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Synthesis and structure of a novel mesomeric betaine 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine ☆

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Abstract

The synthesis and structural characterization by ^{1}H NMR, HRMS, elemental analysis and X-ray crystallography of a novel mesomeric betaine, 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine **8a** are described. The compound **8a** crystallizes in the monoclinic system in the space group $P2_1/n$ with $a = 11.766(2)$, $b = 5.8097(12)$, $c = 12.389(3)$ Å, $\beta = 107.14(3)°$, $V = 809.2(3)$ Å^3, $Z = 4$, $D_{calc} = 1.561$ gcm^{-3}, λ(Cu Kα) = 1.54178 Å, $\mu = 0.953$ mm^{-1} and final $R = 0.0378$ for 1526 reflections. The molecule as a whole has an almost planar conformation and the bond lengths and angles have the values characteristic for π-electron system. The molecular packing in the crystal is influenced by the van der Waals forces and presence of weak π–π interactions. The electronic properties (net charge and MEP distributions and dipole moment) of the molecule **8a** are calculated using AM1 approximation. Twelve dipolar canonical forms for molecule **8a** are presented and their contribution in mesomeric betaine structure of **8a** is discussed (molecular mechanics calculations).

Keywords: Mesomeric betaine; Pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine; X-ray structure

1. Introduction

Annulated 1,2,4-triazine derivatives are present as important core structures in many biologically active compounds, both naturally occurring and synthetic [2,3]. As a part of an ongoing research program into synthesis of heteroaromatic analogues of this system, we were interested in the formation of pyrazolo[4,3-*e*][1,2,4]triazines fused with tetrazole ring. The nitrous acid oxidation of an easily available 5-hydrazino compound **1** [4] appeared to be the method of choice [5]. The initial product of the oxidation, the azido compound **2**, can cyclize to form either linearly fused compound **3a** or angularly fused compound **3b**. In this study, the crystal structure of the tetrazole derivative was clarified by single crystal X-ray analysis [5] revealing the predominant tautomeric structure as linear **3a**, resulting from cyclization of an azido group into N-2 atom of **2** (see Scheme 1).

The propensity of **2** toward cyclization of the azido group into N-2 rather than N-4 prompted us to examine the behavior of 5-azido-2,3-dimethyl-2*H*-pyrazolo[4,3-*e*][1,2,4]triazine **7**. In contrast to compound **2**, the aromatic sextet of π-electrons in 1,2,4-triazine part of the model compound **7** is not retained, and in principle only one kind of intramolecular ring closure of the azido group into N-4 atom leading to **8b** could occur. However, it was found that under thermal conditions compound **7** gave rise to linearly fused betaine **8a**. The structure of **8a** was fully determined by X-ray crystallographic analysis.

Compound **7** was conveniently prepared in the three-step synthesis from 2,3-dimethyl-5-methylsulfanyl-2*H*-pyrazolo[4,3-*e*][1,2,4]triazine **4** by oxidation with potassium manganate (VII), followed by treatment of the resulting 2,3-dimethyl-5-methylsulfonyl-2*H*-pyrazolo[4,3-*e*][1,2,4]triazine **5** with anhydrous hydrazine. The nitrous oxidation of 5-hydrazino compounds **6** thus obtained gave the desired compound **7** (see Scheme 2).

☆ See Ref. [1].

