RING-CHAIN ISOMERISM OF IMINES OF N-MONOSUBSTITUTED 2-BENZOYLBENZENESULFONAMIDES*

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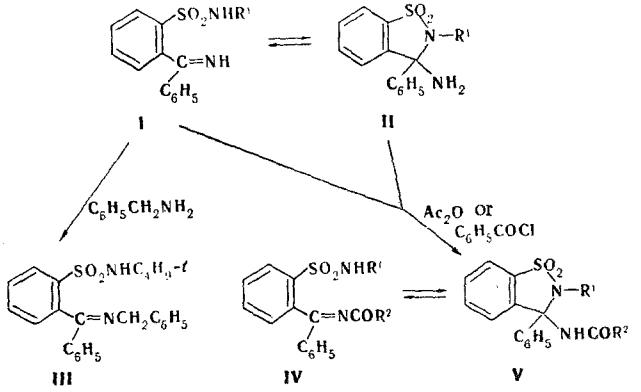
Imines of N-monosubstituted 2-benzoylbenzenesulfonamides or their ring isomers, viz., 3-amino-3-phenylbenzoisothiazoline 1,1-dioxides, were synthesized by condensation of the dilithium derivatives of N-monosubstituted benzenesulfonamides with benzonitrile. Interconversions of the isomers were realized for the N-phenyl derivative. The introduction of bulky isopropyl or tert-butyl substituents at the sulfonamide nitrogen atoms stabilizes the open structure. The ring isomers of the N-acylimines, viz., 3-acylamino-3-phenylbenzoisothiazoline 1,1-dioxides, are formed exclusively in the acylation of both the open and ring isomers.

Little study has been devoted to reactions involving intramolecular nucleophilic addition of a sulfonamido group to the C=N bond [2, 3]. It is known [3] that mixtures of isomeric 2-benzoylbenzenesulfonamide imines (I) and 3-amino-3-phenylbenzoisothiazoline 1,1-dioxides (II) are formed in the condensation of the dilithium derivatives of N-methyl- and N-phenylbenzenesulfonamides with benzonitrile. Open isomer Ib predominates in the case of the anilide, while ring isomer IIa predominates for the N-methylamide.

The aim of the present research was to ascertain the effect of substituents attached to the nitrogen atoms of the sulfonamido and imino groups on the relative stabilities of the open (I, III, and IV) and ring (II and V) isomers formed as a result of intramolecular nucleophilic addition of the sulfonamido N–H group to the C=N bond and to establish the conditions for the interconversions of these isomers.

By condensation of the dilithium derivatives of N-phenyl-, N-benzyl-, N-isopropyl-, and N-tert-butylbenzenesulfonamides with benzonitrile by the method in [3] we obtained, respectively, 2-phenyl- and 2-benzyl-3-amino-3-phenylbenzoisothiazoline 1,1-dioxides (IIb, c) and N-isopropyl- and N-tert-butyl-2-benzoylbenzenesulfonamide imines (Id, e, Table 1).



I, II a $R^1=CH_3$; b $R^1=C_6H_5$; c $R^1=C_6H_5CH_2$; d $R^1=i\text{-}C_3H_7$; e $R^1=t\text{-}C_4H_9$; IV, V a $R^1=C_6H_5$, $R^2=CH_3$; b $R^1=i\text{-}C_3H_7$, $R^2=CH_3$; c $R^1=t\text{-}C_4H_9$, $R^2=CH_3$; d $R^1=R^2=C_6H_5$

In contrast to [3], in which the N-phenyl derivative was obtained in the form of a mixture of isomers Ib and IIb with predominance of open isomer Ib, we obtained ring isomer IIb under the same conditions; this is evidently explained by the ease of the Ib → IIb

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TABLE 1. N-Monosubstituted 2-Benzoylbenzenesulfonamide Imines (Ib, d, e) and 2-Substituted 3-Amino-3-phenylbenzoisothiazoline 1,1-Dioxides (IIb, c)

Compound	mp, °C	IR spectrum (in Nujol), ν, cm^{-1}			Found, %				Empirical formula	Calculated, %				Yield, %
		C=N	SO_2NH	=NH or NH_2	C	H	N	S		C	H	N	S	
Ib	138—140 141,5—143 [3]	1620 sh., 1613	3273	3061	68,0	4,9	8,3	8,0	$C_{19}H_{16}N_2O_2S$	67,8	4,8	8,3	9,5	53
Id*	124—125	1621 sh., 1613	3275	3116	63,5	6,2	9,3	10,7	$C_{16}H_{18}N_2O_2S$	63,6	6,0	9,3	10,6	37
Ie*	99—101	1607	3279	3226	65,1	6,4	8,7	10,4	$C_{17}H_{20}N_2O_2S$	64,5	6,4	8,8	10,1	52
IIb	124—125 127—128 [3]	—	—	3387, 3323	67,9	4,9	8,3	9,2	$C_{19}H_{16}N_2O_2S$	67,8	4,8	8,3	9,5	24
IIc	116—118	—	—	3401, 3324	69,2	5,4	8,2	9,6	$C_{20}H_{18}N_2O_2S$	68,6	5,2	8,0	9,2	13

