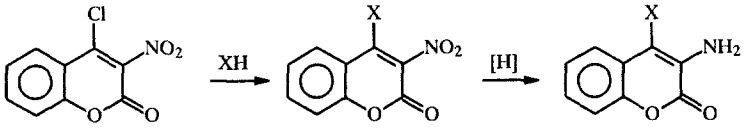
2. S. K. Ogorodnikov and G. S. Idlis, *The Manufacture of Isoprene* [in Russian], Khimiya, Leningrad (1973).
3. S. I. Zhdanov, *Liquid Crystals* [in Russian], Khimiya, Moscow (1979).
4. A. A. Gevorkyan, A. S. Arakelyan, and P. I. Kazaryan, *Khim. Geterotsikl. Soedin.*, No. 8, 1025 (1981).

HETEROCYCLIC BIOANTIOXIDANTS. 3.* EFFECT OF A SUBSTITUENT ON THE RESULT OF THE REDUCTION OF 3-NITRO-4-HETERO-SUBSTITUTED COUMARINS WITH SODIUM HYDROSULFITE

É. A. Parfenov and L. D. Smirnov

The effect of a heterosubstituent on the result of the reduction of 3-nitro-4-substituted coumarins with sodium hydrosulfite, which generally leads to a mixture of three compounds, viz., the product of the reduction of the nitro group to an amino group and products of its replacement by hydrogen or a mercapto group, was studied. The result of the transformation is explained by the stabilizing effect of the heterosubstituent on the reaction intermediate.

To synthesize three types of coumarin reductones [2] V-VII, which contain an amino group in the 3 position and an amino, hydroxy, or mercapto group in the 4 position, we used a synthetic scheme based on nucleophilic substitution of the activated halo group in 3-nitro-4-chlorocoumarin (I) [3] and subsequent reduction of the nitro group in intermediates II-IV.



I II-IV V-VII

II, V a X=NH_2, b X=$NHCH_3$, c X=$NHCH_2CH{=}CH_2$, d X=$NH(CH_2)_2OH$, e X=$NHCH_2C_6H_5$, f X=NHC_6H_5, g X=NHC_6H_4COOH-*o*, h X=$N(C_3H_7)_2$, i X=$N(CH_2)_4$, j X=$N(C_2H_5)_2$; III, VI a X=OH, b X=OCH_3; IV, VII a X=$SCH_2C_6H_5$, b X=SC_6H_4COOH-*o*

Previously, for the synthesis of 3,4-diaminocoumarins V we used catalytic hydrogenation with palladium on carbon [3, 4]; this method has drawbacks, among which are the consumption of a precious metal, as well as the impossibility of introducing of unsaturated groupings and groupings that are sensitive to hydrogenolysis into the composition of the 4-N-substituents in reductones V.

In testing various approaches, we obtained unsatisfactory results in the reduction of 3-nitro-4-aminocoumarins II to the corresponding reductones V with stannous chloride dihydrate in a nonaqueous medium [5] and with sodium borohydride in the presence of hydrogen-transfer catalysts, including Ni(II), Co(II) [6], and Cu(II) [7] salts, as well as nickel and cobalt borides [8]. According to the data in [9], the salt of formic acid with triethylamine reduces the carbon—carbon double bond in 3,6-dinitrocoumarin, whereas it is recommended that the reduction of the nitro group in aromatic compounds be carried out with formic acid or its salts in the presence of a catalyst — palladium on carbon [10]. According to our data, formic acid and its

*See [1] for Communication 2.

All-Union Science Center for the Safety of Biologically Active Substances, Kupavna Moscow Region, 142450.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 329-334, March, 1992. Original article submitted February 12, 1990.

