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SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW PRECURSORS OF MACROCYCLIC CYCLOPHANES: 1,4-BIS (2-R-5,5-DIMETHYL-1,3-DIOXAN-2-YL) BENZENE

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Dedicated to Professor Sorin Mager
on the occasion of his 75th birthday

ABSTRACT. The synthesis and the stereochemistry of some new 1,3-dioxane derivatives of 1,4-diacetylbenzene are reported. The structural analysis carried out using NMR investigations revealed the anancomeric structure of the compounds. The favorable arrangement of the different functions for the participation to the macrocyclisation is insured by the axial orthogonal dispositions of the aromatic group with respect to both 1,3-dioxane rings.

Introduction

The investigations on the stereochemistry of 1,3-dioxane derivatives with aryl groups at position 2 of the heterocycle showed important structural aspects. The A value (free conformational enthalpy) of aryl groups at position 2 of the 1,3-dioxane ring are high (*e.g.* A_{Ph} = 13.04 kJ/mol [1,2]). The 2-aryl-1,3-dioxanes are anancomeric compounds and the conformational equilibrium between I and II is shifted toward I which exhibits the aryl group in the *equatorial* orientation (Scheme 1 [3-5]).

The conformational equilibrium of 2-alkyl,2-aryl-1,3-dioxanes (III, IV; *e.g.* 2-phenyl-2-methyl-1,3-dioxanes, Scheme 1) is shifted toward the conformer exhibiting the aryl group in the *axial* position [1,6-8].

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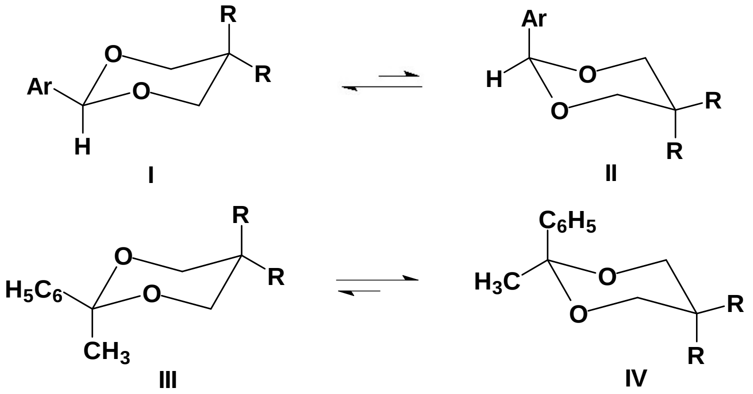
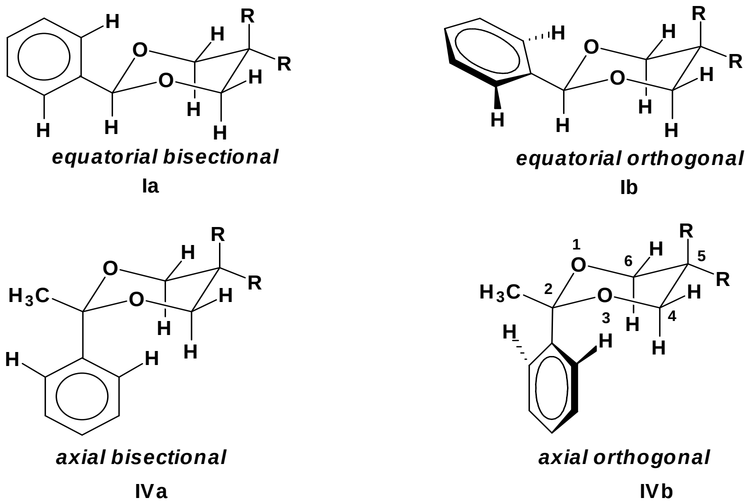


Scheme 1

The higher A value of the methyl group at position 2 (A_{Me} = 16.63 kJ/mol [1]) than the A value of the phenyl group (A_{Ph} =13.04 kJ/mol [1]) at the same position suggests the *axial* preference of the phenyl group. Thermodynamic measurements of 2-methyl-2-phenyl-1,3-dioxanes showed a considerably higher preference of the methyl group for the *equatorial* position (ΔG_{III-IV}^0 = 10.11 kJ/mol [1]) than that calculated from the A- values of methyl and phenyl groups ($\Delta A = A_{Me} - A_{Ph}$ = 3.63 kJ/mol).



