A New Class of 4-(Hydroxyaryl)-1,3-Dithiolium Chlorides

PAUL CHIRITA[1], CRISTIAN GEORGE HRIB[2], ION SANDU[3,4], NECULAI CATALIN LUNGU[5], LAURA GABRIELA SARBU[51], KAMEL EARAR[6*]

[1] University of Craiova, Department of Chemistry, 107I Calea Bucuresti, 200478, Craiova, Romania
[2] Chemisches Institut der Otto-von-Guericke-Universität, Universitätsplatz 2, D-39116 Magdeburg, Germany
[3] Alexandru Ioan Cuza University of Iasi, Arheoinvest Interdisciplinary Platform, 22 Carol I Blvd., 700506, Iasi, Romania
[4] Romanian Inventors Forum, 3 Sf. Petru Movila, 700089, Iasi, Romania
[5] Alexandru Ioan Cuza University of Iasi, Department of Chemistry, 11 Carol I Blvd., 700506, Iasi, Romania
[6] Dunărea de Jos University of Galaţi, Romania, Faculty of Medicine and Farmacy, 35. Al. I. Cuza Str., 800010, Galati, Romania

The synthesis of a new class of 1,3-dithiolium chlorides as potentially water soluble compounds has been accomplished from the corresponding mesoionic 2-(1,3-dithiol-2-ylium)phenolates. These later compounds have been obtained by acid catalyzed cyclocondensation of various substituted 2-(3,5-dibromo-2-hydroxyphenyl)-2-oxoethyldithiocarbamates. The X-Ray structural characterization of 4-(3,5-dibromo-2-hydroxyphenyl)-2-(N,N-diethylamino)-1,3-dithiol-2-ylium chloride is reported.

Keywords: dithiocarbamates, 1,3-dithiolium salts, organic chlorides, X-ray crystallography

An important feature of heterocyclic compounds is represented by their versatility to carry various substituents that bring them a wide range of application [1-3]. Along with a large variety of industrial application, heterocyclic compounds exhibit important implication in therapeutics, due to the possibility of interacting with the human body [4-9]. Between them, sulfur and nitrogen-containing heterocyclic compounds have maintained a special interest for researchers [10-20]. The way a drug is administered will affect how the body absorbs the substance. Each method of administering the drug has different distribution rates. Excluding intravenous methods, a biologically active compound must usually pass through at least one body membrane. Soluble drugs are more rapidly absorbed, because most membranes are lipid-based. The absorption rate is affected by a variety of factors [21]. Drugs taken in a water solution are absorbed more rapidly than drugs taken in other administration form. For this reason, the synthesis of water soluble heterocyclic compounds with potentially biological activities is of general interest. A 1,3-dithiolium derivative has been reported to exhibit biological activity against gram-positive and gram-negative bacteria [22]. Besides the biological interest for the 1,3-dithiolium derivatives, these compounds are known for their reactivity at the C(2)-position towards nucleophiles [23]. Moreover, 1,3-dithiolium salts are important precursors in the synthesis of tetrathiafulvalenes (TTF), that are used as π-electron donors in obtaining organic metals; recent studies have shown the increased role of TTFs as donor groups in intramolecular charge-transfer complexes [24]. In this context, a variety of acceptor units has been investigated, special attention being devoted to the nature of cationic systems. Thus, of special interest are systems where the donor moiety is linked through a π- or σ-bonded bridge to the acceptor moiety [25-32]. Recently, new evidences for the mesoionic character of 2-(1,3-dithiol-2-ylium)phenolates have been reported [33].

In view of these facts, we decided to investigate the synthesis of a new class of 4-(3,5-dibromo-2-hydroxyphenyl)-1,3-dithiolium chlorides as potentially water soluble compounds.

Experimental part

Analysis methods

Melting points were obtained on a Mel-Temp II apparatus. IR spectra were recorded on a Bruker Tensor 27 instrument. UV-Vis spectra were recorded on Varian BioCarry 100 spectrophotometer. NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in ppm downfield from TMS. Elemental analyses (C, H, N, S) were conducted using a CE440 Elemental Analyser; the results were found to be in good agreement (±0.31%) with the calculated values.