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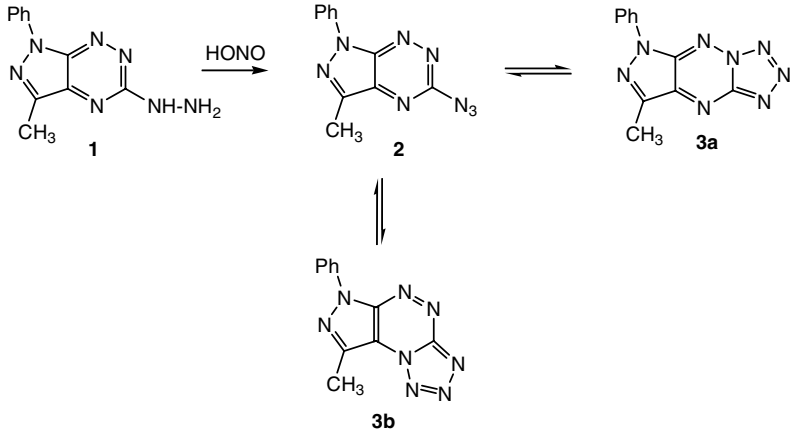
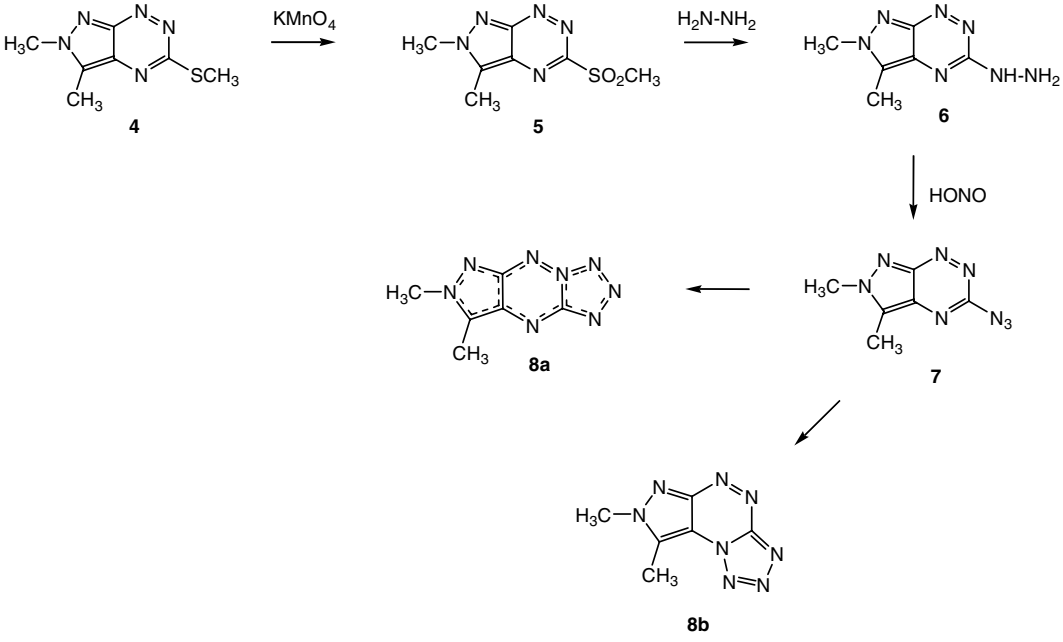


Scheme 1.



Scheme 2.

During recrystallization of **7** from hot ethyl alcohol the color of the ethanolic solution gradually changed from yellow to red and a deep red precipitate of the tetrazole derivative (**8a** or **8b**) was formed. In order to establish whether we are dealing with angularly fused compound **8b** or its linearly fused isomer **8a** it became necessary to confirm its structure by X-ray.

2. Experimental

2.1. General methods

Melting points were determined on Boetius melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer with TMS as internal standard in deuterated solvents. The chemical shifts are given in δ (ppm). Mass spectra were measured on AMD 604 spectrometer. Elemental analysis of C, H and N was recorded on Perkin-Elmer 2400-CHN analyzer and results for the indicated elements were within 0.3% of the calculated values. Compound **4** was prepared according to the literature procedure [4]. Compound **6** was used as a crude product.

2.2. Synthesis of 2,3-dimethyl-5-methylsulfonyl-2H-pyrazolo[4,3-e][1,2,4]triazine *5*

To a solution of **4** (195 mg, 1 mmol) in 20 mL of benzene were added water (30 mL), potassium manganate (VII) (474 mg, 3 mmol), catalytic amounts of tetrabutylammonium bromide (65 mg, 0.2 mmol) and 1.5 mL of acetic acid. The reaction mixture was stirred at rt for 1 h. A saturated solution of $Na_2S_2O_5$ in water was added to the mixture until the purple color disappeared. The organic layer was separated and water phase was extracted with benzene (3×10 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel

using a mixture of chloroform-ethanol (40:1) as eluent and recrystallized from ethanol to give 120 mg (0.53 mmol, 53%) of **5**. Mp 164 °C. ^{1}H NMR ($CDCl_3$) δ: 2.87 (s, 3H), 3.58 (s, 3H), 4.42 (s, 3H). MS (EI 70 eV, *m/z*, %): 227 (1) [M^+], 199 (9), 136 (7), 79 (15), 56 (100); IR (KBr) cm^{-1}: 1320, 1130; Anal. Calcd for $C_7H_9N_5SO_2$: C, 37.00; H, 3.96; N, 30.83. Found: C, 37.11; H, 3.82; N, 31.05.

