Autoassembly of cage structures
9.* Complete autoassembly of dilactones of α,α′-dihydroxy-α,α′-dialkoxycarbonyladipic and -pimelic acids

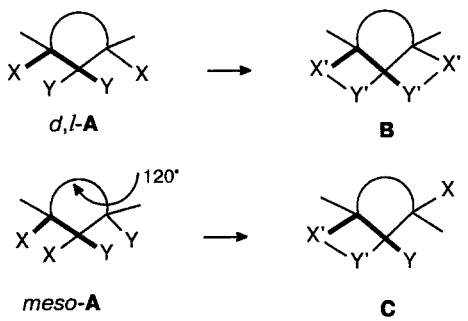
R. G. Kostyanovsky, Yu. I. El'natanov, O. N. Krutius, and V. N. Voznesensky*

N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117977 Moscow, Russian Federation. Fax: +7 (095) 938 2156

Complete autoassembly of dilactones **4**—**6** from dihydroxytetraesters of the type $X_2YC(CH_2)_nCYX_2$ (X = CO_2R, Y = OH, n = 2, 3) was performed in high yields under the conditions of acid or base catalysis. The classic syntheses of the Tröger's base, Meerwein ester, and dilactams were considered from the viewpoint of bicycle autoassembly.

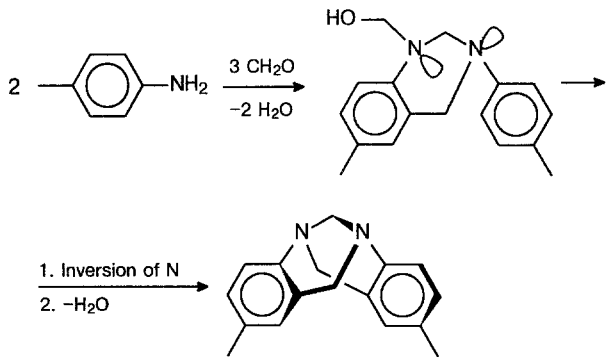
Key words: α,ω-alkylene-bis-tartronates; autoassembly of dilactones of α,α′-dihydroxy-α,α′-dialcoxycarbonyladipic and -pimelic acids; acidic and basic catalysis; NMR, IR, and mass spectra.

For type **A** systems that contain functional groups **X** and **Y** capable of interaction with one another, bicycle **B** can be formed only from *d,l*-**A** since *meso*-**A** produces monocycle C, in which the **X** and **Y** groups are *trans* to each other.



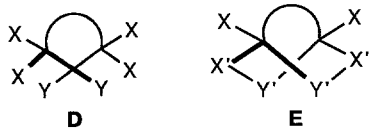
Obviously, this stereo-controlled cyclization is a general method for assembling bicycles. We have studied this principle in detail for the syntheses of dilactones of substituted α,α′-dihydroxyglutaric (DHG)[1—8] and -adipic acids (DHA),[2,9,10] which have been synthesized by N. D. Zelinsky (DHG,[11,12] DHA[13]) and which have attracted the attention of many prominent chemists for over 100 years (DHG,[14—18] DHA[16,17,19—21]).

The formation of a bicycle from *meso*-**A** becomes possible under epimerization conditions. The formation of dilactones in low yields from the *meso*-forms of α,α′-dihidroxy diacids and from their monolactones is explained by their partial epimerization under thermolysis conditions.[2,9,16,19] It can be assumed that the syntheses of the Tröger's base and its derivatives (see Ref. 22 and references therein) are based on the above principle of bicycle autoassembly.



In this case epimerization occurs due to the easy inversion of the N atoms.

The most impressive example is the complete autoassembly of bicycles from type **D** systems, in which the initially occurring cyclization always results in *cis* orientation of the **X** and **Y** groups and consequent cyclization into bicycle **E**.



