Synthesis and Characterization of Some New 2-Methyl-O-Acyl-Oximino-Dibenz[b,e]Oxepins

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This paper is a continuation of our research and presents the chemical modeling that we made on the dibenz[b,e]oxepinic system, with the aim of obtaining new compounds with potential antidepressive action, that contain in the same molecule two pharmacologically active elements: the dibenzoxepin system and the oximinic group. For the new compounds synthesized, we used as intermediate substance 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one, prepared by cyclizing the 2-(4-methyl-phenoxymethyl)-benzoic acid (which resulted from phtalide and potassium p-cresolate). After treating the aforementioned ketone with hydroxylamine hydrochloride, we obtained 2-methyl-11-hydroxyimino-6,11-dihydro-dibenz[b,e]oxepin. This oxime was acylated with different substituted benzoic acid chlorides and we obtained the 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins. We established the optimal reaction conditions to synthesize the new compounds with high purity and yields. The new compounds, which have not been mentioned in the literature concerning this domain, have been characterized by their physical constants (melting point, solubility), structurally by NMR, IR analysis and by elemental analysis. To obtain new compounds from the dibenz[b,e]oxepin series with potential pharmacological action, we synthesized eight new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins. The spectral and elemental analysis confirmed the final and intermediate compounds structures and also the synthesis that we had done.

Keywords: dibenz[b,e]oxepin, ^{1}H-NMR, ^{13}C-NMR

The present application is a continuation-in-part of our research concerning the synthesis and characterization of new O-acyl-dibenz[b,e]oxepins [1-6].

The remarkable pharmacological efficiency of the compounds with dibenz[b,e]oxepinic structure such as Doxepine, known for antidepressive action and low side effects, and the positive results of the previous pharmacological tests effectuated with some substances with the same structure, synthesized by us, led us to obtain new compounds in the dibenz[b,e]oxepin series.

In the case of dibenz[b,e]oxepins previously synthesized, the pharmacological tests relevated that same compounds are psychoactivators and others are sedatives and anxiolitics [7-10].

Furthermore, the antidepressive action will be investigated for a possible use of this substances in therapeutics.

We made the chemical modeling and combined in the same molecule the dibenz[b,e]oxepinic system and the oximinic group, double bound with the carbon from 11-position of this nucleus.

Experimental part

All melting points were recorded with an Electrothermal 9100 apparatus and are uncorrected.

The ^{1}H-NMR spectra were obtained at 300MHz and the ^{13}C-NMR spectra were recorded at 75.075MHz with a Gemini 300BB apparatus using solutions in chloroform-d_1 as solvent and tetramethylsilane as internal standard.

The IR spectra were performed using potassium bromide tablet, with a Biorad FTS 135 apparatus.

The elemental analysis was realized using a Perkin Elmer CHNS/ O Analyser Series II 2400 apparatus.

The synthesis of 2-(4-methyl-phenoxymethyl)-benzoic acid

A solution containing 5.4 g (0.05 mol) of freshly distilled *para*-cresol (Mol wt 108.13) in 30 mL xylene was placed in a round-bottom flask, equipped with a water removing device. Subsequently, 3.10 g (0,055 mol) potassium hydroxide (Mol wt 56,11) were added.

The reaction mixture was refluxed until 0.9 mL resulting water was removed by azeotropic distillation while potassium *para*-cresolate precipitated at the bottom.

6.7 g (0.05 mol) Phtalide (Mol wt 134.14) was added and the mixture was refluxed until it solidified.

The precipitate was heated for solubilisation with 10% potassium hydroxide solution and then was diluted with 50 mL of water.

The aqueous phase was separated and acidulated with 1M hydrochloric acid solution until the mixture became acid (*p*H 3), when 2-(4-methyl-phenoxymethyl)-benzoic acid precipited. The resulting precipitate, which crystallized from water: ethanol (1: 1) mixture, shows a m.p. 126-129^{0}C. 7.2 g of 2-(4-Methyl-phenoxymethyl)-benzoic acid (Mol wt 242.26) resulted (59.5% yield).

