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INTERACTION OF 1,5-DISUBSTITUTED 3-METHYL-2-OXO-2,3-DIHYDRO-1*H*-IMIDAZOLE-4-CARBONITRILES WITH HYDROGEN SULFIDE

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The reaction of 1-alkyl(aryl)-5-alkyl(aryl)amino-3-methyl-2-oxo-2,3-dihydro-1H-imidazole-4-carbonitriles with hydrogen sulfide was investigated. Unexpectedly, this led, after treatment of the reaction products with triethyl orthoformate, to 1,2,4-dithiazol-5-ylidene-5-thioxoimidazolidin-2-one derivatives.

Keywords: dithiazoles, 3-methylimidazol-2-ones, hydrogen sulfide, triethyl orthoformate.

We have shown previously that the interaction of substituted 2-oxo-2,3-dihydro-1*H*-imidazole-4-carbonitriles **1** with hydrogen sulfide in pyridine formed the corresponding thioamides – prospective starting materials for the preparation of analogs of purine bases [1]. The *N*-methyl derivatives **2** react with hydrogen sulfide in a different manner: the reaction does not stop at the stage of forming the expected thioamides **3** or their prototropic isomers **4**, but produce a complex mixture of eleven products, among which are basically (~50%) the 1-R-3-methyl-2-oxo-5-thioxoimidazolidine-4-carbothioamides **5**. Their presence in the reaction mixture was determined by chromato-mass spectrometry: compound **5a** (R_f 0.44, *m/z* 280 $[M+1]^+$); compound **5b** (R_f 0.36, *m/z* 266 $[M+1]^+$); compound **5c** (R_f 0.42, *m/z* 280 $[M+1]^+$). Similar conversion of *N*-substituted imine fragments into thioxy groups by reaction of sulfuring agents has been reported previously in the literature [2, 3]. We did not succeed in isolating compounds **5a–c** in the pure state, but on heating the mixture of the products obtained with sulfuring agents in the presence of triethyl orthoformate derivatives of 1,2,4-dithiazol-3-ylidene **6a–c** were obtained in moderate yields.

The composition and structure of compounds **6a–c** were confirmed by elemental analysis, IR spectroscopy, mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and X-ray crystallography (compound **6a**). The C=O stretching frequencies at ν 1701–1717 cm^{-1} were characteristic for compounds **6a–c.** The H-5' singlet of the

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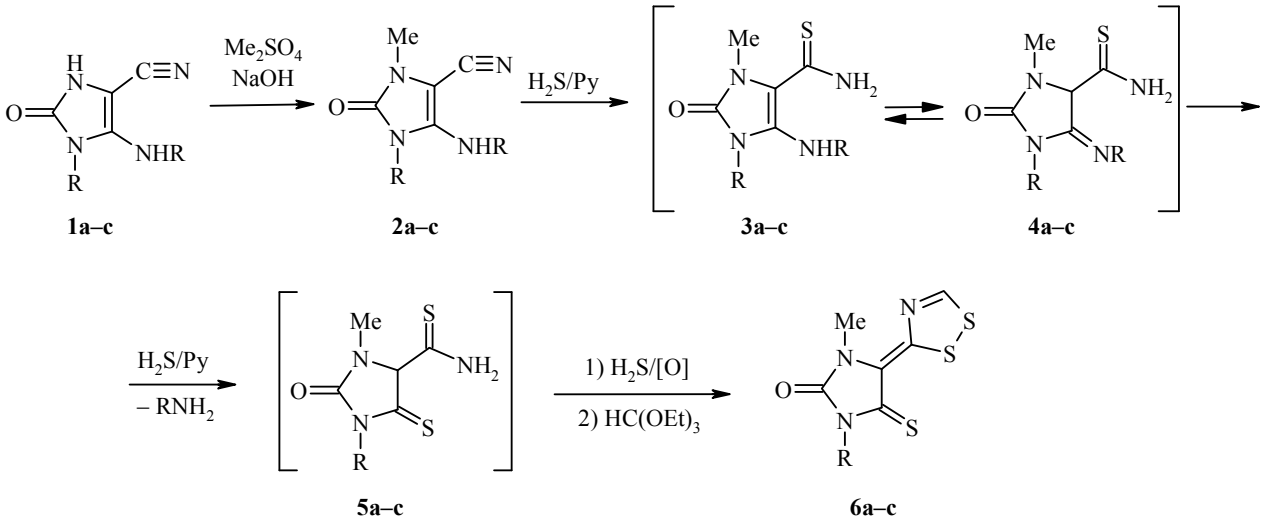
dithiazolylidene unit at δ 9.81–9.86 and the NMe group at δ 3.67–3.73 ppm were present in the ^{1}H NMR spectra. The NMR spectra and the TLC results indicated the presence of a single geometric isomer in the reaction products **6a–c**.



