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OXIDATION OF VINYL DERIVATIVES OF BENZIMIDAZOLE-2-THIONE

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N-Vinylbenzimidazole-2-sulfonic acid, 2-benzimidazolyl vinyl sulfoxide, and 2-benzimidazolyl vinyl sulfone were obtained in high yields by the action of concentrated hydrogen peroxide and acetyl hydroperoxide on N- and S-monovinyl derivatives of benzimidazole-2-thione. N-Vinyl-2-benzimidazolone and a complex mixture of polymeric products are formed in the oxidation of N.S-divinyl-2-mercaptobenzimidazole. It is shown that the reactivity of the sulfur atom depends on the number of vinyl groups and their orientation with respect to the heteroatoms.

We have previously reported [1] the synthesis of 2-benzimidazolyl vinyl sulfide (I) and N,S-divinyl-2mercaptobenzimidazole (II) and their transformations involving the double bond of the vinyl group. In the present research we have studied the oxidation of I and II, as well as benzimidazole-2-thione (III) and N-vinylbenzimidazole-2-thione (IV), in order to obtain new water-soluble vinyl monomers containing oxidized sulfur.

It is known [2] that di(2-benzimidazolyl) disulfide is isolated in the oxidation of thione III with 10% hydrogen peroxide, whereas benzimidazole-2-sulfonic acid (V) is obtained by the action of 30% H₂O₂ in glacial acetic acid or in sodium hydroxide solution.

When we used 78% hydrogen peroxide in glacial acetic acid or 70% acetyl hydroperoxide in ether for the oxidation of III we were unable to isolate the above-indicated disulfide, but sulfonic acid V was obtained in quantitative yield. Oxidation of thione III in acetone gives benzimidazole-2-sulfonic acid (VI), the structure of which is confirmed by the presence of the absorption bands of a SO_2H group in its IR spectrum. The literature data [2-4] on the melting point of acid V are contradictory, apparently in connection with the formation of various hydrated forms of this compound. According to the results of elementary analysis, acids V and VI, which we isolated in the present research, are stable monohydrates with mp~200 and 157°, respectively. The IR spectrum of V contains an intense absorption band at 1043 cm⁻¹ and a doublet at 1200 cm⁻¹, which are characteristic for hydrated sulfonic acids [5]. The bands of the stretching vibrations of the C-H bonds and associated NH and OH groups are superimposed at 2400-3600 cm⁻¹. It was also established by potentiometric titration of an

Irkutsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1670-1673, December, 1975. Original article submitted October 29, 1974.

This material is protected by copyright registered in the name of Plenum Publishing Corporation, 227 West 17th Street, New York, N.Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$7.50. aqueous solution of acid V with 0.1 N NaOH solution that empirical formula $C_7H_6N_2O_3S \cdot H_2O$ corresponds to the investigated compound. The product was 98% pure.

The introduction of a reactive N-vinyl group in the thione III molecule reinforces conjugation of the sulfur atom with the heteroring and may give rise to side processes. The reaction of IV with acetyl hydroperoxide in ether gives N-vinylbenzimidazole-2-sulfonic acid (VIII), in the IR spectra of which the absorption bands of the vinyl group double bond are retained and bands of vibrations of the SO₃H group appear in place of the band due to the vibrations of the thioamide fragment. In the oxidation of N-vinyl compound IV with 78% H_2O_2 in acetone we were unable to isolate monomeric acid VIII. Under these conditions, water-soluble poly (N-vinylbenzimidazole-2-sulfonic acid) (IX) is formed in considerable amounts:



It is interesting to note that IV is converted to polymer X with difficulty under the influence of catalytic amounts of hydrogen peroxide at 20°, whereas acid VIII under the same conditions quite readily gives a polymeric product identical to polymer IX with respect to the IR spectroscopic data. It might be assumed that in the oxidation of thione IV with hydrogen peroxide acid VIII is formed initially and then undergoes polymerization.

Depending on the reaction conditions, in the oxidation of sulfide I we isolated two compounds - 2-benzimidazolyl vinyl sulfoxide (XI) and 2-benzimidazolyl vinyl sulfone (XII) [6]:



The IR spectra of XI and XII contain absorption bands of a vinyl group bonded to a sulfur atom at 1590 cm⁻¹. The vibrations of the SO group in sulfoxide XI are characterized by a band at 1055 cm⁻¹ and the vibrations of the SO₂ group in sulfone XII are characterized by two high intensity bands at 1150 and 1345 cm⁻¹.

The divinyl derivative (II) of benzimidazole-2-thione behaves differently on oxidation. Oxidation under mild conditions leads to elimination of the grouping in the 2 position, as a result of which N-vinyl-2-benzimi-dazolone (XIII) was isolated:



The IR spectrum of XIII contains intense absorption bands at 1650 (C=C) and 1720 cm⁻¹ (C=O).