Synthesis

The synthetic pathway used to obtain 4-(3,5-dibromo-2-hydroxyphenyl)-1,3-dithiolium chlorides **5a-e** is described in scheme 1. Mesoionic phenolates **4** have been synthesized according to the reported procedure [34].

4-(3,5-Dibromo-2-hydroxyphenyl)-2-(N,N-diethylamino)-1,3-dithiol-2-ylium chloride (**5b**)

To 1g (2.36mmol) suspension of mesoionic phenolate **4b** in 10mL acetone a solution of 0.96mL HCl (37%, 11mmol) was added. The reaction mixture was vigorously stirred at rt for 2 h, then filtered and washed with acetone. Recrystallization from ethanol gave colorless crystals; yield 1.06g (98%). Analytical and spectral data of 1,3-dithiolium chlorides **5** are presented in table 1.

X-ray Structure Determination of ***5b****:*

Numerical details are presented in table 2.

The intensity data of **5b** was collected on a Stoe IPDS 2T diffractometer with MoK_α radiation. The data were collected with the Stoe XAREA program using ω-scans [35]. The space groups were determined with the XRED32 program [35]. The structures were solved by direct

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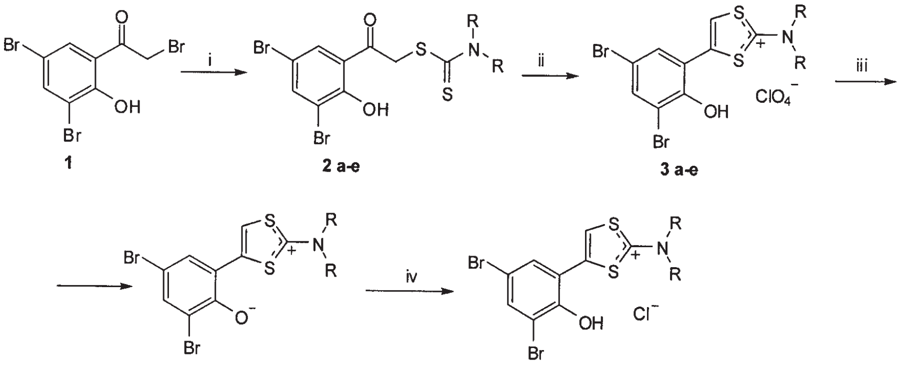
* *email - laura_gabriela84@yahoo.com* *erar_dr.kamel@yahoo.com*



i. $R_2NC(S)S^-$, acetone, reflux; ii. H_2SO_4/AcOH 1:3 (v/v), 80°C, 70% $HClO_4$; iii. aq. $NaHCO_3$; HCl/acetone; iv. 37%HCl, acetone

2, 3, 4, 5	R	R
a	$-CH_3$	$-CH_3$
b	$-CH_2CH_3$	$-CH_2CH_3$
c	$-CH_2-CH_2-CH_2-CH_2-$	
d	$-CH_2-CH_2-CH_2-CH_2-CH_2-$	
e	$-CH_2-CH_2-O-CH_2-CH_2-$	

