TRANSFORMATIONS OF BICYCLIC SYSTEMS CONTAINING AN ISOTHIAZOLE RING

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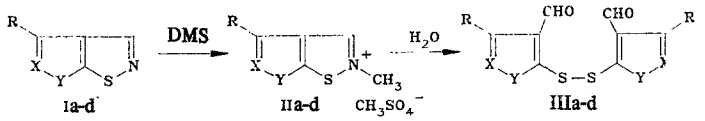
Isothiazolium salts, which are readily hydrolyzed to heterocyclic o-formyl disulfides, were obtained by alkylating bicyclic systems containing an isothiazole ring. The initial isothiazole-containing systems are stable in water and react with nucleophiles such as the hydroxyl ion with opening of the isothiazole ring and formation of o-cyanodisulfides.

Bicyclic systems containing an annelated isothiazole ring [1] have already been obtained by brominating nickel complexes of aminomethylene derivatives of thiones of five-membered heterocyclic compounds. To study their chemical properties, these compounds were introduced into an alkylation reaction by dimethyl sulfate.



I—IIIa-c R=H, X=CC_6H_5; a Y=O; b Y=S; c Y=NCH_3; d R=CH_3, X=N, Y=NC_6H_5

Colorless compounds were isolated from the methylation of 2-phenylfuro- and 2-phenylthieno[3,2-d]isothiazoles Ia,b. Their physicochemical characteristics and data of elemental analysis are listed in Table 1. The alkylation product of 1-methyl-2-phenylpyrrolo[3,2-d] isothiazole could not be isolated in a pure state. This compound is very hygroscopic and decomposes to form bis(4-formyl-5-pyrrolyl) disulfide (IIIc). Compounds IIa,b react with water in a similar way to form the corresponding 4-formyl disulfides IIIa,b. In contrast to compounds Ia-c, alkylation of 1-phenyl-3-methylpyrazolo[3,2-d]isothiazole may proceed at two reaction centers. However, in the reaction with dimethylsulfate, irrespective of its excess, one product is always formed, and according to the PMR spectrum data (Table 2), a structure of the methylation product at the isothiazole ring IId was ascribed to this product. This is also confirmed by the structure of the hydrolysis product, bis(1-phenyl-3-methyl-4-formyl-5-pyrazolyl) disulfide IIId, identical with the disulfide previously obtained by other methods [1, 2].

The high electrophilicity of the carbon atom of the isothiazole ring, and the readiness of the compound to react with water resulting from this electrophilicity, is also confirmed by the PMR spectral data. Thus, comparison of signals of protons at the 3 and 4 positions of the isothiazolium salts IIa,b and the corresponding bicyclic isothiazole-containing systems Ia,b shows that after methylation, the shift into the weak field is $\Delta\delta_{3\text{-H}}$ 0.85 and 0.45, and $\Delta\delta_{4\text{-H}}$ 0.55 and 0.77 ppm, respectively (Table 2).

It should be noted that, as shown by the PMR spectra, the annelated isothiazole ring in compounds Ia-d also plays the role of an electron acceptor, causing an up to 0.4 ppm shift of the 3-H signal of the five-membered ring (Table 2), compared with similar signals in monoheterocyclic compounds (2-phenylfuran 6.62 ppm [3], 2-phenylthiophene 7.22 ppm [4], 4-phenylpyrrole 6.51 ppm [5]). The position of the 4-H signal does not change, it is present in the same region as in isothiazole (8.54 ppm) [6], and is practically independent of the nature of the annelated ring. However, the electrophilicity of the carbon atom in these

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TABLE 1. Physicochemical Characteristics of Isothiazolium Salts IIa-d and 5-Hetaryl Disulfides IIIa-d and Va-d

