INFLUENCE OF SUBSTITUENTS IN SALICYLALDEHYDE MOLECULE ON INTERACTION WITH 2-IMINO-3,5-DIMETHYLTHIAZOLIDINE

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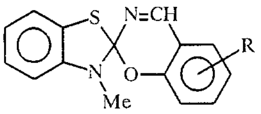
Salicylaldehyde, 5-chlorosalicylaldehyde, or o-vanillin will react with 2-imino-3,5-dimethylthiazolidine to form previously unknown bis(3,5-dimethylthiazolidin-2-ylideneamino)-2-hydroxyphenylmethanes. If strong electron-acceptor groups are present on the aromatic ring, an acid–base interaction takes place. Thus, 3-nitro-5-methoxy-, 3-nitro-5-chloro-, and 3-bromo-5-nitrosalicylaldehyde react with the heterocyclic base to form saltlike complexes, the structure of which has been confirmed by x-ray diffraction.

In recent years, the attention of investigators engaged in the search for new photochromic substances has been attracted to spiro-1,4-oxazines, which, in contrast to spiropyrans [1], are highly resistant to aging [2]. Also, the synthesis of spiro-1,3-oxazines of the type of (I), through the condensation of 2-imino-3-methylbenzothiazoline with aromatic o-hydroxyaldehydes, has been described in a patent [3]. However, nothing was said about photochromic properties of these compounds.



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In view of this background, we undertook the synthesis of spiro-1,3-oxazines (II) from 2-imino-3,5-dimethylthiazolidine (III) and salicylaldehydes (IVa-f). Another factor in choosing the heterocycle III was the possibility of finding new biologically active substances, since it is known that derivatives of this compound have radiation-protective [4] and insecticidal [5] properties, are transferase inhibitors [6], and have been recommended for use in the treatment of diabetes [7].

Our studies showed that the thiazolidine III with salicylaldehyde, 5-chlorosalicylaldehyde, or o-vanillin (IVa-c) forms bisthiazolidine structures (Va-c). When the nitrosalicylaldehydes IVd-f are used in the reaction, saltlike complexes of the type of VI are recovered. A nitro group in the salicylaldehyde molecule apparently changes the character of the interaction with the heterocyclic base by strengthening the acidity of the phenolic hydroxyl, so that the interaction between the original components is entirely of the acid–base type. It has also been established that compounds VId, e, upon heating in chloroform, can be converted to the bisthiazolidine derivatives Vd, e, which again form the original compounds VId, e upon cooling.

The structures of the substances that we obtained were established on the basis of ^{1}H and ^{13}C NMR spectra, IR spectra, elemental analysis, and x-ray structure analysis.

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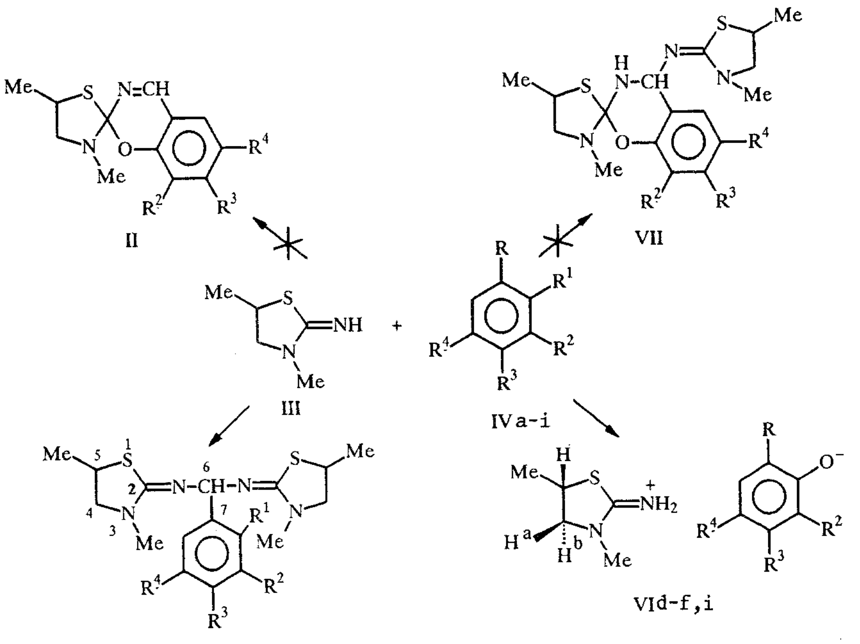