The synthesis of 2-(4-methyl-phenoxymethyl)-benzoyl chloride

4.85 g (0.02 Mol) of 2-(4-methyl-phenoxymethyl)-benzoic acid (Mol wt 242.26), 30 mL of dry 1,2-dichloroethane and 5 g (3 mL) (0.042 mol) of thionyl chloride (Mol wt 119, d_4^{25} 1.638) were placed in a round-bottom flask equipped with

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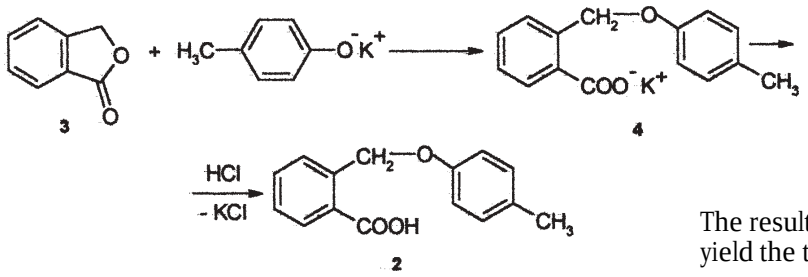


Scheme 1. The synthesis of 2-(4-methyl-phenoxymethyl)-benzoic acid

condenser and drying tube. The mixture was refluxed for 3 hours. The thionyl chloride in excess and the solvent were removed by reduced pressure. For the next step, the 2-(4-methyl-phenoxymethyl)-benzoic acid chloride was used in the crude status.

1,2-Dichloroethane was anhydrized over calcium chloride and distillated at normal pressure.

The synthesis of 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one

2.8 g (0.02 Mol) of anhydrous aluminium chloride (Mol wt 133.6) and 15 mL of 1,2-dichloroethane were placed in a round- bottom flask equipped with stirrer, condenser and drying tube, thermometer and addition funnel.

The suspension was cooled to 0^0C by stirring. The 5.2 g (0.02 mol) of 2-(4-methyl-phenoxymethyl)-benzoyl chloride (Mol wt 260.70), solubilised in 25 mL of 1,2-dichloroethane, was added in portions, with the mixture maintained at 0^0 to 5^0C, during the addition period.

After the acid chloride was added, the reaction mixture was stirred at 5^0 to 20^0C for one hour and then, for another hour at 20^0C.

The reaction mixture was poured into 5% hydrochloric acid solution and stirred until the complex aluminium chloride: ketone has been decomposed.

The organic and aqueous layers were then separated and the organic layer was washed once with 5% sodium hydroxide solution and twice with water, dried (anhyd. calcium chloride), treated with decolorizing charcoal and evaporated under vacuum to yield the 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (Mol wt 224.25), which was recrystallized from hexane (4.25 g, 94.5% yield, m.p. 106- 108^{0}C).

The synthesis of 2-methyl- 11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin

11.2 g (0.05 Mol) of 2-methyl-6,11-dihydro-dibenz[b,e] oxepin-11(6H)-one (Mol wt 224.25) and 10.5 g (0.15 mol) of hydroxylamine hydrochloride (Mol wt 69.5) were boiled under reflux in 100 mL of pyridine for 96 hours. The pyridine is subsequently distilled off in a vacuum, the residue is triturated with water, suction-filtered, dried and recrystallized from isopropanol (7.3 g, 61% yield, m.p. 206-209^{0}C, Mol wt 239.26).

The synthesis of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins (general procedure)

3.83 g (0.016 Mol) of 2-methyl-11-hydroximino-6,11-dihydro-dibenz[b,e]oxepin (Mol wt 239.26) were solubilised in anhydrous benzene by refluxing in a round-bottom flask equipped with condenser and drying tube. To this solution was added dropwise a solution of 0.016 mol acyl chloride in 10 mL anhydrous benzene and 1.27 g (1.3 mL) (0.016 mol) dry pyridine (Mol wt 79.09, d_4^{25} 0.9780) and the mixture was refluxed for two hours.

After cooling and filtered, the solvent was removed by distillation and the residue was triturated with isopropanol. The resulting solid was recrystallized from isopropanol to yield the title compound.