2.3. Synthesis of 2,3-dimethyl-5-hydrazine-2H-pyrazolo [4,3-e][1,2,4]triazine **6**

To a solution of **5** (227 mg, 1 mmol) in dry THF (20 mL) cooled to 0–5 °C anhydrous hydrazine (0.1 mL, 3 mmol) was added. The reaction mixture was stirred at 0–5 °C for 30 min and additional 3 h at rt. After that time the solvent was evaporated *in vacuo* to give 150 mg (0.84 mmol, 84%) of the red solid. The crude product was used for the next step. Mp 218–220 °C. ^{1}H NMR (CD_3OD) δ: 1.65 (s, 2H), 2.59 (s, 3H), 4.18 (s, 3H), 6.92 (s, 1H). IR (KBr) cm^{-1}: 3300, 1550, 1450. MS (EI 70 eV, *m/z*, %): 179 (10) [M^+], 164 (5), 151 (4), 135 (10), 67 (5), 56 (100). HRMS (EI, *m/z*) 180.0984, Calcd for $C_6H_{10}N_7$ [M^+H] 180.0992.

2.4. Synthesis of 5-azido-2,3-dimethyl-2H-pyrazolo [4,3-e][1,2,4]triazine **7**

The solution of **6** (90 mg, 0.5 mmol) in CH_3COOH/H_2O mixture (1:1, 8 mL) was cooled to 0–5 °C and aqueous $NaNO_2$ (70 mg in 2 mL of water) was added dropwise so that the temperature of mixture was kept below 5 °C. After additional stirring for 15 min at 0–5 °C the orange precipitate was filtered off, washed with water and dried at room temperature to give 92 mg (0.48 mmol, 96%) of **7**. Mp 140 °C. ^{1}H NMR ($CDCl_3$) δ: 3.02 (s, 3H), 4.36 (s, 3H). IR (KBr) cm^{-1}: 2145 (N_3). MS (EI 70 eV, *m/z*, %): 190 (35) [M^+], 78 (7), 57 (4), 56 (100), 54 (4). HRMS (EI, *m/z*) 190.07101, Calcd for $C_6H_{10}N_8$ [M^+] 190.07154.

2.5. Synthesis of 6,7-dimethyl-2H-pyrazolo[4,3-e] tetrazolo[4,5-b][1,2,4]triazine **8a**

The azido compound **7** (95 mg, 0.5 mmol) was dissolved in boiling ethanol (5 mL) and the resulting mixture was left to slow crystallization at room temperature. The crystals and dry residue after evaporation of the alcohol were combined and purified on column chromatography using chloroform/ethanol mixture 30:1 as eluent to give **8a** (62 mg, 0.32 mmol, 64%) as a red solid. Mp 148 °C. ^{1}H NMR ($CDCl_3$) δ: 2.70 (s, 3H), 4.29 (s, 3H). MS (EI 70 eV, *m/z*, %): 190 (27) [M^+], 78 (6), 56 (100). HRMS (EI, *m/z*) 190.07189, Calcd for $C_6H_{10}N_8$ [M^+] 190.07154. Anal. Calcd for $C_6H_{10}N_8$: C, 37.90: H, 3.18; N, 58.92. Found: C, 38.08: H, 3.18; N, 58.65.