Similar splitting out of the thiovinyl grouping in the meso position of the azole ring was observed in the oxidation of benzoxazolyl vinyl sulfide [6]. The instability of the C=S bond in divinyl derivative II is due to the effect of two vinyl groups on the conjugation of the sulfur atom with the heteroring.

Raising the temperature and increasing the concentration of the oxidizing agent bring about polymerization of the oxidation product. We isolated a polymeric product (XIV) with mp $250-280^{\circ}$ in the reaction of II with acetyl hydroperoxide in ether at 20°. The absorption bands of vinyl groups are absent in the IR spectrum of polymer XIV, but frequencies of the vibrations of the CH_2 group (2930 and 2810 cm⁻¹) are present. The presence of absorption bands of SO, SO₂, and SO₃H groups constitutes evidence for the presence of oxidized sulfur in the product, and the intense absorption at 1712 cm⁻¹ (C=O) indicates participation of XIII in the polymerization.

It should be noted that oxidization of the vinyl group was not observed in the oxidation of I, II, and IV with peroxides; this is explained by the lower nucleophilicity of the vinyl group as compared with the sulfur atom.

EXPERIMENTAL

The IR spectra of KBr pellets and mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. Concentrated hydrogen peroxide and acetyl hydroperoxide were prepared by the method in [7]. The starting 2-benzimidazolyl vinyl sulfide (I) and N,S-divinyl-2-mercaptobenzimidazole (II) were obtained by the reaction of benzimidazole-2-thione (III) with acetylene under pressure [1, 6].

<u>N-Vinylbenzimidazole-2-thione (IV)</u>. A mixture of 3.03 g (15 mmole) of II and 3.72 g (60 mmole) of ethyl mercaptan in a sealed ampule was heated in a thermostat at 80° for 24 h, after which the mixture was cooled, and the resulting white acicular crystals were removed by filtration and washed with hexane to give 1.9 g (72%) of a product with mp 175° (from benzene). Found %: C 61.5: H 4.6: S 18.2. $C_9H_8N_2S$. Calculated %: C 61.3: H 4.6: S 18.2. IR spectrum, cm⁻¹: 1646 (C=C) and 1512 (HN-C=S).

Benzimidazole-2-sulfonic Acid (V). A 1.1-g (25 mmole) sample of 78% H₂O₂ was added with stirring at 20° to a suspension of 0.75 g (5 mmole) of thione III in 30 ml of glacial acetic acid, after which the mixture was heated to 70° for 4 h. The solvent was then removed by vacuum distillation, the residue was triturated with ether, and the solid material was removed by filtration and dried to give 0.98 g (90%) of white crystals with mp ~200° (mp 365-370° [2]). Found %: C 39.0; H 3.8; S 14.6. C₇H₆N₂O₃S·H₂O. Calculated %: C 38.9; H 3.7; S 14.8.

Benzimidazole-2-sulfinic Acid (VI). A 2-g (46 mmole) sample of 78% H₂O₂ was added dropwise at -5° to a suspension of 1.5 g (10 mmole) of thione III in 30 ml of acetone, after which it was allowed to stand at 20° for 6 h. The resulting precipitate was removed by filtration, washed with acetone, and dried to give 1.56 g (78%) of a product with mp 157°. Found %: C 42.2; H 4.0; S 16.0. C₇H₆N₂O₂S·H₂O. Calculated %: C 42.0; H 4.0; S 16.0. IR spectrum, cm⁻¹: 1050 and 1110-1245 (SO₂H).

<u>N-Vinylbenzimidazole-2-sulfonic Acid (VIII)</u>. A 1.5-g (14 mmole) sample of 70% acetyl hydroperoxide was added dropwise to a solution of 1 g (5.7 mmole) of IV in 30 ml of dry diethyl ether, and the precipitate that formed after 4 h was removed by filtration, washed with ether, and dried to give 1 g (73%) of a product with mp 135°. Found %: C 44.6; H 4.2; S 13.2. $C_9H_8N_2O_3S \cdot H_2O$. Calculated %: C 44.6; H 4.2; S 13.2. IR spectrum, cm^{-1} : 1650 (C=C); 1027, 1060, and 1154-1243 (SO₃H).

Poly (N-vinylbenzimidazole-2-sulfonic) Acid (IX). A 0.7-g (16 mmole) sample of 78% H_2O_2 was added dropwise to a solution of 0.88 g (5 mmole) of thione IV in 20 ml of acetone, after which the mixture was stirred for 4 h. The resulting precipitate was removed by filtration and washed with acetone and ether to give 0.7 g (60%) of a product with mp 260-300°. Found %: C 45.1; H 4.3; S 13.2. ($C_9H_8N_2O_3S \cdot H_2O_n$. Calculated %: C 44.6; H 4.2; S 13.2. IR spectrum, cm⁻¹: 2940 and 2830 (CH₂); 1050 and 1120-1240 (SO₃H).