To implement this simple idea, we have elaborated a synthesis of α,ω-alkylene-bis-tartronates[22,23] by α,ω-bis-

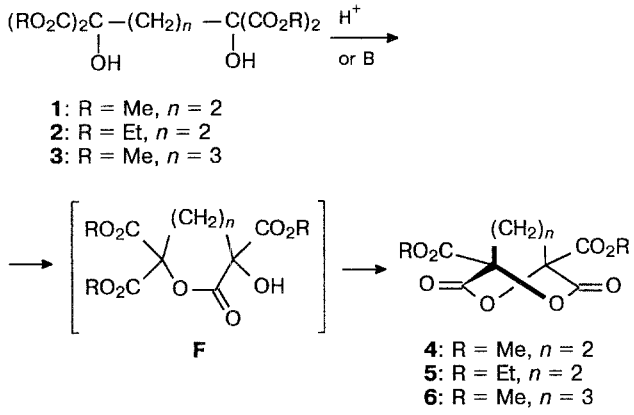
* For communication 8, see Ref. 23.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 327—330, February, 1995.

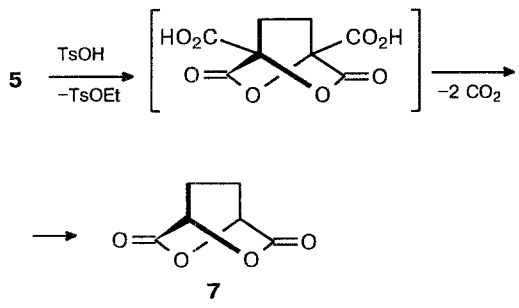
hydroxylation of α,ω-alkylene-bis-malonates followed by hydrolysis and esterification.[23] In addition, it has been found that only the monolactone is formed from methylene-bis-tartronate.[1]

In the present work we performed the cyclization of α,ω-alkylene-bis-tartronates **1—3** (see Ref. 23) into dilactones **4—6** under the conditions of acid (TsOH, refluxing in *o*-xylene) or base catalysis (1,5-diazabicyclo[5.4.0]-undecene-5 (DBU), in benzene, over molecular sieves, at 20 °C) (Scheme 1).

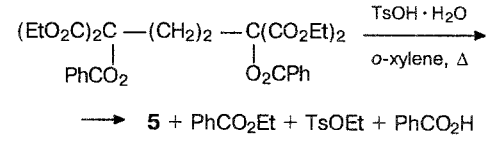
Scheme 1



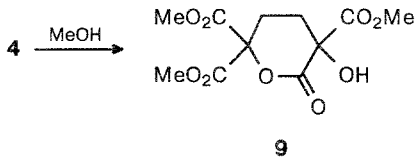
Refluxing 1,2-ethylene-bis-tartronate[1] in toluene with a twofold excess of $TsOH \cdot H_2O$ gave dilactone **5** as well as the dilactone of α,α′-dihydroxyadipic acid **7**. The formation of the latter can be explained by deesterification of dilactone-diester **5** through the action of *p*-toluenesulfonic acid (the ^1H NMR spectrum of the reaction mixture showed the presence of ethyl tosylate) followed by decarboxylation of the dilactonodicarboxylic acid.



According to its melting point, dilactone **7** was found to be identical to that reported in a earlier communication.[21] The formation of dilactone **5** was also detected by the ^1H NMR spectrum of the reaction mixture after refluxing 1,2-ethylene-bisbenzoyloxymalonate (**8**)[23] with TsOH in *o*-xylene for 48 h. In addition to benzoic acid, this procedure gave ethyl benzoate and ethyl tosylate identified by comparing its ^1H NMR spectra with those of authentic samples.



The ^1H NMR spectra of the reaction mixture formed *via* lactonization under mild conditions with DBU display both the signals of the dilactone and monolactone **F**. The structures of dilactones **4—7** were confirmed by spectral data (Fig. 1 and Experimental) and by performing a quantitative transformation of dilactones **4—6** into the original α,ω-alkylene-bistartronates **1—3** by treatment with the corresponding alcohols. In the case of dilactone **4**, the ^1H NMR spectrum of the reaction mixture showed the presence of tetraester **1** along with the corresponding type-**F** monolactone **9** (see Experimental).