2.6. X-ray structure analysis

Red prismatic crystals of **8a** suitable for X-ray diffraction analysis were grown by slow evaporation of an ethanol solution. X-ray data were collected on the Bruker SMART APEX CCD diffractometer at room temperature; crystal sizes: $0.30 \times 0.30 \times 0.10$ mm, ω scans. The multiscan absorption correction was applied (SADABS [6]). The structure was solved by direct methods using SIR92 [7] and refined by full-matrix least-squares with SHELXL97 [8]. All hydrogen atoms were located from $\Delta\rho$ map and their coordinates were refined with isotropic displacement parameters taken as 1.5 times those of the respective parent atoms. All crystal and experimental data are listed in Table 1. Molecular graphics were prepared using ORTEP3 for Windows [9] and XP in SHELXTL-Plus [10], PARST [11] and PLATON [12] were used for geometrical calculations. All calculations were performed using WINGX ver. 1.64.05 package [13].

Table 1
Crystal data and structure refinement for **8a**

Empirical formula	$C_6H_6N_8$
Formula weight	190.19
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell parameters	
a (Å)	11.766(2)
b (Å)	5.8097(12)
c (Å)	12.389(3)
β (deg)	107.14(3)°
V (Å^3)	809.2(3)
Z	4
D_{calc} (g cm^{-3})	1.561
$F(0\,0\,0)$	392
λ (Cu Kα) (Å)	1.54178
Cell parameters from	83 reflections
θ range for lattice parameters (°)	8.50–31.76
Absorption coefficient μ (mm^{-1})	0.953
T_{min}/T_{max}	0.799/0.911
θ range for data collection (°)	4.56–70.53
Index ranges h, k, l	−14/13, −7/7, −14/15
No. of measured reflections	8609
No. of independent reflections	1526 ($R_{int} = 0.0214$)
No. of observed reflections	1474 with $I > 2\sigma(I)$
Refinement method	Full-matrix least-squares on F^2
Final R indices: R, $wR(F^2)$	0.0378, 0.1194
Goodness-of-fit on F^2, S	1.099
Data/parameters	1526/146
Extinction coefficient	0.0125(16)
Largest diff. peak and hole (e Å^{-3})	+0.235 and −0.158
$(\Delta/\sigma)_{max}$	0.000

2.7. Theoretical calculations

The net charge distributions on the atoms, dipole moment and the molecular electrostatic potential (MEP) for 6, 7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine **8a** were calculated at the restricted Hartree-Fock level (RHF) using AM1 semiempirical SCF-MO method [14]. The molecular mechanics studies (MM + force field [15]) were undertaken to calculate the strain energy for all possible dipolar canonical forms of **8a**. All calculations were performed using the program package HYPERCHEM rel. 4.5 [16]. The structures were fully optimized without any symmetry constraint

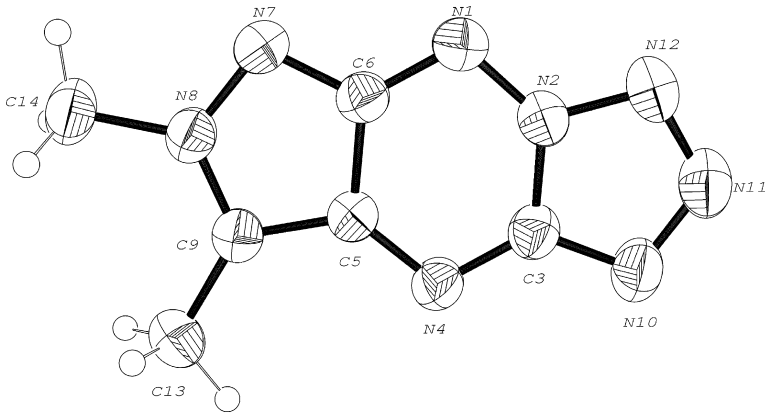


Fig. 1. A view of the molecule **8a** with the atomic labelling. Non-H atoms are represented by displacement ellipsoids of 50% probability.

to a gradient norm of <0.1 and the initial geometries were built from crystallographic data of **8a**.