equatorial bisectional
Ia

equatorial orthogonal
Ib

axial bisectional
IVa

axial orthogonal
IVb

Scheme 2

The equatorial aryl groups exhibit a weak preference for the *bisectional* rotamer (I_a) [9-11] and the axial phenyl group shows the *orthogonal* orientation (IV_b, Scheme 2 [7,8,12-15]). This is consistent with the ^{1}H NMR shifts [7,8].

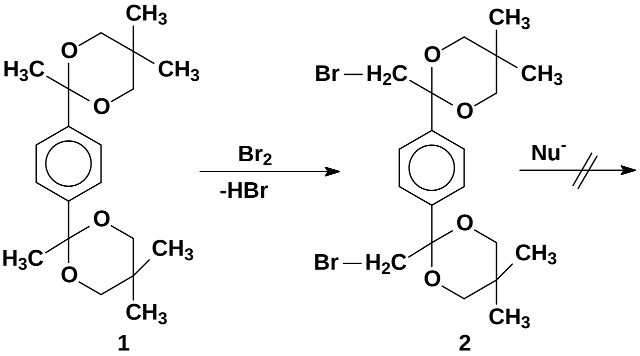
Investigations on the stereochemistry of compounds bearing two 1,3-dioxane rings on the same aromatic system, obtained from benzenedicarboxaldehydes, have revealed the *equatorial* orientation of the aromatic ring for both heterocycles [3-5], while the investigations of similar derivatives of 1,4-diacetylbenzene [16] and of 2,6-diacetylbenzene [17] showed the axial orientation of the aromatic group with respect to both heterocycles. Some of these 1,3-dioxane derivatives were already successfully used in the synthesis of macrocyclic cyclophanes [18, 19]

It was considered of interest to investigate the stereochemistry of new 1,3-dioxane derivatives of 1,4-diacetylbenzene bearing different substituents at the positions 2 and 5 of the 1,3-dioxane rings and to determine the conformational behaviour of the heterocycles, the orientation of the aromatic substituent in both heterocycles, and to identify the possibility to use these compounds for the synthesis of cyclophanes.

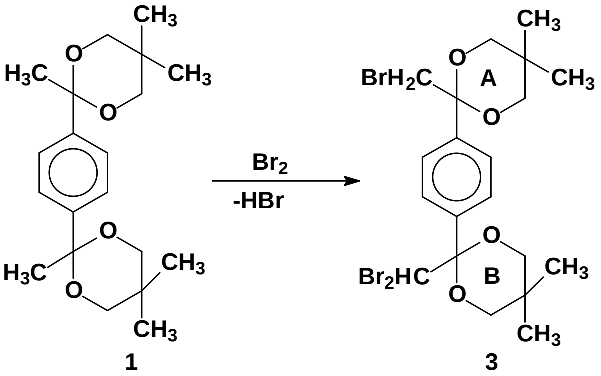
Results and Discussions

In order to obtain new bis(2-R-1,3-dioxan-2-yl) derivatives bearing the 1,4-phenylene unit the 1,3-dioxane derivative **1** [16] was brominated in good yields (Table 1) using the typical procedure for the bromination reaction of cyclic ketals (Scheme 3)[20,21].

The bromination reaction generated as side product the tribrominated derivative **3** (Scheme 4, Table 1), too.



Scheme 3

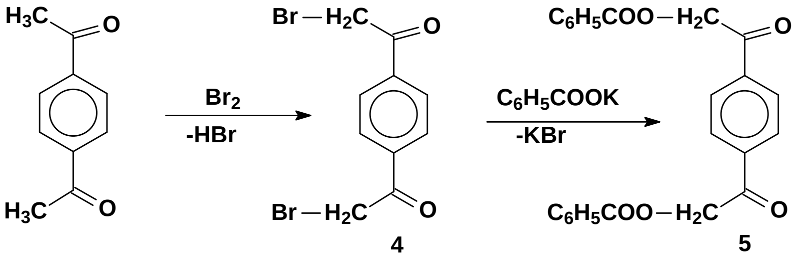


Scheme 4

Dibrominated derivative **2** was reacted with several nucleophyles (*e.g*. HO^-, $C_6H_5COO^-$) in order to have access to other derivatives with appropriate substitution for the macrocyclisation reaction. All the attempts failed and the conclusion was that the steric hindrance of the carbon atoms bearing the bromine substituents is very high and nucleophyle substitutions cannot take place in these positions.