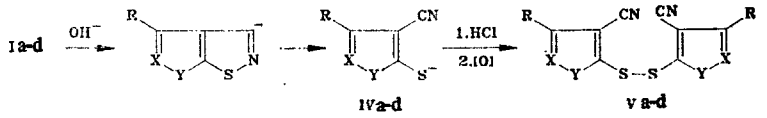
Compound	mp,* deg C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Found, %		Empirical formula	Calculated %		Yield, %
				N	S		N	S	
IIa	213	235 (4,16); 300 (3,95)	1560 (C=C, conjug.), 2870 (CH), 3125 (CH)	4,2	19,4	$C_{13}H_{13}NO_5S_2$	4,3	19,6	74
IIb	245	268 (4,15); 300 sh, 330 sh	1600 (C=C, conjug.), 2880 (CH), 3100 (CH)	4,0	27,7	$C_{13}H_{13}NO_4S_3$	4,1	28,0	80
IId	222	256 (4,06); 300 (3,85), 375 sh	1600 (C=C, conjug.), 2890 (CH), 3050 (CH)	12,2	18,5	$C_{13}H_{15}N_3O_4S_2$	12,3	18,8	80
IIIa	189 [1]	240 (4,65); 277 (4,74); 370 (4,29)	1520 (C=C, conjug.), 1690 (C=O), 2830 (CH), 3115 (CH)	—	—		—	—	88
IIIb	199	260 (4,25); 355 (3,80)	1600 (C=C, conjug.), 1680 (C=O), 2835 (CH), 3100 (CH)	—	29,3	$C_{22}H_{14}O_2S_4$	—	29,2	90
IIIc	156 [1]	260 (4,54); 375 (3,98)	1610 (C=C, conjug.), 1675 (C=O), 2955 (CH), 3115 (CH)	—	—		—	—	86
IIId	126 [2]	230 (4,30); 296 (3,98)	1600 (C=C, conjug.), 1680 (C=O), 2820 (CH), 3070 (CH)	—	—		—	—	88
Va	190	240 (4,51); 310 sh; 365 (4,19)	1590 (C=C, conjug.), 2245 (C≡N), 3120 (CH)	6,8	15,9	$C_{22}H_{12}N_2O_2S_2$	7,0	16,0	77
Vb	197	245 (4,55); 303 (4,34); 370 (4,26)	1490 (C=C, conjug.), 2240 (C≡N), 3100 (CH)	6,3	29,5	$C_{22}H_{12}N_2S_4$	6,5	29,6	76
Vc	176	253 (4,37); 315 sh; 360 (3,96)	1600 (C=C, conjug.), 2235 (C≡N), 2955 (CH), 3070 (CH)	13,0	14,8	$C_{24}H_{18}N_4S_2$	13,1	15,0	73
Vd	197	255 (4,56); 315 (3,82)	1600 (C=C, conjug.), 2240 (C≡N), 2930 (CH), 3030 (CH)	19,6	14,8	$C_{22}H_{16}N_6S_2$	19,6	15,0	53

*Compounds IIa,b,d were crystallized from acetonitrile; IIIa,b,Vc,d from benzene; IIIc from heptane; IIId from petroleum ether; Va from a mixture of chloroform and petroleum ether; and Vb from chloroform.

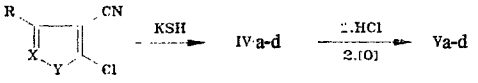
TABLE 2. PMR Spectra of Isothiazoles Ia-d and Isothiazolium Salts IIa-d

Compound	Chemical shifts, ppm (multiplicity)				
	3-H	4-H	1-R	$2\text{-}C_6H_5$	$5\text{-}CH_3$
Ia	7,07 s	8,47 s	—	7,32—7,93 m	—
Ib	7,59 s	8,73 s	—	7,40—7,81 m	—
Ic	6,60 s	8,47 s	3,73 s	7,52 s	—
Id	—	8,51 s	7,38—7,83 m	—	—
IIa	7,85 s	8,95 s	—	7,18—7,64 m	3,60 s
IIb	8,04 s	9,50 s	—	7,22—7,72 m	
IId	—	9,10 s	7,70 s		3,48 s

compounds is insufficient, and they do not react with water, even on prolonged boiling, while with a strong nucleophile (OH^-, $AlkO^-$) the reaction proceeds readily and opening of the isothiazole ring is observed. In the presence of hydroxyl ions, a proton is split off, followed by stabilization of the anion due to opening of the isothiazole ring with the formation of cyanomercaptides. Under experimental conditions these are further oxidized to the corresponding cyanodisulfides.



The intermediate product of this reaction, 4-cyano-5-mercapto derivative IV, was isolated in noticeable amounts in the reaction of pyrazoloisothiazole Id only. The structure of disulfides Va-d was confirmed by an alternative synthesis from chloronitriles, described in [7], according to the following scheme:



During their isolation, the salts of mercaptonitriles of the five-membered heterocyclic compounds, formed at the first stage, are readily oxidized to disulfides. In the IR spectra of these compounds, an intense absorption band of the cyano group at 2235-2245 cm^{-1} is observed, depending on the nature of the heterocycle. The electronic spectra of these compounds are similar in character to the absorption spectra of disulfides with a formyl group IIIa-d. They contain 2-3 intense broad absorption maxima (Table 1).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer (KBr tablets, concentration 0.25-0.40 wt.%). The electronic absorption spectra were recorded on an SF-8 apparatus (1 cm cuvette), using acetonitrile as solvent. The PMR spectra were recorded on a Perkin–Elmer spectrometer, 60 MHz, DMSO, accuracy of measurement of the chemical shifts of ^1H is within ±0.05 ppm. The compounds were identified by the TLC method on Silufol 254.

Compounds Ia-d were obtained by the method described in [1].

The physicochemical characteristics of the compounds synthesized are listed in Table 1.

