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Synthesis, Tautomeric States and Crystal Structure of (Z)-Ethyl 2-Cyano-2-(3H-Quinazoline-4-ylidene) Acetate and (Z)-Ethyl 2-Cyano-2-(2-Methyl-3H-Quinazoline-4-ylidene) Acetate

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Abstract: The new compounds (Z)-ethyl 2-cyano-2-(3H- and 2-methyl-3H-quinazoline-4-ylidene) acetate (**1** and **2,** respectively) were synthesized by multi-step reactions. The structures in a solution have been determined by ^{1}H-NMR spectroscopy and in the crystal form by X-ray analysis. Molecule **1** crystallized in a primitive monoclinic cell, space group $P2_1/c$. The cell dimensions are a=7.970(6) Å, b=7.061(2) Å, c=20.537(7) Å, β=97.69(5)°, V=1145.3(10) Å^3. Molecule **2** crystallized in a triclinic cell, space group P-1, the cell dimensions are a=8.196(5) Å, b=8.997(6) Å, c=9.435(4) Å, α=74.22(4)°, β=89.75(4)°, γ=74.07(5)°, V=641.9(6) Å^3. In both compounds the presence of intra-molecular NH---O=C hydrogen bonding between the nitrogen atom in position 3 of the quinazoline ring and a carbonyl group of the ethyl cyanoacetate residue was proven by quantum-chemical, ^{1}H-NMR and X-ray methods.

Keywords: Quinazolines, activated methylene groups, intramolecular hydrogen bonding, tautomery, quantum-chemical calculations.

Introduction

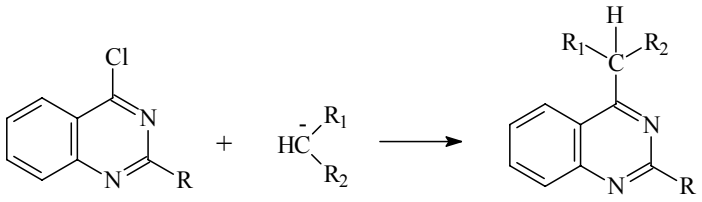
From a theoretical perspective quinazolines are undoubtedly of interest as topics for study because they are multipurpose heterocyclic systems with multiple reactive centers. Among them are found a

series of highly effective agricultural compounds, such as fungicides, bactericides, defoliants and plant growth stimulants [1-3]. Compounds of this class also are used as medicinal drugs with various pharmacological activities [4-5]. It is known that pyrimidine system derivatives that contain activated methylene group residues can exist in different tautomeric forms [6]. The tautomeric state of these substances depends on nature of the substituent's functional group at the C2 atom, the substituent at positions C5 and C6, solvent nature and other factors. There was no data in the literature concerning the tautomeric states of pyrimidine derivatives and their benzene analogs (quinazolines), having substituents at C4 [7]. Because of this the study of possible tautomeric forms of 2-substituted quinazolines containing compounds with an activated methylene group at C4 is of theoretical interest. Moreover, the study of influence on tautomery of the substituent properties at the C-2 position is also interesting. In this paper the synthesis, study of tautomeric states (in solution – by NMR spectroscopy, in crystal state –by X-ray analysis) and the quantum-chemical justification of the presence of tautomeric forms is discussed.

Results and Discussion

Compounds **1** and **2** were obtained by nucleophilic substitution of 4-chloro-2-H(methyl)-3,4-dihydroquinazoline with ethyl cyanoacetate (Figure 1). The reactions proceeded smoothly in boiling dimethylformamide in the presence of sodium hydride for 3 hours, with the yields ranging from 60 up to 75 %.

Figure 1. Structural representation and reaction scheme of compounds **1** and **2**



1. R=H; R_1=CN, R_2=$COOC_2H_5$

2. R=CH_3; R_1=CN, R_2=$COOC_2H_5$

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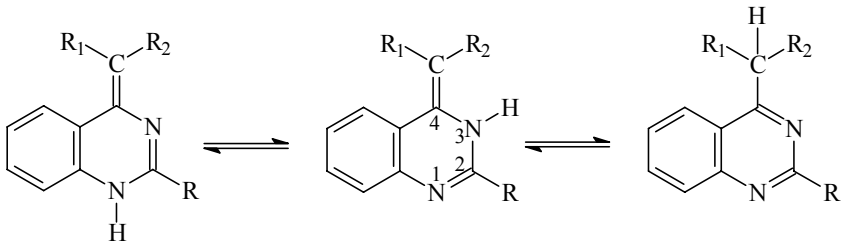
From a theoretical point of view these compounds can exist in three tautomeric forms (Figure 2).

