HETEROCYCLIC BIOANTIOXIDANTS. 2.* INTERACTION OF 3-NITRO-4-SUBSTITUTED COUMARINS WITH MERCAPTANS

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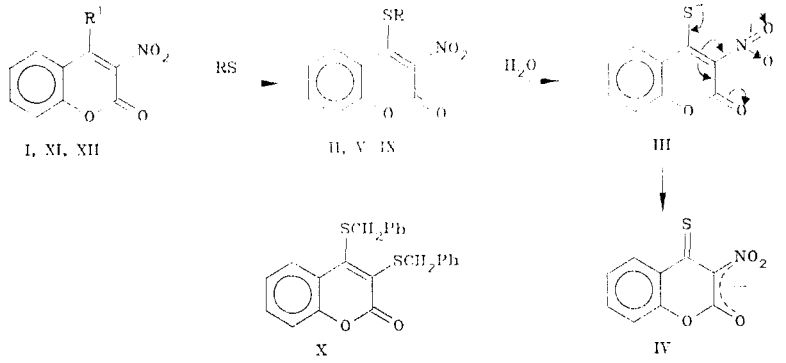
3-Nitro-4-chlorocoumarin forms 3-nitro-4-substituted coumarins when it reacts with an equimolar quantity of benzyl mercaptan or thiosalicylic acid; with excess benzyl mercaptan, it forms 3,4-di-S-benzyl coumarin. 3-Nitro-4-methoxycoumarin under the same conditions, with an equimolar ratio of reagents, forms a mixture of monosubstituted and disubstituted products. A mechanism is proposed for these reactions.

We had concluded previously [1] that the source of instability of 3-nitro-4-mercaptocoumarin (II) is the isomerization of its conjugated base III to the anion of the highly reactive thioketone IV. An attempt to fix the mercaptan II in the form of derivatives V-VII was also unsuccessful. Apparently, the total electron-acceptor effect of the carbonyl and nitro groups activates the S—R bond in the compounds V-VII so much that the compounds readily enter into hydrolytic conversions, and hence the expected derivatives cannot be detected in the reaction mixtures [1].

On this basis, we can conclude that in order to fix the mercaptan II, the derivatives must be selected so that the S—R bond is resistant to hydrolysis.



I R¹=Cl; II R=H; V R=SO_3Na; VI R = 3-nitro-4-coumarinylthio; VII R=COPh; VIII R=CH_2Ph; IX R=*o*-$HOOCC_6H_4$; XI R¹=OMe; XII R¹=NH_2

Actually, according to [2], the chlorocoumarin I in reaction with sodium benzyl mercaptide in ethanol forms the stable S-benzyl derivative VIII. In [3], however, it is stated that the chlorine atom in 3-nitro-4-chlorocoumarin (I) is replaced only in reactions with hard nucleophiles, and that in reactions with soft nucleophiles, in particular with sodium benzyl mercaptide, only the nitro group is replaced.

According to our experimental data, the interaction of equimolar quantities of the chlorocoumarin I and benzyl mercaptan in acetone or DMFA in the presence of pyridine or sodium bicarbonate leads to the formation of 3-nitro-4-S-benzylcoumarin (VIII) with a quantitative yield. Analogously, in a reaction with thiosalicylic acid (1:1 reactant ratio), the only product is 3-nitro-4-S-(o-carboxyphenyl)coumarin (IX).

*For Communication 1, see [1].