3. Results and discussion

3.1. X-ray structure analysis results

The X-ray analysis revealed that the linear tricyclic inner salt with mesomeric betaine structure of the 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine **8a** is formed via ring closure toward N-2 in 5-azido-2,3-dimethyl-2*H*-pyrazolo[4,3-*e*][1,2,4]triazine **7**. View of the molecule **8a** with numbering of atoms is shown in Fig. 1 and selected geometrical parameters are listed in Table 2. The geometry (bond lengths, angles and planarity) of the tricyclic pyrazolotetrazolotriazine skeleton is very similar in **8a** and previously reported related structure of 7-methyl-5-phenyl-1*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine [5]. The molecule of **8a** has a planar conformation as a whole. The pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine ring is planar to within 0.016(1) Å. The methyl substituents lie almost in the plane of this ring with the displacements of 0.075(2) Å for C13 and 0.016(2) Å for C14. The N–N and N–C bond lengths are in the ranges 1.3167–1.3615 and 1.3237–1.3830 Å, respectively, and they have the values intermediate between expected single- and double-bond lengths characteristic for π-electron system.

Table 2
Bond lengths (Å) and angles (°) for **8a**

N(1)–C(6)	1.3256(16)	N(8)–C(9)	1.3406(17)
N(1)–N(2)	1.3348(15)	N(8)–C(14)	1.4571(17)
N(2)–N(12)	1.3441(15)	N(10)–N(11)	1.3362(19)
N(2)–C(3)	1.3830(17)	N(10)–C(3)	1.3406(17)
N(4)–C(5)	1.3237(16)	N(11)–N(12)	1.3167(19)
N(4)–C(3)	1.3330(17)	C(5)–C(9)	1.4109(17)
N(7)–C(6)	1.3459(16)	C(5)–C(6)	1.4518(17)
N(7)–N(8)	1.3615(16)	C(9)–C(13)	1.4779(19)
C(6)–N(1)–N(2)	109.45(11)	N(4)–C(3)–N(10)	130.05(13)
N(1)–N(2)–N(12)	122.84(11)	N(4)–C(3)-N(2)	123.05(11)
N(1)–N(2)–C(3)	127.94(11)	N(10)–C(3)–N(2)	106.90(11)
N(12)–N(2)–C(3)	109.22(11)	N(4)–C(5)–C(9)	131.23(11)
C(5)–N(4)–C(3)	111.64(11)	N(4)–C(5)–C(6)	124.18(11)
C(6)–N(7)–N(8)	102.38(10)	C(9)–C(5)–C(6)	104.59(10)
C(9)–N(8)–N(7)	117.15(11)	N(1)–C(6)–N(7)	124.67(12)
C(9)–N(8)–C(14)	125.21(13)	N(1)–C(6)–C(5)	123.72(11)
N(7)–N(8)–C(14)	117.64(12)	N(7)–C(6)–C(5)	111.61(11)
N(11)–N(10)–C(3)	105.86(12)	N(8)–C(9)–C(5)	104.27(11)
N(12)–N(11)–N(10)	113.23(12)	N(8)–C(9)–C(13)	125.35(12)
N(11)–N(12)–N(2)	104.79(12)	C(5)–C(9)–C(13)	130.33(12)

There are no classical hydrogen bonds present in the crystal structure of **8a**. The molecular packing in the crystal (Fig. 2) is influenced by the van der Waals forces and presence of week π–π interactions. The pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine systems belonging to the inversion related molecules partially overlap each other with the shortest intermolecular contact 3.385(2) Å [symmetry code: (i) = $-x, -y, -z$].

3.2. Theoretical calculations results

According to the definition comprised in [17], "mesomeric betaines are neutral compounds that can exclusively be formulated as dipolar structures, in which the positive and negative charges are delocalized within a common π-electron system. They posses an even number of positive and negative charges and no uncharged covalent structure can be drawn". The molecule of the title 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine **8a** fulfils all requirements for mesomeric betaine structure. The pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine ring system is fully aromatic with 14 π-electrons. The small differentiation of the bond lengths in the tricyclic ring system obtained from X-ray investigation makes impossible precise localization of the positive and negative charges on the atoms and indicates on the delocalization of these charges within π-electron system. The net charge on the atoms, the molecular electrostatic potential (MEP) distribution in the plane of the molecule and the position of the vector of dipole moment calculated using AM1 semiempirical method show that negative charge is mainly delocalized on the N atoms of the triazine and tetrazole rings, while the positive charge is distributed in the pyrazole ring area (Fig. 3).

