

SYNTHESES BASED ON MERCAPTOBENZTHIAZOLE,
 MERCAPTOBENZOXAZOLE, AND
 MERCAPTOBENZIMIDAZOLE

COMMUNICATION 2. REACTION OF 2-BENZOXAZOLYL
 VINYL SULFIDE AND 2-BENZIMIDAZOLYL
 VINYL SULFIDE

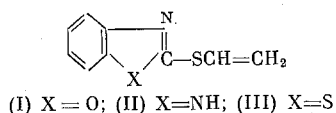
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We reported the synthesis of various substituted benzthiazoles [1, 2] with a view to studying the relationship of their physiological activity with structure. Since it is known that the benzimidazole group is fairly widely distributed in physiologically active compounds and certain substituted 2-mercaptobenzoxazoles possess marked herbicidal activity [3] it seemed of interest to continue the started studies on compounds of the benzoxazole and benzimidazole series. It was also of interest from the point of view of comparing the chemical properties of compounds of these series.

2-Benzoxazolyl vinyl sulfide (I) and 2-benzimidazolyl vinyl sulfide (II) (IR spectra Fig. 1), which were prepared by the vinylation of 2-mercaptobenzoxazole and 2-mercaptobenzimidazole (Schemes 1 and 2), were used as starting substances for this work. This vinylation reaction for the selected compounds proceeded under conditions close to those developed earlier for the synthesis of 2-benzthiazolyl vinyl sulfide (III) [1] with yields of ~60-70%.

During the study of certain reactions of the vinyl sulfides (I) and (II) a significant interaction of atoms remote from one another was noted which led, in particular, to a definite dependence of the properties of the vinyl double bond on the nature of the heteroatom X present in their molecule



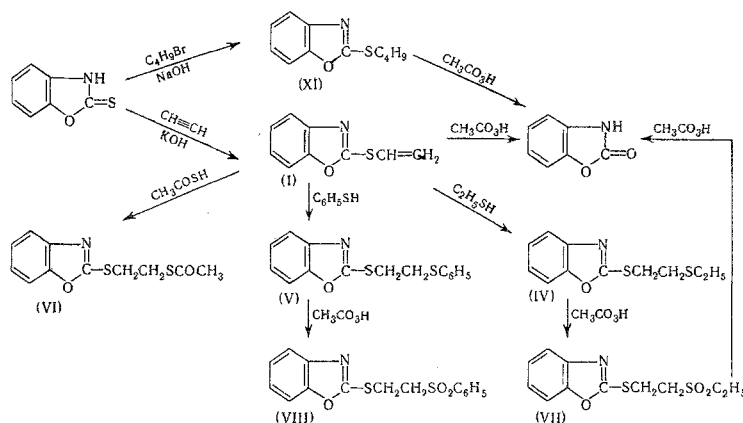
Moreover a great similarity was found in the chemical properties of the vinyl sulfides for which X=O or S. Thus, in free radical addition reactions with a number of thiols, sulfide (I) reacts analogously to 2-benzthiazolyl vinyl sulfide (III) which was described earlier [1] and gives in the presence of azodiisobutyronitrile (AIBN) with ethanethiol, thiophenol, and thiolacetic acid high yields of the adducts (IV)-(VI). This reaction proceeds even more smoothly for benzoxazolyl vinyl sulfide (I) than for the benzthiazole analog (III): in this case the cleavage processes (for example, in the addition of thiolacetic acid in the presence of atmospheric oxygen) which are characteristic of the slower reactions of the latter [1] are not observed

