SULFONATION OF SUBSTITUTED AZOLES WITH SULFUR TRIOXIDE IN DICHLOROETHANE

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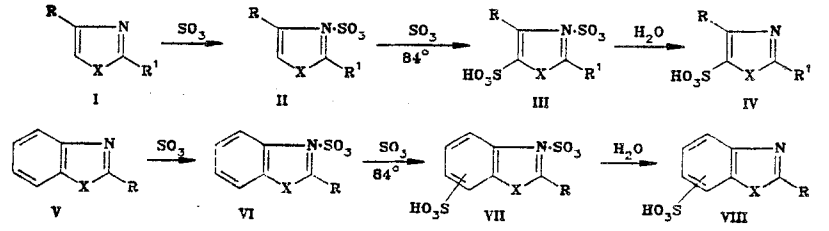
A novel method has been developed for the synthesis of sulfonic acids of five-membered heterocycles containing two heteroatoms, with a solution of sulfur trioxide in 1,2-dichloroethane. High yields of the required products are obtained, under conditions which are mild in comparison with those used in earlier methods. The mechanism of sulfonation is discussed, and some azole·SO_3 complexes have been obtained and described.

Existing methods for the sulfonation of imidazoles and thiazoles are attended by several deficiencies, namely low yields of the sulfonic acids, the severe reaction conditions, and the large excess of sulfonating agent needed. For these reasons, it was of interest to develop new methods for the sulfonation of azoles.

We have examined the reaction of azoles (I) and (V) with a solution of sulfur trioxide in boiling 1,2-dichloroethane. The reaction time varies over a wide range, depending on the reactivity of the substrate. The azolesulfonic acids (IV) and (VIII) were obtained only when at least a threefold excess of sulfur trioxide was used. When the substrate—SO_3 ratio was 1:1 or 1:2, under the above conditions, or under milder conditions, the azole—sulfur trioxide compounds (II) and (VI) were obtained, and could be isolated from the reaction mixtures in high yields. By analogy with other work [10, 11], in which it was shown that compounds of tertiary amines with sulfur trioxide are charge-transfer complexes, and with [12, 13], we also regard compounds (II) and (VI) as complexes. These complexes [(II) and (VI)] are solids which are stable on storage in the absence of moisture, and which have sharp melting points (Table 2). In water, the complexes of thiazoles (IIb-f) and benzothiazole (VIc) decompose to sulfuric acid and the starting materials, but the corresponding imidazole (IIa) and benzimidazole complexes (VIa, b) are quite stable in water, undergoing hydrolysis only on boiling for 5 h. On fusion, complexes (II) and (VI) are converted into the C-sulfonic acids, as when sulfonation was carried out with an excess of sulfur trioxide. The sulfonating activity of (II) and (VI) was examined using a number of substrates which are unstable under severe sulfonating conditions. For example, with complexes (IIb) and (VIc), sylvane was fully sulfonated in 1,2-dichloroethane at 40°, and with (IIb), dextran was fully sulfonated in formamide at 40-45°C.

On the basis of these findings, we consider that the sulfonation of substituted and condensed imidazoles and thiazoles with solutions of sulfur trioxide in aprotic solvents proceeds as follows:



I—IV a X=NH, b—g X=S; a,b R=R¹=H; c R=CH_3, R¹=H; d R=R¹=CH_3; e R=H, R¹=Br; f R=CH_3, R¹=Br; g R=CH_3, R¹=OH; V—VIII a, b X=NH; a R=H; b R=CH_3; c X=S, R=CH_3

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TABLE 1. Literature Methods for the Preparation of Sulfonic Acids (salts) of Thiazoles and Imidazoles

Substrate	Reaction conditions			Position of $-SO_3H$	Yield, %*	Citations
	sulfonating agent	temperature, °C	time, h			
Imidazole	50—60% oleum (fourfold excess)	160	3	4 (5)	83 (barium salt)	[1]
Imidazole	Current SO_3+air	200	2	4 (5)	71	[2]
Benzimidazole	Current SO_3+air	125—180	2	5 (6)	86	[2]
Benzimidazole	20% oleum (20% excess	170—250		5 (6)	—	[3]
Thiazole	20% oleum	170—250		5	—	[4]
2-Bromothiazole	20% oleum	170—250		5	—	[4]
4-Methylthiazole	20% oleum	200		5	—	[5, 6]
2-Bromo-4- methylthiazole	20% oleum	100		5	—	[5, 6]
2,4-Dimethylthiazole	20% oleum	200		5	—	[7]
Benzothiazole	20% oleum	100	4	4, 6, 7	49	[8]

*Yields of most of these compounds are not given in the citations.

