Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2015, **25**, 193–195
Mendeleev Communications

Unexpected formation of (trinitromethyl)pyrazines

Igor L. Yudin,[a] Nadezhda V. Palysaeva,[a] Boris B. Averkiev[b,†] and Aleksei B. Sheremetev*[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: sab@ioc.ac.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

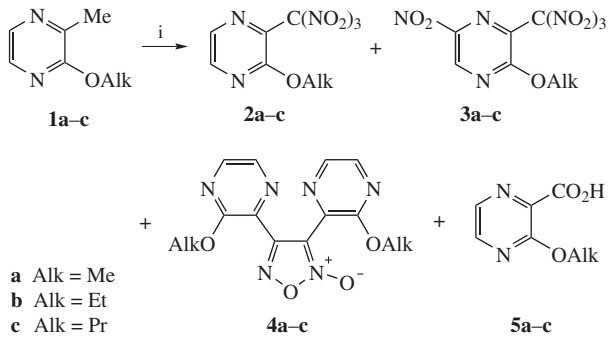
DOI: 10.1016/j.mencom.2015.05.011

Treatment of 2-alkoxy-3-methylpyrazines with HNO_3/H_2SO_4 induces an unusual reaction accompanied by the methyl group nitration with the formation of (trinitromethyl)pyrazines, a structural motif previously unknown in diazine family.

Electrophilic nitration is of great importance in academic research and industrial chemistry.[1] Polynitro derivatives are renowned for their utility in the field of energetic materials.[2] A fundamental challenge in preparing highly nitrated (hetero)aromatic compounds is overcoming the inherent ring deactivation caused by insertion of nitro groups. π-Deficient azines are poorly reactive to electrophiles. Introduction of the nitro group or additional nitrogen atom in the ring further depletes the ring of its π-electrons and lowers its electron density. Nitration of such substrates takes place with great difficulty and only under forcing conditions.[3] On the other hand, a commonly used strategy for facilitating electrophilic nitration is an introduction of electron-donating substituents such as methyl or methoxy groups. Such derivatives require milder nitration conditions, however, sometimes the unwanted oxidation products are formed.

Recent works by our group[4] and others[5] show that electrophilic nitration of 5- and 6-substituted alkoxypyrazines can be an efficient way of generating 3,6- and 3,5-dinitropyrazines, respectively, which find application as precursors for the preparation of energetic compounds suitable for use in insensitive explosive (for example, 2,6-diamino-3,5-dinitropyrazine 1-oxide also referred to as LLM-105) and propellant compositions. We were interested in further expanding the use of alkoxypyrazines for the preparation of novel structures and focused upon the synthesis of polynitro compounds that could be derived from the nitration of 2-alkoxy-3-methylpyrazines **1**. Herein we report the unexpected discovery of an unusual course of nitration onto methyl group of substrates **1**.

Treatment of 2-methoxy-3-methylpyrazine **1a** with a mixture of concentrated nitric and sulfuric acids (1:2) at room temperature, an experiment aimed to insert nitro groups into 5- and 6-positions, gave in fact trinitromethyl compound **2a** in low yield (*ca*. 5%) and recovered starting **1a** (*ca*. 86%). Carrying out the reaction at 35 °C for 12 h brought about product **2a** (*ca*. 9%), 2-methoxy-5-nitro-3-trinitromethylpyrazine **3a** (*ca*. 3%) and 3,4-bis(2-methoxypyrazin-3-yl)furoxan **4a** as minor products (*ca*. 2%) (Scheme 1) after chromatographic separation. Raising temperature to 45 °C (for 3.5–4 h) improved the selectivity towards tetranitro compound **3a** to 34%, and trinitro compound **2a** was minor product (*ca*. 6%); however, these conditions promote oxidative decomposition of the starting materials, intermediates, and products dropping thus the yields.[‡] When compound **1a** was added to a pre-heated mixture of nitric and sulfuric acids (1:2) at 50 °C, the solution gradually became black and neither trinitromethyl compounds **2a** or **3a** nor furoxan **4a** were detected in the reaction mixture. Substrates containing ethoxy or propoxy groups, **1b** and **1c**, gave no appreciable yield of the desired trinitromethyl



Scheme 1 *Reagents and conditions*: i, HNO_3/H_2SO_4 (1:2), 45 °C.

