithium reagent with carbonyl group oxygen was shown to favor *syn*-metallation, and solvated anion must be more stable in chelate structure **13** (17).

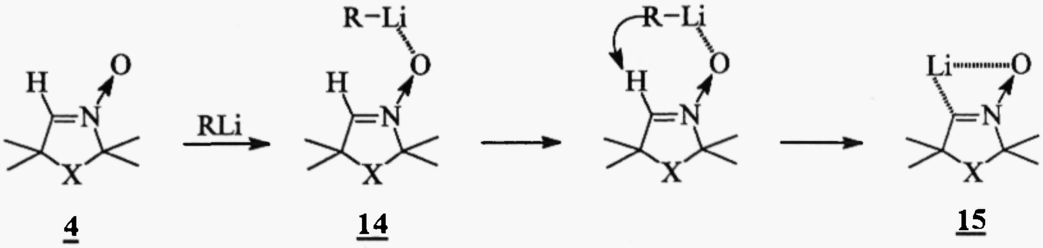


12



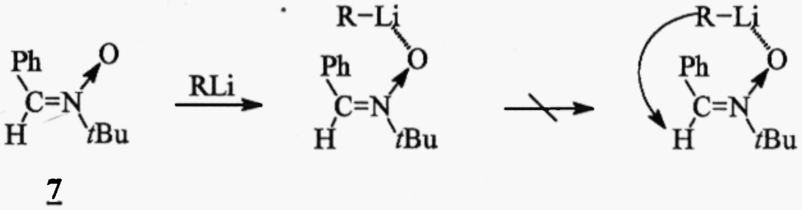
13

The data, mentioned above, along with the many other ones, unified with the concept of complex-induced proximity effect (CIPE), that enabled to account for some regio- and stereochemical results in organolithium chemistry (18). If assume, that aldonitrones metallation is a CIPE-controlled process, it becomes evident that the formation of the complex 14 **(Scheme 4)** between the organolithium compound and the nitrone group oxygen directs the metallation and "kinetically" favors metallation in *syn*-position solely, while the formation of chelate **15** should favor the resulting anion stabilization.



Scheme 4

Aldonitrone group configuration in 7 also allows for complex formation, but makes impossible the abstraction of hydrogen atom, located at C=N bond other side.



Scheme 5

Conclusions: The results, received in this work, allow for the statement, that the cyclic aldonitrones of pyrroline, 3-imidazoline and 2*H*-imidazole series metallation can be used as a method of their activation towards electrophilic reagents. This conclusion is likely to be extendible also to those acyclic aldonitrones, which exist in solution as an equilibrium mixture of *E*- and *Z*-forms.

Acknowledgements: We thank the *Russian Foundation for Basic Researches* (grant No. 97-03-32864a) for financial support and Drs. *V. Reznikov* and *I. Kirilyuk* for helpful discussions.

Experimental: Melting points (uncorrected) were measured using a Kofler plate. IR spectra were recorded on a UR-20 and Specord-IR in KBr. Raman spectra were recorded on a

Table 1: Characteristics of the synthesized compounds.

No.	IR (KBr) $\tilde{\nu}$, cm^{-1}	UV λ_{max}/nm (ε)	m.p., [° C]	Found, [%] C	H	N	Brutto formula	Calculated, [%] C	H	N	Yield, [%]
8a	1500 (C=N)	232 (7600) 317 (7600)	196-197 [a]	62.35	10.13	18.08	$C_{16}H_{30}N_4O_2$	61.89	9.67	18.05	65
8b	1500, 1512 (C=N)	235 (11600) 315 (2600)	128-130 [b]	69.96	9.64	9.58	$C_{16}H_{28}N_2O_2$	71.00	9.29	9.20	70
10a	1520, 1570 (C=N)	238 (9200) 281 (7400)	165-167 [c]	73.81	6.41	15.56	$C_{22}H_{22}N_4O$	73.71	6.20	15.63	70
10b	1512, 1535, 1540 (C=N)	218 (66500) 267 (23000) 303 (9600) 370 (5000)	256-258 [d]	67.99	5.95	14.52	$C_{22}H_{22}N_4O_3$	67.67	5.69	14.35	80

[a] Hexane : EtOAc, 1:6. - [b] Hexane. - [c] Hexane : EtOAc, 3:1. - [d] Hexane : EtOAc, 1:5.

Table 2: ^1H and ^{13}C NMR data of the synthesized compounds.