Results and Discussions

For the new compounds synthesis we used as intermediate substance 2-methyl-6,11-dihydro-dibenz [b,e]oxepin-11(6H)-one (**1**).

The synthesis has three stages.

1. *The synthesis of 2-(4-methyl-phenoxymethyl)-benzoic acid* (scheme 1)

In the first stage, the 2-(4-methyl-phenoxymethyl)-benzoic acid (**2**) was prepared by treating the phtalide (**3**) with potassium *para*-cresolate in xylene.

The resulted potassium salt of 2-(4-methyl-phenoxymethyl)-benzoic acid (**4)** has a good solubility in an aqueous solution of 10% sodium hydroxide and it can be separated from xylene. The acid **2** is precipitated using a mineral acid solution.

The potassium salt of *para*-cresol was obtained using the *para*-cresol and potassium hydroxide in xylene, the resulting water being removed by azeotropic distillation.

The reactions are presented in the scheme 1.

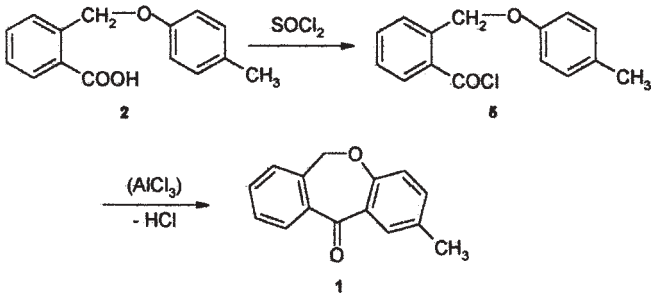
2. *The synthesis of 2-methyl-6,11-dihydro-dibenz[b,e] oxepin-11(6H)-one* (scheme 2)

The 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one (**1**) was synthetized by a Friedel-Crafts cyclization of the 2-(4-methyl-phenoxymethyl)-benzoic acid chloride (**5**) in dry 1,2-dichloroethane.

The acid chloride **5** resulted by refluxing the acid **2** with thionyl chloride in excess (the most favorable is 25%), but can be obtained also by using different anhydrous solvents as reaction medium, like 1,2-dichloroethane.

The desired ketone can be prepared directly from the acid **2** using various agents for anhydrization (e.g. polyphosporic acid), but the yields was smaller.

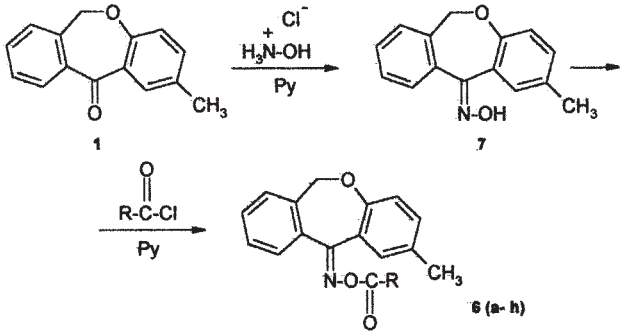
The scheme 2 presents the mentioned reactions.



Scheme 2. The synthesis of 2-methyl-6,11-dihydro-dibenz[b,e]oxepin-11(6H)-one

3. *The synthesis of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins (scheme 3)*

The new compounds (**6**) were prepared by acylation of the 2-methyl-11-hydroximino-6,11-dihydro-dibenz[b,e] oxepin (**7**) with different benzoic acid chlorides, in dry benzene, in the presence of anhydrous pyridine as a proton fixator.



Scheme 3. The synthesis of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins

The oxime **7** resulted by treating the ketone **1** with hydroxylamine hydrochloride in the presence of pyridine.

The reactions are presented in the scheme 3 and the structures of the new compounds (6a-h) are presented in table 1.

The structure, molecular formula, molecular weight, melting point and yield of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins are presented in table 1.

The new compounds are solid, crystallized, white or light yellow, soluble at normal temperature in acetone, benzene, toluene, xylene, chloroform, dichloromethane and dichloroethane, by heating in inferior alcohols, insoluble in water.