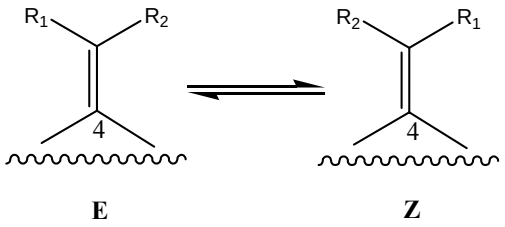
Figure 2. Possible tautomeric states for compounds **1** and **2**.



A **B** **C**

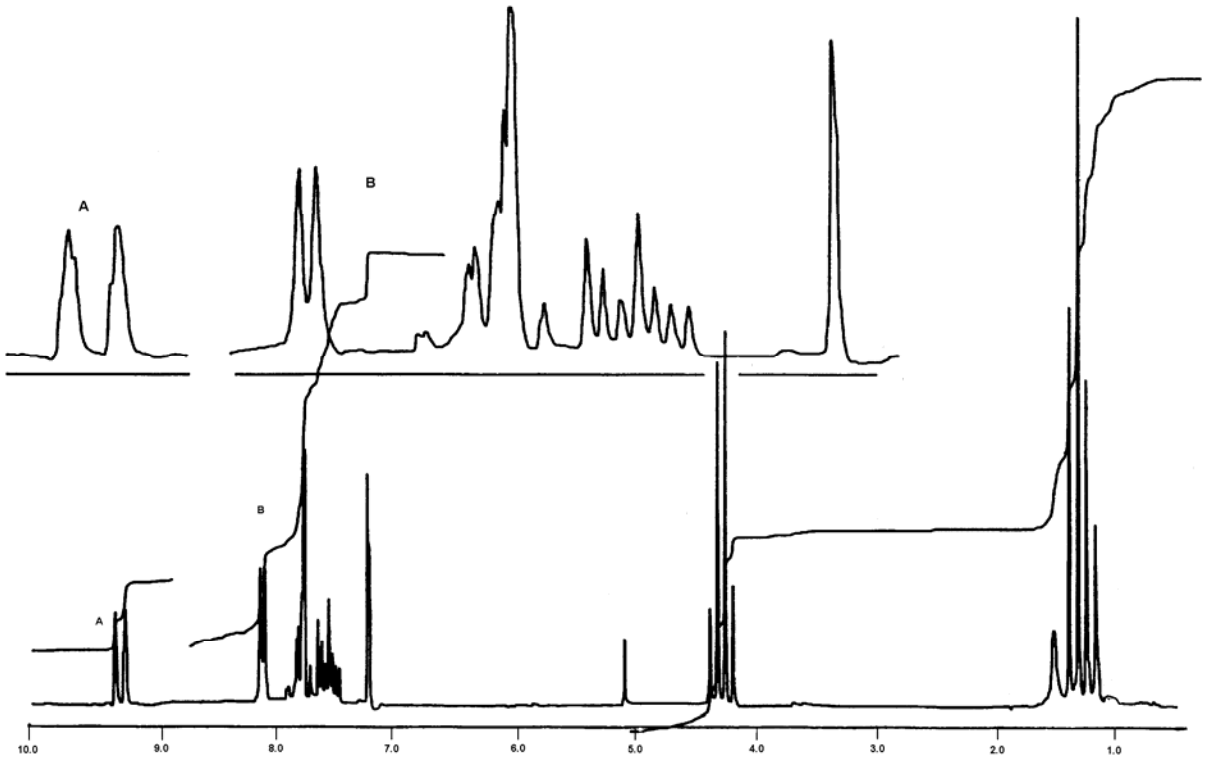
Moreover, in tautomeric forms **A** and **B** two geometrical isomers – the E and Z-forms - (i.e., the double bond conformers A', B') can exist (Figure 3).

Figure 3. Two geometrical isomers of compounds **1** and **2**.



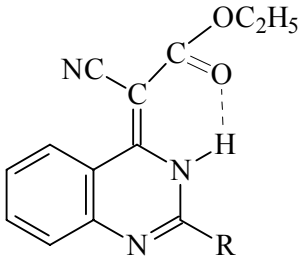
NMR and X-ray crystallography were used to elucidate the structures of the products. The ^{1}H-NMR spectra have been interpreted on the basis of proton-proton correlations (Figure 4).

