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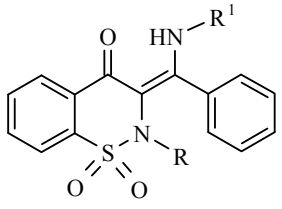
AZOMETHYNE DERIVATIVES OF 1,3-BENZOTHIAZINE 1,1-DIOXIDE

O. Yu. Korshunov[1], E. V. Sennikova[1]*, K. A. Lysenko[2], G. S. Borodkin[1], and A. D. Garnovskii[1]

The Schiff's bases 2-alkyl-4-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxides have been synthesized for the first time, their structures in solution and in the crystalline state and their ability to form complexes have been investigated. The unusual condensation reaction of 1,2-benzothiazine 1,1-dioxide with ethyl orthoformate and 4-aminoantipyrine has been observed.

Keywords: azomethynes, benzothiazine dioxide, isomers, X-ray structural analysis, tautomerism.

In a continuation of the synthesis, and investigation of the structure and complex-forming ability of azomethyne derivatives of 1,2-benzothiazine 1,1-dioxide **1** [1-3], we have obtained for the first time and characterized Schiff's bases of type **2.**



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R = H, Alk; R^1 = Ar, Het

In distinction from the synthesis of compounds **1** from β-diketones and primary amines, the synthesis of **2** is achieved by condensation of 2-alkyl-4-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxides **3** with primary amines and ethyl orthoformate.

* To whom correspondence should be addressed, e-mail: evsennikova@yandex.ru.

[1]Scientific Research Institute of Physical and Organic Chemistry, Southern Federal University, Rostov-on-Don 344090, Russia.
[2]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 119991, Russia; e-mail: kostya@xray.ineos.ac.ru

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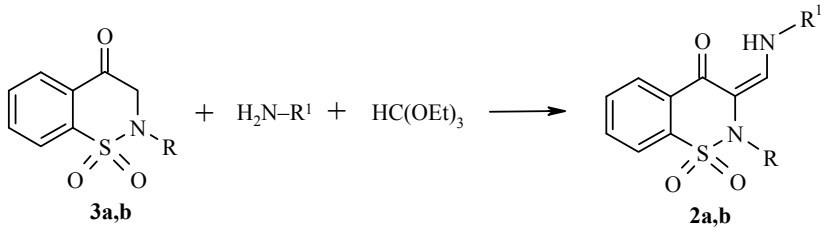
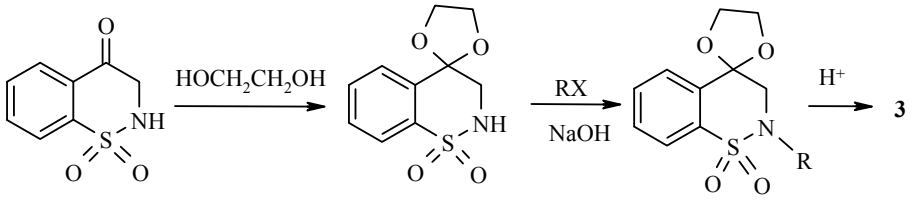
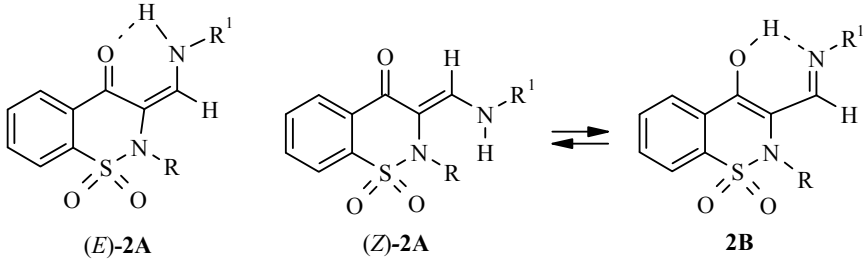


2,3 a R = Me, **b** R = Et; **2 a** R^1 = 4-MeC_6H_4, **b** R^1 = 2-pyridyl

The alkyl-substituted starting materials were obtained *via* three-stage synthesis form 4-oxo-3,4-dihydro-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide.



For the compounds studied in this work the following tautomeric forms are possible: ketoamines with (*E*)/(*Z*)-isomers (**A**) and the enolimines (**B**).