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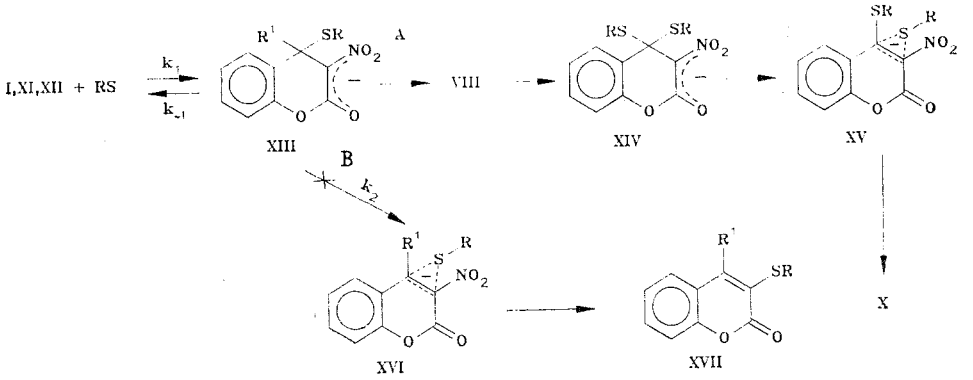
When a molar excess (2:1) of benzyl mercaptan is brought into the reaction, the only product is 3,4-di-S-benzyl coumarin (X), in agreement with the data of [2]. At the same time, in the interaction of equimolar quantities of 3-nitro-4-methoxycoumarin (XI) and benzyl mercaptan, we observed the formation of a mixture of mono- and di-S-substituted coumarins VIII and X, which is contradictory to the data of [2].

The results should be interpreted on the basis of specific mechanistic features of substitution in this activated coumarin system. Since the splitting—addition mechanism should be eliminated from consideration, in our examination of the carbanion mechanism [4] we should first of all consider stabilization of the intermediate anion XIII as a result of significant delocalization of charge.



Three paths are possible for this conversion: decomposition into the original reactants with a rate constant k_{-1}; decomposition with elimination of substituent R^1 (path A); and decomposition with elimination of the nitro group (path B). With a highly nucleophilic substituent R^1, the second variant is preferred; this is confirmed by our experiment on the interaction of equivalent quantities of the chlorocoumarin I with benzyl mercaptan or thiosalicylic acid. With a lower nucleophilicity of the substituent R^1, the slower decomposition of the intermediate XIII with the formation of the mono-S-substituted coumarin VIII creates the prerequisites for simultaneous existence of the intermediates XIII and XIV in the reaction mixture, these intermediates containing a tetrahedral carbon atom in position 4.

Particular attention should be given to the mechanism of the α-substitution process, which in the case of activated vinyl systems has been studied far less than the mechanism of β-substitution. According to [5], the mechanism includes a nonclassical bridge structure in which the bridge atom expands its electron shell above an octet. Only soft bases are capable of this.

Our experimental data are in accord with these concepts. Actually, replacement of the nitro group in the coumarins I and XI has been successful only in the reaction with benzyl mercaptan, but not by the action of excess methanol, as in obtaining compound XI from the coumarin I. Although the statement of Tabakovic et al. [3] regarding substitution of the nitro group in compound I by benzyl mercaptan and other soft nucleophiles is refuted by experiment, the theoretical possibility of selective α-substitution of 3,4-disubstituted coumarins apparently still remains valid. This reaction can be realized if conversion of the intermediate XIII through path B competes effectively with the other possible paths. The difference between schemes A and B is that in the first case, the bridge structure XV is obtained from the predecessor XIV, in which the role of the bridge can be played by either of the two RS groups in position 4, whereas in the second case, in the formation of the structure XVI, the predecessor XIII includes only one such group, which is to say that the probability of realizing the first scheme is higher.

The course of the process with scheme A through the formation of the product VIII could be suppressed by a further lowering of the nucleofuge properties of the substituent R^1. In order to test this prediction, we carried out the interaction of 3-nitro-4-aminocoumarin (XII) with potassium ethylxanthate in DMFA medium, and with potassium thiocyanate in alcohol; but in both cases, we recovered quantitatively the original coumarin XII. In this case, $k_2 << k_1$; and in a preparative experiment, it becomes impossible to observe the formation of the product XVII.