The complexes (II) and (VI) formed initially are further sulfonated to (III) and (VII), which on treatment with water are readily hydrolyzed to the sulfonic acids (IV) and (VIII). The presence of complex-bound SO_3 in (III) and (VII) is confirmed by their ability to sulfate alcohols. The formation of sulfonic acids (IV) and (VIII) from the intermediates (III) and (VII) occurs almost instantaneously in all cases. The dichloroethane layer on completion of the reaction contains no SO_3, which is all bound in the solid which separates. Following solution of this solid in water, the aqueous solution contains the sulfonic acids (IV) or (VIII) together with sulfuric acid in an amount corresponding to the SO_3 taken up, as shown by differential titration of the mixtures of sulfonic and sulfuric acids, and the quantitative determination of sulfuric acid as $BaSO_4$. The structures of (IV) and (VIII) were confirmed by IR and PMR spectroscopy. Thus, the IR spectra of the barium salts of sulfonic acids (IV) and (VIII) (Table 3) showed strong absorption for the symmetrical (1050-1110 cm^{-1}) and asymmetrical stretching vibrations (1170-1205 cm^{-1}) of the SO_2 group, and S—O vibrations at 610-680 cm^{-1}. The PMR spectra of these salts contain no signals for a proton attached to carbon in the 5-position of thiazoles, the 4(5)-position of imidazoles, or the 5(6)-positions of benzimidazoles.

Sulfonation of 2-hydroxy-4-methylthiazole takes place very rapidly, and it was not possible to isolate the intermediate complex, in contrast to unsubstituted thiazole, which did not give a sulfonic acid under these conditions. Sulfonation of 2-methylbenzothiazole gave two isomeric sulfonic acids, the positions of the sulfonic acid groups in which have not yet been established.

The use of standard methods of electronic spectroscopy did not lead to any unambiguous conclusions as to the structures of these compounds, since the presence of the sulfonic acid group has little effect on their electronic absorption spectra. However, the addition of the sulfo-group changes the shape of the molecule, as shown by linear dichroism (LD) studies [14-17]. This method has been used to show differences in the structures of complexes and sulfonic acids in the case of benzimidazole (Va), 5(6)-benzimidazolesulfonic acid (VIIIa), benzimidazole·sulfur trioxide (VIa), and 2-methyl-5(6)-benzimidazolesulfonic acid (VIIIb).

The spectrum of (Va) (Fig. 1a) consists of three absorption bands, and is analogous to that reported in [22]. The first long-wavelength band (285-260 nm) results from the superposition of two systems of electron-vibratory transitions, and the second is seen at 260-240 nm. In the shorter wavelength region there are, to judge from the spectral course of the dichroism, at least two electronic transitions of different polarization in the molecule. The introduction of a sulfo-group into (Va) [compound (VIIIa)] results spectroscopically in a small bathochromic shift of all the absorption bands, by "leveling out" of the vibratory structure (Fig. 1b) and improvement of the orientation of the molecules in the polymer matrix. In the spectrum of the complex (VIa), the positions of the absorption maxima are identical with those in the spectrum of (Va), but the intensity of the absorption at 285-260 nm is reduced. According to the LD spectra, the orientation of the molecules of complex (VIa) in extended films is poorer than with the sulfonic acid (VIIIa). It appears that the addition of the sulfo-group to the azole molecules increases its extension (since the C—S bond is in the