Va-e,g,h

Va-e,g,h, VId-f, and ia-h R = CHO; a-f,i $R^1 = OH$; a $R^2 = R^3 = R^4 = H$; b $R^2 = OCH_3$, $R^3 = R^4 = H$; c $R^2 = R^3 = H$, $R^4 = Cl$; d $R^2 = NO_2$, $R^3 = H$, $R^4 = OCH_3$; e $R^2 = NO_2$, $R^3 = H$, $R^4 = Cl$; f $R^2 = Br$, $R^3 = H$, $R^4 = NO_2$; g $R^1 = R^2 = R^3 = R^4 = H$; h $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$; i $R = R^2 = R^4 = NO_2$, $R^3 = H$

In the PMR spectra of compounds Va-e (Table 1), there are two doublets of C-methyl groups of the thiazolidine fragments at ~ 1.4 ppm with $J_{CH3,H} = 5.9\text{-}6.6$ Hz, and also two singlets of N-methyl groups at ~ 3 ppm. The signal of the proton of the =N−CH group is located in the 5.24-5.43 ppm region. The doubling of signals of the protons of the heterocycles is difficult to determine, in view of their multiplicity (in Table 1 we have listed shifts for the centers of gravity of the multiplets). The phenolic hydroxyl is coupled by intramolecular hydrogen bonding, apparently with both nitrogen atoms of the C=N fragments at once, under the condition of rapid rotation of the phenol ring around the simple C−C bond, as evidenced by the presence of a broadened signal at ~ 11 ppm.

In the ^{13}C NMR spectrum of compound Vb (see Experimental section) there are unresolved, broadened, double-intensity signals of C-methyl and N-methyl groups, signals of the methoxy-substituted phenol ring, and also paired signals of carbon atoms of $CH-CH_2$ and C=N groups and the sp^3-hybridized carbon atom $C_{(6)}$ (δ = 86.90 and 87.04 ppm). The doubling of signals of the thiazolidine rings of the compounds V that is detected by means of ^1H and ^{13}C NMR spectra, in combination with the doubling of the signal of the $C_{(6)}$ atom in the ^{13}C NMR spectrum, evidently cannot be attributed to nonequivalence of the two heterorings in V, but rather to the simultaneous existence of these substances in the form of an equimolar mixture of geometric isomers with different orientation (E, Z) of the two thiazolidine fragments relative to the C=N bonds.

According to [2], heterocyclic methylene bases can interact with salicylaldehydes to form products consisting of two molecules of the base and one molecule of the aldehyde — so-called dicondensed spirodihydropyrans. In our case as well, there is a possibility of obtaining "dicondensed" spiro compounds with the structure of VII, isomeric with the bis-products V. However, evidence in favor of formation of the bis-products, apart from the NMR data we have already discussed, may be found in the closeness of values of the chemical shifts of protons of the $N-CH_3$ groups of the original base III and the products V, including those obtained by condensation of the thiazolidine III with benzaldehyde and anisaldehyde, i.e., compounds Vg and Vh respectively, for which closure of the spiro ring is impossible, owing to the absence of OH groups (see Tables 1 and 2). Let us also note that the formation of compounds of the type of VII should be accompanied by an upfield shift (by about 0.2 ppm) of the signal of the N-methyl group of the heterocyclic fragment containing the spiro carbon atom [8] — but no such shift is observed in the present case. Additional evidence for the structure V is the closeness of values of the chemical shifts of carbon atoms of the C=N groups in the ^{13}C NMR spectra of compound Vb (δ = 159.84, 160.01 ppm) and the base III (δ = 164.5 ppm; see Experimental section).

In the IR spectra of the compounds V there are bands corresponding to absorption by the C=N group at 1640-1670 cm^{-1} and associated hydroxyls at 3000-3200 cm^{-1}.