N	^{13}C δ [ppm]	^1H δ, [ppm]
8a	23.67, 23.89 (CH_3); 26.94 (NCH_3); 64.59 (C5); 90.06 (C2); 137.68 (C=N→O)	1.42 (s, 12 H, 4 CH_3); 1.46 (s, 12 H, 4 CH_3); 2.31 (s, 6 H, 2 NCH_3)
8b	27.62, 28.97 (CH_3); 41.41 (C5); 50.96 (CH_2); 73.08 (C3); 140.72 (C=N→O)	1.38 (s, 12 H, 4 CH_3); 1.43 (s, 12 H, 4 CH_3); 2.03 (s, 4 H, 2 CH_2)
10a	23.23, 24.07 (CH_3); 101.52 (C2'); 104.83 (C2); 127.02 (C-o); 127.90 (C'-o); 128.39 (C-m); 128.50 (C'-m); 131.20 (C-p); 130.65 (C'-p); 131.40 (C-i); 131.92 (C'-i); 132.60 (O=N→O); 155.04, 163.48, 164.28 (C=N)	1.63 (s, 12 H, 4 CH_3); 7.2-7.45 (m, 6 H, aromatic H); 7.5-7.6 (m, 4 H, aromatic H)
10b	23.96, 24.11 (CH_3); 97.96 (C2'); 102.28 (C2); 123.92 (C-i); 125.22 (C'-i); 126.41 (C-o); 128.33 (C-m); 129.40 (C'-o); 129.69 (C'-m); 130.53 (C'-p); 130.95 (C-p); 131.33 (C=N→O); 135.07, 135.22 (PhC=N→O); 156.93 (C=N)	1.65 (s, 6 H, 2 CH_3); 1.84 (s, 6 H, 2 CH_3); 7.34-7.38 (m, 6 H, aromatic H); 7.65-7.75 (m, 4 H, aromatic H)

Bruker IFS-66 equipped with FRA-106 Raman unit. UV spectra were recorded on a Specord UV-VIS in ethanol. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200SY and Bruker AC-200 (200 Mhz and 50.32 Mhz, for ^1H and ^{13}C, respectively) at 300 K. Both for ^1H and for ^{13}C NMR $CDCl_3$ as a solvent was used, δ_H = 7.24, δ_C = 76.69. Imidazoline **4a** was prepared according to a literature procedure (19a), 2*H*-imidazoles **5a** and **5b** - correspondingly according to procedures (11,19b), 4*H*-imidazole **6** - according to procedure (19c). Element analysis of the synthesized compounds was performed in the Microanalysis Laboratory of the Novosibirsk Institute of Organic Chemistry. Molecular weight of **8a** was determined by an ebullioscopy procedure in $CHCl_3$. Data on IR- and UV-spectra, element analysis, melting points and yields of the synthesized compounds are summarized in **Table 1**. ^1H and ^{13}C NMR data of the synthesized compounds are summarized in **Table 2**.

Aldonitrones Metallation (general procedure): The LDA or *n*-BuLi ether solution (25 ml, $9.5 \cdot 10^{-3}$ mol) was placed under argon in three-necked flat-bottomed flask fitted with magnetic stirrer, dropping funnel and thermometer, and cooled up to -70°. Then the solution of **4-7** ($1.9 \cdot 10^{-3}$ mol in 10 ml of ether) was added dropwise for 15 min upon the stirring. The reaction mixture was stirred for 10 min at -70°, allowed to warm-up to room temperature and decomposed with 10 ml of H_2O. Ether layer was separated, aqueous phase was extracted with $CHCl_3$ (3 × 10 ml), the combined organic layers were dried ($MgSO_4$), then the solvent was evaporated in a rotary evaporator. Thin-layer chromatographic separation of residue on silica gel with $CHCl_3$ +0.5 % CH_3OH as eluent gave **8a,b** and **10a,b**.

NMR Experiment on Isotope Exchange: The solutions of **4a**, **5a** and **7** ($6 \cdot 10^{-5}$ mol) in 2 ml of CD_3OD containing $8 \cdot 10^{-5}$ mol of CD_3ONa were kept at room temperature. ^1H-NMR spectra were recorded on a Bruker WP-200SY in 2 h intervals.

References:

(1) A preliminary account of this work has been reported in: *Abstracts of 11-th International Conference on Organic Synthesis (ICOS-11)*, Amsterdam, p. 343 (1996).