Spectral data

The structures of the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins were established through NMR and IR spectroscopy.

The ^{1}H-NMR spectra of the new dibenz[b,e]oxepins are divided into two spectra corresponding to the oxepinic system and to the acyl radical attached to the oximino group.

The protons of the methyl group situated in the second position of dibenz[b,e]oxepin nucleus gives a singlet signal in the range 2.24- 2.37 ppm.

The presence of an oxygen in the 5th position makes possible the existence of sin-anti isomery, materialised in our spectra through the dedoublation of the protons and the carbons signals, but the diference between chemical shifts of the methylene group is insignificant.

The most unscreened proton is H^1, and the most screened is H^4.

The individual attribution of the H^1-H^4 protons were done using the connectivity H-H experiments **(COSY).** This experiment wasn't possible for the protons H^7-H^{10} because of their signals (multiplets) overlapping in the range 7.29-7.63 ppm.

For the protons H^{14}-H^{18} the complete attributions were made (except the 6e compound), the most unscreened protons being H^{14} and H^{18} which are situated in the *ortho* position.

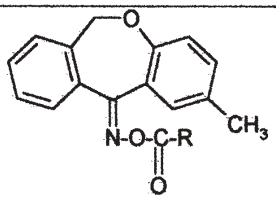
The most important ^{1}H- NMR spectral values (δ, ppm, J, Hz) for the compounds, are presented in table 2.

The ^{13}C-NMR spectra were recorded in $CDCl_3$. The carbon atoms attributions outcame from the spectra recorded by complete decoupling and sequence pulse APT (Attached Proton Test), and also from two-dimensional heteronuclear correlation experiments (COSY H-^{13}C or HETCOR).

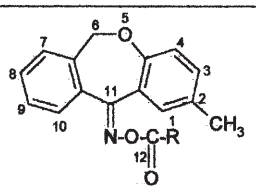
The carbon atoms were identified by 2D experiments because the protons H^1-H^4 have well-defined attributions. The methyl group produces a signal at 20.2-20.3 ppm. The methylene group (C^6) appears in the range 70.4-70.5 ppm, the differences between the chemical shifts of the two sin-anti isomers being unsignificant.

In the oxepinic system, the carbon atom C^4 is the most screened tertiary carbon atom and the C^{4a} is the most unscreened quaternary carbon atom, because of the presence of the oxigen atom.

Table 1
THE NEW COMPOUNDS CHARACTERISTICS



No.	R	Molecular formula	Molecular weight	Melting point (^{0}C)	Yield(%)
6a.	-C_6H_4F (2)	$C_{22}H_{16}FNO_3$	361.36	176.2- 178.6	53.1
6b.	-C_6H_4F (3)	$C_{22}H_{16}FNO_3$	361.36	170.4- 172.1	63.5
6c.	-C_6H_4Cl(2)	$C_{22}H_{16}ClNO_3$	377.82	140.5- 142.5	56.7
6d.	-C_6H_4Cl(4)	$C_{22}H_{16}ClNO_3$	377.82	184.3- 186	76.6
6e.	-C_6H_4Br (2)	$C_{22}H_{16}BrNO_3$	422.27	130.4- 132.7	67.8
6f.	-C_6H_4Br (3)	$C_{22}H_{16}BrNO_3$	422.27	164.4-166.9	73.3
6g.	-C_6H_4Br (4)	$C_{22}H_{16}BrNO_3$	422.27	186.3- 188.1	71.5
6h.	-C_6H_4I (2)	$C_{22}H_{16}INO_3$	469.27	150.1- 152.6	57.7