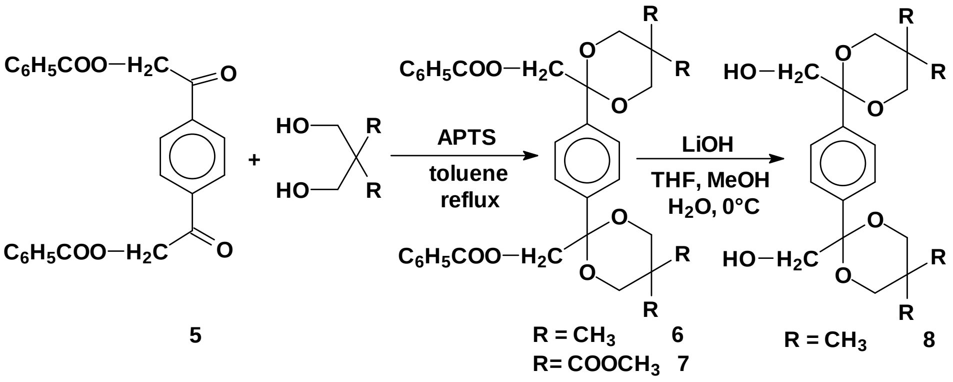
Due to this result we changed our strategy and we decided to obtain first the desired derivatives of 1,4-diacetylbenzene and then to use these derivatives for the synthesis of the 1,3-dioxane rings.

In the first step we brominated in good yields 1,4-diacetylbenzene with bromine in acetic acid [22] and after that we carried out the substitution of bromine atoms of the dibrominated derivative **4** with $C_6H_5COO^-$ (Scheme 5, Table 1), and we obtained the diester **5**.



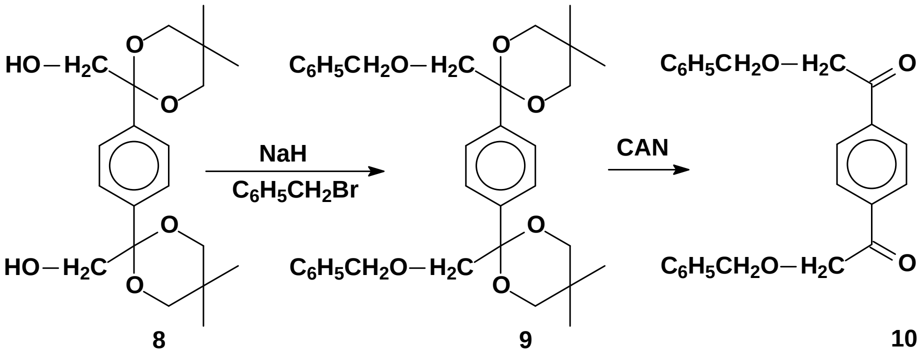
Scheme 5.

The dibenzoate derivative **5** was subjected to the condensation reaction with neopentylglycol or with dimethyl-bis(hydroxymethyl)malonate (Scheme 6, Table 1) in order to obtain the 1,3-dioxane diester **6** and hexaester **7**. The diester **6** was deprotected with LiOH at 0℃, to give diol **8**.



Scheme 6

Diol **8** was used to obtain the protected α,α'-dihidroxi-1,4-diacetylbenzene **10**, *via* the di-1,3-dioxane derivative **9** (Scheme 7, Table 1).



Scheme 7

Table 1.
Results of the synthesis of compounds **2**, **3** and **5-10**

Compound	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**
Yields %	75	15	92	52	74	91	78	86

Compounds **2**, **3**, **7**, **9**, **10** are new ones, while compounds **5**, **6**, **8** were already reported [19].