TABLE 1

Compound No.	bp, °C (p mm Hg) or mp, °C (solvent)	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	S		C	H	S	
I	97-99 (3)	61,07	4,25	18,37	C ₉ H ₇ NOS	61,00	3,98	18,06	70
II	159-161 (benzene - alcohol)	61,38	4,65	18,08	C ₉ H ₈ N ₂ S	61,33	4,57	18,19	66
IV	149-150 (3)	55,26	5,78	26,42	C ₁₁ H ₁₃ NOS ₂	55,19	5,47	26,79	94
V	48-48,5 (petroleum ether)	62,41	4,52	22,51	C ₁₀ H ₁₃ NOS ₂	62,68	4,56	22,83	92
VI	141-142,5 (3)	52,11	4,53	25,57	C ₁₁ H ₁₁ NOS ₂	52,15	4,38	25,31	72
VII	88,2-88,6 (alcohol)	48,78	4,93	23,30	C ₁₁ H ₁₃ NO ₃ S ₂	48,67	4,83	23,63	97
VIII	99,8-101 (alcohol)	56,35	4,15	20,11	C ₁₅ H ₁₃ NO ₃ S ₂	56,42	4,10	20,08	90
IX	118-119 (benzene - heptane)	56,07	5,91	26,45	C ₁₁ H ₁₄ N ₂ S ₂	55,41	5,91	26,90	50
X	164,5-165,5 (alcohol)	51,60	4,02	14,65	C ₉ H ₈ N ₂ O ₂ S	51,92	3,87	15,40	60
XI	122,5-123,5 (3)	63,88	6,50	15,25	C ₁₁ H ₁₃ NOS	63,77	6,28	15,46	90

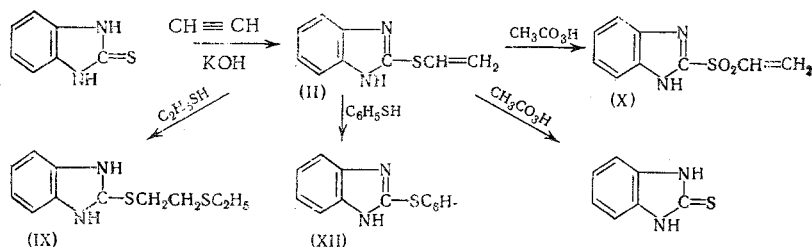
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya*, No. 3, pp. 670-675, March, 1969. Original article submitted April 11, 1968.

Scheme 1



As regards the benzimidazolyl sulfide (II) (Scheme 2), only in its reaction with ethanethiol were we successful in preparing the adduct (IX) in a yield of ~ 50%. The formation of 2-thiophenylbenzimidazole (XII) (i.e. an unusual transesterification) was observed in the reaction of the sulfide (II) with thiophenol. The same treatment with thiolacetic acid, even with the strict exclusion of atmospheric oxygen, caused decomposition of the sulfide molecule and the liberation of 2-mercaptobenzimidazole

Scheme 2

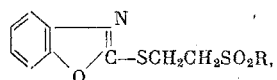


Thus, cleavage reactions of the group in position 2 are more characteristic for the benzimidazole derivatives than addition to the side chain double bond. The latter is evidently distinguished in this case by a reduced reactivity.

Several similar reactions were observed previously [4] in the case of nucleophilic substitution of a chlorine atom situated in position 2 of various heterocyclic systems by amino or alkoxy-groups. At the same time it is difficult to accept that the thiols react in our case as nucleophiles. It was shown in the work cited that the ease of substitution of the group in position 2 under nucleophilic conditions very clearly increases in the order: benzimidazole < benzthiazole < benzoxazole [4]. At the same time we only observed the exchange of the $\text{SCH}=\text{CH}_2^*$ group by the SC_6H_5 group in the benzimidazole series.

The results of the oxidation reaction under mild conditions (peracetic acid in ether, temperature -12 to -10°C) also proved to be unexpected for the same vinyl sulfides (I) and (II) and also the adducts (IV), (V), (VI), and (XI) obtained based on them. Thus, during the oxidation of the vinyl sulfide (I), which contained the oxazole ring, cleavage of the molecule occurred and, instead of the expected sulfone, 2-hydroxybenzoxazole was formed (q.v. Scheme 1). Adducts (IV) and (V) based on the vinyl sulfide (I) and which contain two sulfur atoms in the side chain gave the monosulfones (VII) and (VIII) even in excess peracetic acid. The introduction of only two oxygen atoms into the side chain during the oxidation was confirmed by elementary analysis and the formation of the sulfonyl group by the IR spectrum (Fig. 2).