‡ *Nitration of compound* **1a** *(general procedure)*. 2-Methoxy-3-methylpyrazine **1a** (3.72 g, 30 mmol) was added slowly to a stirred mixture of HNO_3 (5.5 ml, 100%) and H_2SO_4 (11 ml, 98%) at 30–35 °C. The reaction mixture was heated at 45 °C for 4 h. Afterwards, it was poured over *ca*. 50 g of crushed ice and extracted with EtOAc (3×50 ml). Combining the organic layers, washing with brine, drying ($MgSO_4$), and removal of solvent afforded a mixture of products.

The residue was subjected to column chromatography [eluting with hexane–EtOAc, 50:1 → 5:1, R_f(**2a**) > R_f(**3a**) > R_f(**4a**) > R_f(**5a**)] to give pure products.

2-Methoxy-3-(trinitromethyl)pyrazine **2a**: yield 6%, mp 90–91 °C. ^{1}H NMR ($CDCl_3$) δ: 4.07 (s, 3H), 8.29 (d, 1H, *J* 2.56 Hz), 8.52 (d, 1H, *J* 2.57 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.2 (OMe), 126.6 [$C(NO_2)_3$], 128.2 [$CC(NO_2)_3$], 136.2, 146.8, 158.8 (*C*OMe). ^{14}N NMR ($CDCl_3$) δ: –36.1 (NO_2). MS (70 eV), *m/z*: 259 (2) $[M]^+$, 213 (100) $[M-NO_2]^+$. Found (%): C, 27.88; H, 1.89; N, 26.95. Calc. for $C_6H_5N_5O_7$ (%): C, 27.81; H, 1.94; N, 27.03.

2-Methoxy-5-nitro-3-(trinitromethyl)pyrazine **3a**: yield 34%, mp 77–78 °C, ^{1}H NMR ($CDCl_3$) δ: 4.27 (s, 3H), 9.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 57.1 (OMe), 125.1 [$C(NO_2)_3$], 130.0 (CH), 132.7 [$CC(NO_2)_3$], 151.4 (CNO_2), 157.6 (*C*OMe). ^{14}N NMR ($CDCl_3$) δ: –23.0 (br., CNO_2), –38.7 [$C(NO_2)_3$]. MS (70 eV), *m/z*: 304 (1) $[M]^+$, 258 (100) $[M-NO_2]^+$. Found (%): C, 23.76; H, 1.27; N, 27.55. Calc. for $C_6H_4N_6O_9$ (%): C, 23.70; H, 1.33; N, 27.63.

3,4-Bis(3-methoxypyrazin-2-yl)furoxan **4a**: yield 4%, mp 221–222 °C. ^{1}H NMR (DMSO-d_6) δ: 4.06 (3H), 4.12 (3H), 8.27–8.30 (2H), 8.48–8.50 (2H). ^{13}C NMR (DMSO-d_6) δ: 54.8, 55.1 112.8, 142.9, 143.7, 144.2, 144.5, 144.6, 146.8, 154.3, 158.6, 158.8. MS (70 eV), *m/z*: 302 (23) $[M]^+$, 286 (34) $[M-O]^+$, 256 (65) $[M-O-NO]^+$, 135 (100). Found (%): C, 47.74; H, 3.38; N, 27.73. Calc. for $C_{12}H_{10}N_6O_4$ (%): C, 47.69; H, 3.33; N, 27.81.

3-Methoxypyrazine-2-carboxylic acid **5a**: yield 14%, this compound in all respects corresponds to literature data.

† Present address is School of Natural Sciences and Mathematics, Stockton University, Galloway, New Jersey, 08205, USA.