The structural analysis was carried out using NMR investigations. The spectra of **2**, **3**, **6-9** exhibit different signals for the axial and equatorial protons of the 1,3-dioxane rings and for the similar groups located on it (Table 2).

Table 2.
NMR data for compounds **2**, **3** and **6-9**

Compound	4’(4”)-H; 6’(6”)-H		5’(5”)-CH_3		5’(5”)-$COOCH_3$	
	ax.	eq.	ax.	eq.	ax.	eq.
2	3.45	3.52	1.36	0.63	-	-
3	3.40	3.55	1.36	0.63	-	-
6	3.47	3.47	1.30	0.60	-	-
7	3.98	4.62	-	-	3.71	3.64
8	3.47	3.52	1.29	0.63	-	-
9	3.48	3.54	1.31	0.61	-	-

The NMR data suggest the anancomeric structure of these derivatives and the axial orthogonal orientation of the aromatic ring.

Conclusions

New 1,3-dioxane derivatives were obtained in good yields by condensation reactions or using the α, α’ bromination reaction of cyclic ketals. The NMR based structural analysis of these derivatives revealed the rigid structure for all compounds and the axial orientation of the aromatic ring with respect to both saturated heterocycles. The reported derivatives are important precursors for the synthesis of cyclophane derivatives.

Experimental

^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz), COSY, HMQC, and HMBC spectra, were recorded at *rt* in $CDCl_3$ on a Bruker 300 MHz spectrometer, using the solvent line as reference. Mass spectra were recorded on an ATI Unicam Automass.

Melting points were measured with a Kleinfeld melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was conducted on silica gel 60 F_{254} TLC plates purchased from Merck. Preparative column (flash) chromatography was performed using PharmPrep 60 CC (40-63 µm) silica gel purchased from Merck. Chemicals were purchased from Aldrich or Acros and were used without further purification.

General Procedure for the Synthesis of Compounds 2 and 3

The 1,3-dioxane derivative (2.1 mmol) and dry dichloromethane (40 ml) were introduced into a three-necked flask equipped with a reflux condenser, a thermometer and a dropping funnel. Bromide (9.25 mmol) in 10 ml dry dichloromethane was added drop wise, under magnetically stirring, to this mixture cooled into an ice bath at 0-5ºC, the ensuing reaction being monitored initially by the fading of the solution color. After the addition of the bromide, the ice bath was removed and the stirring was continued for 1h, the contents in the flask being allowed slowly to reach room temperature (20-25ºC). The mixture was evaporated *in vacuum* and the residue was crystallized from ethanol.

1,4-Bis(2’-bromomethyl-5’,5’-dimethyl-1’,3’-dioxan-2’-yl)benzene (2)
White solid, m.p.=164-5℃, yield 75% (flash chromatography, elution: DCM/pentane/diethyl acetate 1/3/0.1 v/v, Rf = 0.60). ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm): 0.63 (6H, s), 1.36 (6H, s), 3.45 (4H, d, *J*=10.6 Hz), 3.46 (4H, s), 3.52 (4H, d, *J*=10.6 Hz), 7.51 (4H, s). ^{13}**C-NMR** (75 MHz, $CDCl_3$, δ ppm): 21.9 (CH_3) 23.0 (CH_3), 30.2 (C_{quat}), 40.8 (CH_2), 72.2 (CH_2), 98.9 (C_{quat}), 128.44 (CH), 137.8 (C_{quat}). **MS** (EI, 70 eV); m/z (rel. int., %): 493 (2) $[M+H]^+$, 477 (10), 399 (100).

