Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2013, **23**, 176–178
Mendeleev Communications

2-Methyl-11-nitro-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one: synthesis, crystal structure and tautomerism in dipolar aprotic solvents

Valentina F. Sedova, Viktor P. Krivopalov, Yurii V. Gatilov and Oleg P. Shkurko*

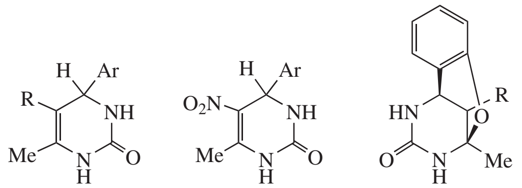
N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 383 9752; e-mail: oshk@nioch.nsc.ru

DOI: 10.1016/j.mencom.2013.05.020

Condensation of salicylaldehyde with nitroacetone and urea yields one diastereomer of the title compound. In DMF or DMSO solutions, this compound undergoes oxadiazocine ring opening leading to the equilibrium between its 2*R,6*S**,11*S**- and 2*R**,6*S**,11*R**-diastereomers and 4-(2-hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-one.**

3,4-Dihydropyrimidin-2(1*H*)-ones exhibit a wide range of biological activities, in particular, modulation of calcium channels.[1] 5-Alkoxycarbonyl-4-aryl-6-methyl-3,4-dihydropyrimidin-2-ones **1** possess a pharmacological profile similar to that of the classical calcium channel blockers and antihypertensive activity resembling that of dihydropyridine drugs.[2] Replacement of the ester group in compounds **1** with a nitro group gives rise to 4-aryl-6-methyl-5-nitro-3,4-dihydropyrimidin-2-ones **2** that show low levels of toxicity and a significant hypotensive effect.[3]

Syntheses of compounds **1**, **2** were based on the modified Biginelli reaction.[4] Behaviour of salicylaldehydes in this reaction is rather complicated as compared with other aromatic aldehydes. Thus the three-component Biginelli condensation of substituted salicylaldehydes with β-dicarbonyl compounds and urea may yield ordinary cyclocondensation products **1** and/or products of their further transformation to 11-R-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4-(3*H*)-ones **3**.[5] However, no data pertaining to the combined usage of α-nitro ketones and salicylaldehyde in the aforementioned reaction have been reported so far.

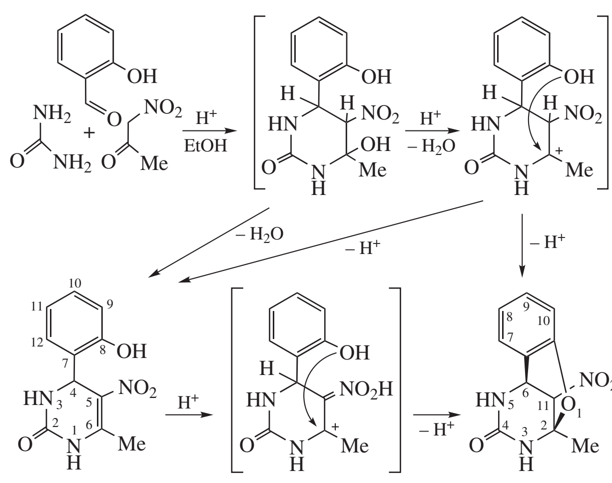


1 **2** **3**

R = C(O)Alk, C(O)OAlk

In this work, the reaction of salicylaldehyde with nitroacetone and urea was studied. This reaction was performed by simultaneous heating of the reactants in a 1 : 1.05 : 2 ratio in boiling ethanol in the presence of catalytic amounts of concentrated HCl. The compound obtained was snow-white solid, in contrast to yellow or light yellow 4-aryl-6-methyl-5-nitro-3,4-dihydropyrimidin-2-one **2**.[3] The IR spectra showed the absorption bands of stretching vibrations of the groups NH, C=O, NO_2, C–O–C, whereas the band assignable to OH vibration (in KBr and oil) was absent. This fact revealed an evidence of the formation of 2-methyl-11-nitro-5,6-dihydro-2*H*-2,6-methano-1,3,5-benzoxadiazocin-4(3*H*)-one **4** (Scheme 1).