The structure of these sulfones must correspond with formula



since an attempt to oxidize them further in the same way as the oxidation of the simpler 2-alkylthiobenzoxazoles [for example the 2-thiobutyl derivative (XI)] always leads to the one and the same result — cleavage

* The over-all increase of rate in this series is very large and consists of approximately 6 orders.

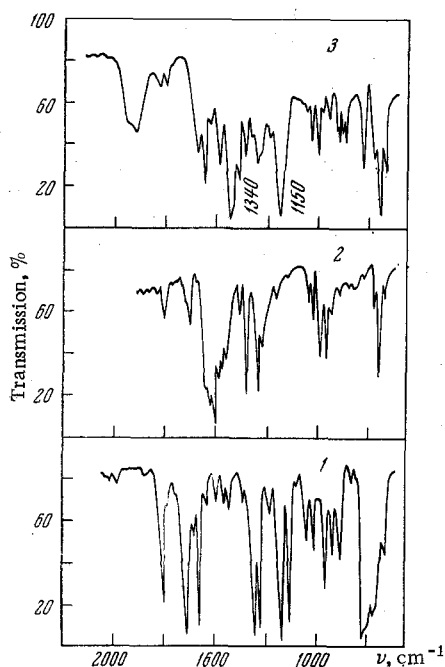


Fig. 1. IR Spectra: 1) 2-Benzoxazolyl vinyl sulfide (I); 2) 2-benzimidazolyl vinyl sulfide (II); 3) 2-benzimidazolyl vinyl sulfone (X)

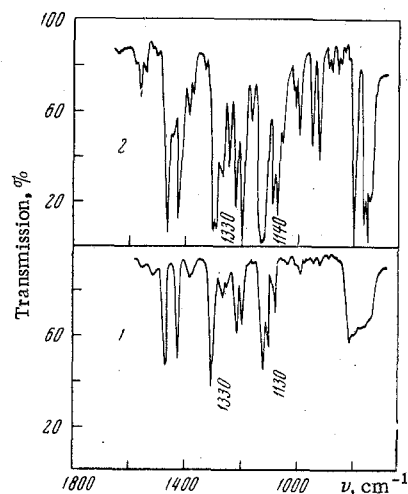
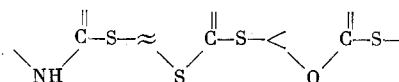


Fig. 2. IR Spectra: 1) β -Ethylthioethyl-2-benzoxazolyl sulfone (VII); 2) β -phenylthioethyl-2-benzoxazolyl sulfone (VIII).

of the side chain and formation of 2-hydroxybenzoxazole (q.v. Scheme 1). It should be noted that under the oxidation conditions adopted by us, cleavage of the side chain was never observed in the analogous derivatives of the benzthiazole series [1]. However there is an indication of the cleavage of the 2-hydroxyethylthio group during the oxidation of the corresponding sulfides under drastic conditions [5]. In spite of the fact that all the derivatives of benzimidazole are difficultly soluble substances, and their reactions are obliged to be carried out under heterogeneous conditions, the vinyl sulfide (I) gave, on oxidation, the expected vinyl sulfone (X) (q.v. Fig. 1). The oxidation of the dithioether (IX) under these conditions led to the formation of a complex mixture of products which were not investigated further.

The data presented evidently indicates that in oxidation reactions of the sulfur atom situated in position 2 of the compounds studied the following order of conjugation with the adjacent fragments of the heterorings is shown



Probably this considerably hinders the oxidation of the sulfur atom in the oxazole derivatives.

The study of the dependence of the physiological activity of the prepared compounds on structure will form the subject of a separate communication.