1-(2’-dibromomethylene-5’,5’-dimethyl-1’,3’-dioxan-2’-yl)-4-(2’’-bromomethyl-5’’,5’’-dimethyl-1’’,3’’-dioxane-2’’-yl)benzene (3)
White solid, m.p.=134-5℃, yield 15% (flash chromatography, elution: DCM/pentane : 3/1 v/v, Rf = 0.52). ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm): 0.63 (6H, s), 1.36 (6H, s), 3.40 (4H, d, *J*=10.9 Hz), 3.46 (2H, s), 3.55 (4H, d, *J*=10.9 Hz), 6.88 (1 H, s) 7.63 (2H, d, *J*=8.3 Hz) 8.16 (2H, d, *J*=8.3 Hz) ^{13}**C-NMR** (75 MHz, $CDCl_3$, δ ppm): 21.8 (CH_3) 22.9 (CH_3), 30.2 (C_{quat}), 49.6 (CH), 40.1 (CH_2), 72.3 (CH_2), 98.6 (C_{quat}), 128.6 (CH), 130.4 (CH), 131.4 (C_{quat}) 143.9(C_{quat}). **MS** (EI, 70 eV); m/z (rel. int., %): 475,477 (2.5), 391,393 (49), 314 (12), 305 (14), 209 (11), 104

General Procedure for the Synthesis of Compound 7

2,2-dicarboxymethyl-1,3-propanediol (11 mmol) and ketone **5** (5 mmol) with catalytic amounts of *p*-toluenesulphonic acid (0.1 g) were solved in 200 mL toluene. The mixture was refluxed and the water produced in the reaction removed using a Dean-Stark trap. When 80 % of the water had been separated, the mixture was cooled to room temperature and the catalyst was neutralized (under stirring 0.5 h) with CH_3-COONa powder in excess (0.2 g). The reaction mixture was washed twice with 100 mL of water. After drying over $MgSO_4$, the benzene was removed and **7** was purified by flash chromatography.

1,4-Bis[2’-benzoyloxymethyl-5’,5’-bis(carboxymethyl)-1,3-dioxan-2’-yl]benzene (7)
White solid, m.p.= 245-6℃, yield 74% (flash chromatography, elution: DCM, Rf = 0.43. ^{1}**H-NMR** (300 MHz,$CDCl_3$, δ ppm): : 3.64 (6H, s), 3.71 (6H, s), 3.98 (4H, d, *J*=11.3 Hz) 4.31 (4H, s) 4.62 (4H, d, *J*=11.6 Hz) 7.42 (4H, dd, overllaped *J*=7.2 Hz, *J*=7.5 Hz) 7.54 (2H, t, *J*=7.5 Hz) 7.60 (4H, s,) 8.0 (4H, d, *J* = 7.2 Hz). ^{13}**C-NMR** (75 MHz, $CDCl_3$, δ ppm): 53.16 (CH_3) 53.19 (CH_3), 53.23 (C_{quat}), 63.8 (CH_2), 69.2 (CH_2), 100.4 (C_{quat}) 128.4 (CH), 128.6 (CH), 129.9 (C_{quat}), 130.0 (CH), 133.2 (CH) 136.5 (C_{quat}), 165.9 (CO), 166.9 (CO), 168.1 (CO). **MS** (EI, 70 eV); m/z (rel. int., %): 616(100) [M-134], 442 (40).

General Procedure for the Synthesis of Compound 9

To a suspension of NaH (8.4 mmol) in dry THF (50 mL), diol **8** (2.1 mmol) in 10 ml THF was added under argon. The mixture was heated to reflux and benzyl bromide (2.1 mmol) solved in 5 mL THF was added slowly to the

NaH solution. Reflux of the solvent was continued for 5h, after which the system was brought to room temperature and the solid phase removed by filtration. The solvent was evaporated and the crude product was solved in CH_2Cl_2 (20 mL) and then washed twice with water (20 mL). After drying over magnesium sulfate, the solvent was removed and the crude product was purified by crystallization from ethanol.

1,4-Bis(2'-benzyloxymethyl-5',5'-dimethyl-1,3-dioxan-2'-yl)benzene (9)
White solid, yield 76% **^{1}H-NMR** (300 MHz,$CDCl_3$, δ ppm): 0.61 (6H, s), 1.31 (6H, s), 3.48 (4H, d, *J*=10.6 Hz) 3.54 (4H, d, *J*=10.6 Hz), 3.56 (4H, s), 4.54 (4H, s) 7.11-7.23 (10H, m, overlapped signals), 7.50 (4H, s). **^{13}C-NMR** (75 MHz, $CDCl_3$, δ ppm): 22.05 (CH_3), 30.4 ($\underline{C}H_3$), 31.1 (C_{quat}), 71.6 (CH_2), 73.8 (CH_2), 77.25 (CH_2) 100.9 (C_{quat}), 127.38-127.42 (**CH**) 128.2 (CH), 132.3 (C_{quat} 1-C, 4-C), 137.5 (C_{quat}).