In addition, the ^{1}H and ^{13}C NMR spectra of this compound in DMF-d_7 revealed the formation of the only product and were



5 **4**

Scheme 1 The tandem Biginelli and intramolecular oxa-Michael reactions.

in agreement with the O-bridge structure of **4**. Conclusions pertaining to the formation of methanobenzoxadiazocine are based on the appearance of H-6, H-11 signals and also the characteristic signals of atoms C-2, C-6 and C-11 (Table 1). The separated compound was stable in a solid state as well as in ethanol solution.

The spacial structure of compound **4** was established by X-ray analysis[†] (Figure 1) indicating its 2*R**,6*S**,11*S**-configuration

Table 1 Chemical shifts of characteristic signals in ^{1}H and ^{13}C NMR spectra of compounds **4a** and **4b** in DMF-d_7 (δ/ppm).

NMR	Signal	**4a**	**4b**
^{1}H	Me	1.95 (s)	1.94 (s)
	H-6	5.06 (dd, *J* 3.5 and 4.1 Hz)	5.01 (dd, *J* 2.6 and 5.1 Hz)
	H-11	5.74 (d, *J* 3.2 Hz)	5.69 (d, *J* 2.7 Hz)
	NH-5	7.65 (d, *J* 4.0 Hz)	7.77[a]
	NH-3	8.15 (br. s)	8.00 (br. s)[b]
^{13}C	Me	23.48	24.63
	C-6	50.67	47.66
	C-11	80.25	81.10
	C-2	83.45	82.75
	C-10	117.45	117.48
	C-10a	154.82	155.57

[a] The signal is adjacent to the NH-3 signal of compound **5**. [b] The signal is adjacent to the signal of DMF.

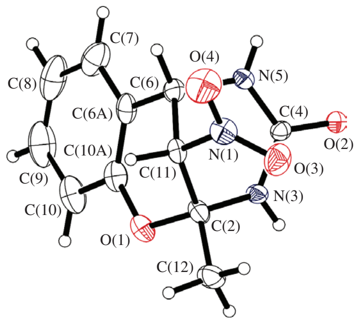
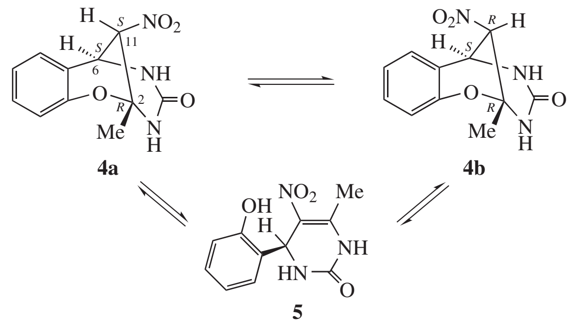


Figure 1 X-ray crystal structure of **4a** (ORTEP view). Displacement ellipsoids are drawn at 50% probability level.

(diastereomer **4a**). As a result of a pseudoaxial position of the O-bridged aromatic ring, it has a fixed, approximately perpendicular orientation [87.2(1)°] relative to the hexahydropyrimidine cycle. The heterocycle exhibits a slightly asymmetrical half-chair conformation, in which four atoms C-2, N-3, C-4 and N-5 are nearly planar; whereas the atoms C-6 and C-11 are displaced considerably from this plane to the opposite sides [0.390(5) and –0.445(5) Å]. In the case when the oxygen bridge O-1 and the aromatic ring aligned under the heterocyclic ring (configuration 2*R**,6*S**), the methylene bridge C-11 resided above the ring plane and the axially oriented nitro group connected to atom C-11 occurred in *cis*-disposition with respect to the urea fragment (configuration 11*S**). In the crystal, enantiomeric molecules are assembled in zigzag centrosymmetric chains along the *a* axis *via* hydrogen bonds N(3)–H···O(2) [H···O 2.01(4) Å, N–H···O 173(4)°] and N(5)–H···O(2) [2.06(4) Å, 175(4)°].