In DMSO solution these azomethynes exist in the form of mixtures of the (*E*)/(*Z*)-isomers of the imino ketone tautomer **2A**, which is in agreement with literature data [6,7]. In the ^{1}H NMR spectrum, the proton signal of the CH group is recorded as two doublets in the 8.11-8.32 ppm region, and the signal of the NH proton appears as two doublets at 10.15 ((*Z*)-isomer) and 12.04 ppm ((*E*)-isomer). Introduction of a pyridine substituent in molecule **2** (R = Et, R^1 = 2-pyridyl) lead to the almost complete disappearance of the (*E*)-isomer in DMSO solution.

With the objective of determining the structure of the molecules in the crystalline state 2-methyl-4-oxo-3-(*p*-tolyl)aminomethylidene-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (**2a**) was studied by X-ray structural analysis.

In the crystalline phase this compound exists in the form of 3-aminomethylene-4-oxo tautomer ((*E*)-isomer). The hydrogen atom localized on the exocyclic nitrogen atom lies in the plane of the basic fragment of the molecule and participates in an intramolecular NH···O hydrogen bond.

The azomethine derivatives obtained form complexes with 3*d* metals.

Very unexpectedly the product of the interaction of 2-ethyl-4-oxo-3,4-dihydro-2H-1,2-benzothiazine-1,1-dioxide (**3b**) with ethyl orthoformate and 4-aminoantipyrine did not form complexes with metals. In its ^{1}H NMR spectrum (DMSO) the signals of the protons of the proposed =CH-NH groups appear as two monoprotonic singlets at 5.91 and 6.44 ppm. The structure of this compound was determined by X-ray structural analysis.

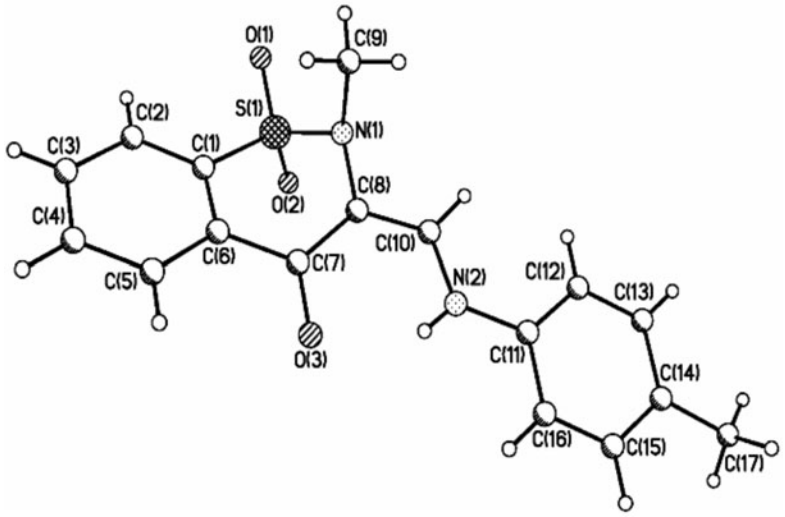


Fig. 1. Structure of 2-methyl-4-oxo-3-(*p*-tolyl)aminomethylidene-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (**2a**).

Table 1. Some Bond Lengths (*d*) and Bond Angles (ω) in Compound **2a**

Bond	*d*, Å	Angle	ω, deg
C(7)–O(3)	1.242	C(7)–C(8)–C(10)	124.14
C(8)–C(10)	1.378	C(8)–C(10)–N(2)	122.79
C(10)–H(10)	0.997	H(10)–C(10)–N(2)	115.97
C(10)–N(2)	1.339	H(2)–N(2)–C(10)	110.49
N(2)–H(2)	0.780		
N(2)–C(11)	1.415		