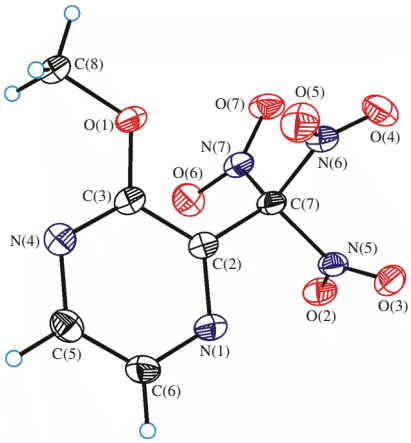


Figure 1 The general view of molecule **2a** with the atom numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

pyrazines. For example, treatment of the ethoxypyrazine **1b** with the nitration mixture at 45 °C gave tetranitro product **3b** in 2.5% yield.

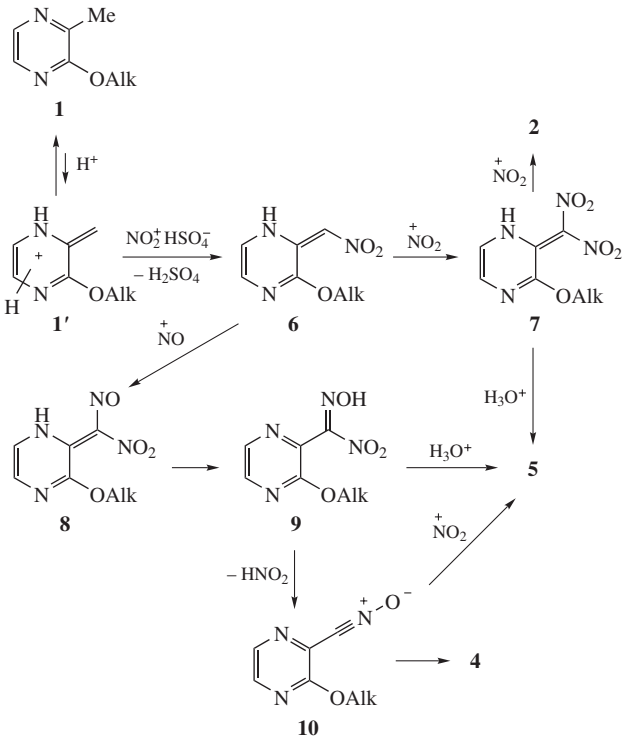
In contrast, there is a report[6] that nitric acid in trifluoroacetic anhydride at room temperature converts parent 2-methylpyrazine to 5-nitro-2-methylpyrazine in 12.7% yield and recovery 60% unreacted starting material.

Compared with starting compound **1a**, the ^{1}H and ^{13}C NMR spectra of all products isolated from this reaction displayed the disappearance of methyl group signals, and the appearance of signals characteristic of trinitromethyl at δ ~ 125 ppm for compounds **2a** and **3a**. Structure of **2a** was confirmed by single crystal X-ray diffraction analysis (Figure 1).§ The ^{13}C NMR spectra of **4a** displayed the expected signals characteristic of the furoxan ring at δ ~ 113 and 154 ppm, that are also consistent with those reported for similar 3,4-dipyrazinylfuroxans.[7]

Due to effect of the methoxy group, the bond distances at N(4) are unequal: the N(4)–C(5) is 1.348(2) Å, while the N(4)–C(3) is 1.322(2)Å. Orientation of the trinitromethyl moiety is so that the nitrogen atom of a nitro group N(5) is in the plane of the pyrazine ring [the N(1)–C(2)–C(7)–N(5) torsion angle is 3.5(2)°], while the N(1)–C(2)–C(7)–N(6) and N(1)–C(2)–C(7)–N(7) torsion angles are 114.0(2) and 121.49(14)°, respectively, that is defined by steric repulsion with the adjacent methoxy group. On the contrary, for recently described 2-trinitromethyl-5-methylpyridine,[8] the trinitromethyl moiety has more freedom, and is oriented so that one of N=C–C–N torsion angles is close to 90°; therefore, all three nitro groups are out of the heterocycle plane.