1a–c **2a–c** **3a–c** **4a–c** **5a–c** **6a–c**

1–6 a R = Bn, **b** R = Ph, **c** R = 4-MeC_6H_4

To examine the spatial structure of products **6a–c** we carried out an X-ray crystallographic study of compound **6a** (Fig. 1). The central N(1)–N(2)–C(1-3) five-membered heterocycle is planar with in limits of 0.05 Å, and the distribution of bond lengths and valence angles (Table 1) indicates the conjugation of the nonbonded electron pair of atoms N(1) and N(2) with the π-system of the bonds C=O, C=S, and C=C in the heterocycle. Thus the sums of the valence angles at the nitrogen atoms are equal to 360°, whereas all of the formally single C–C and C–N bonds within the ring are considerably shortened in comparison with standard values for single bonds, which indicates the delocalization of the electron density within bonds of the heterocycle. Very similar geometric characteristics were found previously for 5-benzylidene-3-methyl-1-phenyl-1,3-diazacyclopentan-2-one-4-thione [4], but in the compound we have studied the C(2)–C(3) bond is shortened by 0.06 Å which is apparently connected to stabilization of the structure by secondary interactions. The dithiazole heterocycle is actually coplanar with the central 5-membered ring because of effective conjugation. In the structure of molecule **6a**, intramolecular attractive interaction between atom S(1) of the dithiazole ring and atom S(3) to a distance of 2.802 Å is to be observed that is characteristic of similar systems [5].

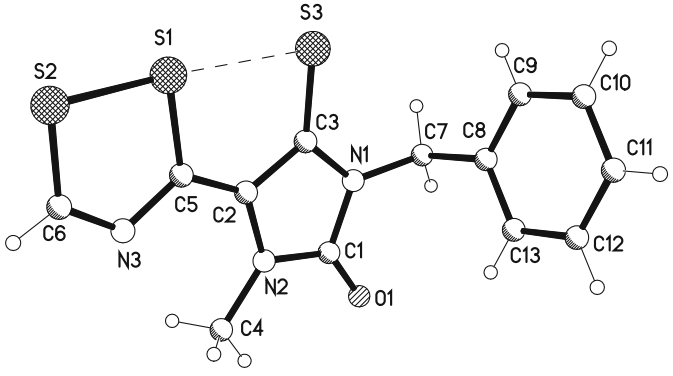


Fig. 1 Overall form of compound **6a** molecule

TABLE 1. Basic Bond Lengths (*l*) and Valence Angles (ω) in Compound **6a**

Basic valence lengths	*l*, Å	Bond angles	ω, deg
C(1)–N(1)	1.399(3)	N(2)–C(1)–N(1)	106.6(2)
C(3)–N(1)	1.369(3)	C(3)–N(1)–C(1)	110.2(2)
C(1)–N(2)	1.360(3)	C(1)–N(2)–C(2)	109.6(2)
C(2)–N(2)	1.405(3)	N(1)–C(3)–C(2)	106.8(2)
C(2)–C(3)	1.411(3)	N(2)–C(2)–C(3)	106.8(2)
C(3)–S(3)	1.665(2)	N(1)–C(3)–S(3)	127.0(2)
C(2)–C(5)	1.372(3)	C(2)–C(3)–S(3)	126.23(19)
C(5)–N(3)	1.362(3)	C(6)–N(3)–C(5)	115.7(2)
C(6)–N(3)	1.286(3)	N(3)–C(5)–S(1)	117.69(18)
C(5)-S(1)	1.778(2)	C(2)–C(5)–S(1)	120.09(19)
C(6)–S(2)	1.707(3)	N(3)–C(6)–S(2)	122.1(2)
S(1)–S(2)	2.1055(10)	C(5)–S(1)–S(2)	91.56(9)
S(1)···S(3)	2.802(1)	C(6)–S(2)–S(1)	92.93(10)
		S(2)–S(1)···S(3)	176.6(2)

The combination in one molecule of the pharmacophoric dithiazolylidene [6, 7] and 5-thioxoimidazolidin-2-one [8] fragments makes the compounds **6a–c** potential objects for exploration as bioregulators for various effects.