(2) a) S.-I. Murahashi, J. Sun, T. Tsuda, *Tetrahedron Lett.* 34, 2645-2648 (1993).

b) A. Reznikov, L.A. Vishnivetskaya, L.B. Volodarskii, *Russ. Chem. Bull.* 42, 889-890 (1993).

c) Y. Ukaji, Y. Kenmory, K. Inomata, *Tetrahedron Assymetry* 7, 53-56 (1996).

d) P. Merino, A. Lanaspa, F. L. Mershan, T. Tejero, *J. Org. Chem.* 61, 9028-9032 (1996).

(3) a) J. J. Tufariello In *1,3-Dipolar Cycloaddition Chemistry*, (Ed.: A. Padwa) Wiley-Interscience, New-York, Vol. 2, Chapter 9, 83-168 (1984).

b) P. N. Confalone, E. M. Huie, *Org. React.* 36, 1-173 (1988).

(4) P. Beak, D. B. Reitz, *Chem. Rev.* 78, 275-316 (1978).

(5) a) D. Seebach, D. Enders, *Angew. Chem. Int. Ed. Ingl.* 14, 15-32 (1975).

b) D. Seebach, W. Lubosch, *Angew. Chem. Int. Ed.* 15, p. 313 (1976).

(6) D. G. B. Boocock, R. Darcy, E. F. Ullman, *J. Amer. Chem. Soc.* 90, 5945-5946 (1968).

(7) R. F. C. Brown, V. M. Clark, M. Lamchen, Sir A. Todd, *J. Chem. Soc.* p. 2116-2122 (1959).

(8) I. A. Grigor'ev, M. M. Mitasov, G. I. Shchukin, I. K. Korobeynicheva, L. B. Volodarskii, *Zhurn. Org. Khim.* 13, 1532-1537 (1977).

(9) C. Berti, M. Colonna, L. Greci, *Tetrahedron* 32, 2147-2156 (1976).

(10) Bands assignment in Raman spectrum to the symmetric and asymmetric ones is made according the work: V. T. Alexanjan, E. V. Sobolev, *Dokl. Akad. Nauk SSSR* 150, 1062-1065 (1963).

(11) I. A. Kirilyuk, I. A. Grigor'ev, L. B. Volodarskii, *Izv. Akad. Nauk SSSR. Ser. Khim.* 9, 2113-2122 (1991).

(12) N. N. Zatsepina, I. F. Tupitsyn, A. I. Belyashova, E. A. Medyantseva, I. M. Andreeva, V. I. Minkin, *Reakts. Sposobn. Org. Soedin.*, *12*, 223-234 (1975); *Chem. Abstr.*, 85, 32286u (1976).

(13) J. Bjorgo, D. R. Boyd, D. C. Neill, W. B. Jennings, *J. Chem. Soc. Perkin Trans I*, 254-259 (1977).

(14) a) P. Beak, B. G. McKinnie, D. B. Reitz, *Tetrahedron Lett.*, 1839-1842 (1977).

b) P. Beak, W. J. Zajdel, *J. Amer. Chem. Soc.* 106, 1010-1018 (1984).

c) A. I. Meyers, D. A. Dickman, T. R. Bailey, *J. Amer. Chem. Soc.* 107, 7974-7978 (1985).

(15) N. G. Rondan, K. N. Houk, P. Beak, W. J. Zajdel, J. Chandrasekhar, P. v. R. Schleyer, *J. Org. Chem.* 46, 4108- 4101 (1981).

(16) a) M. Al-Aseer, P. Beak, D. Hay, D. J. Kempf, S. Mills, et al., *J. Amer. Chem. Soc.* 105. 2080-2082 (1983).

b) A. I. Meyers, W. F. Rieker, L. M. Fuentes, *J. Amer. Chem. Soc.* 105, 2082-2083 (1983).

c) D. R. Hay, Z. Song, S. G. Smith, P. Beak, *J. Amer. Chem. Soc.* 110, 8145-8153 (1988).

(17) R. D. Bach, M. L. Braden, G. J. Wolber, *J. Org. Chem.* 48, 1509-1514 (1983).

(18) P. Beak, A. I. Meyers, *Acc. Chem. Res.* 19, 356-363 (1986).

(19) a) I. A. Grigor'ev, G. I. Shchukin , V. V. Martin, V. I. Mamatyuk, *Khim. Geter. Soed.* 2,

247- 259 (1985).

b) I. A. Kyrilyuk, I. A. Grigor'ev, L. B. Volodarskii, *Izv. Akad. Nauk SSSR. Ser. Khim.* 9, 2122-2127 (1991).

c) I. A. Grigor'ev, I. A. Kyrilyuk, L. B. Volodarskii, *Khim. Geter. Soed.* 12, 1640-1648 (1988).

Received February 16, 1998