TABLE 1. Characteristics of Compounds Va-e, g, h

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm ($CDCl_3$)										Yield, %
			C—CH_3	N—CH_3	4-H^a, 4-H^B	5-H	6-H	8-R^1	9-R^2	10-R^3	11-R^4	12-H	
Va	$C_{17}H_{24}N_4OS_2$	175...177	1,40, 1,44	2,91, 2,92	3,1, 3,7	3,5	5,27	11,09	6,83	7,11	6,74	7,16	43
Vb	$C_{18}H_{26}N_4O_2S_2$	185...190	1,41, 1,44	2,92, 2,93	3,1, 3,7	3,6	5,31	11,46	3,85		6,7...6,8		43
Vc	$C_{17}H_{22}ClN_4OS_2$	170...172	1,43, 1,45	2,92, 2,93	3,1, 3,7	3,6	5,24	11,10	6,75	7,05	—	7,13	25
Vd	$C_{18}H_{25}N_5O_4S_2$	165...167	1,42, 1,45	2,94, 2,95	3,1, 3,7	3,6	5,40	~10,3*	—	7,35	3,78	7,20	45
Ve	$C_{17}H_{22}ClN_5O_3S$	—	1,46	2,99, 3,00	3,2,	3,5...3,9	5,43	~9,0*	—	7,95	—	~7,2	—
Vg	$C_{17}H_{24}N_4S_2$	167...169	1,38, 1,42	2,94, 2,95	3,0, 3,7	3,5	5,18	7,51		7,2...7,3		7,51	52
Vh	$C_{18}H_{26}N_4OS_2$	140...143	1,41	2,95	3,1, 3,7	3,5	5,15	7,45	6,83	3,78	6,83	7,45	48

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*Compound Vd, and to a greater degree Ve, are present in a mixture with the salts VId and VIe; as a result, a common exchange signal of OH and $=N^+H_2$ is observed; also, owing to the presence of the o-nitro group, an equilibrium is possible between the two H-chelate forms OH...N=C and OH...ONO.

TABLE 2. Characteristics of Salts VId-f, i, and also 2-Imino-3,5-dimethylthiazolidine III

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm ($CDCl_3$)								Yield, %
			C—CH_3	N—CH_3	4-H^a, 4-H^B	5-H	$=N^+H_2(=NH)$	CHO	4'-H	6'-H	
VId*	$C_{13}H_{17}N_3O_5S$	124...126	1,44	3,02	3,30, 3,76	3,76	8,71	10,46	7,84	7,68	51
VIe^{2*}	$C_{12}H_{14}ClN_3O_4S$	118...119	1,47	3,15	3,48, 3,93	3,85	8,64	10,40	8,14	7,84	63
VIf	$C_{12}H_{14}BrN_3O_4S$	169...170	1,46	3,05	3,33, 3,79	3,79	—^{3*}	9,99	8,52	8,65	84
VIi	$C_{11}H_{13}N_5O_7S$	173...174	1,60	3,44	3,72, 4,17	4,08	—^{3*}	—	8,99	8,99	65
III	$C_5H_{10}N_2S$	—	1,43	2,92	3,22, 3,63	3,75	5,67	—	—	—	32

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*δ_{OCH3} = 3.86 ppm.

*SSCC: $J_{CH3,5\text{-}H}$ = 6.58 Hz; $J_{4\text{-}H^a,5\text{-}H}$ = 4.75 Hz; $J_{4\text{-}H^b,5\text{-}H}$ = 7.31 Hz; $J_{4\text{-}H^a,4\text{-}H^b}$ = 10.60 Hz. Similar SSCC values observed for all VI compounds.

*No signal detected, owing to poor solubility of compound.