EXPERIMENTAL

IR spectra of KBr tablets were recorded on a Vertex-70 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AVANCE DRX-500 instrument (500 and 125 MHz respectively) in DMSO-d_6 solutions with TMS as internal standard. Chromato-mass spectra were obtained with a high-resolution Agilent 1100 liquid chromatograph equipped with a diode matrix and a mass selective detector (Agilent LC/MSD SL). Parameters of the chromato-mass analysis: column Zorbax SB-C18 1.8 μm, 4.6×15 mm (PN 821975-932); solvents: A – acetonitrile–water, 95:5, 0.1% trifluoroacetic acid, B – 0.1% trifluoroacetic acid; eluent flow 3 ml/min; injection volume – 1 μl; UV detectors – 215, 254, 285 nm; method of ionization – chemical ionization at atmospheric pressure (APCI), scanning range *m/z* 80–1000. Melting points measured with Fisher-Johns apparatus.

1-Benzyl(phenyl)-5-benzyl(phenyl)amino-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazole-4-carbonitriles 2a,b were prepared by method [1].

3-Methyl-1-(4-methylphenyl)-5-[(4-methylphenyl)amino]-2-oxo-2,3-dihydro-1*H*-imidazole-4-carbonitrile (2c) was prepared analogously to compounds **2a,b.** Yield 70%; mp 173–175°C. IR spectrum, ν, cm^{-1}: 1698 C=O (band with shoulder), 2206 (CN), 3026–3212 (NH). ^{1}H NMR spectrum, δ, ppm: 2.32 (3H, s, CH_3); 2.41 (3H, s, CH_3); 3.33 (3H, s, NCH_3); 6.96–7.41 (8H, m, H Ar); 8.21 (1H, s, NH). Mass spectrum, *m/z*: 319 $[M+1]^+$. Found, %: C 71.49; H 5.58; N 17.69. $C_{19}H_{18}N_4O$. Calculated, %: C 71.68; H 5.70; N 17.60.

(4*E*)-1-R-4-(3*H*-1,2,4-Dithiazol-3-ylidene)-3-methyl-5-thioxoimidazolidin-2-ones 6a–c (General Method). The corresponding compound **2a–c** (5 mmol) was dissolved in a mixture of pyridine (10 ml) and triethylamine (1 ml), a rapid flow of hydrogen sulfide was passed in for 1 h, the mixture was stirred for 2 h at 20–25°C, water (50 ml) was added and the mixture was extracted with dichloromethane (3×10 ml). The dichloromethane was evaporated in vacuum and the oil formed was dissolved in triethyl orthoformate (10 ml), boiled for 4 h, the precipitate formed was filtered off, washed with diethyl ether and recrystallized from dioxane.

(4*E*)-1-Benzyl-4-(3*H*-1,2,4-dithiazol-3-ylidene)-3-methyl-5-thioxoimidazolidin-2-one (6a). Yield 41%; mp 178–180°C. R_f 0.69. IR spectrum, ν, cm^{-1}: 1494, 1568, 1701 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.67

(3H, s, NCH_3); 5.06 (2H, s, CH_2); 7.25–7.43 (5H, m, H Ph); 9.81 (1H, s H-5'). ^{13}C NMR spectrum, δ, ppm: 39.5, 45.8, 126.1, 128.08, 128.12, 129.0, 136.2, 153.7, 159.9, 171.0, 171.4. Mass spectrum, *m/z*: 322 $[M+1]^+$. Found, %: C 48.67; H 3.51; N 13.21; S 30.07. $C_{13}H_{11}N_3OS_3$. Calculated, %: C 48.57; H 3.45; N 13.07; S 29.93.

(4*E*)-4-(3*H*-1,2,4-Dithiazol-3-ylidene)-3-methyl-1-phenyl-5-thioxoimidazolidin-2-one (6b). Yield 35%; mp 219–221°C. R_f 0.63. IR spectrum, ν, cm^{-1}: 1309, 1399, 1421, 1488, 1565, 1717 (C=O). ^1H NMR spectrum, δ, ppm: 3.73 (3H, s, NCH_3); 7.45–7.58 (5H, m, H Ph); 9.85 (1H, s, H-5'). ^{13}C NMR spectrum, δ, ppm: 31.5, 116.1, 127.6, 128.5, 130.5, 137.1, 153.8, 160.1, 171.2, 171.5. Mass spectrum, *m/z*: 308 $[M+1]^+$. Found, %: C 46.72; H 2.84; N 13.56; S 31.45. $C_{12}H_9N_3OS_3$. Calculated, %: C 46.88; H 2.95; N 13.67; S 31.29.