Solutions of sample **4a** in DMSO or DMF gradually changed their colour with time from colourless to yellow along with changes in its spectral pattern. These changes occurred more rapidly in the DMSO solution as compared to the less polar DMF. Immediately after the dissolution of compound **4** in DMF-d_7, its ^{1}H and ^{13}C NMR spectra contained the signals of diastereomer **4a**‡ only (Table 1); however, after 20 min, additional signals of diastereomer **4b**‡ near the signals of diastereomer **4a** emerged. The proximity of proton H-11 to the aromatic ring in the structure **4a** (configuration 11*S**) initiated a slight deshielding effect as compared to the structure **4b** (configuration 11*R**). The signals ^{13}C-11 for both diastereomers **4a** and **4b** are observed in the field of ~81 ppm that well keeps within area of 75–85 ppm characteristic of α-nitroalkanes.[6]

Table 2 The equilibrium between dihydropyrimidinone **5** and methanobenzoxadiazocine diastereomers **4a**,**b** in DMF-d_7.[a]



Entry	Time after dissolving/h	Ratio of **4a**:**4b**:**5**
1	0.17	99:<1:<1
2	0.33	93:3:4
3	4	60:9:31
4	24	16:10:74
5	96	15:10:75

[a] The values obtained upon relative intensities of ^{1}H NMR signals of H-6, H-11 for compounds **4a**,**b** and signal of H-4 for compound **5**.

Along with the specified signals above, the ^{1}H signals of 4-(2-hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-one **5**‡ emerged as well (see Scheme 1): δ 5.95 (d, H-4, *J* 3.0 Hz), 7.78 (d, NH-3, *J* 2.5 Hz), 9.98 (s, OH), 10.06 (s, NH-1), which correlate with data[3(a)] for 2-methoxyphenyl analogue of compound **5**. In the ^{13}C NMR spectrum the signals of Me, C-4, C-9, C-5, C-6 and C-8 of compound **5** were observed at 19.70, 51.57, 116.36, 123.10, 151.50 and 156.15 ppm, respectively. While the fraction of diastereomer **4a** decreased rapidly, the amount of diastereomer **4b** and dihydropyrimidinone **5** grew (see Table 2). After 24 h, the ratio **4a**:**4b**:**5** became 16:10:74. This unambiguously attests to the fact that the oxadiazocine ring of these compounds can be easily opened by the C–O bond in highly polar aprotic medium. Finally, the equilibrium between dihydropyrimidinone **5** and methanobenzoxadiazocine diastereomers **4a**,**b** was established.

† *Crystal data for* **4a**: $C_{11}H_{11}N_3O_4$, M = 249.23, monoclinic, space group $P2_1/n$, a = 7.2169(12), b = 18.811(3) and c = 9.0227(14) Å, β = 111.987(6)°, V = 1135.8(3) Å^3, Z = 4, d_{calc} = 1.457 g cm^{-3}, T = 150(2) K, μ = 0.113 mm^{-1}, λ = 0.71073 Å. Data collection yielded 9854 reflections resulting in 1987 unique, 1393 with $I > 2\sigma(I)$, $2\theta < 50°$. Full-matrix least-squares refinement led to a final R = 0.0565, wR_2 = 0.1859 and GOF = 1.078. Intensity data were measured on Bruker Kappa Apex II with CCD area detector.

CCDC 885775 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.

‡ *General procedure.* A mixture of 12.5 mmol of nitroacetone, 12 mmol of salicylaldehyde, 25 mmol of urea, 1.25 ml conc. HCl and 25 ml of ethanol was heated using an oil bath at 95 °C for 6 h. The mixture was cooled and the precipitate was filtered off, washed with water and ethanol. Then it was dried and crystallized from EtOH. NMR spectra were recorded in DMF-d_7 on a Bruker AM-400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), the internal standard was the signal of DMF-d_7 (δ_H 2.74, δ_C 30.10 ppm).

2-Methyl-11-nitro-5,6-dihydro-2H-2,6-methano-1,3,5-benzoxadiazocin-4(3H)-one **4**: 45% yield, mp 229–232 °C (EtOH). IR (KBr ν/cm^{-1}): 3415, 3221 (NH), 1701 (C=O), 1553, 1371 (NO_2), 1244 (C–O). UV [EtOH, λ_{max}/nm (log ε)]: 202 (4.40), 274 (3.17), 280 (3.15). MS (DFS, EI, 70 eV), *m/z* (%): 249 (33) [M]$^+$, 232 (100) [M – OH]$^+$. HRMS, *m/z*: 249.0745 ($C_{11}H_{11}N_3O_4$ required *m/z* 249.0744). Found (%): C, 53.01; H, 4.44; N, 16.68. Calc. for $C_{11}H_{11}N_3O_4$ (%): C, 53.01; H, 4.45; N, 16.86.