In spite of the presence of the methoxy group and unsubstituted carbon atoms at the pyrazine ring, packing density of the crystal **2a** is relatively high (1.722 g cm^{-3} at 110 K). Visual analysis of the crystal packing (Figure 1S, see Online Supplementary Materials) reveals the presence of the close intermolecular contacts: O(3)···O(7) [2.824(3) Å], and O(5)···H(6) [2.53(3) Å]. For more detailed understanding of the crystal packing we used an approach based on consideration of pair intermolecular energies of the closest environment of the central molecule[9] for which we used M052X functional that was successfully applied for different heterocyclic compounds in recent studies.[10] The results obtained (Table 1S) clearly show crucial role that the trinitromethyl moiety[11] plays in the stabilization of the dense crystal packing. The strongest intermolecular interaction is provided by C(6)–H(6)···O(5) H-bond (involving the nitro group) and interaction between oxygen atoms of the nitro groups and π-density of the pyrazine ring. The closest O···O contact mentioned above is also formed between oxygens of the nitro groups, while the energy of interaction involving the methoxy group is the weakest.

The formation of these products was rationalized by the mechanism shown in Scheme 2. First, nitration of the starting methylpyrazine **1** induced by participation of the enamine form **1′**[12] could give mononitro intermediate **6**,¶ which would be expected to exist in the enamine form shown since the nitro group is electron withdrawing.[14] Subsequent step-by-step nitration affords trinitromethyl derivative **2**. Alternatively, attack on the intermediate **6** by nitrous acid could give nitroso intermediate **8**. The latter would then undergo isomerization to nitrolic acid **9**. The nitrous acid liberated upon heating compound **9** generated nitrile oxide **10**. The latter dimerized to the furoxan **4**.[7] Intermediates **7**, **9** and **10** are susceptible to hydrolysis resulting in acid **5** as the by-product.



Scheme 2

There are only a few reports of direct nitration of a methyl group at a (het)arene to the trinitromethyl group. The first[15] such transformation in low (1–6%) yields was nitration of methylbenzenes to (trinitromethyl)benzenes by applying nitrogen oxides disclosed by Titov[15(a)] and Petrovich.[15(b)] In 1992, Deady and Quazi reported a nitration of a fused methylisoquinoline with sulfuric acid solutions of potassium nitrate to the corresponding (trinitromethyl)isoquinoline in moderate yields (31%).[16] Bellamy

§ *Crystal data for* **2a**: $C_6H_5N_5O_7$, orthorhombic crystals, space group *Pbca*, a = 12.427(2), b = 11.839(2) and c = 13.588(2) Å, V = 1999.0(6) Å^3, Z = 8, M = 259.15, d_{calc} = 1.722 g cm^{-3}, μ = 0.159 mm^{-1}, $F(000)$ = 1056. Intensities of 15591 reflections were measured with a Bruker SMART CCD difractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scans, $2\theta < 60°$] at 110 K. The structure was solved by the direct methods and refined by the full-matrix least-squares procedure in anisotropic approximation. 2921 independent reflections (R_{int} = 0.0545) were used in the refinement procedure that was converged to wR_2 = 0.1252 calculated on F^2_{hkl} [GOF = 1.018, R_1 = 0.0505 calculated on F_{hkl} using 2260 reflections with $I > 2\sigma(I)$].

CCDC 1055062 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

¶ Pyrazinylidene cyanoacetic esters are mono-nitrated by mixtures of HNO_3 at α-C-atom of the side chain in good yields.[13]

and co-workers prepared 2,4-dimethoxy-6-trinitromethyl-1,3,5-triazine (57%) from 2,4-dimethoxy-6-methyl-1,3,5-triazine using HNO_3/H_2SO_4 mixture.[17] More recently, Katritzky *et al*.[8] obtained 5-methyl-2-trinitromethylpyridine in 10% yield on the nitration of 2,5-lutidine with nitric acid in trifluoroacetic anhydride. No previous installation of trinitromethyl group onto pyrazine ring has been documented.

The attachment of trinitromethyl groups to an azine backbone is a highly desirable process but one of the most difficult to achieve in practice. Studies on heterocycles bearing trinitromethyl group have provided extensive information which is relevant to the design and development of new high energetic materials.[18] In this regard, pyrazine derivatives are the benchmark family of energetic materials whose properties can be tuned through the chemical modification. The incorporation of trinitromethyl group into the backbone provides deep insights into the structure–property relationships.

