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BENZOXAZINES AND RELATED COMPOUNDS

6.* NITRATION OF 2,4,4-TRISUBSTITUTED 4H-1,3-BENZOTHIAZINES

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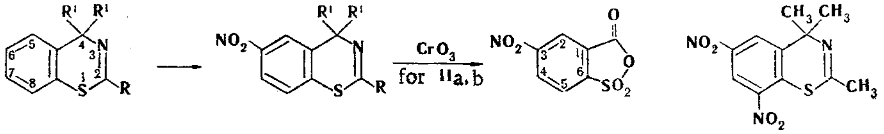
4H-1,3-Benzothiazines have so far been little-investigated compounds [1, 2] (see also [3]), and there are no data on electrophilic substitution reactions in this system.

In order to synthesize 2,4,4-trisubstituted 4H-1,3-benzothiazines (Ia-k) with a nitro group in the aromatic ring we realized the nitration of compounds (Ia-k) with a mixture of equimolar amounts of nitric acid (d = 1.5) and concentrated sulfuric acid at room temperature. In all cases the mononitro derivatives (IIa-k) were isolated (Table 1).



Ia-k IIa-k III IV

I, II a $R=R^1=CH_3$; b $R=CH_3$, $R^1=C_2H_5$; c $R=CH_3$, $R^1=p\text{-}C_3H_7$; d $R=C_2H_5$, $R^1=CH_3$; e $R=R^1=p\text{-}C_3H_7$; f $R=p\text{-}C_4H_9$, $R^1=CH_3$; g $R=p\text{-}C_4H_9$, $R^1=C_2H_5$; h $R=p\text{-}C_4H_9$, $R^1=p\text{-}C_3H_7$; i $R=i\text{-}C_4H_9$, $R^1=CH_3$; j $R=C_6H_5$, $R^1=CH_3$; k $R=4\text{-}ClC_6H_4$, $R^1=CH_3$

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*For Communication 5, see [1].

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TABLE 1. 2,4,4-Trisubstituted 6-Nitro-4H-1,3-benzothiazines

Compound	R	R'	mp, °C (solvent for crystallization)	R_f	Found, %				Molecular formula	Calculated, %				Molecular weight (by mass spectrometry)	Yield, %
					C	H	N	S		C	H	N	S		
IIa	CH_3	CH_3	74—75 (methanol)	0,38	—	—	11,8	13,6	$C_{11}H_{12}N_2O_2S$	—	—	11,8	13,2	236,0	85
IIb[a]	CH_3	C_2H_5	58—59 (ether)	0,42	59,3	6,1	10,6	11,7	$C_{13}H_{16}N_2O_2S$	59,1	6,1	10,6	12,1	264,6	74
IIc	CH_3	p-C_3H_7	50—52 (hexane)	0,54	61,6	6,8	9,7	11,2	$C_{15}H_{20}N_2O_2S$	61,6	6,9	9,6	11,0	292,3	90
IId	C_2H_5	CH_3	71—72 (hexane)	0,40	—	—	11,2	12,8	$C_{12}H_{14}N_2O_2S$	—	—	11,2	12,8	250,1	80
IIe[a]	p-C_3H_7	p-C_3H_7	32—33	0,59	—	—	8,9	10,1	$C_{17}H_{24}N_2O_2S$	—	—	8,8	10,0	320,6	86
IIf[b]	p-C_4H_9	CH_3	—	0,55	—	—	10,0	11,4	$C_{14}H_{18}N_2O_2S$	—	—	10,0	11,5	279,0	63
IIg[b]	p-C_4H_9	C_2H_5	—	0,58	—	—	9,4	10,1	$C_{16}H_{22}N_2O_2S$	—	—	9,2	10,4	—	80
IIh[b]	p-C_4H_9	p-C_3H_7	—	0,61	—	—	8,0	9,8	$C_{18}H_{26}N_2O_2S$	—	—	8,4	9,6	—	67
IIi[b]	i-C_4H_9	CH_3	—	0,53	—	—	9,7	11,4	$C_{14}H_{18}N_2O_2S$	—	—	10,0	11,5	279,0	89
IIj	C_6H_5	CH_3	102—104 (heptane)	0,51	—	—	9,2	11,0	$C_{16}H_{14}N_2O_2S$	—	—	9,4	10,8	299,0	70
IIk[c]	4-ClC_6H_4	CH_3	134—135 (heptane)	0,55	—	—	8,4	9,5	$C_{16}H_{13}ClN_2O_2S$	—	—	8,4	9,6	—	65

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[a] UV spectrum, λ_{max} (lg ε): IIb, 235 (inflection), 328 (3.95); IIe, 233 (3.95, inflection), 340 nm (3.91). [b] Liquids.
[c] Found: Cl 10.8%. Calculated: Cl 10.7%.