(2R,6S*,11S*)-Diastereomer* **4a**. ^{1}H NMR, δ: 1.95 (s, 3H, Me), 5.06 (dd, 1H, H-6, *J* 3.5 and 4.1 Hz), 5.74 (d, 1H, H-11, *J* 3.2 Hz), 6.88 (d, 1H, H-10, *J* 8.3 Hz), 7.00 (dt, 1H, H-8, *J* 0.8 and 7.5 Hz), 7.29 (dt, 1H, H-9, *J* 1.6 and 8.3 Hz), 7.34 (dd, 1H, H-7, *J* 1.6 and 7.5 Hz), 7.65 (d, 1H, NH-5, *J* 4.0 Hz), 8.15 (br. s, 1H, NH-3). ^{13}C NMR, δ: 23.48 (Me), 50.67 (C-6), 80.25 (C-11), 83.45 (C-2), 117.45 (C-10), 122.14 (C-8), 125.11 (C-6a), 129.58 (C-9), 130.68 (C-7), 150.86 (C-4), 154.81 (C-10a).

(2R,6S*,11R*)-Diastereomer* **4b**. ^{1}H NMR, δ: 1.94 (s, 3H, Me), 5.01 (dd, 1H, H-6, *J* 2.6 and 5.1 Hz), 5.69 (d, 1H, H-11, *J* 2.7 Hz), 6.88 (d, 1H, H-10, *J* 8.3 Hz), 7.02 (dt, 1H, H-8, *J* 0.8 and 7.5 Hz), 7.25 (dt, 1H, H-9, *J* 1.6 and 8.3 Hz), 7.37 (dd, 1H, H-7, *J* 1.6 and 7.5 Hz), 7.77 (m, 1H, NH-5), 8.00 (br. s, 1H, NH-3). ^{13}C NMR, δ: 24.63 (Me), 47.66 (C-6), 81.10 (C-11), 82.75 (C-2), 117.48 (C-10), 122.59 (C-8), 124.42 (C-6a), 129.83 (C-9), 130.71 (C-7), 150.96 (C-4), 155.57 (C-10a).

4-(2-Hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1H)-one **5**. ^{1}H NMR, δ: 2.64 (s, 3H, Me), 5.95 (d, 1H, H-4, *J* 3.0 Hz), 6.78 (t, 1H, H-11, *J* 7.8 Hz), 6.94 (d, 1H, H-9, *J* 7.8 Hz), 7.13 (t, 1H, H-10, *J* 8.0 Hz), 7.14 (d, 1H, H-12, *J* 7.8 Hz), 7.78 (d, 1H, NH-3, *J* 2.5 Hz), 9.98 s (1H, OH), 10.06 (s, 1H, NH-1). ^{13}C NMR, δ: 19.70 (Me), 51.57 (C-4), 116.36 (C-9), 119.58 (C-11), 123.10 (C-5), 128.31 (C-7), 128.41 (C-10), 129.65 (C-12), 151.50 (C-6), 151.56 (C-2), 156.15 (C-8).

For NMR spectra of the compounds mixtures (Figures S1–S9), see Online Supplementary Materials.

It is possible to assume that the formation of the O-bridged structures with the predominant *cis*-orientation of nitro group relative to the urea fragment (configuration 11*S**) occurs under kinetically controlled conditions of the oxa-Michael addition reaction. When the equilibrium is established, the form **a** becomes dominant. This is in agreement with the higher thermodynamic stability of this form (8 kcal mol^{-1}), as calculated by PRIRODA program (DFT/PBE/3z method).[7]

The behaviour of compound **4a** in DMSO solution was similar to its behaviour in DMF, however, the observed transformations proceeded quicker. After dissolution of this compound in more polar DMSO-d_6 solvent, the equilibrium **4a** : **4b** : **5** (5 : 4 : 91) was reached within ~0.5 h and remained constant within a month. Attempts to isolate the tautomer **5** from this mixture were unsuccessful. When the solution was poured in water and kept for several days at room temperature, the precipitated material was a 94 : 6 mixture of compounds **4** and **5**.

In summary, the revealed tautomerism of compounds **4** and **5** gives more insight into the structures and properties of the products of classical Biginelli reaction.

This work was supported by the Siberian Branch of the Russian Academy of Sciences (SB RAS) (grant no. 93). MS, IR and NMR spectra were recorded at the Chemical Service Center of the SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.05.020.