EXPERIMENTAL SECTION

2-Mercaptobenzoxazole (synthesized by the known method [6]) and 2-mercaptobenzimidazole (technical domestic company "Chemapol," ChSSR) served as starting compounds for the synthesis of 2-benzoxazolyl vinyl sulfide (I) and 2-benzimidazolyl vinyl sulfide (II). In the majority of cases the oxidation of sulfides was carried out with concentrated peracetic acid (70-75%) in absolute ether solution at a temperature of -10 to -12°C . The other reaction conditions are given in the experimental description. Melting points were determined on a Koffler apparatus. All melting points are uncorrected. IR spectra were measured by UR-10 spectrophotometer in CCl_4 solution [compounds (I), (VII), and (VIII)] or as KBr discs [compounds (II) and (X)].

2-Benzoxazolyl Vinyl Sulfide (I). A mixture of 15 g of 2-mercaptobenzoxazole and 1 g of KOH in 300 ml of dioxane was stirred in a rotating autoclave of 1 liter capacity. The mixture was saturated with acetylene. The heating at 170 - 175°C (maximum pressure 40 atm) was maintained for 5 h. After removal of the dioxane the residue was dissolved in ether, washed with water, and dried over Na_2SO_4 . This yielded 12.2 g of sulfide (I) as a slightly mobile yellow liquid with bp 97 - 99° (3 mm); n_D^{20} 1.6221; d_4^{20} 1.2142. Found: MR 51.87; Calculated MR 51.41.

2-Benzimidazolyl Vinyl Sulfide (II) was prepared similarly to sulfide (I). The heating was conducted at 170–180°C (maximum pressure 20 atm) for 3 h. After working up, the solid residue was washed on the filter with benzene. From 10 g of 2-mercaptobenzimidazole was obtained 7 g of the sulfide (II) (Table 1).

Reaction of the Vinyl Sulfides (I) and (II) with Ethanethiol, Thiophenol, and Thiolacetic Acid. The reactions were carried out with benzene dilution in sealed glass ampoules in a nitrogen atmosphere at 78–80°C for 20–24 h. The initiator was AIBN (0.25–0.75%). The sulfides (1 mole) and thiols (2–2.5 mole) used in the reaction were freshly distilled in a stream of nitrogen. The properties and yields of the compounds prepared are given in Table 1.

β -Acetylthioethyl-2-benzoxazolyl Sulfide (VI). A mixture of 3.54 g of sulfide (I) and 7.6 g of thiolacetic acid was heated in the presence of 0.025 g of AIBN for 24 h. The yield of compound (VI) was 3.6 g (72%).

Compound (VI) was prepared in the same yield on heating 1.77 g of sulfide (I) with 1.52 g of thiolacetic acid (0.01 g of AIBN) without removal of atmospheric oxygen and without a preliminary distillation of the components.

Oxidation of 2-Benzoxazolyl Vinyl Sulfide (I). A solution of 3 g of sulfide (I) in 30 ml of ether was treated with 3.4 g of peracetic acid (72%). The reaction mixture was left overnight. After working up, 2 g (~90%) of 2-hydroxybenzoxazole was obtained with mp 136–137.5°. Found: C 62.20; H 3.70%. $C_7H_5NO_2$. Calculated: C 62.22; H 3.70%. There was present in the IR spectrum of 2-hydroxybenzoxazole frequencies attributable to its isomeric form, benzoxazolone, (q.v. Table 1), the doublet with frequencies at 1740 and 1780 cm^{-1} is characteristic for the C=O group and the broad band with absorption maximum approximately at 3250 cm^{-1} is characteristic for an NH group. According to the data of [7] the mp is 137–138°C.

If the work up of the reaction mass is carried out immediately after the addition of the peracetic acid, the sulfide (I) is recovered unchanged.

β -Ethylthioethyl-2-benzoxazolyl Sulfone (VII). A mixture of 0.5 g of compound (IV) in 20 ml of absolute ether was treated with 0.92 g of peracetic acid (71%, isolation on the same day). The yield was 0.54 g of sulfone (VII). There were absorption bands at 1140 and 1330 cm^{-1} in the IR spectrum of (VII) (q.v. Fig. 2) which are characteristic of the SO₂ group. If the reaction mixture was left overnight without working up, decomposition of the sulfone molecule (VII) occurred with the partial formation of 2-hydroxybenzoxazole (demonstrated by TLC).