Scheme 1. Synthesis of 1,3-dithiolium chlorides **5**

Table 1

ANALYTICAL AND SPECTRAL DATA OF 1,3-DITHIOLIUM CHLORIDES **5**

	M.p., °C	η, %	IR-ATR, cm^{-1}	NMR (DMSO-*d6*), ppm
5a	226-227 dec.	96	3191, 1548, 1410, 1289, 1120, 851, 775, 624, 575	*^{1}H NMR* δ : 3.57 (6H, s, $2CH_3$); 7.71 (1H, d, H-4); 7.76 (1H, d, H-6, J_{H4-H6}=2.3 Hz); 8.07 (1H, s, H-5); 11.42 (1H, s, OH). *^{13}C NMR* δ : 47.1, 47.9, 112.4, 114.9, 122.9, 123.4, 130.9, 134.2, 136.4, 150.1, 187.9
5b	227-228 dec.	98	3054, 1551, 1411, 1290, 1175, 1079, 825, 604	*^{1}H NMR* δ : 1.38 (6H, t, $2CH_3$); 3.87 (2H, q, CH_2); 3.90 (2H, q, CH_2); 7.70 (1H, d, H-4); 7.78 (1H, d, H-6, J_{H4-H6}=2.4 Hz); 8.15 (1H, s, H-5); 11.58 (1H, s, OH). *^{13}C NMR* δ : 17.0, 53.2, 54.2, 112.6, 114.6, 123.1, 123.3, 130.4, 133.8, 136.9, 150.7, 188.1
5c	227-228 dec.	95	3047, 2878, 1548, 1454, 1254, 1111, 821, 614	*^{1}H NMR* δ : 2.30 (4H, m, $2CH_2$); 3.80 (4H, m, $2CH_2$); 7.70 (1H, d, H-4); 7.74 (1H, d, H-6, J_{H4-H6}=2.4 Hz); 8.05 (1H, s, H-5); 11.54 (1H, s, OH). *^{13}C NMR* δ : 26.0, 26.4, 56.1, 56.5, 112.4, 114.7, 123.5, 123.8, 130.1, 140.1, 136.9, 150.5, 187.5
5d	234-235 dec.	97	3056, 2921, 1531, 1485, 1385, 1248, 825, 619, 525	*^{1}H NMR* δ : 1.80 (6H, m, $3CH_2$); 3.90 (4H, m, $2CH_2$); 7.69 (1H, d, H-4); 7.73 (1H, d, H-6, J_{H4-H6}=2.4 Hz); 8.09 (1H, s, H-5); 11.48 (1H, s, OH). *^{13}C NMR* δ : 21.5, 24.9, 25.0, 56.1, 57.8, 112.0, 114.4, 122.8, 123.1, 130.3, 133.5, 136.8, 150.2, 187.8
5e	229-230 dec.	92	3223, 2989, 1541, 1477, 1405, 1263, 1105, 884, 639, 535	*^{1}H NMR* δ : 3.90 (8H, m, $4CH_2$); 7.70 (1H, d, H-4); 7.74 (1H, d, H-6, J_{H4-H6}=2.4 Hz); 8.10 (1H, s, H-5); 11.46 (1H, s, OH). *^{13}C NMR* δ : 54.1, 54.5, 64.7, 112.4, 114.8, 122.5, 123.0, 130.4, 133.2, 136.5, 150.9, 188.4

methods (SHELXS-97) and refined by full matrix least-squares methods on F^2 using SHELXL-97 [36,37].

CCDC-1036553 contains the supplementary crystallographic data for compound **5b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Results and discussions

A retrosynthetic analysis for the target 1,3-dithiolium chlorides indicate that the suitable precursors are the corresponding mesoionic 1,3-dithiolium phenolates. These compounds have been synthesized following a three step procedure (scheme 1). The first one involve the reaction of 2-bromo-1-(3,5-dibromo-2-hydroxy-phenyl)ethan-1-one (**1**) with various salts of dithiocarbamic acid, readily available from the reaction of secondary amine with carbon disulfide [38]. The cyclo-condensation of thus obtained phenacyl dithiocarbamates **2** under acidic condition provided 1,3-dithiolium derivatives. Using a concentrated sulfuric acid-glacial acetic acid (1:3 v/v) mixture the cyclization of dithiocarbamates **2** takes place under mild reaction conditions [40-49]. After 10 min at 80°C the homogeneous reaction mixture was cooled to room

Table 2
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR **5b**

Identification code	ip422	
Empirical formula	$C_{13}H_{14}Br_2ClNOS_2$	
Formula weight	459.64	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 8.3455(17) Å	α= 90°
	b = 17.157(3) Å	β= 93.35(3)°
	c = 11.074(2) Å	γ = 90°
Volume	1582.9(5) $Å^3$	
Z	4	
Density (calculated)	1.929 Mg/m^3	
Absorption coefficient	5.547 mm^{-1}	
F(000)	904	
Crystal size	0.33 x 0.24 x 0.12 mm^3	
Theta range for data collection	2.19 to 29.23°	
Index ranges	-11<=h<=10, -23<=k<=23, -15<=l<=15	
Reflections collected	17514	
Independent reflections	4276 [R(int) = 0.0945]	
Completeness to theta = 29.23°	99.3 %	
Absorption correction	Sphere	
Max. and min. transmission	0.1165 and 0.0901	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4276/0/185	
Goodness-of-fit on F^2	1.191	
Final R indices [I>2sigma(I)]	R1 = 0.0535, wR2 = 0.1231	
R indices (all data)	R1 = 0.0614, wR2 = 0.1270	
Largest diff. peak and hole	1.706 and -1.682 e.$Å^{-3}$	