TABLE 3. Coordinates of Atoms and Structure of VIII*

Atom	x	y	z	Atom	x	y	z
$S_{(1)}$	0,2748(1)	0,0305(6)	0,8248(3)	$H_{(2)}$	0,357(2)	0,062(2)	1,137(2)
$N_{(1)}$	0,2220(2)	-0,015(2)	1,0219(7)	$H_{(3)}$	0,328(1)	0,092(2)	0,901(2)
$N_{(2)}$	0,2918(2)	0,016(2)	1,1148(7)	$H_{(4)}$	0,393(2)	0,0000(0)	0,858(2)
$C_{(1)}$	0,2609(2)	-0,018(2)	1,0022(8)	$H_{(4.1)}$	0,356(2)	0,096(2)	0,826(2)
$C_{(2)}$	0,3328(7)	-0,024(2)	1,0710(9)	$H_{(5)}$	0,316(2)	0,001(2)	0,343(2)
$C_{(3)}$	0,3273(4)	0,006(2)	0,900(1)	$H_{(5.1)}$	0,258(1)	0,0000(0)	0,250(2)
$C_{(4)}$	0,3577(3)	0,005(2)	0,807(1)	$H_{(6)}$	0,505(1)	0,000(2)	0,912(2)
$C_{(5)}$	0,2886(3)	0,022(2)	1,2774(8)	$H_{(7)}$	0,114(2)	-0,001(2)	0,293(2)
$O_{(1)}$	0,0341(2)	-0,021(2)	0,3482(6)	$H_{(9)}$	0,050(2)	-0,001(2)	0,619(2)
$O_{(2)}$	0,0679(3)	0,108(1)	0,8835(8)	$H_{(12)}$	0,206(1)	-0,000(2)	0,519(2)
$O_{(3)}$	0,1272(2)	-0,012(2)	0,9527(6)	$H_{(13)}$	0,016(2)	0,0000(0)	0,144(2)
$O_{(4)}$	0,1789(2)	0,002(2)	0,7459(6)	$H_{(131)}$	0,450(2)	0,424(2)	-0,137(2)
$O_{(5)}$	0,1875(2)	-0,006(2)	0,3048(6)	Molecules of water and chloroform (without H atoms)			
$N_{(3)}$	0,1004(2)	-0,013(2)	0,8546(7)	$O_{(6)}$	0,4685(8)	-0,030(2)	0,055(2)
$C_{(6)}$	0,1448(2)	0,007(2)	0,4943(7)	$C_{(14)}$	0,4624(3)	0,004(2)	0,479(1)
$C_{(7)}$	0,1087(2)	-0,013(2)	0,3921(8)	$Cl_{(1)}$	0,3910(2)	0,010(2)	0,427(1)
$C_{(8)}$	0,0715(2)	-0,012(2)	0,4406(8)	$Cl_{(2)}$	0,4245(6)	-0,042(2)	0,240(2)
$C_{(9)}$	0,0701(2)	-0,007(2)	0,5912(8)	$Cl_{(3)}$	0,4806(7)	-0,037(2)	0,854(2)
$C_{(10)}$	0,1056(2)	-0,004(2)	0,6975(8)	$Cl_{(4)}$	0,4637(6)	-0,031(2)	0,306(2)
$C_{(11)}$	0,1453(2)	0,009(2)	0,6532(8)	$Cl_{(5)}$	0,5021(7)	-0,038(2)	0,431(1)
$C_{(12)}$	0,1835(2)	-0,009(2)	0,4372(9)	$Cl_{(6)}$	0,4607(7)	-0,018(2)	0,672(2)
$C_{(13)}$	0,0355(3)	-0,017(2)	0,1944(9)	$Cl_{(7)}$	0,5034(6)	-0,028(2)	0,277(2)
$H_{(1)}$	0,219(1)	0,001(2)	1,122(2)	$Cl_{(8)}$	0,4222(6)	0,000(2)	0,528(2)
$H_{(1,1)}$	0,195(2)	0,000(2)	0,919(2)	$Cl_{(9)}$	0,4287(6)	0,006(2)	0,378(2)

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*Populations (m) of crystallographic positions of all atoms of the salt amount to 0.5 m (06) = 0.25; each chlorine atom in the molecule is disordered among three positions; therefore, m ($Cl_{(1)}$ – $Cl_{(9)}$) = 0.166.