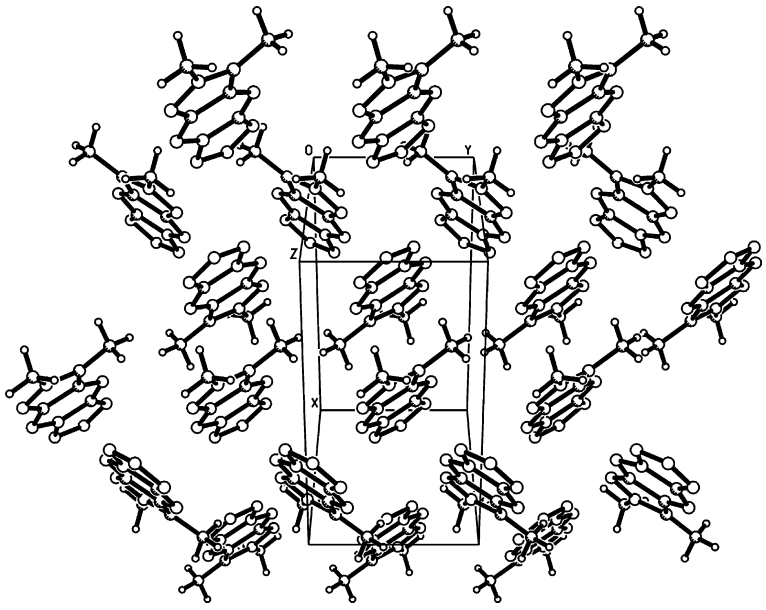


Fig. 2. Unit-cell packing in crystal of **8a**.

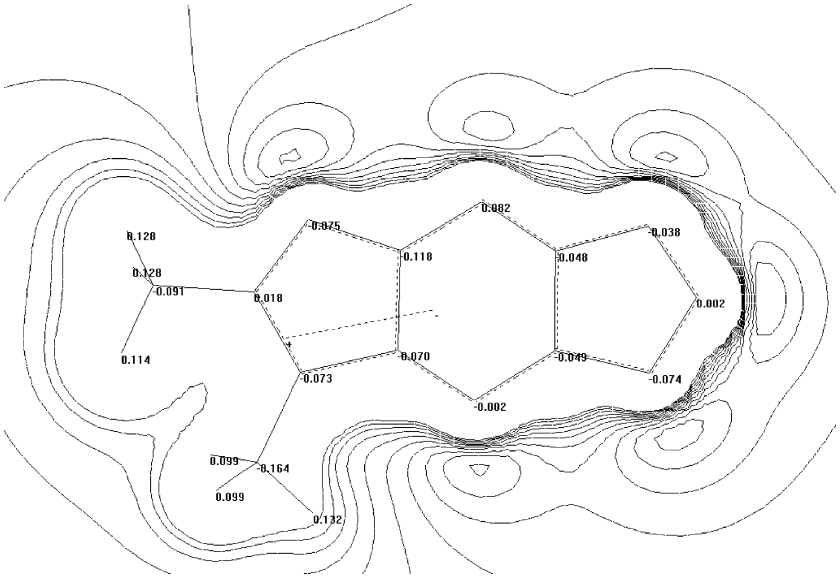
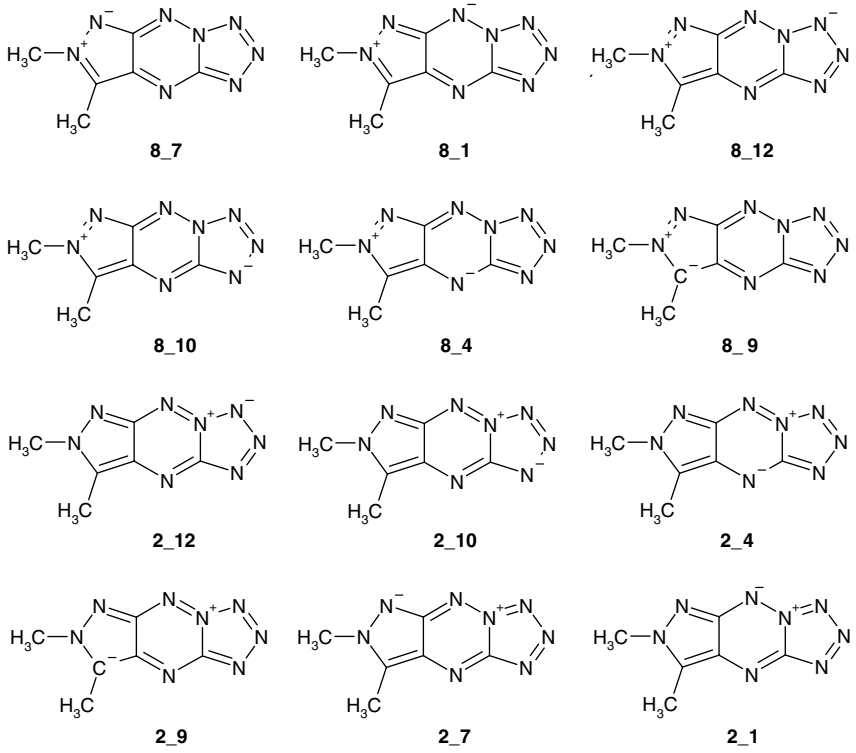