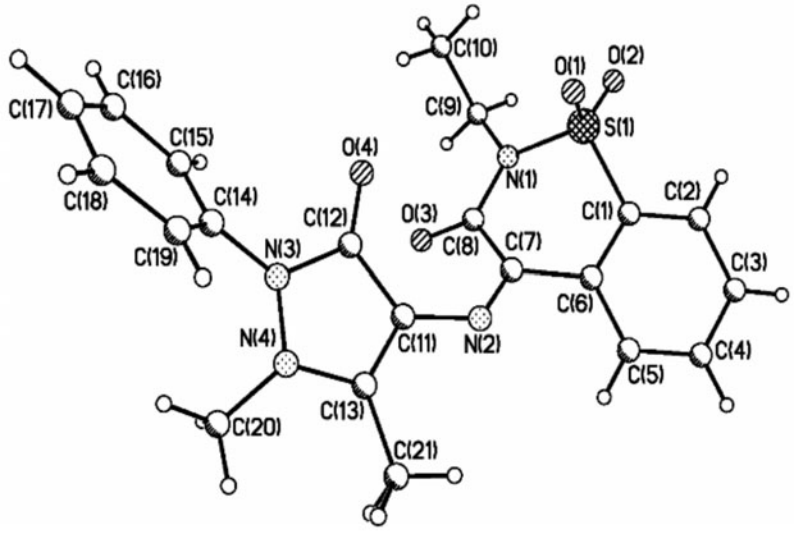
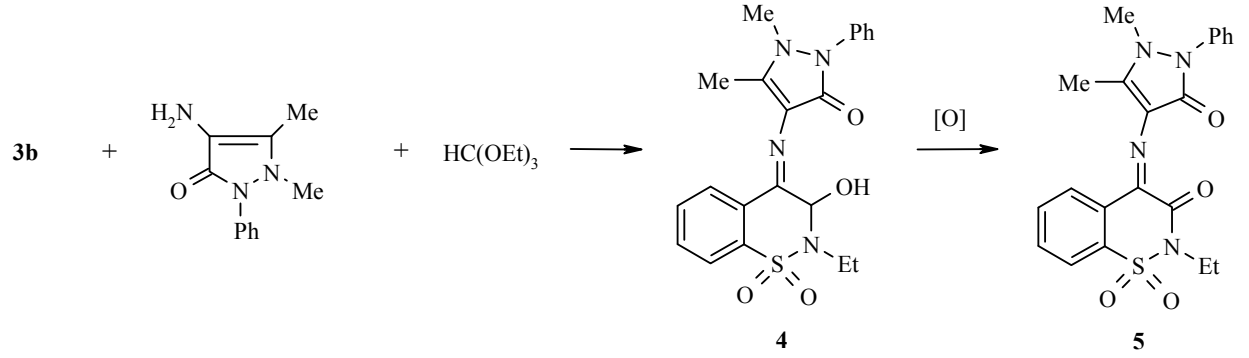


Fig. 2. Structure of 4-(4-antipyryl)imino-2-ethyl-3-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (**5**)

The presence in the ^{1}H NMR spectrum of signals in the 5.91-6.44 ppm region is explained by the fact that the compound **4** formed during the reaction is rapidly oxidized into 4-(4-antipyiryl)imino-2-ethyl-3-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (**5**).

Table 2. Some Bond Lengths (*d*) and Bond Angles (ω) in Compound **5**

Bond	*d*, Å	Angle	ω, deg
C(8)–O(3)	1.213	O(3)–C(8)–C(7)	121.33
C(7)–N(2)	1.284	C(8)–C(7)–N(2)	125.26
C(11)–N(2)	1.375	C(7)–N(2)–C(11)	125.55
C(11)–C(13)	1.371	N(1)–C(8)–O(3)	121.44
C(11)–C(12)	1.462	N(2)–C(11)–C(12)	129.39
C(12)–O(4)	1.227	N(2)–C(11)–C(13)	121.40
		N(2)–C(7)–C(6)	117.61



EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions were recorded with a Varian Unity-300 spectrometer (300 MHz) with the residual protons of the solvent acting as internal standard.

X-ray Crystallographic Studies were carried out with a Bruker AXS Smart 1000 CCD at the Center for X-ray Crystallography (A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences). Structures were solved by direct methods using the SHELX 97 suite of programs [8]. Crystals of 2-methyl-4-oxo-3-(*p*-tolyl)aminomethylidene-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (**2a**) are monoclinic, $C_{17}H_{16}N_2O_3S$, at a temperature of 296 K: a = 15.8385(9), b = 7.6340(4), c = 13.6084(8) Å, β = 114.41(10)°, V = 1498.33(15) Å^3, Z = 4, space group $P2_1/c$, μ(MoKα) = 0.71073 mm^{-1}. Crystals of 4-(4-antipyryl)imino-2-ethyl-3-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (**5**) are monoclinic at a temperature of 102 K: a =15.8125(12), b = 7.7933(5), c = 17.0518(11) Å, β = 108.343(5)°, V = 1994.6 (2) Å^3, Z = 4, space group $P2_1/c$, μ(MoKα) = 0.71073 mm^{-1}.

4-Oxo-3,4-dihydro-2H-1,2-benzothiazine-1,1-dioxide (3, R = H**)** was synthesized by a known method [9].