(4*E*)-4-(3*H*-1,2,4-Dithiazol-3-yliden)-3-methyl-1-(4-methylphenyl)-5-thioxoimidazolidin-2-one (6c). Yield 37%; mp 221–223°C. R_f 0.65. IR spectrum, ν, cm^{-1}: 1403, 1421, 1488, 1518, 1568, 1716 (C=O). ^1H NMR spectrum, δ, ppm: 2.40 (3H, s, CH_3); 3.73 (3H, s, NCH_3); 7.29 (4H, s, H Ar); 9.86 (1H, s, H-5'). ^{13}C NMR spectrum, δ, ppm: 39.4, 39.5, 126.6, 127.8, 130.3, 132.1, 139.0, 153.3, 160.3, 171.2, 171.3. Mass spectrum, *m/z*: 322 $[M+1]^+$. Found, %: C 48.61; H 3.29; N 13.15; S 29.84. $C_{13}H_{11}N_3OS_3$. Calculated, %: C 48.57; H 3.45; N 13.07; S 29.92.

X-Ray structural study of a monocrystal of compound 6a with dimensions 0.06×0.22×0.28 mm at room temperature using a Bruker Apex II diffractometer (λ MoKα radiation, graphite monochromator, θ_{max} 26.31°, segment of the sphere $-8 \le h \le 13$, $-9 \le k \le 8$, $-21 \le l \le 22$). 7857 reflections were collected of which 2809 were independent (average *R* factor 0.0367). Absorptions were correlated using the SADABS program using the multiscanning method (T_{min}/T_{max} = 0.8659/0.9689). The crystal of compound **6a** was monoclinic, space group $P2_1/c$, a = 10.5041(8), b = 7.2532(4), c = 18.3171(10) Å, β = 93.701(4)°, V = 1392.64(15) $Å^3$, Z = 4, d_c = 1.533, μ = 0.530 mm^{-1}, F(000) 664. The structure was solved by direct method with refinement by least squares analysis in the full matrix anisotropic approximation using the SHELXS97 and SHELXL97 programs [9, 10]. Hydrogen atoms were found and refined isotropically. In the refinement 1980 reflections with $I > 2\sigma(I)$ were used, 225 refined parameters, number of reflections per parameter 8.8, the weighting scheme used was $\omega = 1[\sigma^2(Fo^2) + (0.0289P)^2 + 0.5289P]$ where $P = (Fo^2 + 2Fc^2)/3$, the ratio of the maximal (average) shift to the error in the last cycle 0.041(0.002). The final values of the divergence factors for reflections with $I > 2\sigma(I)$, $R_1(F) = 0.0384$, $wR_2(F^2) = 0.0743$, $R_1(F) = 0.0694$, $wR_2(F^2) = 0.0867$, *GOOF* 1.02 for all independent reflections. The residual electron density from the difference Fourier after the last cycle of refinement were 0.23 and –0.25e/$Å^3$. The results of the X-ray crystallographic study have been deposited in the Cambridge Crystallographic Data Center (deposit CCDC 805442).

REFERENCES

1. S. A. Chumachenko, O. V. Shablykin, A. P. Kozachenko, T. V. Osadchuk, and V. S. Brovarets, *Khim. Geterotsikl. Soedin.,* 410 (2011). [*Chem. Heterocycl. Comp.,* **47**, 410 (2011)].
2. E. Ziegler, C. Mayer, and J. G. Zwainz, *Z. Naturforsch.,* **30b**, 760 (1975).
3. L. Skrzypek, *Heterocycles*, **51**, 2111 (1999).
4. J. P. Declercq, G. Germain, M. van Meerssche, J. A. Falmagne, S. D. Carter, and L. Ghosez, *Bull Soc. Chim. Belge,* **89**, 661 (1980).
5. H. Graubaum, G. Lutze, and M. Ramm, *Phosphorus, Sulfur, Silicon, Relat. Elem.,* **84**, 83 (1993).
6. T. Raj, R. K. Bhatia, R. K. Sharma, V. Gupta, D. Sharma, and M. P. S. Ishar, *Eur. J. Med. Chem.,* **44**, 3209 (2009).
7. T. Raj, R. K. Bhatia, A. Kapur, M. Sharma, A. K. Saxena, and M. P. S. Ishar, *Eur. J. Med. Chem.,* **45**, 790 (2010).
8. A. M. Sh. El-Sharief and Z. Moussa, *Eur. J. Med. Chem.,* **44**, 4315 (2009).
9. G. M. Sheldrick, *SHELXS97. Program for Crystal Structure Solution,* Göttingen, Germany, 1997.
10. G. M. Sheldrick, *SHELXL97. Program for Crystal Structures Refinement,* Göttingen, Germany, 1997.