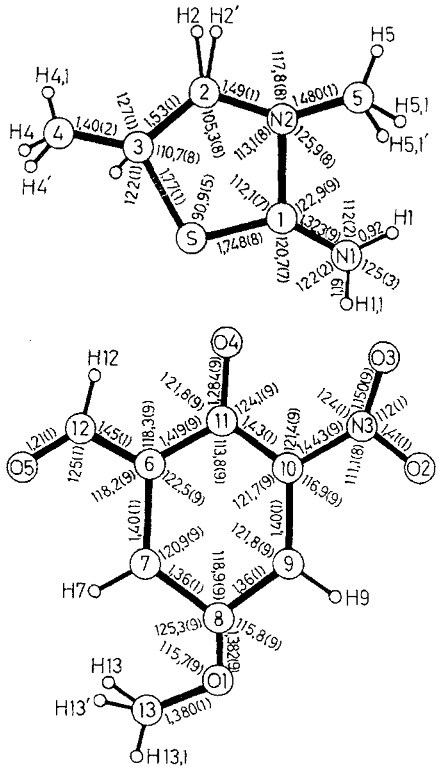

Fig. 1. Structure of salt VId.

The structure of VId — the product of interaction of 2-imino-3,5-dimethylthiazolidine III with 3-nitro-5-methoxysalicylaldehyde — was established on the basis of PMR data (see Table 2) and the results of an x-ray structure analysis of its crystal solvate VIII (see Fig. 1 and Table 3). This substance is a salt, formed as a result of proton transfer from the hydroxyl group of the aldehyde to the imino group of the base. The conformations of the cation and the anion are planar; they are positioned in a disordered manner close to the mirror plane of symmetry (space group C 2/m). In the crystal structure of VId, the ions form a chain-layered packing through two types of hydrogen bonds. A strong hydrogen bond $N_{(1)}-H_{(1.1)}...O_{(4)}$ is realized between the protonated imino group and the negatively charged oxygen atom of the anion. The distance $H_{(1.1)}...O_{(4)}$ is 1.54 Å, and the angle $N_{(1)}-H_{(1.1)}...O_{(4)}$ is 167°. A weaker hydrogen bond $N_{(1)}-H_{(1)}...O_{(5)}$ is formed by the carbonyl group of the anion and the cation of a neighboring molecule, which is translationally identical to the first. The distance $H_{(1)}...O_{(5)}$ is 1.93 Å, and the angle $N_{(1)}-H_{(1)}...O_{(5)}$ is 170°.

In the PMR spectra of the salts based on 3-nitro-5-methoxy-, 3-nitro-5-chloro-, and 3-bromo-5-nitrosalicylaldehydes VId-f, the signals of the protons of the N-methyl substituents and the $CH-CH_2$ groups are shifted downfield by ~0.1-0.25 ppm (Table 2). A still greater downfield shift of the protons of these same groups (~0.5 ppm) is observed when the acidity of the OH group is increased in the case of 2-imino-3,5-dimethylthiazolidine picrate VIi.

The bisthiazolidine derivatives Va-c and the salts VId-f have thermochromic properties. Upon melting, they take on a deep color that disappears upon cooling. Compounds Va-c also manifest thermochromic properties in chloroform, ethyl acetate, and acetone solutions.

Thus, in the interaction of 2-imino-3,5-dimethylthiazolidine with salicylaldehydes, either bisthiazolidine derivatives V or salts VI may be formed. The direction of the reaction depends on the electronic character of the substituents in the aldehyde molecule.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded in a Bruker WP-200-SY NMR spectrometer, with TMS as an internal standard. The IR spectra were taken in a Specord IR-75 instrument, in white mineral oil.

The results of elemental analyses of compounds Va-c, g, h and VId-f, i for contents of C, H, Br, N, and S matched the calculated values.