EXPERIMENTAL

The IR spectra were taken in a Perkin—Elmer 580 instrument in tablets with KBr. The TLC was performed on standard Silufol UV-254 plates.

The elemental analyses of the compounds for C, H, N, and S were consistent with the calculated values.

3-Nitro-4-methoxycoumarin (XI) was obtained by a method given in [2]; 3-nitro-4-aminocoumarin (XII) was obtained by amination of the chlorocoumarin I [6].

Interaction of 3-Nitro-4-chlorocoumarin (I) with Benzyl Mercaptan. A. To a suspension of 2.26 g (10 mmoles) of the chlorocoumarin I in 10 ml of acetone, a solution of 1.24 g (10 mmoles) of benzyl mercaptan and 0.8 ml (10.4 mmoles) of pyridine in 5 ml of acetone (18-20°C) was added dropwise with stirring over a period of 20 min, after which the stirring was continued for 1 h, and 40 ml of water was added. The precipitated crystals were separated by filtration, washed with water, and dried in air, obtaining 3-nitro-4-S-benzylcoumarin (VIII), mp 150-151°C (acetone—ethanol); according to [2], mp 153-155°C (benzene); R_f 0.53 (benzene—ethyl acetate, 19:0.7), R_f 0.35 (hexane—ether, 1:1). IR spectrum, ν, cm^{-1}: 1720 (C=O), 1605 (Ar), 1589 (C=C), 1540 and 1529 (NO_2). Yield 2.90 g (93%).

B. The reaction was performed in DMFA with the same ratio of reactants, using sodium bicarbonate in place of pyridine. The yield of the coumarin VIII was 88%.

C. In the same manner as in method **A**, 2.26 g (10 mmoles) of compound I was brought into reaction with 2.48 g (20 mmoles) of benzyl mercaptan in the presence of 1.6 ml (20.8 mmoles) of pyridine in acetone. Obtained 3,4-di-S-benzylcoumarin (X) with a yield of 3.64 g (93.4%), mp 89-90°C (ethanol—water); according to [2], mp 90°C; R_f 0.54 (hexane—ether, 2:1). IR spectrum, ν, cm^{-1}: 1720 (C=O), 1602, 1584 (C=C).

Interaction of 3-Nitro-4-chlorocoumarin (I) with Thiosalicylic Acid. This was carried out by method **B**, using two molar equivalents of sodium bicarbonate. The reaction mixture, after completing the reaction, was diluted with water, and the product was separated by the addition of concentrated HCl. Obtained 3-nitro-4-S-(o-carboxyphenyl)coumarin (IX, $C_{16}H_9NO_6S$), mp 253-254°C (water). IR spectrum, ν, cm^{-1}: 2500-3500 (OH), 1743- and 1683 (C=O), 1604 and 1594 (C=C); δ_{OH} 1548 cm^{-1}. Yield 94%.

Interaction of 3-Nitro-4-methoxycoumarin (XI) with Benzyl Mercaptan. This reaction was carried out by method **B**, using triethylamine. After diluting the reaction mixture with water, the semiliquid substance that was precipitated was triturated with a small quantity of alcohol. The resulting solid substance (0.39 g) was recrystallized from a mixture of 3 ml of methanol and 2 ml of acetone, obtaining 0.09 g of the coumarin VIII, mp 147-148°C, identical to the coumarin VIII synthesized in the previous experiment as determined by the IR spectrum and chromatographic mobility. The mother solution was evaporated down, and the residue was deposited in a chromatographic column with silica gel and eluted, first with 5% and 10% mixtures of ether with hexane, then with chloroform. From the first fractions, the coumarin X was recovered, and from the subsequent fractions another 0.05 g of the coumarin VIII. The total yield of the coumarin VIII was 0.14 g (23%). The yield of the coumarin X was 0.24 g (63%). On the basis of the melting point, IR spectrum, and chromatographic mobility, this compound was identical to compound X obtained in the preceding experiment.

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