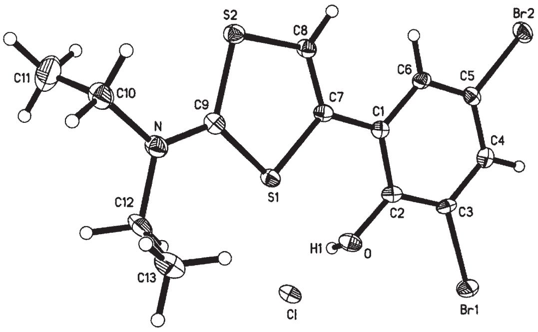


Fig.1.Molecular structure of compound **5b**. Ellipsoids represent 5o% probability levels. Selected molecular dimensions (A,): N-C(9) 1.300(5), S(1)-C(9) 1.719(4), S(2)-C(9) 1.727(4), N-C(9)-S(2) 122.1(3), N-C(9)-S(1) 122.4(3), S(2)-C(9)-S(1) 115.4(2)

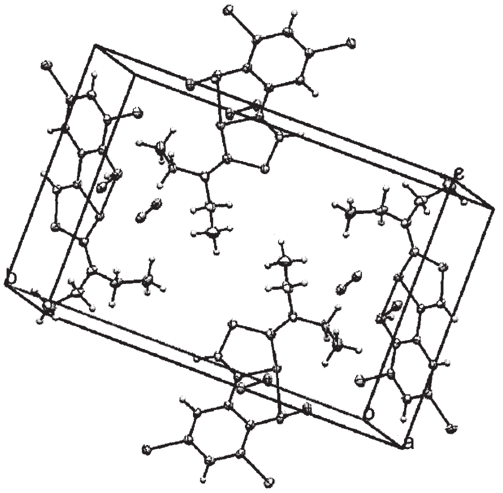


Fig. 2. The packing diagram of compound **5b**

temperature and 70% $HClO_4$ and water were added. Treatment of perchlorates **3a-e**, under heterogeneous conditions, with saturated aqueous sodium hydrogen carbonate solution provides 4,6-dibromo-2-[2-(dialkylamino)-1,3-dithiol-2-ylium-4-yl]phenolates **4a-e**, in quantitative yields as yellow compounds. Using the interconversion possibilities between the mesoionic phenolates and their salts, we have been able to isolate a new class of 1,3-dithiolium chlorides. Thus, by the treatment of an acetone suspension of mesoionic phenolates **4** with 37% hydrochloric acid 4-(3,5-dibromo-2-hydroxyphenyl)-1,3-dithiol-2-ylium chlorides **5** have been isolated as colorless crystalline products. The molecular structure of the new compounds was proved by analytical and spectral data (table 1).

Furthermore, the structure of 4-(3,5-dibromo-2-hydroxyphenyl)-2-(*N,N*-diethylamino)-1,3-dithiol-2-ylium chloride (**5b**) was unambiguously proved by X-ray crystallography (fig. 1). In this compound, the benzene and 1,3-dithiolium planes form a dihedral angle of only 3.53°; the two rings are practically planar and this value confirms the previous assumptions that the presence of a substituent at the C(5) of 1,3-dithiolium ring induces significant deviation from planarity [50-52]. The recorded data confirms the double bonding character of the C(9)-N bond (numbering from fig. 1); the lenght of C(9)-N bond is 1.300A°, shorter than N-C(10) and N-C(12) that are essentially σ-bonds (1.4 A°). A hydrogen bond was found between the phenolic O-H group and the chlorine counter-anion. The packing diagram that indicates inter-elemental cell hydrogen bonds is presented in figure 2 .