The data from the PMR spectra (in carbon tetrachloride) for the aromatic part of the nitro derivatives (IIa-k) show that the nitro group enters at position 6 or 7 (the presence of one signal for a proton with a meta constant and two signals for vicinal protons). Thus, in the PMR spectrum of compound (IIa) there are signals at 7.3 (d, J = 8 Hz), 8.1 (q, J_1 = 8 Hz, J_2 = 2.5 Hz), and 8.3 ppm (d, J = 2.5 Hz). An analogous set of signals for the protons of the benzene ring is observed in compounds (IIb-k). In order to determine the position of the nitro group (6 or 7) more precisely compounds (IIa, b) were oxidized with chromic anhydride in sulfuric acid. As a result we obtained the 3-nitrosulfobenzoic anhydride (III) with mp 210-212°C, which corresponds to published data [4] and differs greatly from the constant (110-112°C) of the 4-nitro isomer. From this it follows that the nitro group in compounds (IIa-k) occupies position 6. The PMR spectra for the aliphatic part of the molecules (IIa-k) do not differ in character from the spectra of the initial compounds [1]. (A small downfield shift of certain signals is sometimes served.) For example, in the spectrum of compound (IIa) there are two singlets at 1.6 (6H) and 2.3 ppm (3H) for the protons of the 4-$(CH_3)_2$ and 2-CH_3 groups respectively. The spectrum of (IId) is characterized by a singlet at 1.6 ppm for the proton of 4-$(CH_3)_2$ and, accordingly, triplet and quadruplet signals at 1.1 and 2.5 ppm for the CH_3 and CH_2 protons of the ethyl group. It is interesting to note that in compounds in which there are more bulky radicals than methyl at position 4 the signal of the 5-H proton is shifted upfield by 0.3 ppm, and this can be explained by additional screening of the 5-H proton from the bulky substituents. In the IR spectra of compounds (II) there are $\nu_{NO_2}{}^{s}$ (1345-1360 cm^{-1}) and $\nu_{NO_2}^{as}$ (1523-1538 cm^{-1}) vibrations; the frequencies for the stretching vibrations of the C=N group differ little from those in the initial compounds.

In system (I) the orientation of the entering nitro group is clearly determined by the concerted effect of the substituent of the first kind at position 1, i.e., the alkylthio group, and by the effect of the group at position 4 containing a protonated aminomethyl fragment, which is considered (e.g., see [5]) to be largely meta-directing.

In compounds (IIj, k), for which it can be assumed that the nitro group enters the aryl residue at $C_{(2)}$ and not at the benzene ring of the benzothiazine system, it is easy to establish by means of the PMR spectra that the nitro group is in the benzothiazine part of the molecule (the presence of a doublet with J = 2.5 Hz at 8.4-8.6 ppm, which belongs to the 5-H proton). Here the decrease in the activity of the aryl radicals at position 2 compared with the benzene ring of benzothiazine as a result of the protonation of the imino group conjugated with the aryl residue clearly has an effect.

The use of 3 mole of nitric acid (8 h, 40°C) in the case of compound (Ia) leads to the formation of the 6,8-dinitro derivative (IV), in which the position of the nitro groups is clearly established by means of the PMR spectrum (two doublets from 5-H and 7-H with J = 2.5 Hz at 8.5 and 8.9 ppm respectively). It is not clear why the introduction of a second nitro group into compound (Ib), which contains two ethyl groups at position 4, requires even more drastic reaction conditions; after 11 h at 100°C the nitro compound is only formed to the extent of 33%, as determined by the PMR spectrum.

Thus, electrophilic substitution in the case of nitration in the series of compounds (I) occurs at position 6, as occurred in the case of 2,4,4-trialkyl-4H-1,3-benzoxazines [6]. It should be noted that the nitro derivatives (II) are considerably more stable than their oxygen analogs [6]. [For example, hydrolysis products are formed in the latter case when the acid reaction mass is added to water [6], while compounds (II) remain unchanged.] This fact makes it possible to use the nitro derivatives (II) for various chemical transformations in the presence of acidic agents.