0009-3122/92/2803-0274$12.50

TABLE 1. Characteristics of the Reduction Products

Compound	Empirical formula	mp,* °C	IR spectrum (KBr), ν, cm^{-1}			Yield, %
			NH_2, NH, OH	C=O	C=C, Ar	
Vc	$C_{12}H_{12}N_2O_2$	80...81	3364, 3303	1668	1626, 1586, 1564**, 3090...3000 (=CH—)	72
Vd	$C_{11}H_{12}N_2O_3$	102	3400...3245	1661	1619, 1599, 1565, 1540**,***	74
VIb	$C_{10}H_9NO_3$	83...84	3488...3318	1702...1692	1637, 1591	35
VIIa	$C_{16}H_{13}NO_2S$	101...102	3472, 3364	1711, 1693	1606, 1580	27
VIIb	$C_{16}H_{11}NO_4S \cdot 1{,}5H_2O$	226...227	3454, 3352	1704	1609, 1585	21
VIII	$C_{10}H_8O_3$	120...122	—	1700...1683	1620, 1602	28
Xa	$C_{16}H_{12}O_2S$	177...178	—	1718	1603, 1592	42
Xb	$C_{16}H_{10}O_4S$	224...225	3500...2500 (δ_{OH} 1562)	1684	1611, 1587	25
XI	$C_{16}H_{10}O_4S_2 \cdot H_2O$	337...338	3500...2500 (δ_{OH} 1560)	1701	1617, 1602	19

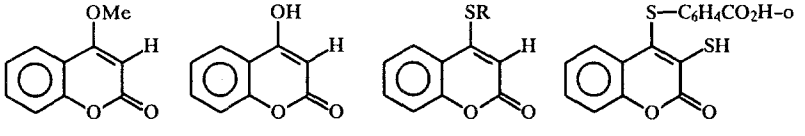
*The compounds were crystallized: Vc from 60% methanol, VIb and VII from 10% methanol, VIIa from ethanol—chloroform (5:1), Xa from ethanol—dioxane (2:1), and the remaining compounds from water.

**Superimposition of the δ_{NH} band is possible.

***ν, cm^{-1} (DMSO): 1696 (C=O), 1622 and 1578 (C=C).

ammonium and sodium salts do not react with 3-nitro-4-diethylaminocoumarin (IIj) at 18-20°C even with the addition of Raney nickel, but in the presence of palladium on carbon 3-amino-4-diethylaminocoumarin (Vj) is formed in 60-70% yield. When we used another hydrogen donor — sodium hypophosphite monohydrate — we were also able to carry out the reduction of the nitro group to an amino group in the presence of Raney nickel. However, reduction by this method [1] was accompanied by the formation of a small amount of a difficult-to-separate impurity with an unestablished structure.

The most satisfactory results were obtained when we turned to the use of sodium hydrosulfite as the reducing agent and when we carried out the reaction in an aqueous organic solvent in the presence of a weak base. In this case, after dilution of the reaction mixture with excess water, one can isolate the reduction products, which, as a rule, do not require additional purification. We used this method to obtain 3,4-diaminocoumarins Va-i. The reduction of 3-nitro-4-hydroxycoumarin (IIIa) with sodium hydrosulfite proceeded just as unambiguously — with the formation of only one product, 3-amino-4-hydroxycoumarin (VIa). The reduction of 3-nitro-4-methoxycoumarin (IIIb) under the same conditions leads to a mixture of the expected 3-amino-4-methoxycoumarin (VIb) and a product of replacement of the nitro group in starting coumarin IIIb by hydrogen — 4-methoxycoumarin (VIII).



VIII IX X XI

X a R=$CH_2C_6H_5$, b R=C_6H_4COOH-*o*

The ratio of products VIb and VIII depends on the conditions under which the reaction is carried out: 3-amino-4-methoxycoumarin (VIb) predominated in aqueous methanol with added sodium acetate, while 4-methoxycoumarin (VIII) predominated when sodium acetate was replaced by sodium bicarbonate.

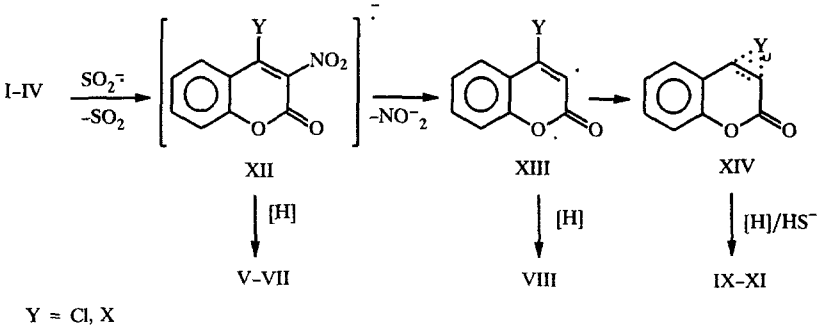
3-Nitro-4-chlorocoumarin (I) is hydrolyzed quite readily in weakly alkaline media to give 3-nitro-4-hydroxycoumarin (IIIa) [2]. If it is assumed that the rate of hydrolysis of 3-nitro-4-chlorocoumarin (I) under the conditions of its reduction with

sodium hydrosulfite (in an aqueous medium with added pyridine) is higher than the rate of reduction of the nitro group, the formation of 3-amino-4-hydroxycoumarin (VIa) as the only product should have been expected. In fact, the only product that was isolated from the reaction mixture in the reduction of coumarin I was 4-hydroxycoumarin (IX). This result makes it possible to assert that replacement of the chlorine atom by a hydroxy group in I is completed after its reduction.