References

1 (*a*) C. O. Kappe, *Eur. J. Med. Chem.*, 2000, **35**, 1043; (*b*) M. Brands, R. Endermann, R. Gahlmann, J. Krüger and S. Raddatz, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 241; (*c*) H. Prokopcova, D. Dallinger, G. Uray, H. Y. K. Kaan, V. Ulaganathan, F. Kozielski, C. Laggner and C. O. Kappe, *ChemMedChem*, 2010, **5**, 1760; (*d*) Y. N. Mabkhot, N. A. Kheder and A. M. Farag, *Heterocycles*, 2011, **83**, 609; (*e*) Suresh and J. S. Sandhu, *ARKIVOC*, 2012, (i), 66.

2 (*a*) J. J. Baldwin, S. M. Pitzenberger and D. E. McClure, *US Patent 4675321*, 1987 (*Chem. Abstr.*, 1987, **107**, 242619); (*b*) K. Atwal, *US Patent 4684655*, 1987 (*Chem. Abstr.*, 1987, **107**, 176066); (*c*) R. O. Vitolinya and A. A. Kimenis, *Pharm. Chem. J.*, 1989, **23**, 213 (*Khim.-Farm. Zh.*, 1989, **23**, 285); (*d*) G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz and M. F. Malley, *J. Med. Chem. Lett.*, 1992, **35**, 3254; (*e*) C. O. Kappe, *Molecules*, 1998, **3**, 1; (*f*) K. Singh, D. Arora, D. Falkowski, Q. Liu and R. S. Moreland, *Eur. J. Org. Chem.*, 2009, 3258; (*g*) K. Singh, D. Arora, D. Falkowski, Q. Liu and R. S. Moreland, *Mini-Rev. Med. Chem.*, 2009, **9**, 95.

3 (*a*) G. Ya. Remennikov, S. S. Shavaran, I. V. Boldyrev, L. K. Kurilenko, B. M. Klebanov and V. P. Kukhar, *Khim.-Farm. Zh.*, 1991, **25** (3), 35 (in Russian); (*b*) G. Ya. Remennikov, S. S. Shavaran, I. V. Boldyrev, N. A. Kapran, L. K. Kurilenko, V. G. Shevchuk and B. M. Klebanov, *Pharm. Chem. J.*, 1994, **28**, 322 (*Khim.-Farm. Zh.*, 1994, **28**, 25); (*c*) G. Ya. Remennikov, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1997, **33**, 1369 (*Khim. Geterotsikl. Soedin.*, 1997, 1587).

4 S. V. Vdovina and V. A. Mamedov, *Russ. Chem. Rev.*, 2008, **77**, 1017 (*Usp. Khim.*, 2008, **77**, 1091).

5 (*a*) J. Svetlik, V. Hanus and J. Bella, *J. Chem. Res. (S)*, 1991, **1**, 4; (*b*) N.-Y. Fu, Y.-F. Yuan, Z. Cao, S.-W. Wang, J.-T. Wang and C. Peppe, *Tetrahedron*, 2002, **58**, 4801; (*c*) J. Svetlik, L. Veizerova and V. Kettmann, *Tetrahedron Lett.*, 2008, **49**, 3520; (*d*) E. M. H. Abbas, S. M. Abdallah, M. H. Abdoh, H. A. Tawfik and W. S. El-Hamouly, *Turk. J. Chem.*, 2008, **32**, 297; (*e*) M. M. Kurbanova, *Russ. J. Org. Chem.*, 2010, **46**, 599 (*Zh. Org. Khim.*, 2010, **46**, 606); (*f*) Q. Cheng, Q. Wang, X. Xu, M. Ruan, H. Yao and X. Yang, *J. Heterocycl. Chem.*, 2010, **47**, 624.

6 H.-O. Kalinowski, S. Berger and S. Braun, in *Carbon-13 NMR Spectroscopy*, J. Wiley and Sons, New York, 1988, p. 239.

7 (*a*) D. N. Laikov, *Chem. Phys. Lett.*, 1997, **281**, 151; (*b*) D. N. Laikov and Yu. A. Ustynyuk, *Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 820 (*Izv. Akad. Nauk, Ser. Khim.*, 2005, 804).

Received: 24th January 2013; Com. 13/4054