Fig. 3. Net charge distribution on the atoms (e), MEP distribution in the plane of the fused tricyclic system (starting value: −0.12 eV, step: 0.02 eV) and dipole moment vector (10.14 D) calculated for **8a** (AM1 approximation).

There are twelve possible dipolar canonical structures for the analysed molecule **8a**, indicated on Scheme 3 as **n_m**, where **n** and **m** are the atoms numbers with positive and negative charges, respectively. One can see that the positive charge occurs only at N2 or N8 atoms, while the negative one can be localized in both causes at N1, N4, N7, C9, N10 and N12 atoms. No common atoms for the delocalization of the positive and negative charge exist. Thus, the 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine **8a** may be classified as cross-conjugated mesomeric betaine CCMB [17].

The energy minimization and geometry optimization for all canonical structures of the molecule **8a** were performed using the molecular mechanics method. The strain energy (E_i) for each structure was calculated and the percentage (p_i) of it in the hybrid mesomeric betaine structure was estimated using a non-generate Boltzmann distribution (Table 3). As it can be seen from Table 3, the ratio of the contributions of the canonical forms positive charged on N2 and N8 atoms is about 9:1 with clear predomination of two canonical forms **2_1** and **2_4** exceeding 70%. This result is to be expected, because the intramolecular ring closure of the azido group in **7** into N-2 atom leading to **8a** should give rise to charge migration mainly in the tetrazolotriazine part of the molecule retaining the aromatic sextet of π-electrons in pyrazole ring. Similar effects are observed



Scheme 3.

Table 3
The strain energy (E_i, MMX molecular mechanics approximation) and percentage (p_i) for **m_n** canonical forms of molecule **8a**

Canonical form	E_i (kJ mol^{-1})	p_i (%)
8_7	155.54	0.29
8_1	152.11	1.26
8_12	154.16	0.54
8_10	155.16	0.36
8_4	149.17	4.20
8_9	155.12	0.37
2_12	149.72	3.36
2_10	150.85	2.11
2_4	144.28	31.35
2_9	149.97	3.03
2_7	146.41	13.09
2_1	143.69	39.97

in angular [1,2,4]triazolo[3,4-c][1,2,4]benzotriazines and linear [1,2,4]triazolo[4,3-b][1,2,4]benzotriazines, where the equilibrium between angular and linear isomers goes via antiaromatic diazirines involving charge migration in the heterocyclic rings area in the acting mechanism of valence bond isomerization [18].

4. Conclusion

In this paper, we have proved that the linearly fused 6,7-dimethyl-2*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine **8a** is obtained from cyclization of an azido group into N-2 atom of 5-azido-2,3-dimethyl-2*H*-pyrazolo[4,3-*e*][1,2,4]triazine **7**. The molecule **8a** has the mesomeric betaine structure of CCMB type. Among twelve possible dipolar canonical forms of **8a** those with positive charge on N2 atom give predominant contribution to the mesomeric betaine structure providing for charge migration in the area of the tetrazolotriazine part of **8a**. The structure of **8a** was established by X-ray crystallography.

5. Supplementary materials

CCDC-603862 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

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