*PMR spectrum (CD_3OD), ppm: Id: 0.98 [d, J = 6 Hz, 6-H, $(CH_3)_2$] and 7.3-8.1 (m, 9H, aromatic protons); Ie: 1.11 [s, 9H, $(CH_3)_3$] and 7.2-8.1 (m, 9H, aromatic protons).

TABLE 2. 2-Substituted 3-Acylamino-3-phenylbenzoisothiazoline 1,1-Dioxides (Va-d)

Compound	mp, °C	IR spectrum, ν, cm^{-1}					Found, %				Empirical formula	Calculated, %				Yield, %
		in Nujol				in dioxane										
		C=O (amide I)	amide II	N—H		C=O (V)	C=O, C=N (IV)	C	H	N	S		C	H	N	S	
Va	210—211 (dec.)	1698 сл., 1672	1532	3259, 3197 sh		—	1628	66,3	4,8	7,2	8,2	$C_{21}H_{18}N_2O_3S$	66,6	4,8	7,4	8,5	88
Vb*	227—228 (dec.)	1677	1540	3287, 3214 sh		1707	1639	62,7	6,0	8,2	8,3	$C_{18}H_{20}N_2O_3S$	62,8	5,8	8,1	9,3	98
Vc*	208—209	1679	1521	3224, 3210 sh		1710	1640	63,2	6,3	7,2	8,7	$C_{19}H_{22}N_2O_3S$	63,7	6,2	7,8	8,9	98
Vd	204—206	1679	1516	3314, 3204 sh		1693	—	70,9	4,8	6,4	7,0	$C_{26}H_{20}N_2O_3S$	70,9	4,6	6,4	7,3	80

*PMR spectrum (in CD_3OD), ppm: Vb: 1.38 and 1.57 [two doublets, J = 6.8 Hz, 6H, $(CH_3)_2$], 2.03 (s, 3H, $COCH_3$), and 7.2-7.8 (m, 9H, aromatic protons); Vc: 1.47 [s, 9H, $(CH_3)_3$], 2.04 (s, 3H, $COCH_3$), and 7.1-7.8 (m, 9H, aromatic protons).

isomerization. We found that the Ib → IIb isomerization is easily realized by refluxing in an ethanol solution of triethylamine.

Isomerization in the opposite direction (IIb → Ib) proceeds thermally in the case of brief heating of ring isomer IIb to 140°C or even during recrystallization from carbon tetrachloride or ethanol.

We were unable to realize thermal isomerization for the ring isomer of the N-benzyl derivative (IIc → Ic). This difference from the N-phenyl derivative is evidently explained by the fact that the phenyl group reduces the nucleophilicity of the sulfonamide nitrogen atom and stabilizes the open structure [2, p. 174].

The presence of bulky isopropyl and tert-butyl substituents attached to the sulfonamido nitrogen atom stabilizes the open structure. We were unable to realize I → II isomerization for sulfonamides Id, e under alkaline-catalysis conditions.

Both series of isomers are easily identified from their IR spectra: The spectra of the crystalline open isomers I contain a C=N band at 1607-1621 cm^{-1}, a narrow band of a sulfonamido N—H group at ∿3275 cm^{-1}, and a broader band of an imino N—H group at ∿3100 cm^{-1}; a C=N band is absent in the spectra of ring isomers II, but a characteristic doublet of symmetrical and asymmetrical stretching vibrations of an NH_2 group is observed at 3000-3500 cm^{-1} (Table 1).

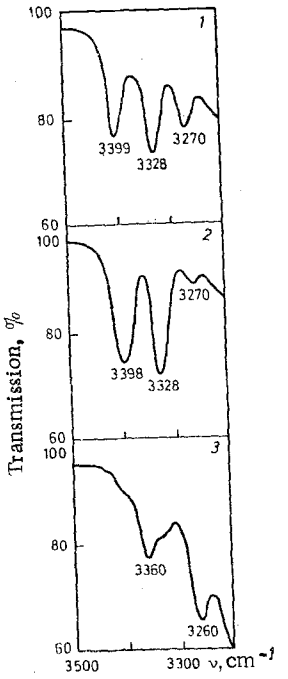

Fig. 1. IR spectra at 3200-3500 cm^{-1} recorded for solutions in methylene chloride (c = 0.1 M, l = 0.62 mm): 1) IIb; 2) IIc; 3) Id.