<u>2-Benzimidazolyl Vinyl Sulfoxide (XI)</u>. A 0.24-g (5 mmole) sample of 78% H_2O_2 was added at -5° to 0.88 g (5 mmole) of sulfide I in 15 ml of acetone, after which the mixture was allowed to stand at 20-22° for 2 days. The solvent was then removed by distillation, and the residue was washed with ether to give 0.8 g (83%) of a product with mp 122° (from ethanol). Found %: C 56.1; H 4.3; S 16.6. $C_9H_3N_2OS$. Calculated %: C 56.2; H 4.2; S 16.7.

<u>2-Benzimidazolyl Vinyl Sulfone (XII)</u>. A 0.88-g (5 mmole) sample of sulfide I in 30 ml of diethyl ether was treated with 1.5 g (15 mmole) of 70% acetyl hydroperoxide, initially at -10° and subsequently at 20°. After 2 days, the resulting precipitate was removed by filtration to give 0.62 g (60%) of a product with mp 167° (from ethanol) (mp 164.5-165.5° [6]). Found %: C 51.9; H 4.1; S 15.2. C₉H₈N₂O₂S. Calculated %: C 51.9; H 3.9; S 15.4.

<u>N-Vinyl-2-benzimidazolone (XIII)</u>. A 2.3-g (20 mmole) sample of 30% H₂O₂ was added at 20° to a solution of 4 g (20 mmole) of divinyl derivative II in 30 ml of acetic anhydride, after which the mixture was allowed to stand for 2 days. The solvent was then removed by distillation, and the residue was subjected to chromatography (with a column filled with Al₂O₃, elution with CHCl₃) to give 0.9 g (28%) of white crystals of XIII with mp 152° (from benzene) (mp 152-153° [8]). Found %: C 67.6; H 4.9; N 17.4. C₉H₈N₂O. Calculated %: C 67.4; H 5.0; N 17.5.

Oxidation of N.S-Divinyl-2-mercaptobenzimidazole (II). A 1.5-g (14 mmole) sample of 70% acetyl hydroperoxide was added dropwise at -10° to a solution of 1 g (5 mmole) of II in 20 ml of diethyl ether, after which the mixture was allowed to stand at 20-22° for 2 days. The solvent was then removed by distillation, the residue was triturated with dry acetone, and the solid material was removed by filtration to give 0.5 g of polymer XIV with mp 250-280°. Found %: C 49.2; H 4.6; S 17.0. IR spectrum, cm⁻¹: 1040 (SO); 1130, 1320 (SO₂); 1150-1220 (SO₃H).

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BEHAVIOR OF N, S-DIVINYL-2-MERCAPTOBENZIMIDAZOLE

IN THE THIYLATION REACTION

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N,S-Divinyl-2-mercaptobenzimidazole reacts with thiols under free-radical initiation conditions at both vinyl groups to give β -addition products, whereas it reacts with sulfur dioxide to give a stable complex. N-Vinylbenzimidazole-2-thione was obtained by heating the divinyl derivative of benzimidazole-2-thione in the presence of a mercaptan without a catalyst. The former on reaction with thiols under the influence of azobisisobutyronitrile readily forms N-(β -alkylthio)eth-ylbenzimidazole-2-thiones; in the presence of ionic catalysts, N-(α -alkylthio)ethylbenzimidazole-2-thiones are formed.

Thiols readily react with N-vinylbenzimidazole in the presence of free-radical initiators to give β -addition products [1]. The attachment of a vinyl group to the sulfur atom in the benzimidazole-2-thione molecule complicates the course of the thiylation reaction, in which connection one observes splitting out of the grouping in the 2 position of the heteroring [2]. The aim of the present research was the synthesis of a number of sulfides from N.S-divinyl-2-mercaptobenzimidazole (I) for subsequent testing of their biological activity. Moreover, we also proposed to obtain new sulfur-containing vinyl monomers, i.e., to direct the addition of the thiol to one of the vinyl groups of I in order to make it possible to subsequently synthesize polymeric preparations with prolonged action.

The thiylation of divinyl derivative I was investigated under homolytic and heterolytic conditions. Ethyl, propyl, butyl, and phenyl mercaptans were used as the thiols.

It was found primarily that disulfides of mercaptobenzimidazoles (II-V) are formed in yields up to 80% in the reaction of I with mercaptans in the presence of azobisisobutyronitrile (AIBN). Ultraviolet irradiation of the reaction mixture does not change the direction of the reaction.

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