The ^1H NMR spectra of dilactones **4,5,7** contain an AA′BB′ system of ethylene fragment protons, like in the case of the dilactone of α,α′-dihydroxy-α,α′-dimethyladipic acid (see Fig. 1), whose structure has been determined by X-ray diffraction analysis.[10] The ^1H NMR spectrum of dilactone **5** indicates geminal non-equivalence of the methylene protons of the ester groups (see Fig. 1) due to asymmetric induction of the chiral dilactone skeleton (*cf.* Ref. 24). The ^{13}C NMR spectra of dilactones **4—7** correspond to mutual equivalence of the carbon atoms in the substituents and in the skeleton of the symmetrical dilactone system. The IR spectra of dilactones **4—7** contain well-resolved carbonyl bands typical of lactones, dilactones (*cf.* Refs. 6,7,9), and ester groups. The EI mass spectra of dilactones **4—7** contain M^+ peaks, and the chemical ionization mass spectrum of dilactone **5** contains an MH^+ peak (100 %).

It can be assumed that the above principle of complete autoassembly is the basis for the classical synthesis of the Meerwein ester[25,26]* and 3,7-diazabicyclo-[3.3.1]nonane-2,6-diones[28] (Scheme 2). In the former case, the synthesis is likely to involve double intramolecular acylation, partial hydrolysis, and decarboxylation, while the latter synthesis probably occurs through double intramolecular amidation.

* The dienol structure of the Meerwein ester has been established by X-ray diffraction.[27]

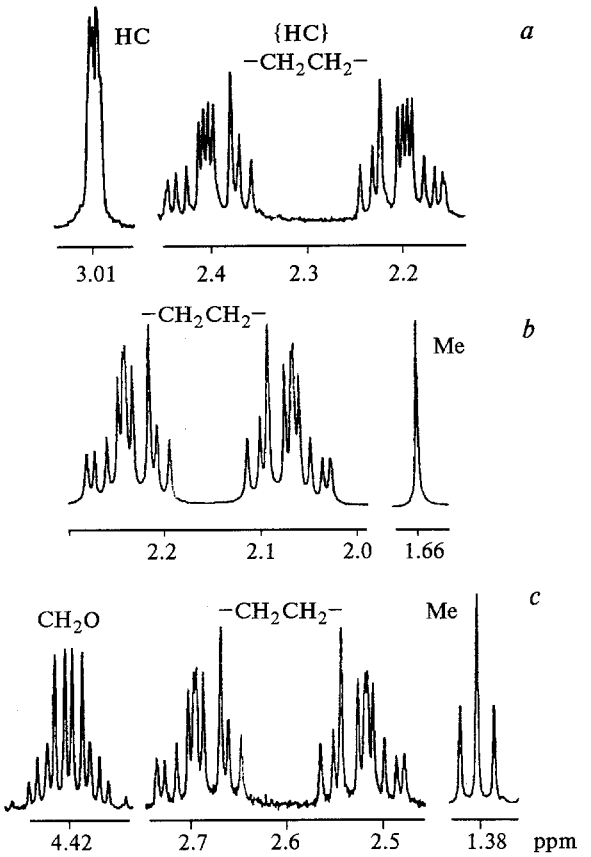
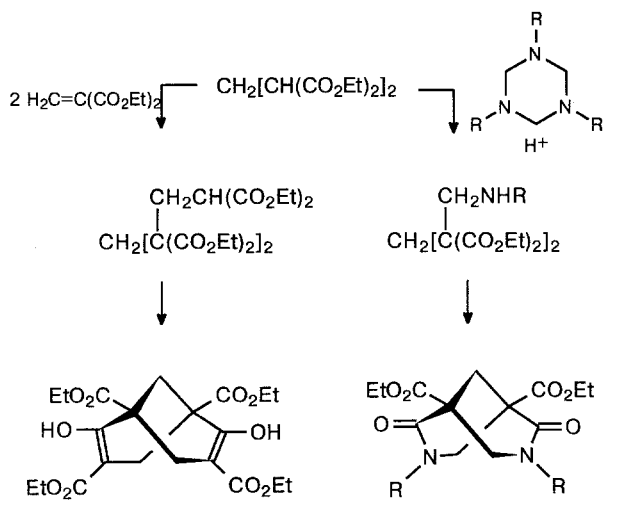


Fig. 1. ^1H NMR spectra of dilactones **5** and **7** (the latter spectrum was obtained with decoupling from the methine protons) (*a*,*c*) and the dilactone of α,α′-dihydroxy-α,α′-dimethyladipic acid (*b*).