It is apparent from the IR spectra of Id and IIb, c recorded for solutions in methylene chloride (Fig. 1) that for the N-phenyl derivative and to an even greater extent for the N-benzyl derivative the Ib, c $\rightleftarrows$ IIb equilibria are shifted to favor the ring form (NH_2 bands at 3400 and 3330 cm^{-1}), whereas for N-isopropylsulfonamide Id it is shifted virtually completely to favor the open form (3360 and 3260 cm^{-1}).

In order to introduce substituents at the imine nitrogen atom we studied the transimination of imines Ib, d, e with benzylamine, aniline, and 4-nitroaniline in solutions in ethanol, butanol, and pyridine, as well as in benzene or toluene in the presence of catalytic amounts of p-toluenesulfonic acid. However, we were able to accomplish transimination only when we refluxed a butanol solution of N-tert-butylsulfonamide Ie with benzylamine for 6 h (see [4, 5]). The IR spectrum of N-tert-butyl-2-benzoylbenzenesulfonamide N-benzylimine (III) contains a C=N band at 1621 cm^{-1} and a band of a sulfonamide N–H group at 3309 cm^{-1} which confirm open structure III. In an attempt to accomplish the transimination of sulfanilide Ib by refluxing a solution of it in benzene or toluene with aniline in the presence of p-toluenesulfonic acid we observed Ib → IIb isomerization.

It is curious that N-acyl derivatives with only ring structures (Va-d, Table 2) are formed in the acylation of both open isomers Ib, d, e and ring isomer IIb. The introduction of an electron-acceptor group at the imino nitrogen atom in sulfonamide molecule I increases the electrophilicity of the carbon atom of the C=N bond so much that intramolecular addition of the sulfonamido N–H group to this bond becomes possible even when such bulky substituents as the tert-butyl group are attached to the nitrogen atom. We have previously observed [6] a similar effect of electron-acceptor substituents attached to the keto group during a study of the ring-chain isomerization of N-tert-alkyl-2-aroylbenzamides.

An amide I band at 1680 cm^{-1} (in the spectrum of amide Va this band has a low-intensity high-frequency satellite), an amide II band, and one or two N–H bands are observed in the IR spectra of crystalline 3-acylamino-3-phenylbenzoisothiazoline 1,1-dioxides (Va-d, Table 2). The splitting of the amide I and N–H bands is evidently due to the formation of intermolecular hydrogen bonds in the crystalline state. Only one intense band in the region of the stretching vibrations of double bonds is observed at 1628 cm^{-1} in the IR spectrum of acetamide Va recorded for a solution in dioxane. This band can be assigned to the absorption of C=O and C=N bonds in the conjugated C=N–C=O system (IV) [7]. It is apparent from

the IR spectrum that in dioxane solution the IVa ⇄ Va equilibrium is shifted completely to favor the open form. Bands at 1710 cm^{-1} (amide I in ring isomer V) and 1640 cm^{-1} are observed in the spectra of dioxane solutions of acetamides Vb and Vc, which confirms the existence of the IV ⇄ V equilibrium.

In the case of acetamide Vc we demonstrated that only one high-frequency band at 1704 and 1698 cm^{-1}, respectively, appears in more polar solvents, viz., acetonitrile and dimethyl sulfoxide (DMSO), than dioxane. Consequently, an increase in the polarity of the solvent shifts the equilibrium to favor the ring form.

The spectrum of a dioxane solution of benzamide Vd contains only an amide I band at 1693 cm^{-1} and an amide II band at 1514 cm^{-1}, i.e., under the influence of the more potent electron-acceptor benzoyl group the equilibrium is shifted completely to favor the ring form.

Judging from the PMR spectra, acetamides Vb, c in solution in CD_3OD exist completely in the ring form. The signals of the methyl protons of the tert-butyl or isopropyl group are shifted ∿0.4 ppm to the weaker-field side on passing from the open structure (Id, e) to the ring structure of acetamides Vb, c. We observed a similar shift on passing from N-tert-butyl-2-acylbenzamides to 2-tert-butyl-3-hydroxyisoindolinones [8]. The splitting of the signal of the protons of the $(CH_3)_2$ groups in the spectrum of Vb into two doublets is due to the diastereotopic character of the methyl groups that is associated with the chiral character of the molecule.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in Nujol and hexachlorobutadiene and of solutions in methylene chloride, dioxane, acetonitrile, and DMSO were recorded with a Specord 751R spectrometer. The PMR spectra of solutions in CD_3OD (0.01 mole/liter) were obtained with a Bruker Physik WH-90 DS spectrometer (90 MHz) with hexamethyldisiloxane as the internal standard.