This work was supported by the Russian Science Foundation (project no. 14-13-01153). We are grateful to Dr. K. Yu. Suponitsky for helpful discussions.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.011.

References

1 (*a*) *Industrial and Laboratory Nitrations, ACS Symposium Series 22*, eds. L. F. Albright and C. Hanson, American Chemical Society, Washington, DC, 1976; (*b*) K. Schofield, *Aromatic Nitration*, Cambridge University Press, Cambridge, 1980; (*c*) G. A. Olah, R. Malhotra and S. C. Narang, *Nitration: Methods and Mechanisms*, VCH, Weinheim, 1989; (*d*) *Nitro Compounds: Recent Advances in Synthesis and Chemistry*, eds. H. Feuer and A. T. Nielsen, VCH, Weinheim, 1990; (*e*) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, Weinheim, 2001.

2 J. P. Agrawal and R. D. Hodgson, *Organic Chemistry of Explosives*, Wiley, Hoboken, 2007.

3 V. L. Rusinov and O. N. Chupakhin, *Nitroaziny (Nitroazines)*, Nauka, Moscow, 1991 (in Russian).

4 (*a*) V. A. Tartakovskii, O. P. Shitov, I. L. Yudin and V. A. Myasnikov, *USSR Patent SU 1703645*, 1991; (*b*) I. L. Yudin, A. B. Sheremetev, O. P. Shitov and V. A. Tartakovskii, *Mendeleev Commun.*, 1995, 196; (*c*) B. B. Averkiev, M. Yu. Antipin, I. L. Yudin and A. B. Sheremetev, *J. Mol. Struct.*, 2002, **606**, 139; (*d*) I. L. Yudin, A. B. Sheremetev, B. B. Averkiev and M. Yu. Antipin, *J. Heterocycl. Chem*., 2005, **42**, 691.

5 (*a*) S. P. Philbin, R. W. Millar and R. G. Coombes, *Propellants Explos. Pyrotech.*, 2000, **25**, 302; (*b*) A. J. Bellamy and P. Golding, *Cent. Eur. J. Energ. Mater*., 2007, **4** (3), 33; (*c*) A. J. Bellamy and P. Golding, *Cent. Eur. J. Energ. Mater*., 2008, **5** (2), 3.

6 R. Murugan, E. F. V. Scriven, G. F. Hillstrom and P. K. Ghoshal, *PCT Int. Appl. WO 02090328*, 2002.

7 (*a*) Y.-N. Li, Z.-Z. Zhang, Y.-S. Zhou, B. Chen and B.-Z. Wang, *Chin. J. Explos. Propellants*, 2009, **32** (6), 40; (*b*) L. S. Postnikov, *Chem. Nat. Compd.*, 2010, **46**, 72 (*Khim. Prirod. Soedin.*, 2010, 64); (*c*) Y.-N. Li, Z.-Z. Zhang, Y.-P. Ji and Y.-I. Wang, *Hanneng Cailiao (Chin. J. Energ. Mater.)*, 2010, **18** (1), 7; (*d*) Y. Li, Z. Zhang, Y. Zhou, B. Wang and Y. Shang, *Acta Chim. Sinica*, 2011, **69**, 701.

8 A. R. Katritzky, E. F. V. Scriven, S. Majumder, R. G. Akhmedova, A. V. Vakulenko, N. G. Akhmedov, R. Murugan and K. A. Abboud, *Org. Biomol. Chem.*, 2005, **3**, 538.

9 (*a*) A. B. Sheremetev, S. G. Zabusov, T. R. Tukhbatshin, N. V. Palysaeva and K. Yu. Suponitsky, *Chem. Heterocycl. Compd.*, 2014, **50**, 1154 (*Khim. Geterotsikl. Soedin*., 2014, 1250); (*b*) K. Yu. Suponitsky, K. A. Lyssenko, I. V. Ananyev, A. M. Kozeev and A. B. Sheremetev, *Cryst. Growth Des*., 2014, **14**, 4439.