EXPERIMENTAL

The UV spectra were recorded in alcohol (c = $2.5 \cdot 10^{-5}$ to $1 \cdot 10^{-4}$ M) on a Perkin-Elmer 402 spectrophotometer. The IR spectra were recorded on DS-301 and UR-10 spectrometers in carbon tetrachloride, in Vaseline oil, or in tablets with potassium bromide. The PMR spectra were recorded in carbon tetrachloride on a Varian T-60 instrument. The molecular weights were determined on a Varian MAT-112 instrument. The purity of the obtained compounds was monitored by TLC on aluminum oxide of grade II activity in the 1:2 ether–petroleum ether system.

Compounds (Ie, h-k) were obtained by the method in [1]. Data on the compounds are given in Table 2.

TABLE 2. 2,4,4-Trisubstituted 4H-1,3-Benzothiazines*

Compound	R	R¹	mp, °C	R_f	IR spectrum, $\nu_{C=N}$, cm⁻¹	Found, %			Molecular formula	Calculated, %			Yield, %
						Cl	N	S		Cl	N	S	
Ie	p-C_3H_7	p-C_3H_7	—	0,64	1652	—	5,0	11,4	$C_{17}H_{25}NS$	—	5,1	11,6	47
Ih	p-C_4H_9	p-C_3H_7	—	0,66	1650	—	4,7	11,2	$C_{18}H_{27}NS$	—	4,8	11,1	76
Ii	*i*-C_4H_9	CH_3	—	0,60	1640	—	5,9	13,9	$C_{14}H_{19}NS$	—	6,0	13,8	78
Ij	C_6H_5	CH_3	85—87	0,61	—	12,2	4,6	11,4	$C_{16}H_{15}NS \cdot HCl$	12,2	4,8	11,1	61
Ik	4-ClC_6H_4	CH_3	144—146	0,60	—	21,9	4,2	9,9	$C_{16}H_{14}ClNS \cdot HCl$	21,9	4,3	9,9	81

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*Compounds (Ie, h, i) are liquids, and compounds (Ij, k) were isolated as the hydrochlorides. (For the method of isolation and purification, see [1].)

2,4,4-Trisubstituted 6-Nitro-4H-1,3-benzothiazines (IIa-k). To a solution of 0.02 mole of benzothiazine (I) in 40 ml of concentrated sulfuric acid, while cooling (with the temperature kept at ∿ 20°C), we added 0.025 mole of nitric acid (d = 1.5) in portions. The mixture was left for 48 h, added to ice, made alkaline with a solution of sodium hydroxide, and extracted with benzene. The benzene solution was washed with water and evaporated, and compounds (IIa-k) were obtained. The liquids (IIf-i) were purified by the method in [1] by column chromatography on aluminum oxide of grade II activity with a 1:4 mixture of benzene and heptane as eluent. Data on compounds (IIa-k) are given in Table 1.

2,4,4-Trimethyl-6,8-dinitro-4H-1,3-benzothiazine (IV). To a solution of 3.8 g (0.02 mole) of the benzothiazine (Ia) in 38 ml of concentrated sulfuric acid, while cooling, we added 2.6 ml (0.06 mole) of nitric acid (d = 1.5) in portions. The mixture was kept at 40°C for 8 h, added to ice, made alkaline with a solution of sodium hydroxide, and extracted with benzene. The extract was washed with water, and 4 g (71.6%) of the dinitro derivative (IV) was isolated from the benzene solution by evaporation; mp 125-126°C (from alcohol), R_f 0.21. Found, %: C 47.2; H 4.2; N 14.8; S 11.6. $C_{11}H_{11}N_3O_4S$. Calculated, %: C 47.0; H 4.0; N 14.9; S 11.4. IR spectrum (in potassium bromide: 1335 and 1350 (ν^s of two NO_2), 1525 and 1540 (ν^{as} of two NO_2), 1660 cm⁻¹ (ν C=N).

3-Nitrosulfobenzoic Anhydride (III). To a solution of 1 g (4 mmole) of compound (IIa, b) in 10 ml of 50% sulfuric acid we added 3 g of chromic anhydride. The mixture was heated to boiling and left at 20°C for 12 h. It was then added to water and extracted with ethyl acetate. The ethyl acetate solution was washed with water and evaporated, and 0.4 g (48%) of the anhydride (III) was obtained; mp 210-212°C. Published data [4]: mp 212-218°C. Found, %: N 6.5; S 14.1. $C_7H_3NO_6S$. Calculated, %: N 6.1; S 14.0.

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