Conclusions

The synthesis of water soluble 4-(3,5-dibromo-2-hydroxyphenyl)-2-dialkylamino-1,3-dithiol-2-ylium chlorides has been accomplished from the corresponding mesoionic phenolates. The latter compounds have been synthesized by cyclocondensation of 1-(3,5-dibromo-2-hydroxyphenyl)-2-(*N,N*-dialkylaminocarboditioate)-ethan-1-ones, followed by base treatment. The X-Ray structural characterization of 4-(3,5-dibromo-2-hydroxyphenyl)-2-(*N,N*-diethylamino)-1,3-dithiol-2-ylium chloride is presented.

Acknowledgments: This work was supported by a grant of the Romanian National Authority for Scientific Research, CNDI– UEFISCDI, project number 51/2012.

References

1. NEKRASOV, D. D., Chemistry of Heterocyclic Compounds, **37**, 2001, p. 263.

2. NORMAN, S. R., Drug Development Res., **69**, 2008, p. 15.

3. SPERRY, J. B., Wright, D. L., Current Opinion in Drug Discovery and Development, **8**, 2005, p. 723.

4. GOSAV, S., BIRSA, M. L., Rom. Rep. Phys., **66**, 2014, p. 411.

5.BELEI, D., ABUHAIE, C., BICU, E., JONES, P. G., HOPF, H., BIRSA, M. L., Synlett, **23**, 2012, p. 545.

6.GOSAV, S., PRAISLER, M., Birsa, M. L., Int. J. Mol. Sci., **12**, 2011, p. 6668.

7.BELEI, D., BICU, E., JONES, P. G., BIRSA, M. L., J. Heterocycl. Chem., **48**, 2011, p. 129.

8.SARBU, L. G., BIRSA, A., HOPF, H., BIRSA, M. L., Phosphorus, Sulfur, and Silicon, and the Related Elements, **186**, 2011, p. 1246.

9.GOSAV, S., BIRSA, M. L., Acta Chem. Iasi, **18**, 2010, p. 150.

10.BELEI, D., BICU, E., JONES, P. G., BIRSA, M. L., Synlett, **2010**, p. 931.

11.SARBU, L.G., HOPF, H., GRUENENBERG, J., BIRSA, M.L., Synlett, **26**, 2015, p. 87.

12.SARBU, L.G., BICU, E., HOPF, H., BIRSA, M.L., Rev. Chim. (Bucharest), **65**, no. 4, 2014, p. 398.

13.BAHRIN, L.G., LUCA, A., BIRSA, M.L., Rev. Chim. (Bucharest), **65**, no. 2, 2014, p. 199.

14. BIRSA, M.L., SANDU, I., BAHRIN, L.G., Rev. Chim. (Bucharest), **65**, no. 2, 2014, p. 174.

15.SARBU, L.G., BIRSA, M.L., Acta Chem. Iasi, **19**, 2011, p. 125.

16.BELEI, D., BICU, E., BIRSA, M.L., Acta Chem. Iasi, **17**, 2009, p. 197.

17.BIRSA, M.L., An. Stiint. Univ. ¸Al.I. Cuza¸ Iasi, **8**, 2000, p. 325.

18.SELIGER, H., CASCAVAL, A., BIRSA, M.L., An. Stiint. Univ. ¸Al.I. Cuza¸ Iasi, **5**, 1997, p. 129.

19.SARBU, L.G., HOPF, H., JONES, P.G., BIRSA, M.L., Beilstein J. Org. Chem., **10**, 2014, p. 2550.

20.MARIN, L., ARVINTE, A., Mat. Plast., **50**, no. 1, 2013, p. 23.

21.MAISTO, S.A., GALIZIO, M., CONNORS, G.J., Drug Use and Abuse, 5th ed., Thomson Wadsworth, Belmont, 2008.

22.BAHRIN, L.G., APOSTU, M.O., BIRSA, M.L., STEFAN, M., Bioorg. Med. Chem. Lett., **24**, 2014, p. 2315.

23. BIRSA, M.L., Synth. Commun., **33**, 2003, p. 3071.

24. BRYCE, M.R., GREEN, A., MOORE, A.J., PEREPICHKA, D.F., BATSANOV, A.S., HOWARD, J.A.K., LEDOUX-RAK, I., GONZALES, M., MARTIN, N., SEGURA, J.L.,GARIN, J., ORDUNA, J., ALCALA, R., VILLACAMPA, B., Eur. J. Org. Chem., **2001**, p. 1927.