2-Alkyl-substituted 4-oxo-3,4-dihydro H-1,2-Benzopthiazine 1,1-Dioxides 3a,b (General Method). A mixture of 4-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (0.1 mol), ethylene glycol (0.5 mol), and *p*-toluenesulfonic acid (0.001 mol) in toluene (50 ml) was boiled for 6 h with azeotropic removal of water. The precipitate of the ethyleneketal of 4-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1dioxide was filtered off and washed with methanol. It was dissolved in DMF (30 ml) and finely dispersed NaOH was added, the mixture was stirred for 1 h at 50°, cooled to room temperature and a 1.2-fold excess of methyl iodide or ethyl bromide was added. The reaction mixture was kept at room temperature for 24 h and poured into water. The precipitate was filtered off, washed with water and methanol and dissolved in a mixture of methanol (50 ml) and 9% HCl (50 ml). The mixture was boiled with removal of the solvent until the mixture became turbid, cooled, and the precipitate was filtered off.

2-Methyl-4-oxo-3,4-dihydro-2H-1,2-benzothiazine-1,1-dioxide (3a). Yield 55%; mp 107°C [10].

2-Ethyl-4-oxo-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (3b). Yield 55%; mp 84°C [10].

Synthesis of the Azomethynes 2a,b and 5 (General Method). A suspension of the corresponding methylene-active compound (0.01 mol), triethyl orthoformate (0.01 mol), and the amine (0.01 mol) in ethylene glycol (10 ml) was heated at 150°C until the distillation of ethanol became stopped, then the temperature was raised to 180°C and kept there for 20 min. After cooling, the precipitate was filtered off and washed with methanol.

2-Methyl-4-oxo-3-(*p*-tolyl)aminomethylidene-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (2a). Yield 55%; mp 180°C (MeCN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97 (3H, s, CH_3); 2.4 (3H, s, CH_3); 7.12-8.26 (8H, m, Ar); 8.11 and 8.32 (combined 1H, both d, *J* = 13.0 and *J* = 13.1, =C<u>H</u>NH); 10.15 and 12.06 (combined 1H, both d, *J* = 14.5 and *J* = 12.9, NH). Found, %: C 61.19; H 4.31; N 8.79. $C_{16}H_{14}N_2O_3S$. Calculated, %: C 61.13; H 4.49; N 8.91.

2-Ethyl-3-(2-pyridyl)aminomethyliden-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide (2b). Yield 48%; mp 205°C (MeOH–MeCN mixture). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 3.26 (2H, quin., *J* = 7.2, $C\underline{H}_2CH_3$); 7.01 (1H, dd, ^3J = 6.7, ^4J = 1.8, H-5 pyridine); 7.31 (1H, d, *J* = 8.2, H-3 pyridine); 7.68 (1H, m, H-4 pyridine); 7.79-8.18 (4H, m, Ar); 8.32 (1H, dd, ^3J = 4.8, ^4J = 1.3, H-6 pyridine); 9.02 (1H, d, *J* =13.0, =C<u>H</u>NH); 10.52 (1H, d, *J* = 13.0, =CHN<u>H</u>). Found, %: C 59.02; H 4.40; N 8.60. $C_{16}H_{15}N_2O_3S$. Calculated, %: C 58.36; H 4.60; N 8.50.

4-(4-Antipyryl)imino-2-ethyl-3-oxo-3,4-dihydro-2H-1,2-benzothiaxine 1,1-dioxide (5). Yield 45%; mp 198°C. Initial ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 (3H, t, *J* = 8.1, $CH_2C\underline{H}_3$); 2.11 (3H, s, CH_3); 3.12 (3H, s, CH_3); 3.47 (2H, quin., *J* = 8.1, $C\underline{H}_2CH_3$); 5.92 (1H, s, =C<u>H</u>OH); 6.43 (1H, s, OH); 7.19-7.89 (9H, m, Ar). Found, %: C 59.06; H 5.26; N 13.02. $C_{21}H_{22}N_4O_4S$. Calculated, %: C 59.14; H 5.20; N 13.14.

^{1}H NMR spectrum after standing for 3 h in DMSO-d_6 solution, δ, ppm (*J*, Hz): 0.96 (3H, t, *J* = 8.1, $CH_2C\underline{H}_3$); 2.24 (3H, s, CH_3); 2.87 (3H, s, CH_3); 3.62 (2H, q, *J* = 8.1, $C\underline{H}_2CH_3$); 7.21-7.96 (9H, m, Ar). Found, %: C 59.36; H 4.68; N 13.24. $C_{21}H_{20}N_4O_4S$. Calculated, %: C 59.42; H 4.75; N 13.20.

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