Figure 4. NMR spectrum of compound 1 (zones A and B also shown in expanded view).



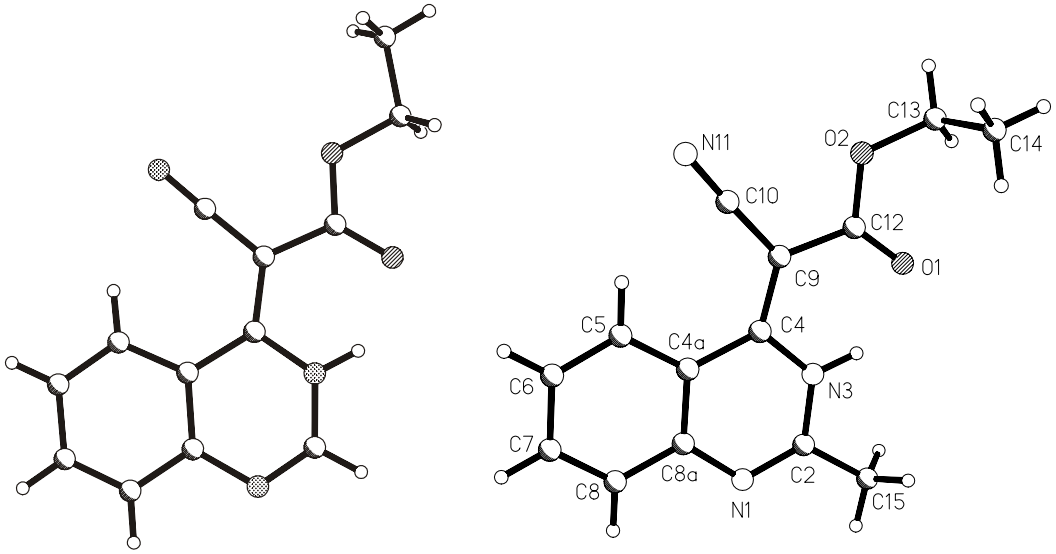
Both compounds have a downfield signal at 14.15 ppm, corresponding to the NH group in position 3. The downfield shift of the NH signal testifies to the interaction of the NH group proton with the oxygen atom of the carbonyl group of the substituent at C4. However, in this case the strong intramolecular NH--O=C hydrogen bonding also confirms the presence in solution of the tautomeric form **B** (Figure 5). If there were a significant presence of tautomer **A** at room temperature the NH group signal would be observed at more strong fields, near 10-12 ppm, but not such peak is observed.

Figure 5. Intramolecular hydrogen bond formation



The downfield shift of the H5 proton signal (approximately by 1.5 ppm) in comparison with the signals of the other aromatic protons in both compounds may be explained by the close spatial presence of the CN group, which causes a deshielding effect due to carbon-nitrogen π-bonding (Figure 6). With the purpose of obtaining unambiguous evidence of the structures and determination of their conformations in crystal form the X-ray structural analysis of these substances was carried out. The determined structures are shown in Figure 6.

Figure 6. ORTEP plots of compounds **1** and **2** in crystal state.



Interesting with regards to the tautomery question is the geometry of the pseudo-aromatic substituted pyrimidine ring, in particular of nodal atoms C2, C4 and C9. In compounds **1** and **2** the quinazoline skeleton with substituents in position C4 on the whole has a planar geometry to within 0.06 Å (with the exception of the C14 methyl group). The planarity of the molecules and the sum of valence angles (360°) at C4 and C9 indicate that atoms C4 and C9 have sp^2-hybridization. Further, by comparing the lengths of the valence bonds from nodal atoms C4 and C9, it is possible to note that the C4-C9 bonds (1.405 in **1** and 1.398 in **2**) are much shorter than a single bond and are identical to aromatic benzene ring bonds. These data indicate that the double bond is in the C4=C9 position.

By comparison of C2-N1 (1.276 in **1** and 1.290 in **2**) and C2-N3 bond lengths (1.360 in **1** and 1.366 in **2**) and the experimentally determined location of the H atom at N3 we may state that in the molecules examined the formal double bond in pyrimidine ring is at N1=C2, like in the related quinazoline alkaloids [8, 9]. Thus, in the crystalline state molecules **1** and **2** exist in the tautomeric form **B** with double bonds at positions N1=C2 and C4=C9. The trend towards averaging of these heterobonds in the pyrimidine ring specifies the presence of coupling between the π-electrons of the double bonds with the lone pair electrons of atoms N1 and N3.