25.BIRSA, M.L., GANJU, D., J. Phys. Org. Chem., **16**, 2003, p. 207.

26.BIRSA, M.L., ASAFTEI, I.V., Monat. Chem., **139**, 2008, p. 1433.

27.BIRSA, M.L., HOPF, H., Synlett, **2007**, p. 2753.

28.BIRSA, M.L., HOPF, H., Synlett, **2009**, p. 3000.

29.BIRSA, M.L., HOPF, H., Heteroatom Chem., **21**, 2010, p. 126.

30.BIRSA, M.L., JONES, P.G., HOPF, H., Synlett, **2011**, p. 259.

31.LUNGU, N.C., SANDU, I., CHIRITA, P., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no. 7, 2013, p. 697.

32.HOPF, H., JONES, P.G., NICOLESCU, A., BICU, E., BIRSA, M.L., BELEI, D., Chem. Eur. J., **20**, 2014, p. 5565.

33.SARBU, L.G., LUNGU, C.N., ASAFTEI, I.V., SANDU, I., BIRSA, M.L., Rev. Chim. (Bucharest), **65**, no. 3, 2014, p. 325.

34.BUHACEANU, R., LUNGU, C.N., FORNA, N.C., ASAFTEI, I.V., CHIRITA, P., BIRSA, M.L., Rev. Chim. (Bucharest), **64**, no. 9, 2013, p. 960.

35.*** Stoe, XAREA Program for Xray Crystal Data collection, (XRED32 included in XAREA) (Stoe,2002).

36.SHELDRICK, G. M., SHELXL-97 Program for Crystal Structure Refinement, Universität Göttingen (Germany) **1997**.

37.SHELDRICK, G. M., SHELXS-97 Program for Crystal Structure Solution, Universität Göttingen (Germany) **1997**.

38.BRAVERMAN, S., CHERKINSKY, M., BIRSA, M. L., Science of Synthesis, **18.2**, Georg Thieme Verlag, Stuttgart, 2005, p 55.

39.BIRSA, M. L., Synth. Commun., **32**, 2002, p. 115.

40.BIRSA, M. L., Sulfur Lett., **26**, 2003, p. 155.

41.BELEI, D., FORNA, N. C., SANDU, I., BIRSA, M. L., Rev. Chim. (Bucharest), **65**, no. 1, 2014, p. 80.

42.SELIGER, H., HAPP, E., CASCAVAL, A., BIRSA, M. L., NICOLAESCU, T., POINESCU, I., COJOCARIU, C., Eur. Polym. J., **35**, 1999, p. 827.

43.BIRSA, M.L., An. St. Univ. Al. I. Cuza Iasi, s. Chimie, **6**, 1998, p. 57.

44.BIRSA, M.L., An. St. Univ. Al. I. Cuza Iasi, s. Chimie, **7**, 1999, p. 341.

45.BIRSA, M.L., An. St. Univ. Al. I. Cuza Iasi, s. Chimie, **7**, 1999, p. 349.

45.BIRSA, M.L., An. St. Univ. Al. I. Cuza Iasi, s. Chimie, **8**, 2000, p. 71.

46.BIRSA, M.L., An. St. Univ. Al. I. Cuza Iasi, s. Chimie, **8**, 2000, p. 329.

47. BIRSA, M.L., Synth. Commun., **31**, 2001, p. 1271.

48.BIRSA, M.L., JONES, P.G., BRAVERMAN, S., HOPF, H., Synlett, **2005**, p. 640.

49.SARBU, L.G., BIRSA, M.L., Acta Chem. Iasi, **19**, 2011, p. 125.

50.SERBEZEANU, D., VLAD-BUBULAC, T., HAMCIUC, C., AFLORI, M., BRUMA, M., Mat. Plast., **48**, no. 2, 2011, p. 117.

51. SARBU, L.G., SANDU, I., BAHRIN, L.G., BALAN, A., APOSTU, M.O., Rev. Chim. (Bucharest), **66**, no. 1, 2015, p. 55.

52.SARBU, L.G., APOSTU, M.O., SANDU, I.G., MANEA, L. R., BAHRIN, L.G., Rev. Chim. (Bucharest), **65**, no. 11, 2014, p. 1327

Manuscript received: 22.01.2015