β -Phenylthioethyl-2-benzoxazolyl Sulfone (VIII). (VIII) was obtained by treating 0.5 g of compound (V) in 20 ml of absolute ether with 0.5 g of peracetic acid (78%). The yield of sulfone (VIII) was 0.5 g (90%). The IR spectrum is given in Fig. 2.

β -Ethylthioethyl-2-benzimidazolyl Sulfide (IX). A mixture of 1.35 g of sulfide (II) and 1.6 g of ethanethiol diluted with 10 ml of benzene and 90 ml of dioxane was heated in the presence of AIBN for 10 h. The yield was 0.9 g (50% of compound (IX)).

Reaction of 2-Benzimidazolyl Sulfide (II) with Thiophenol. A mixture of 0.5 g of sulfide (II) and 3.13 g of thiophenol diluted with 15 ml of benzene (0.02 g of AIBN) was heated. The yield was 0.39 g (67%) of 2-thiophenylbenzimidazole with mp 198–200°C. Found: C 69.29; H 4.66; S 14.47%. $C_{13}H_{10}N_2S$. Calculated: C 68.98; H 4.45; S 14.17%. According to the data of [8] the mp is 201°C. 2-Thiobenzimidazole is also formed on carrying out the reaction without solvent.

Reaction of Benzimidazolyl Vinyl Sulfide (II) with Thiolacetic Acid. A mixture of 0.5 g of sulfide (II) and 2.16 g of thiolacetic acid diluted with 15 ml of benzene was heated in the presence of 0.02 g of AIBN. The yield was 0.33 g (78%) of 2-mercaptobenzimidazole with mp 300.5–302 deg (in a sealed capillary). A sample mixed with authentic material did not give a depression of the melting point. According to the data of [9] the mp is 298°C.

2-Benzimidazolyl Vinyl Sulfone (X). On treating 1 g of sulfide (II) with 1.5 g of peracetic acid (59%), 0.73 g (60%) of sulfone (X) was isolated. There were adsorption bands at 1140 and 1340 cm^{-1} which are characteristic for the SO₂ group in the IR spectrum of (X).

2-Thiobutylbenzoxazole. Alkylation of 2-mercaptobenzoxazole (0.1 mole) in alcoholic NaOH solution (0.1 mole) with butyl bromide (0.1 mole) gave 12 g (90%) of sulfide (XI) with bp 122.5–123.5° (3 mm); n_D^{20} 1.5689.

Oxidation of 2-Thiobutylbenzoxazole (XI). The oxidation was carried out as described above. The reaction mixture was kept overnight in the refrigerator. On recommencing the stirring at room temperature an exothermic reaction was observed (without resinification). From 5.2 g of sulfide (XI) 3 g (90%) of 2-hydroxybenzoxazole was obtained with mp 136-137°C. A sample mixed with an authentic specimen did not give a depression of melting point.

SUMMARY

1. The vinylation reaction of 2-mercaptobenzoxazole and 2-mercaptobenzimidazole is studied.
2. A number of sulfides and sulfones with sulfur atoms in the side chain, are prepared under reaction conditions developed on the basis of the heterocyclic vinyl sulfides.
3. Together with the usual free radical addition of thiols to the C=C double bonds of the prepared vinyl sulfides, the unexpected reaction of substitution of the S-vinyl group by the thiophenyl radical was found in the case of 2-benzimidazolyl vinyl sulfide.
4. The sulfur atom adjacent to the oxazole ring in 2-benzoxazolyl vinyl sulfide in contrast to 2-benzimidazolyl vinyl sulfide is not oxidized to the sulfone under mild conditions; under more vigorous conditions cleavage occurs with the formation of 2-hydroxybenzoxazole.

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