Scheme 2



Experimental

NMR spectra were recorded on a Bruker WM-400 spectrometer (^1H 400.13; ^{13}C 100.62 MHz) in $CDCl_3$, using $SiMe_4$ as the internal standard. Electron impact (EI) and chemical ionization (CI) mass spectra were obtained on VG 7070 E and KRATOS MS-30 mass spectrometers at an ionizing voltage of 70 eV. IR spectra were recorded in $CHCl_3$ on a UR-20 spectrophotometer. Elemental analyses were performed on a CHNOS-1106 analyzer manufactured by KARLO-ERBA Strumentazione. Melting points were determined on a Boetius RNMK-0.5 hot stage at a heating rate of 4—5 °C min^{-1}.

We used dry solvents as well as freshly-prepared and freshly-purified reagents in the syntheses.

1,4-Dimethoxycarbonyl-2,5-dioxabicyclo[2.2.2]octane-3,6-dione (4). A. A mixture of tetramethyl 1,2-ethylene-bistartronate **1** (see Ref. 23) (1.0 g, 3.11 mmol) and $TsOH \cdot H_2O$ (1.2 g, 6.32 mmol) in *o*-xylene with b.p. 144 °C (200 mL) was boiled for 1.3—3 h using a reflux condenser equipped with a trap for water separation. The solvent was then evaporated, and the residue was heated in boiling benzene (50 mL) and cooled. The crystals that precipitated were filtered off, the mother liquor was concentrated, and the residue was washed with cold ether (2 × 20 mL) and dried *in vacuo* to give 0.73 g (91 %) of product **4**. Double sublimation of the latter *in vacuo* at 140 °C (1 Torr) gave white plate crystals with m.p. 188—189 °C. Found (%): C, 46.3; H, 3.97. $C_{10}H_{10}O_8$. Calculated (%): C, 46.51; H, 3.88. IR, ν/cm^{-1}: 1760 (C=O), 1795 (C=O) ring, 3050 (CH). ^1H NMR, δ: 2.62 (m, AA′BB′, Δν = 69; $^2J_{AB} = {}^2J_{A'B'} = -15.1$ Hz; $^3J_{AB'} = {}^3J_{A'B} = 11.12$ Hz; $^3J_{AA'} = 2.96$ Hz; $^3J_{BB'} = 6.23$ Hz; 4 H $(CH_2)_2$;* 3.96 (s, 6 H, MeO). $^{13}C\{H\}$ (CD_3CN), δ: 26.65 (s, CH_2); 53.87 (s, MeO); 82.31 (s, C—O); 163.03 (s, C=O); 163.2 (s, C=O); $^{13}C\{H\}$ ($(CD_3)_2SO$), δ: 24.73 (t, CH_2, $^1J = 141.7$ Hz); 53.44 (q, MeO, $^1J = 149.7$ Hz); 81.56 (s, C—O); 162.21 (m, C=O, $^3J = 3.6$ Hz).

B. A mixture of tetramethyl 1,2-ethylene-bistartronate **1** (0.1 g, 0.31 mmol) and a catalytic amount of 1,5-diazabicyclo[5.4.0]-undecene-5 (DBU) in dry benzene (100 mL) was kept for 90 h at 20 °C with 5 Å sieves calcined *in vacuo*. The sieves were filtered off and washed with benzene (2 × 20 mL). The filtrate was concentrated, the residue was washed with cold ether (3 × 15 mL) and dried *in vacuo* to give 70 mg (87 %) of dilactone **4**, which was then sublimed at 140 °C (1 Torr).