TABLE 2. Properties of Azole–Sulfur Trioxide Complexes

Compound*	T_{mp}, °C	ν, cm^{-1}			Found, %				Empirical formula	Calculated, %				Yield, %
		SO_2		S–O	C	H	N	S		C	H	N	S	
		as	*s*											
IIb	119–121	1160	1060	580	21,1	2,1	8,2	39,4	$C_3H_3NO_3S_2$	21,8	1,8	8,5	38,7	94
IIc	93–96	1150	1050	680	—	—	—	—	$C_4H_5NO_3S_2$	26,8	2,7	7,8	35,8	82
IId	139–141	1170	1030	590	29,7	4,0	6,6	32,1	$C_5H_7NO_3S_2$	31,0	3,6	7,2	33,1	63**
IIe	—	1180	1040	570	—	—	—	—	$C_2H_2BrNO_3S_2$	14,7	0,8	5,7	26,2	73
IIf	—	1165	1065	580	—	—	—	—	$C_4H_4BrNO_3S_2$	18,6	1,6	5,4	24,8	94
VIb	192–194	1175	1040	720	45,8	3,9	13,5	15,0	$C_8H_8N_2O_3S$	45,2	3,7	13,2	15,0	89
VIc	165–167	1150	1045	590	42,0	3,9	6,1	28,2	$C_8H_8NO_3S_2$	41,9	3,1	6,1	27,9	92

*The elemental composition of (IIc, e, f) and the melting points of (IIe, f) are not given as a result of their high hygroscopicity.
**Yield on sulfur trioxide (substrate in threefold excess).

TABLE 3. Properties of Barium Salts of (IVc-g) and (VIIIa-c)

Compound	Sulfonation time, h	T_{mp}, °C (decomp.)	ν, cm^{-1}			UV spectrum, λ_{max}, nm (log ε) in H_2O	PMR spectrum, δ, ppm*	Found, %				Empirical formula	Calculated, %				Yield, %
			SO_2		S–O			C	H	N	S		C	H	N	S	
			as	*s*													
IVc	5	215	1180	1110	650	246 (3,91)	8,92 (2-H); 2,59 (CH_3)	19,8	1,7	5,2	26,3	$C_8H_8BaN_2O_6S_4$	19,5	1,6	5,6	26,0	95
IVd	5,8	257	1205	1050	685	248 (4,00)	2,62 (2-CH_3); 2,52 (4-CH_3)	23,2	2,8	5,0	24,1	$C_{10}H_{12}BaN_2O_6S_4$	23,0	2,3	5,3	24,6	70
IVe	4	235	1170	1060	610	256 (4,03)	6,64 (4-H)	11,8	0,8	4,0	20,1	$C_6H_2BaBr_2N_2O_6S_4$	11,5	0,3	4,5	20,5	38
IVf	4	233	1180	1085	680	261 (3,99)	1,22 (CH_3)	14,0	1,2	4,4	19,0	$C_8H_6BaBr_2N_2O_6S_4$	14,7	0,9	4,1	19,6	35
IVg	0,5	203	1200	1050	670	252 (3,99)	2,32 (4-H)	18,4	1,8	5,8	24,5	$C_8H_6BaN_2O_6S_4$	18,2	1,5	5,3	24,3	97
VIIIa	2	>300	1160	1060	680	252 (3,93), 276 (3,82)	8,22 (2-H)	32,1	2,2	10,3	12,6	$C_{14}H_{10}BaN_4O_6S_2$	31,6	1,9	10,5	12,0	60
VIIIb	4	>300	1175	1095	680	250 (3,85), 280 (3,88)	2,28 (CH_3); 8,13 (4-H)	34,4	2,7	10,3	11,6	$C_{16}H_{14}BaN_4O_6S_2$	34,3	2,5	10,0	11,4	85
VIIIc**	2	>300	1180	1125	620	256 (4,26), 286 (3,56), 296 (3,45)	3,02 (CH_3); 2,98 (CH_3)	33,0	2,8	4,4	20,8	$C_{16}H_{12}BaN_2O_6S_4$	32,4	2,0	4,7	21,6	83

*Singlet signals given. In the PMR spectrum of (VIIIa), the doublet signals for the 4-H and 7-H protons are seen at 8.42 and 7.58 ppm, J_{46} = 4.0, J_{76} = 9.0 Hz, and the quartet for the 6-H proton at 7.91 ppm, J_{64} = 4.0, J_{67} = 9.0 Hz. In the spectrum of (VIIIb), the doublet signal for the 6-H and 7-H protons lies at 7.88 ppm, J_{67} = 5.0 Hz. In the case of (VIIIc), only the signals for the methyl groups in the mixture are shown.
**Mixture of isomeric products.