The methyl groups (-C(14)H_3) are located differently with regards to the plane of the quinazoline skeletons. In molecule **1** the methyl group is slightly turned out from this plane (the torsion angle is -175.8), while in **2** it is located practically perpendicular (-81.2) as a consequence of the effect of the packing factor. From Figure 6 it is seen that molecules are in the Z form. The planarity of the molecules and the Z-form of the cyanoacetate ester substituent in position C4 favors the formation of intramolecular H-bonding, such as N-H...O, between the relatively syn-located atoms N3 and O1 (N3...O1 distance 2.594 and 2.592 Å, H...O 1.844 and 1.782 Å, N3-H-O1 angle 140.82 and 140.66°, respectively, in **1** and **2**).

*Determination of the most stable tautomeric form of compound **1** by a computational approach.*

The ability of the MNDO [10], AM1 [11], and PM3 [12] semiempirical molecular orbital methods to reproduce the structure of a series of aromatic heterocycles has been examinated earlier. It has been found that AM1 parameters are superior to either MNDO or PM3 for this class of compounds [13]. We chose the AM1 method, based on the structure determination mentioned above, to be the computational tool considered in the present study of 2-substituted quinazoline-4 derivatives. Therefore, the AM1 parameters could be a good choice for quinazoline derivatives from both structural and energetic points of view. AM1 was thus used to calculate relative stability energies, dipole moments, charges on atoms, energies of HOMO and LUMO molecular orbitals, electrostatic potentials and electron densities on atoms.

No detailed structural information was available for any of these compounds, but it was interesting to see to what extent the relative stabilities within the various tautomers were reproduced by semi-empirical method AM1 (Table 1). The results of AM1 calculations for tautomerization energies are satisfactory and they exhibit a good correlation with the experimental data [14] so that its use is recommended, in particular for high molecular weight compounds [15].

It is known, that the given compounds can be present in several tautomeric forms [16-17], corresponding to different protonation sites. In this case, 2-substituted-quinazoline-4 appears in 3 tautomeric forms as shown in Figure 2, at the ring nitrogen atoms (N1 or N3), and at the carbonyl atom of substituent (C9).

A check of which form from three possible tautomeric ones was the most stable has been carried out by a semiempirical calculation by AM1 method. For the tautomeric structures parameters such as heat of formation, dipole moment and ionization potential have been calculated (Table 1).

Table 1. The Heat of formation (ΔH_f), Dipole moments and Ionization potentials for tautomeric forms (A-C) of compound **1**, calculated by AM1 in gas phase (ε=1).

Tautomer	Ionization potential	Dipole moment, D	Heat of formation, ΔH_f, (kcal/mol)
A	8.75	6.80	15.14
B	8.91	2.79	7.09
C	9.74	4.45	10.41

Table 1 shows that among the possible tautomers of compound **1** (tautomers **A** – **C**, Figure 2) tautomer **B** is calculated to be significantly more stable as it possesses the minimal energy. The difference in relative energy between tautomers ranges from 3.32 - 8.05 kcal/mol. The formation of hydrogen bonding also is seen on orientation of the substituent in space in the calculations. In tautomers **A** and **C** it is located perpendicular to the quinazoline skeleton, and in tautomer **B** - planar. The C=O group is directed aside the NH proton (r =2.03 Å). The N-H···O distance is rather short, implying a strong hydrogen bonding. Taking into account the similarity of the investigated structures, all these conclusions following from semiempirical calculations of compound **1** can also be applied to compound **2** with confidence.

Conclusions

Syntheses of two quinazolines, distinguished by the type of the substituent at position 2 of the quinazoline rings, was carried out. By X-ray structural analysis and NMR spectroscopy methods it was shown that in molecules of (Z)-ethyl 2-cyano-2-(3H- and 2-methyl-3H-quinazolin-4-ylidene)acetate in the crystalline state and in solution the tautomeric form **B** with double bonds in positions N(1)=C(2) and C(4)=C(9) exists.

Formation of NH---O=C intramolecular hydrogen bonding makes the the form **B** the most stable and energetically favorable, which explains its preferred presence both as crystal and in solution. Semiempirical calculations on the AM1 level satisfactorily reproduce the energetics of the tautomeric equilibrium. The results clearly indicate that 2-substituted quinazoline-4 derivatives in the gas phase exist predominantly in the tautomeric form **B**. This result is in agreement with available experimental data in liquid phase (^{1}H-NMR) and X-ray analysis.