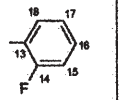
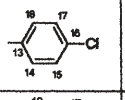
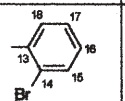
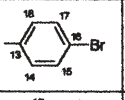
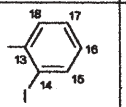
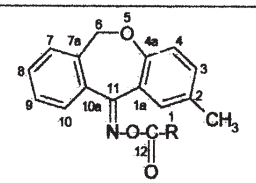
-CH_3	R	H^3	H^4	H^5	H^6	H^7	H^8	H^9	H^{10}	H^{14}	H^{15}	H^{16}	H^{17}	H^{18}
2.32 s		7.69 d 2.5	7.15 dd 8.4; 2.5	6.80 d 8.4	5.16 s	7.40- 7.55 m			7.61 m	-	7.09 ddd 9.7; 8.3; 1.1	7.40- 7.55 m	7.19 td 9.3; 7.6; 1.0	7.87 td 7.6; 1.9
2.32 s		7.70 d 2.4	6.81 d 8.4	7.17 dd 8.4; 2.4	5.17 s	7.35- 7.58 m				7.68- 7.71 m	-	7.26 tdd 8.4; 2.7;1.1	7.39 ddd 9.3; 8.2; 5.5	7.35- 7.58 m
2.31 s		7.70 d 2.4	6.80 d 8.4	7.15 dd 8.4; 2.3	5.15 s	7.35- 7.56 m			7.54 dt 6.7; 1.5	-	7.35- 7.46 m		7.24 m	7.61 dd 7.9; 1.7
2.31 s		7.68 d 2.3	6.80 d 8.4	7.15 dd 8.4; 2.3	5.16 s	7.44- 7.57 m				7.81 d 8.7	7.37 d 8.7	-	7.37 d 8.7	7.81 d 8.7
2.24 s		7.62 d 2.3	6.72 d 8.4	7.08 dd 8.4; 2.3	5.1 s	7.30- 7.55 m								
2.32 s		7.69 d 2.2	6.81 d 8.4	7.17 dd 8.4; 2.2	5.16 s	7.46- 7.61 m				8.01 t 1.8	-	7.82 dt 7.8; 1.4	7.28 t 8	7.67 dt 7.8; 1.4
2.37 s		7.74 d 2.2	6.86 d 8.4	7.22 dd 8.4; 2.2	5.22 s	7.52- 7.63 m				7.79 d 8.5	7.8 d 8.5	-	7.8 d 8.5	7.79 d 8.5
2.24 s		7.63 d 2.3	6.73 d 8.4	7.17 dd 8.4; 2.3	5.1 s	7.29- 7.40 m			7.45 m	-	7.89 dd 7.9; 1.2	7.05 td 7.8; 1.7	7.25 td 7.8; 1.2	7.45 dd 7.8; 1.1

Table 2
^{1}H-NMR DATA FOR THE COMPOUNDS 6a-h (δ ppm, J Hz)



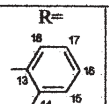
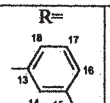
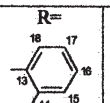
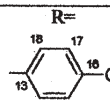
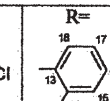
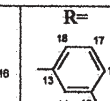
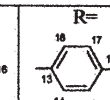
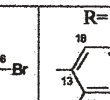
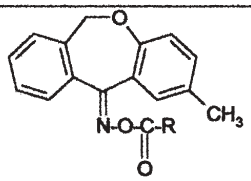
	R= 	R= 	R= 	R= 	R= 	R= 	R= 	R= 
C^1	130.3	130.3	130.2	130.6	130.3	130.6	130.5	130.4
C^{1a}	117.3	118.9	118.9	119.1	119.0	119.0	119.0	119.1
C^2	130.7	130.6	130.7	130.6	130.7	130.8	130.8	130.7
C^3	133.6	133.7	133.6	133.7	133.6	133.7	133.7	133.7
C^4	116.8	116.4	119.7	119.8	119.7	119.8	119.7	119.7
C^{4a}	155.4	155.4	155.3	155.5	155.4	155.5	155.4	155.4
C^5	70.5	70.5	70.4	70.5	70.5	70.5	70.5	70.5
C^7	128.4	128.3	128.3	127.9	128.3	127.8	128.3	128.4
C^{7a}	134.5	134.4	134.3	134.5	134.4	134.4	134.4	134.5
C^8	130.7	130.3	131.0	130.5	130.5	130.4	130.5	130.6
C^9	128.4	128.4	128.4	127.9	128.4	127.9	128.6	128.4
C^{10}	128.2	127.9	128.0	127.2	128.0	127.7	127.8	127.8
C^{10a}	132.7	132.9	130.7	130.9	132.8	130.6	130.6	130.8
C^{11}	163.4	160.8	163.1	162.9	163.6	162.3	163.0	164.1
C^{12}	164.8	164.8	165.1	164.7	165.3	164.9	164.7	165.3
C^{13}	119.1 (21.0)	132.9 (8.8)	132.7	133.7	132.8	133.0	133.7	141.4
C^{14}	161.7 (261.0)	116.7 (20.5)	133.7	131.0	121.7	133.7	131.1	94.1
C^{15}	117.1 (21.1)	164.1 (246.2)	130.5	128.9	132.6	122.6	131.9	141.4
C^{16}	134.8 (9.0)	116.6 (23.1)	133.6	139.9	134.3	136.2	127.5	133.7
C^{17}	124.1	125.5 (3.2)	126.5	128.9	127.0	130.1	131.9	128.0
C^{18}	128.2 (12.8)	125.4	131.2	131.0	131.0	128.1	131.1	132.7
2-CH_3	20.2	20.3	20.2	20.2	20.2	20.2	20.3	20.2