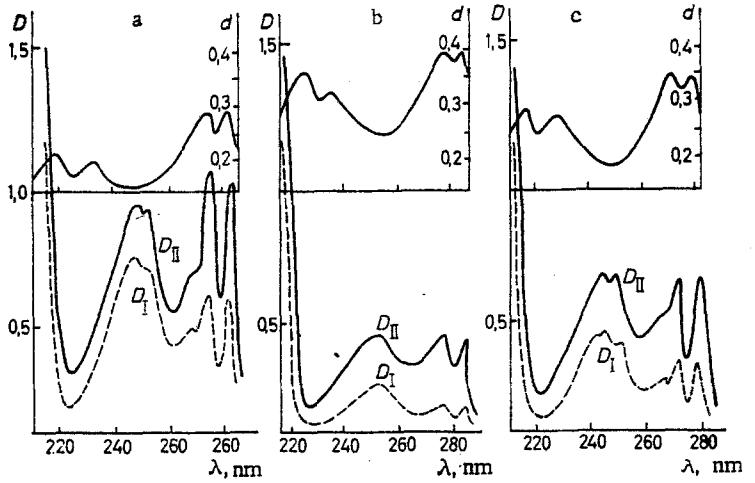


Fig. 1. Absorption spectra in polarized light, and dichroism spectra: a) benzimidazole (Va), b) 5(6)-benzimidazolesulfonic acid (VIIIa), c) benzimidazole·sulfur trioxide (VIa).

TABLE 4. Orientation and Polarization Parameters for Electronic Transitions in Molecules (Va), (VIa), and (VIIIa, b)*

Molecule	Orientational parameters*					Transition	λ, nm	d	β°	φ_1°	φ_2°
	S	c_1, nm	B	C	φ_0°						
Va	1,29	0,835	0,63	0,91	−15	I	274	0,28	36	21	−51
						II	246	0,12	49	44	−77
						III	220	0,21	<46	31	−61
						IV	~214	~0,17	~>52	~37	~−67
VIIIa	1,545	1,02	0,74	0,965	−17	I	276	0,37	35	18	−52
						II	250	0,23	48	31	−65
						III	228	0,35	38	21	−55
						IV	220	0,30	~>44	27	−61
VIIIb	1,70	1,44	0,745	0,95	−17	I	278	0,41	32	15	−49
						II	250	0,26	44	27	−61
						III	236	0,31	39	22	−56
						IV	224	0,21	>48	31	−65
VIa**	1,38	0,99	0,66	0,945	−36	I	273	0,30	40	4	−104
						II	246	0,17	55	11	−89
						III	220	0,18	54	18	−90
						IV	215	0,21	51	15	−93

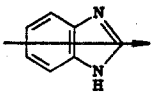
*For (Va), (VIa), and (VIIIa, b), A = 0.905.
**The shape factor, orientation parameters, and angle φ_0 were calculated for the hypothetical planar structure of the complex (VIa').

same plane as the aromatic ring), and improves the orientation of the molecules in the film, as is seen from the increase in the dichroism values for all the absorption bands. The much poorer orientation of the molecules of complex (VIa) in the extended film gives grounds for supposing that in this instance the N–S bonds are not disposed in the plane of the aromatic ring. We have made a similar suggestion previously [9], on the basis of the PMR spectra.

In order to resolve this problem, quantitative calculations were also carried out for the polarization of the electronic transitions, using structural models [14-16], which take into account the dependence of the orientational distribution of the molecules in the film on their shapes (Table 4). According to the structural model, the orientational distribution of the molecules introduced into the extended polymer films is governed by the degree of orientation of the "structural elements" in the polymer, consisting of straightened and mutually parallel segments of the molecules relative to the axis of extension, described by the parameter A, and also by the packing of the introduced molecules within the "structural elements" of the polymer. The latter is governed by the anisotropic forces between the inserted molecules and the macromolecule segments, and is dependent on the shapes and sizes of the molecules introduced. This packing is defined by parameters B and C. Parameter B de-

fines the orientation of the molecules by their long axes, and parameter C the orientation of their planes parallel to the axes of the "structural elements" of the polymer. Parameter B is largely dependent on the shape (degree of extension) of the introduced molecules. A measure of the extension of the molecules is provided by the "shape factor" $s = c_1/b_1$. This is the ratio of the length of the flat molecule c_1 to its width b_1, obtained from the Stewart molecular model [18] taking into account the bond lengths, valence angles, and effective spheres of all the atoms. The validity of the use of structural models in similar molecules has been confirmed experimentally [19-21], including studies of the effects of sulfogroups on the orientation of sulfoanthraquinones [19].