10 (*a*) K. Yu. Suponitsky, K. A. Lyssenko, M. Yu. Antipin, N. S. Aleksandrova, A. B. Sheremetev and T. S. Novikova, *Russ. Chem. Bull., Int. Ed*., 2009, **58**, 2129 (*Izv. Akad. Nauk, Ser. Khim*., 2009, 2065); (*b*) K. Yu. Suponitsky, A. E. Masunov and M. Yu. Antipin, *Mendeleev Commun.*, 2009, **19**, 311; (*c*) K. Yu. Suponitsky, Y. Liao and A. E. Masunov, *J. Phys. Chem. A*, 2009, **113**, 10994; (*d*) A. B. Sheremetev, N. S. Aleksandrova, K. Yu. Suponitsky, M. Yu. Antipin and V. A. Tartakovsky, *Mendeleev Commun*., 2010, **20**, 249; (*e*) A. B. Sheremetev, I. L. Yudin, N. V. Palysaeva and K. Yu. Suponitsky, *J. Heterocycl. Chem*., 2012, **49**, 394; (*f*) K. Yu. Suponitsky and A. E. Masunov, *J. Chem. Phys*., 2013, **139**, 094310; (*g*) A. V. Vologzhanina, A. A. Golovanov, D. M. Gusev, I. S. Odin, R. A. Apreyan and K. Yu. Suponitsky, *Cryst. Growth Des*., 2014, **14**, 4402.

11 (*a*) A. B. Sheremetev, I. L.Yudin and K. Yu. Suponitsky, *Mendeleev Commun*., 2006, 264; (*b*) M. Gobel and T. M. Klapotke, *Adv. Funct. Mater*., 2009, **19**, 347; (*c*) A. B. Sheremetev, N. S. Aleksandrova, N. V. Palysaeva, M. I. Struchkova, V. A. Tartakovsky and K. Yu. Suponitsky, *Chem. Eur. J.*, 2013, **19**, 12446.

12 O. A. Zagulyaeva and I. V. Oleinik, *Chem. Heterocycl. Compd.*, 1995, **31**, 715 (*Khim. Geterotsikl. Soedin*., 1995, 816).

13 (*a*) I. V. Oleinik and O. A. Zagulyaeva, *Mendeleev Commun*., 1994, 50; (*b*) I. V. Oleinik and O. P. Shkurko, *Russ. Chem. Bull*., 1997, **46**, 1351 (*Izv. Akad. Nauk, Ser. Khim.*, 1997, 1407).

14 (*a*) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya and D. A. Efremov, *Nitroalkenes: Conjugated Nitro Compounds*, Wiley, Chichester, 1994; (*b*) S. Rajappa, *Tetrahedron*, 1999, **55**, 7065; (*c*) L. Simkova, F. Liska and J. Ludvik, *Curr. Org. Chem*., 2011, **15**, 2983.

15 (*a*) A. I. Titov, *Zh. Obshch. Khim*., 1948, **18**, 534 (in Russian); (*b*) I. I. Petrovich, *Zh. Obshch. Khim*., 1959, **29**, 407 (in Russian); (*c*) S. S. Novikov and L. I. Khmel'nitskii, *Usp. Khim*., 1957, **26**, 459 (in Russian).

16 L. W. Deady and N. H. Quazi, *Aust. J. Chem.*, 1992, **45**, 2083.

17 A. J. Bellamy, N. V. Latypov and P. Goede, *J. Chem. Res., M.*, 2003, 943.

18 (*a*) O. V. Lebedev, L. V. Epishina, T. S. Novikova, N. N. Makhova, T. I. Godovikova, S. P. Golova, A. V. Shastin, E. A. Arnautova, T. S. Pivina and L. I. Khmel'nitskii, in *International Annual Conference of ICT*, *29th (Energetic Materials)*, Karlsruhe, 1998, pp. 56.1–56.12; (*b*) A. V. Shastin, T. I. Godovikova and B. L. Korsunskii, *Russ. Chem. Rev*., 2003, **72**, 279 (*Usp. Khim*., 2003, **72**, 311); (*c*) Q. Wu, W. Zhu and H. Xiao, *Struct. Chem.*, 2013, **24**, 1725.

Received: 24th February 2015; Com. 15/4572