1,4-Diethoxycarbonyl-2,5-dioxabicyclo[2.2.2]octane-3,6-dione (5). A. A mixture of tetraethyl 1,2-ethylene-bistartronate **2** (see Ref. 23) (0.5 g, 1.32 mmol) and $TsOH \cdot H_2O$ (0.52 g, 2.74 mmol) in *o*-xylene (200 mL) was boiled for 1.3—3 h using a reflux condenser equipped with a trap for water separation. The reaction mixture was worked-up as in the previous procedure (method *A*) to give 0.32 g (84.7 %) of product **5**. Sublimation *in vacuo* at 120 °C (1 Torr) gave the product as white crystals, m.p. 139—140 °C. Found (%): C, 49.86; H, 4.96. $C_{12}H_{14}O_8$. Calculated (%): C, 50.35; H, 4.90. IR, ν/cm^{-1}: 1750 (C=O), 1780 (C=O) ring, 3070 (CH). ^1H NMR, δ: 1.4 (t, 6 H, Me, $^3J = 7.3$ Hz); 2.6 (m, AA′BB′, Δν = 69.9, $^2J_{AB} = {}^2J_{A'B'} = -15.24$ Hz; $^3J_{AB'} = {}^3J_{A'B} = 11.16$ Hz; $^3J_{AA'} = 2.99$ Hz; $^3J_{BB'} = 6.01$ Hz; 4 H, $(CH_2)_2$)*; 4.41 (m, ABX_3, Δν = 14.3; $^2J_{AB} = -10.9$ Hz; 4 H, OCH_2). ^{13}C NMR, δ: 13.82 (qt, Me, $^1J = 127.7$ Hz; $^2J = 2.5$ Hz); 25.53 (tt, $(CH_2)_2$, $^1J = 141.7$ Hz; $^2J = 5.8$ Hz); 63.5 (tq, CH_2O, $^1J = 149.3$ Hz; $^2J = 4.4$ Hz); 81.3 (t, C—O, $^2J = 3.6$ Hz); 162.06 (t, CO_2Et, $^3J = 3.3$ Hz); 162.19 (q, C=O, $^3J = 8.4$ Hz). MS, *m/z* (CI in CH_4): 287 $[M^+ + H]$ (100 %).

B. A mixture of tetraethyl 1,2-ethylene-bistartronate **2** [23] (0.4 g, 1.06 mmol) and $TsOH \cdot H_2O$ (0.76 g, 4 mmol) in dry toluene (100 mL) was refluxed for 48 h. The excess of $TsOH \cdot H_2O$ was filtered off, the mother liquor was concen-

* From a computer analysis of the AA′BB′ spectrum (iteration analysis using the PANIC program).

trated, and the dark residue was extracted with chloroform (3×30 mL). The extract was concentrated, and the residue was washed with cold ether (3×30 mL), dried *in vacuo*, and sublimed at 120 °C (1 Torr) to give 0.1 g (33 %) of dilactone **5**. The dark residue obtained after extraction with chloroform was dried and sublimed *in vacuo* at 90 °C (3 Torr) to give 30 mg (20 %) of the dilactone of α,α'-dihydroxyadipic acid (**7**) as white needle crystals with m.p. 130—132 °C (*cf.* Ref. 21). IR, ν/cm^{-1}: 1800 (C=O), 3105 (CH). ^{1}H NMR, δ {H, 4.99}: 2.31 (m, AA'BB', Δν = 80.2, $^2J_{AB} = {}^2J_{A'B'} = -14.99$ Hz; $^3J_{AB'} = {}^3J_{BA'} = 10.87$ Hz; $^3J_{AA'} = 2.84$ Hz; $^3J_{BB'} = 5.82$ Hz; 4 H, $(CH_2)_2$).* Work-up of the ethereal solution obtained by washing the residue gave ethyl tosylate, ^{1}H NMR, δ: 1.32 (t, 3 H, $MeCH_2$, $^3J = 7.2$ Hz); 2.46 (s, 3 H, MeC_6H_4); 4.1 (q, 2 H, CH_2O); 7.33 (d, 2 H, H(3), $^3J = 8.1$ Hz); 7.78 (d, 2 H, H(2)).