2-Phenylfuro[3,2-d]-5-methylisothiazolium Methylsulfate (IIa). A mixture of 0.20 g (1 mmole) of 2-phenylfuro[3,2-d]isothiazole and 0.19 g (15 mmoles) of freshly distilled dimethyl sulfate is heated to 90-100°C, and then held at this temperature up to solidification of the reaction mixture. The mixture is cooled and is crystallized from acetonitrile, and 0.24 of product are obtained.

Compounds IIb-d were obtained under the same conditions.

Bis(2-phenyl-4-formyl-5-furyl) Disulfide (IIIa). A 0.33-g portion (1 mmole) of compound IIa is dissolved in 10 ml of water, and after a few minutes the precipitate is filtered. Yield, 0.36 g (88%). Compounds IIIb,d are obtained in a similar way. Bis(1-methyl-2-phenyl-4-formyl-5-pyrrolyl) disulfide is obtained by treating compound IIc with water, without isolating it from the reaction mixture. Disulfides IIIa-d were identified with previously obtained samples [1] by the TLC method and by a mixed melting point probe.

Bis(2-phenyl-4-cyano-5-furyl) Disulfide (Va). A. A solution of 0.4 g (2 mmoles) of compound Ia in 50 ml of ethanol and 5 ml of a 10% aqueous sodium hydroxide is boiled for 3 h. After the solvent has been distilled, the mixture is acidified, washed with water, and dried. Yield, 0.31 g (77%).

Compounds Vb-d are obtained under the same conditions.

During alkaline hydrolysis of compound Id, 1-phenyl-3-methyl-4-cyano-5-mercaptopyrazole (IVd) was additionally isolated. Yield, 0.13 g (30%), mp 110°C (from heptane). IR spectrum 2240 (C≡N), 2575 cm^{-1} (S–H). UV spectrum, λ_{max} (log ε): 240 sh, 257 (4.40), 317 nm (3.76). Found: N 19.4; S 14.8%. $C_{11}H_9N_3S$. Calculated: N 19.5; S 14.9%.

B. A 0.41-g portion (2 mmoles) of 2-phenyl-4-cyano-5-chlorofuran is dissolved in 20 ml of ethanol, 1.2 ml of an aqueous solution of potassium hydrosulfide is added, and the mixture is boiled for 1 h. The solvent is distilled, and the residue is dissolved in 20 ml of water, and acidified by 10% HCl. Yield, 0.36 (90%) of product.

The remaining compounds were obtained in a similar way. The disulfides were identified by the TLC method, by the mixed melting point probe, and according to data of IR and UV spectroscopy.

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CYCLIC HYDROXAMIC ACIDS OF THE INDOLE SERIES

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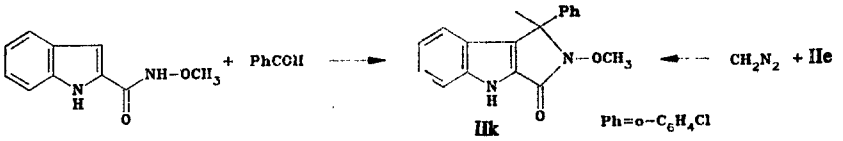
A convenient method was developed for obtaining 2-N-hydroxy-3-keto-1-phenyl-1,3-dihydropyrrolo[3,4-b]indoles by reaction of indole-2-hydroxamic acid with substituted benzaldehydes. Complex compounds of trivalent iron salts with cyclic hydroxamic acids were isolated.

Using a principle for building tricyclic indoles [2,3] previously suggested by us we obtained cyclic hydroxamic acids of the indole series by the method

The process keeps mixtures of reagents in alcohol, saturated with HCl, at room temperature. After a short period of standing the solvent was distilled off to dryness, and the colorless crystalline residue was purified by crystallization from alcohol or acetonitrile. The yields were from 45 to 70%. The elementary composition of the compounds obtained indicates the addition of one molecule of aldehyde to one molecule of indole with loss of water. The compounds have the properties of weak acids, i.e, they dissolve in basic solutions and are isolated unchanged on acidification with acetic acid, which indicates the retention of the >CONOH hydroxamic acid fragment in the molecule formed.

Acetylation of compounds (IIa, e) with boiling acetic anhydride leads to the formation of 2-acetoxy derivatives (IIh, i) not soluble in bases and having lower melting points.

Cyclic hydroxamic acids (IIa, e) are readily alkylated by diazomethane giving 2-methoxy derivatives (IIj,k). For the purpose of establishing the direction of methylation we obtained the methylated derivative (IIk) by an alternate synthesis from the methyl ester of indole-2-hydroxamic acid:



The absence of a melting point depression and the agreements of the Rf and the spectra of the compounds obtained by both methods testifies to their identity and unequivocally shows the direction of methylation.

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