General Procedure for the Synthesis of Compound 10

To a stirred solution of **9** (6 mmol) in MeCN (3mL) and water (3mL) was added solid cerium ammonium nitrate (CAN, 18 mg, 4 mol %). The solution was heated at reflux for 2 h. After cooling at room temperature, water (10 mL) was added and the mixture was extracted with dichloromethane (3x20 mL). The organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuum*. The crude product was further purified by crystallization from acetone.

1,4-Bis(2'-benzyloxymethyl) benzene (10)
White solid, yield 86%. **^{1}H-NMR** (300 MHz,$CDCl_3$, δ ppm): 4.68 (4H, s), 4.74 (4H, s) 7.31 -7.37 (10H, overlapped signals) 7.98 (4H, s).

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REFERENCES

1. Anteunis M.J.O., Tavernier D., Borremans F., *Heterocycles* **1976**, *4*, 293
2. Kleinpeter E., *Advances in Heterocyclic Chemistry*, **1998**, *69*, 217
3. Grosu I., Mager S., Plé G., Plé N., Toscano A., Mesaroş E., Martinez E., *Liebigs Annalen/Recueil*, **1997**, *3*, 345
4. Grosu I., Mager S., Mesaroş E., Plé G., *Heterocyclic Commun.*, **1998**, *4*, 53
5. Grosu I., Mager S., Toupet L., Plé G., Mesaroş E., Mihiş A., *Acta Chem. Scand.*, **1998**, *52*, 366
6. Grosu I., Mager S., Plé G., Mesaroş E., Gegö C., Dulău A., *Rev. Roum. Chim.*, **1999**, *44*, 467
7. Mager S., Grosu I., *Stud. Univ. "Babeş-Bolyai", Chemia*, **1988**,*33*, 47
8. Grosu I., Plé G., Mager S., Mesaroş E., Dulău A., Gegö C., *Tetrahedron*, **1998**, *54*, 2905
9. De Kok A.J., Romers C., *Recl. Trav. Chim. Pays-Bas*, **1970**, *89*, 313

10. Collins P.M., Travis A.S., Tsiquaye K.N., Lindley P.F., Perrat D., *J. Chem. Soc. Perkin Trans. 1*, **1974**,1895
11. Nader F.W., *Tetrahedron Lett*., **1975**, *14*,1207
12. Keller M., Langer E., Lehner H., *Monatsh. Chem*.,**1976**, *107*, 949
13. Kellie G.M., Murray-Rust P., Riddell F.G., *J. Chem. Soc. Perkin Trans. 2*, **1972**, 2384
14. Nader F.W., *Tetrahedron Lett.*, **1975**, *14*,1591
15. Drewes S.E., Drewes M.W., McNaught I.J., *S. Afr. Tydskr. Chem*., **1985**, *38*,101
16. Grosu I., Muntean L.,Toupet L., Plé G., Pop M., Balog M., Mager S., Bogdan E., *Monatsh. Chem.* **2002**, *133*, 631
17. Balog M., Tötös S., Florian C.M., Grosu I., Plé G., Toupet L., Ramondenc Y., Dincă N., *Heterocyclic Commun.* **2004**, *10,* 139
18. Balog M., Grosu I., Plé G., Ramondenc Y., Condamine E., Varga R. A., *J. Org. Chem*., **2004**, *69*, 1337
19. Bogdan N., *manuscript in preparation*
20. Grosu I., Camacho B. C., Toscano A., Plé G., Mager S., Martínez R., Gavino R. R., *J. Chem. Soc. Perkin Trans. 1*, **1997**, 775
21. Bogdan E., Grosu I., Mesaroş E., Toupet L., Plé G., Mager S., Muntean L., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 3635
22. Grosu I, Toupet L., Plé G., Mager S., Mesaroş E., Varga A., Bogdan E., *Monatsh. Chem*., **2000**, *131*, 277