Acknowledgments

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Experimental

General

NMR spectra were obtained on a Tesla BS567A spectrometer (100 MHz), equipped with a 5-mm detector. Approximately 0.05M solutions of the studied compounds in deuterochloroform ($CDCl_3$) were used for recording of spectra at 25 °C. TMS was utilized as the internal standard.

(Z)-ethyl 2-cyano-2-(3H-quinazolin-4-ylidene)acetate (**1**). A mix of dimethylformamide (12 mL, 5.6 mmol), ethyl cyanoacetate (0.6 mL, 5.6 mmol) and sodium hydride (0.14 g, 5.6 mmol) was stirred at room temperature for 30 min., then 4-chlorquinazoline (0.92 g, 5.6 mmol) was added to the reaction mixture and the reaction was continued for about 8 hours at 110-115 °C. After refrigerating, water was added to the reaction mixture and the crystals formed were filtered off. The aqueous filtrate was extracted with chloroform, the extract dried over anhydrous sodium sulphate and then the chloroform was distilled off. Recrystallization was from petroleum ester. Yield: 0.85g (63.5 %), m.p. 178-179 °C; ^{1}H-NMR: 14.15 (1H, br.s, NH), 9.30 (1H, d, ArH, J=8.5 Hz; 1.3 Hz), 8.15 (d, 1H, H_2, J=3 Hz), 7.90-7.42 (3H, m, ArH, J=8.5 Hz; 6 Hz; 3 Hz; 1.3 Hz), 4.30 (2H, q, OCH_2, J=7.5 Hz), 1.55 (H, br. s., CH), 1.33 (3H, t., $\underline{CH_2}\underline{CH_3}$, J=7.5 Hz)

(Z)-ethyl 2-cyano-2-(2-methyl-3H-quinazolin-4-ylidene)acetate (**2**). A mixture of dimethylformamide (12 mL, 5.6 mmol), ethyl cyanoacetate (0.6 mL, 5.6 mmol) and sodium hydride (0.14 g, 5.6 mmol) was stirred at room temperature for 30 min. Then 2-methyl-4-chlorquinazoline (1g, 5.6 mmol) was added to the reaction mixture and the reaction was continued for about 8 hours at 110-115 °C. After refrigerating water was added to the reaction mixture and the crystals formed were filtered off. The aqueous solution was extracted with chloroform, the extract dried over anhydrous sodium sulphate and the chloroform distilled off. Recrystallization was from heptane. Yield - 1g (71.5 %), m.p. 147-148 °C. ^{1}H-NMR 14.15 (1H, br.s, NH), 9.05 (1H, d, ArH, J=7.6 Hz; 1.5 Hz), 7.75 (1H, m, ArH, J=8.5 Hz; 7.6 Hz; 1.3 Hz), 7.58 (1H, d, ArH, J=7.1 Hz; 2.1 Hz), 7.42 (1H, m, ArH, J=8.5 Hz; 7.1 Hz; 2.1), 4.26 (2H, q, OCH_2, J=7.5 Hz), 2.50 (3H, br. s., 2-CH3), 1.33 (3H, t., $\underline{CH_2}\underline{CH_3}$, J=7.5 Hz)

X-ray structural analysis

Single crystals of compounds **1** and **2** were grown for X-ray analysis from methanol and ethanol at room temperature. The crystals are transparent. The crystals of **1** have a plate form. The crystals of **2** are shaped like elongated prisms. The unit cell parameters were determined on a Stoe Stadi-4 diffractometer. Intensities of reflections were measured on the same diffractometer using graphite monochromated MoKα-radiation, in the $\omega/2\theta$ scan mode. Reduction of intensities is carried out by program XRED [18], absorption effects were not corrected. Final cell parameters are given in Table 2 along with other information regarding data collection and refinement. Structures were solved by direct methods and refined by least-squares method in full-matrix isotropic-anisotropic approaching. All calculations were performed using the SHELXTL [19] crystallographic software package of Bruker Analytical X-ray Systems. Coordinates of H atoms are determined experimentally from difference synthesis of electron density (ED). Atomic coordinates and equivalent displacement

parameters have been deposited with CCDC as supplementary information [20]. Location of coordinates of H atoms at heteroatom N3 from difference synthesis of ED has allowed defining the tautomeric form of molecules in a crystal.

Table 2. Crystal data, experimental and refinement parameters for compounds **1** and **2**.