N-Monosubstituted 2-Benzoylbenzenesulfonamide Imines (Id, e) and 2-Substituted 3-Amino-3-phenylbenzoisothiazoline 1,1-Dioxides (IIb, c) (Table 1). The synthesis was carried out at 0°C with constant stirring in solution in freshly distilled (over lithium aluminum hydride) tetrahydrofuran (THF) in an argon atmosphere. A 75-mmole sample of n-butyllithium in ether, prepared by the method in [3], was added in the course of 1 h to a solution of 25 mmole of N-monosubstituted benzenesulfonamide in 50 ml of THF [100 ml of THF in the case of N-(tert-butyl)benzenesulfonamide], and the mixture was allowed to stand for 30 min. A 4.1-ml (40 ml) sample of benzonitrile was then added, and the mixture was allowed to stand for 1 h. A 50-ml sample of 14% hydrochloric acid was then added, and the organic layer was separated and extracted with three 50-ml portions of 14% hydrochloric acid. The hydrochloric acid extracts were neutralized with potassium carbonate and extracted with ether. The ether extracts were dried with magnesium sulfate and evaporated, and the resulting oil was placed in a refrigerator for crystallization. The product was recrystallized from ethanol (Id and IIc), a mixture of benzene with hexane (IIb), or a mixture of ether with hexane (Ie).

The individuality of the compounds was confirmed by thin-layer chromatography (TLC) on Silufol UV-254 plates [elution with ethyl acetate–hexane (3:5)].

N-Phenyl-2-benzoylbenzenesulfonamide Imine (Ib, Table 1). A 0.3-g sample of 3-amino-2,3-diphenylbenzoisothiazoline 1,1-dioxide (IIb) was heated at 140°C for 10 min, after which the mixture was cooled rapidly. The product was recrystallized from a mixture of anhydrous dioxane with hexane.

The Ib → IIb Isomerization. A) A solution of 0.3 g of sulfonamide Ib and 3 ml of triethylamine in 5 ml of ethanol was refluxed for 2 h, after which it was evaporated *in vacuo*, and the resulting oil was treated with 2-3 ml of ethanol, during which it began to crystallize. Ring isomer IIb, with mp 117-118°C, was obtained in 57% yield. The IR spectrum was identical to the spectrum of IIb obtained by the method presented above.

B) A solution of 0.67 g (2 mmole) of sulfonamide Ib, 0.37 ml (4 mmole) of aniline, and catalytic amounts of p-toluenesulfonic acid in 6 ml of anhydrous benzene was refluxed for 2 h, after which it was evaporated *in vacuo*, and the residue was treated with a small amount of ethanol, during which it began to crystallize. Ring isomer IIb, with mp 125-

126°C, was obtained in 79% yield. The IR spectrum was identical to the spectrum of IIb obtained by the method presented above.

N-tert-Butyl-2-benzoylbenzenesulfonamide N-Benzylimine (III). A solution of 0.62 g (2 mmole) of sulfonamide Ie and 0.22 ml (2 mmole) of benzylamine in 20 ml of butanol was refluxed for 6 h, after which it was evaporated *in vacuo*, and the residue was recrystallized from a mixture of anhydrous ether with hexane to give a product with mp 116-117°C in 14% yield. IR spectrum, ν: 1621 (C=N) and 3309 cm^{-1} (N–H). Found: C 71.0; H 6.5; N 7.0; S 7.6%. $C_{24}H_{26}N_2O_2S$. Calculated: C 70.9; H 6.4; N 6.9; S 7.9%.

2-Substituted 3-Acetamido-3-phenylbenzoisothiazoline 1,1-Dioxides (Va-c, Table 2). A 0.1-ml sample of acetic anhydride was added to a hot saturated solution of 1 mmole of the sulfonamide (Ib, d, e) or ring isomer IIb in anhydrous benzene, and the mixture was heated at 100°C until a precipitate developed (1-3 min), after which it was cooled, and the precipitated Va-c were separated.

3-Benzamido-2,3-diphenylbenzoisothiazoline 1,1-Dioxide (Vd, Table 2). A 0.12-ml (1 mmole) sample of benzoyl chloride was added to a solution of 0.34 g (1 mmole) of 3-amino-2,3-diphenylbenzoisothiazoline 1,1-dioxide (IIb) and 0.15 ml (1 mmole) of triethylamine in 4 ml of benzene, and the mixture was maintained at 20°C for 24 h. The precipitate was separated, washed with benzene, dried, and suspended in water. Colorless crystals of Vd were separated.

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