C. A mixture of 1,2-ethylene-bis-benzoyloxymalonate **8** (1.2 g, 2.05 mmol) (see Ref. 23) and $TsOH \cdot H_2O$ (0.78 g, 4.1 mmol) in *o*-xylene (100 mL) was refluxed for 150 h. The ^{1}H NMR spectrum of the reaction mixture indicated that it contained dilactone **5** (which was not isolated), benzoic acid, ethyl benzoate, and ethyl tosylate (see method **B**). $PhCO_2H$, ^{1}H NMR, δ: 7.47 (dt, 2 H, H(3), $^3J = 8.1$ Hz); 7.61 (t, 1 H, H(4)); 8.12 (dd, 2 H, H(2)); $PhCO_2Et$, ^{1}H NMR, δ: 1.42 (t, Me, 3 H, $J = 7.1$ Hz); 4.38 (q, 2 H, CH_2O); 7.42 (dt, 2 H, H(3), $^3J = 8.1$ Hz); 7.53 (t, 1 H, H(4)); 8.03 (dd, 2 H, H(2)).

1,4-Dimethoxycarbonyl-2,5-dioxabicyclo[3.2.2]nonane-3,6-dione (6). A mixture of tetramethyl 1,3-propylene-bis-tartronic acid **3** [23] (0.6 g, 1.79 mmol) and $TsOH \cdot H_2O$ (0.7 g, 3.68 mmol) in *o*-xylene (150 mL) was refluxed for 62 h with a trap for water separation. The reaction mixture was worked-up as described above (method **A**) to give 0.34 g (70 %) of product **6**, which was sublimed *in vacuo* at 140 °C (2 Torr) to give white crystals with m.p. 166—167 °C. IR, ν/cm^{-1}: 1760 vw (C=O), 1780 vw (C=O) ring, 2900 (CH). ^{1}H NMR, δ: 2.0 (q, 2 H, $C-CH_2C$, $^3J = 6.7$ Hz), 2.5 (ddt, ABX_2, 4 H, CH_2CCH_2, Δν = 124, $^2J = -15.3$ Hz); 3.92 (s, 6 H, MeO).

The reaction of dilactone 4 with methanol. A mixture of dilactone **4** (20 mg) and MeOH (0.3 mL) in $CDCl_3$ (0.5 mL) was kept for two weeks at 20 °C. After 4 days, the ^{1}H NMR spectrum indicated the formation of α-hydroxy-α,δ,δ-tris-methoxycarbonyl-δ-valerolactone (**F**, see the text).

2-Hydroxy-2,5,5-tris-methoxycarbonyl-δ-valerolactone (9). ^{1}H NMR, δ: 1.94 (ddd, 1 H, 3a, $^2J_{ab} = -14.8$ Hz; $^3J_{ac} = 8$ Hz, $^3J_{ad} = 4.8$ Hz); 2.26 (ddd, 1 H, 3b, $^2J_{ba} = -14.8$ Hz, $^3J_{bd} = 9.0$ Hz, $^3J_{bc} = 4.6$ Hz); 2.47 (m, 4c and 4d); 3.82 (s), 3.83 (s) and 3.84 (s) (MeO).

After two weeks, the ^{1}H NMR spectrum contained only the signals of tetramethyl 1,2-ethylene-bis-tartronic acid (**1**) (see Ref. 23).

This study was financially supported by NATO (Grant LG 921193), the Russian Foundation for Basic Research (Grant No. 94-03-08730), and the International Science Foundation (Grant MCO 000).