Parameter	**1**	**2**
Empirical formula	$C_{13}H_{11}N_3O_2$	$C_{14}H_{13}N_3O_2$
Formula weight	241.25	255.27
Crystal size (mm)	0.90 x 0.80 x 0.10	0.80 x 0.30 x 0.20
Crystal system	Monoclinic	Triclinic
Space group	P 2_1/c	P-1
Z	4	2
a, Å	7.970(6)	8.196(5)
b, Å	7.061(2)	8.997(6)
c, Å	20.537(7)	9.435(4)
α	90	74.22(4)
β	97.69(5)	89.75(4)
γ	90	74.07(5)
V, Å^3	1145.3(10)	641.9(6)
d_{call}, g/cm^3	1.399	1.321
Theta range	2.4<θ<26.0°	2.3<θ<26.0°
μ_{exp} (cm^{-1})	0.098	0.091
Reflections collected	2247	2526
Number of reflections with **I**>2σ (**I**)	1644	1674
R1 (**I**>2σ(**I**) and for all)	0.0523 (0.0777)	0.0714 (0.1092)
WR2 (**I**>2σ(**I**) and for all)	0.1197 (0.1387)	0.1539 (0.1821)
Max. diff. peak and hole	0.166 and –0.181 eÅ^{-3}	0.209 и –0.261 eÅ^{-3}

References

1. Shakhidoyatov Kh. M.; Irisbaev, A.; Abdullaev, N. P. Synthesis of potential growth regulators of plants in series of the N-substituted lactams and quinazolines; *Growth regulators of plants and herbicides*. Fan: Tashkent, **1978**; pp. 166-195
2. Yaxontev, L. N.; Liberman, S. S.; Jiharyova, G. P.; Kuzmina, K. K. *Chem.-Pharm. J.* **1977**, *5*, 14-26
3. Michael, J. P. *Nat. Prod. Rep.,* **2002**, *19*, 742–760
4. Bhattacharjee, A.K.; Skanchy, D.J.; Jennings, B.; Hudson, T.H.; Brendle, J.J.; Werbovetz, K.A.; *Bioorg. Med. Chem.* **2003**, *10*, 1979-89
5. Gupta, C. M.; Bhaduri, A.P.; Khanna, N. M., *J. Med. Chem.* **1968**, *11*, 392-395
6. Abdullaev, N. P.; Kayumov, K.; Shakhidoyatov, K. M. *Uzb. Khim. J.* **1997**, *2*, 29-34

7. Fathalla, W.; Cajan, M.; Marek, J.; Pazdera, P. *Proceedings of ECSOC-5, The Fifth International Electronic Conference on Synthetic Organic Chemistry*, http://www.mdpi.org/ecsoc-5.htm, September 1-30, **2001**, A0049
8. Tashkhodjaev, B.; Turgunov, K. K.; Dyakonov, A. L.; Belova, G. A.; Shakhidoyatov, Kh. M. *Khim. Prirod. Soedin.* **1995**, 410
9. Turgunov, K. K.; Tashkhodjaev, B.; Molchanov, L. V.; Aripov, Kh. N. *Khim. Prirod. Soedin*. **1995**, 849
10. Pople, J. A.; Santry, J. P.; Segal, G. A. *J. Chem. Phys.* **1965**, *43*, S129
11. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909
12. Stewart, J. P. P. *J. Comput. Chem*. **1989**, *10*, 209.
13. Zahedi, M. *J. Mol. Struct. (THEOCHEM)* **1998**, *452*, 125-131
14. Sygula, A.; Buda, A. *J. Mol. Struct. (THEOCHEM)* **1985,** *121*, 133
15. Sygula, A. *J. Chem. Res., Synop*. **1989**, 56
16. Koryakova, O. V.; Sattarova, V. V.; Sevenard, D. V.; Khomutov, O. G.; Pashkevich, K. I. *Russ. J. Gen. Chem.* **2003**, *73*, 141-144
17. Csányi, D.; Hajós, G.; Timári, G.; Riedl, Z.; Kotschy, A.; Kappe, T.; Párkányi, L.; Egyed, O.; Kajtár-Peredy, M.; Holly, S. *Eur. J. Org. Chem.* **2002**, *1*, 133-138
18. XRED 1.09. Data Reduction program for Stadi-4 and IPDS. STOE & Cie GmbH (**1997**)
19. Sheldrick, G. M. *Acta Crystallogr.* **1993**, *A49*, 53
20. CCDC 240414 and CCDC 240415 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or via the URL http://www.ccdc.cam.ac.uk/conts/retrieving.html)

Sample availability: Available from the authors.

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