According to [14-16], the position of the molecular axis of orientation of compounds is given by the angle φ_0 with the preferred axis, firmly attached to the molecular skeleton. For the present molecules, this axis passes through atom $C_{(2)}$ of the heterocycle:



The angle between the directions of the moments of the electronic transitions and the preferred axis $\varphi_{1,2} = \varphi_0 \pm \beta$, where β is the angle between the direction of the transition moment and the molecular axis of orientation, as calculated by the expression given in [15].

The angles φ_0 and φ are read off relative to the preferred axis in the present compounds against a clock hand. If the change in dichroism is due solely to a change in the shape of the molecules, not to their spectra, then calculation must give the same angles for the analogous electronic transitions in the different molecules for all the compounds. This reasoning was confirmed by calculating the directed moments of the electronic transitions using a structural model, as shown in Table 4 for compounds in which the appropriate molecular fragment in (Va), (VIIIa), and (VIIIb) is planar.

If, however, the N–S bond in (VIa) were situated in the plane of the ring, then the shape factor and the orientational parameters for this structure should have the values given in Table 4. Since the shape factor for this hypothetical form ($s = 1.38$) is greater than for (Va) ($s = 1.29$), the molecule of the complex must have a poorer orientation than that of (Va), and the angles for all the compounds should be the same for all the compounds. However, the dichroism of absorption band 1 for the electronic transition in (Va) and (VIa) is virtually identical, and consequently the molecules are oriented in the same way, and the angles φ for complex (VIa) are different from the same angles in the sulfonic acids. The structural model is unacceptable for nonplanar molecules, and the orientational parameters given for the hypothetical planar structure of the complex cannot be used for calculating the angles for the three-dimensional compound. Hence, these findings show unambiguously that the bond between the sulfo-group and the nitrogen atom in the complex does not lie in the plane of the aromatic ring.

EXPERIMENTAL

IR spectra were obtained on a UR-20 apparatus in vaseline oil, and the PMR spectra of solutions in D_2O on a Tesla BS-487 (80 MHz), with tert-butanol as internal standard. The polymer films were prepared from a 5% solution of polyvinyl alcohol (PVA) in water, with the addition of the required amounts of aqueous solutions of the sulfonic acids (VIIIa, b) or the complex (VIa), by drying in glass cells. PVA films containing benzimidazole were obtained by sorption of (Va) from an alcoholic solution by the polymer film. The films obtained were subjected to fourfold uniaxial extension to a thickness of 20 μm with constant loading, the temperature being gradually raised from 100 to 120°C. The absorption spectra of the extended films in polarized light with an electrical vector parallel to the axis of extension of film $D_{1\parallel}(\lambda)$ and perpendicular to this axis $D_{\perp}(\lambda)$ were measured on an SF-26 spectrophotometer fitted with a polarizer. The spectral course of the dichroism $d(\lambda)$ was calculated by the formula given in [17].

Azole–Sulfur Trioxides (IIa-f) and (VIa-c). To a solution or suspension of 5 mmole of the azole in 10 ml of dry dichloroethane was added with stirring and cooling at from −5° to 0°C 5 mmole of SO_3 (for 1 g, 5 mmole of SO_3), in 10 ml of dichloroethane. The colorless solid which separated was filtered off, washed on the filter with dichloroethane, acetone, and ether, dried, and kept in a desiccator over P_2O_5. The properties of complexes (IIb-f) and (IVb, c) are given in Table 2, and those of (IIa) and (VIa) in [9].

Azolesulfonic Acids (IVa, c-g) and (VIIIa-c) (Table 3). To a solution or suspension of 10 mmole of the azole in 10 ml of dichloroethane was added with stirring a solution of 30 mmole of SO_3 in 10 ml of dichloroethane. The azole·SO_3 complex which separated, which became oily on heating, was boiled for 6 h 30 min, until the oil had been converted completely into the solid, colorless sulfonic acid. The solution was decanted, the solid dissolved in 30-50 ml of water, treated with $BaCO_3$, the $BaSO_4$ filtered off, the filtrate concentrated to a volume of 10-15 ml, the barium salt of the azolesulfonic acid precipitated with 100 ml of a mixture of ethanol and acetone (1:1), washed with acetone and ether, and dried over P_2O_5. The sulfonic acid (IVa) has been described previously [9].

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