Table 3
^{13}C-NMR DATA FOR THE COMPOUNDS 6a-h (δppm)

Table 4

THE ELEMENTAL ANALYSIS



No.	R	C%		H%		N%	
		c.	e.	c.	e.	c.	e.
6a.	-C_6H_4F (2)	73.06	72.82	4.43	4.40	3.87	3.92
6b.	-C_6H_4F (3)	73.06	73.21	4.43	4.38	3.87	3.87
6c.	-C_6H_4Cl (2)	69.87	69.64	4.23	4.21	3.71	3.79
6d.	-C_6H_4Cl (4)	69.87	70.03	4.23	4.27	3.71	3.68
6e.	-C_6H_4Br (2)	62.52	62.69	3.79	3.87	3.32	3.31
6f.	-C_6H_4Br (3)	62.52	62.38	3.79	3.84	3.32	3.35
6g.	-C_6H_4Br (4)	62.52	62.17	3.79	3.79	3.32	3.29
6h.	-C_6H_4I (2)	56.26	56.41	3.41	3.43	2.98	2.92

The signal corresponding to the C^{12} atom appears in the range 164.7-165.3 ppm and the signal of C^{11} can be found in the range 160.8- 164.1 ppm.

For exemplification, we present in the table 3, the ^{13}C-signal attributions for the new compounds.

In the IR spectra the caracteristic bands for the new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins are (cm^{-1}): -CH_2-O- (νCH_2 sym: 2848.3- 2867.6; νCH_2 asym: 2921.7-2929.4; δCH_2 sym: 1349.8- 1380; δCH_2 asym: 1487.7- 1490.2; νC-O-C sym: 1002.4- 1008.5; νC-O-C asym: 1287- 1291.3); -CH_3 (νCH_3 sym: 2848.3-2867.6; νCH_3 asym: ~ 2960); -O-C=O (νC=O: 1754.2- 1760.4; νC-O 1224.7- 1253.1); νC=N: 1612.2- 1650; aromatic rings (ν=C-H: 3018.1- 3045.2; νC=C: 1555.3- 1612.2); νC-F: 1059.3- 1077.1; νC-Cl: 743.5- 749.4; νC-Br: 592- 597,1.

The elemental analysis is presented in table 4.

The spectral data using ^1H-NMR, ^{13}C-NMR, IR spectroscopy and the elemental analysis confirmed the structure of the obtained compounds.

Conclusions

- Following the synthesis of new compounds with potential pharmacological activity, we obtained eight new 2-methyl-O-acyl-oximino-dibenz[b,e]oxepins.

- The compounds are prepared by acylating 11-oximino-2-methyl-6,11-dihydro-dibenz[b,e]oxepin with different halo substituted benzoic acid chlorides.

- The obtained compounds have been characterized by some physical properties.

- The ^1H-NMR, ^{13}C-NMR, IR spectral parameters and elemental analysis confirm the structure of the prepared compounds.

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Manuscript received: 5.11.2006