References

1. R. G. Kostyanovsky, Yu. I. El'natanov, O. N. Krutius, and I. I. Chervin, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 2002 [*Russ. Chem. Bull.*, 1994, **43**, 1884 (Engl. Transl.)].
2. R. G. Kostyanovsky, Yu. I. El'natanov, V. P. Leshchinskaya, and I. I. Chervin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 2637 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 2420 (Engl. Transl.)].
3. I. V. Vystorop, Yu. I. El'natanov, I. I. Chervin, V. N. Voznesenskii, and R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 2428 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1988, **37**, 2190 (Engl. Transl.)].
4. R. G. Kostyanovsky, V. P. Leshchinskaya, Yu. I. El'natanov, A. E. Aliev, and I. I. Chervin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 408 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 355 (Engl. Transl.)].
5. R. G. Kostyanovsky, I. V. Vystorop, A. E. Aliev, Yu. I. El'natanov, V. N. Voznesenskii, V. I. Zav'yalov, and R. A. Karakhanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 891 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 801 (Engl. Transl.)].
6. I. V. Vystorop, Yu. I. El'natanov, and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1591 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1227 (Engl. Transl.)].
7. I. V. Vystorop, A. B. Zolotoi, V. M. Anisimov, V. G. Kartsev, and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1992 1601 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1235 (Engl. Transl.)].
8. I. V. Vystorop, G. V. Shustov, A. Rauk, and R. G. Kostyanovsky, *Mendeleev Commun.*, 1994, 97.
9. R. G. Kostyanovsky and Yu. I. El'natanov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 650 [*Russ. Chem. Bull.*, 1994, **43**, 599 (Engl. Transl.)].
10. A. B. Zolotoi, S. V. Konovalikhin, L. O. Atovmyan, I. V. Vystorop, Yu. I. El'natanov, and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1965 [*Russ. Chem. Bull.*, 1994, **43**, 1854 (Engl. Transl.)].
11. N. D. Zelinsky, *Chem. Ber.*, 1891, **24**, 4006.
12. N. D. Zelinsky and L. A. Chugaev, *Chem. Ber.*, 1895, **28**, 2940.
13. N. D. Zelinsky and W. Isaev, *Chem. Ber.*, 1896, **29**, 819.
14. K. Auwers and H. Kauffmann, *Chem. Ber.*, 1892, **25**, 3221.
15. A. Hantzsch, *Gründriss der Stereochemie*, Verlag von Eduard Trewendt, Breslau, 1893, 37.
16. R. Fittig, *Liebigs Ann. Chem.*, 1907, **353**, 1.
17. K. Freudenberg, W. F. Bruce, and E. Gauf, *Liebigs Ann. Chem.*, 1934, **510**, 206.
18. J. A. Elvidg, R. P. Linstead, and J. F. Smith, *J. Chem. Soc.*, 1952, 1026.
19. A. R. Mattocs, *J. Chem. Soc.*, 1964, 4845.
20. O. Wallach, *Liebigs Ann. Chem.*, 1908, **362**, 261.
21. H. R. LeSueur, *J. Chem. Soc.*, 1908, **93**, 716.
22. R. G. Kostyanovsky, O. N. Krutius, and Yu. I. El'natanov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 2185 [*Russ. Chem. Bull.*, 1994, **43**, 2065 (Engl. Transl.)].
23. R. G. Kostyanovsky, Yu. I. El'natanov, and O. N. Krutius, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 2190 [*Russ. Chem. Bull.*, 1994, **43**, 2070 (Engl. Transl.)].
24. S. N. Balasubrahmanyam and M. Sivarajan, *Tetrahedron Lett.*, 1971, 3355.
25. H. Meerwein and W. Schürmann, *Liebigs Ann. Chem.*, 1913, **398**, 196.
26. H. Meerwein, F. Kiel, G. Klösgen, and E. Schoch, *J. Prakt. Chem.*, 1922, **104**, 161.
27. M. D. Radkliffe, A. Gutierrez, J. F. Blount, and K. Mislow, *J. Am. Chem. Soc.*, 1984, **106**, 682.
28. G. Darnbrough, Ph. Knowles, S. P. O'Connor, and F. J. Tierney, *Tetrahedron*, 1986, **42**, 2339.

* From a computer analysis of the AA'BB' spectrum (iteration analysis using the PANIC program).

Received August 11, 1994;
in revised form October 10, 1994