X-ray Structure Analysis of Crystals of VIII. The crystal structure of VIII is formed by the salt VId and molecules of water and chloroform. All of the atoms are disordered relative to the plane m; apart from this, the water molecule is disordered relative to the center of inversion, and each chlorine atom in the chloroform molecule is disordered among three positions. The dark-red flat-needle crystals of VId are monoclinic, a = 33.045(2), b = 6.830(8), c = 8.948(4) Å, β = 98.60(3)°, V = 2004.37 Å^3, Z = 4. $C_{13}H_{17}N_3O_5 \cdot 0.5\,H_2O \cdot CHCl_3$ space group C 2/m, d = 1.524 g/cm^3. The intensities of 1275 independent reflections with $I > 2\sigma(I)$ were measured in a KM-4 automatic four-circle diffractometer (Mo Kα radiation, graphite monochromator, $\Theta/2\Theta$ scanning to Θ_{max} = 10°). The structure was deciphered by the direct method by means of the program SHELX-86 [10]. The coordinates of the hydrogen atoms were determined objectively from a Fourier difference synthesis; the coordinates were refined by the full-matrix least-squares method in the anisotropic approximation for the nonhydrogen atoms and the isotropic approximation for the hydrogen atoms. The coordinates listed in Table 3 correspond to the final values R = 0.078 and R_ω = 0.081.

2-Imino-3,5-dimethylthiazolidine (III) was obtained from allyl thioisocyanate by a method described in [9]. Colorless oil. ^{13}C NMR spectrum ($CDCl_3$): 20.27 (5-CH_3), 32.63 (N$-CH_3$), 37.77 ($C_{(5)}$), 61.16 ($C_{(4)}$), 164.54 ppm ($C_{(2)}$).

Bis(3,5-dimethylthiazolidin-2-ylidenamino)-2-hydroxyphenylmethane (Va). To a solution of 1.17 g (0.009 mole) of the thiazolidine III in 5 ml of heptane, a solution of 1.04 g (0.009 mole) of salicylaldehyde IVa in 15 ml of heptane was added. The mixture was allowed to stand for 3 h at room temperature. The crystalline precipitate of the product Va was filtered off and washed with heptane. Obtained 1.30 g of compound Va.

Analogously, from III and the corresponding substituted salicylaldehydes IVb, c, g, h, obtained bis(3,5-dimethylthiazolidin-2-ylideneamino)arylmethanes Vb, c, g, h; from III and the nitro-substituted aldehydes IVd-f the salts VId-f; and from III and picric acid the picrate of III (VIi). In the synthesis of compounds Vb, c, g, h and VId, e, in place of heptane, absolute benzene was used. ^{13}C NMR spectrum of compound Vb ($CDCl_3$): 19.96 (5-CH_3), 33.76 (N$-CH_3$), 55.71 (O$-CH_3$), 159.84, 160.01 ($C_{(2)}$), 59.75, 59.92 ($C_{(4)}$), 38.27, 38.44 ($C_{(5)}$), 86.90, 87.07 ($C_{(6)}$), 128.77 ($C_{(7)}$), 148.40 ($C_{(8)}$), 146.21 ($C_{(9)}$), 110.46 ($C_{(10)}$), 119.87 ($C_{(11)}$), 117.68 ppm ($C_{(12)}$).

Bis(3,5-dimethylthiazolidin-2-ylideneamino)-2-hydroxy-3-nitro-5-methoxyphenylmethane (Vd). Refluxed 0.10 g (0.31 mmole) of the salt VId in 1 ml of chloroform for 10 min. Then 3 ml of hot heptane was added to the reaction mixture, and the solvent was slowly evaporated at room temperature. The resulting mixture of red crystals of the original salt VId and yellow crystals of the bis-product Vd was sorted by means of tweezers under a microscope. Obtained 0.03 g of compound Vd.

Bis(3,5-dimethylthiazolidin-2-ylideneamino)-2-hydroxy-3-nitro-5-chlorophenylmethane (Ve). Refluxed 0.27 g (0.81 mmole) of the salt VId in 4 ml of chloroform, for 45 min. Then added 7 ml of hot carbon tetrachloride. The crystals that formed upon cooling the reaction mixture were filtered off and washed with carbon tetrachloride, obtaining 0.2 g of a 3:1 mixture of the original salt VIe and the bis-product Ve (determined from the ratio of integral intensities of the signals in the ^{1}H NMR spectrum).

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