Like IIIb, 3-nitro-4-(benzylthio)coumarin (IVa) upon reduction with sodium hydrosulfite under similar conditions is also converted to a mixture of two compounds — 3-amino-4-(benzylthio)coumarin (VIIa) and 4-(benzylthio)coumarin (Xa); the ratio of the products depends on the solvent selected. However, replacement of the benzyl residue in starting coumarin IVa by a 2-carboxyphenyl residue leads to a different result — the formation of, in addition to the expected products, viz., 3-amino-4-(2-carboxyphenylthio)coumarin (VIIb) and a product of replacement of the nitro group by hydrogen (Xb), a product of a new transformation pathway, viz., 3-mercapto-4-(2-carboxyphenylthio)coumarin (XI).

The individuality and structures of the reduction products obtained were confirmed by the melting points (for the known compounds), the results of analytical chromatography and elementary analysis, and the IR and PMR spectra (Table 1). The IR spectra of diaminocoumarins V are in agreement with the literature data [3]. A characteristic feature of 3-aminocoumarins V-VII is the presence of two absorption bands of stretching vibrations of an NH_2 group at 3300-3500 cm^{-1}. A signal of an olefinic proton in the PMR spectra of the products of replacement of the nitro group by hydrogen is observed at $\approx$6 ppm, which makes it possible to assign 4-substituted coumarin VIII-X structures to them, since the $C_{(4)}$—H signal should show up at substantially weaker field [15]. The presence of a mercapto group in coumarin XI was confirmed by, in addition to the results of elementary analysis, precipitation in the form of the copper(I) salt, reaction with $PdCl_2$, and catalytic acceleration of the iodine—azide reaction. At the same time, the results of elementary analysis and the IR spectroscopic data (the absence of an intense absorption band at 1090 cm^{-1}) do not confirm the alternative sulfinic acid structure that might have developed as a result of attack by the sulfoxylate ion HSO_2^-, since the latter can be generated in sodium hydrosulfite solutions [16].

The results obtained in the reduction of 3-nitro-4-hetero-substituted coumarins I-IV with sodium hydrosulfite provide evidence for the important directing effect of the heterosubstituent in the 4 position on the result of the transformation of the nitro-olefin fragment of the coumarin molecule. Depending on the type of heterosubstituent in the 4 position, three types of transformations with the participation of the nitro group are possible: reduction to NH_2; replacement by hydrogen under the influence of chlorine, sulfur, and, to a lesser extent, oxygen; and replacement by a mercapto group (noted only in the presence of sulfur). The described effect evidently does not have literature analogies [16], although examples of the reductive cleavage of the γ-C—NO_2 bond, which has as its result replacement of the nitro group by hydrogen or an S-nucleophile, including a mercapto group, are quite well known [17, 18]. An $S_{RN}1$ mechanism has been formulated for transformations of this sort for nitro-substituted aliphatic compounds [19].



Considering the ability of sodium hydrosulfite solutions to generate the powerful one-electron-transfer agent, the sulfur dioxide anion radical, via the equation $S_2O_4^{2-} \rightleftarrows 2SO_2^{-\cdot}$ [20] and hydrogen sulfide in a more complex chain of transformations [21], a similar scheme may also be assumed for the transformations of 3-nitro-4-heterosubstituted coumarins I-IV under the influence of sodium hydrosulfite solutions.

According to this scheme, the result of the reaction is determined by the relative stabilities of the two reaction intermediates, viz., anion radical XII or free-radical particle XIII, which develops after cleavage of the $C_{(3)}$—N bond. A comparison of nitrogen and oxygen as the substituent atoms in the 4 position of the starting nitrocoumarin makes it possible to assert that the more electronegative oxygen atom should polarize the $C_{(3)}$—N bond to a greater extent and thereby assists in its cleavage, which was also observed in the reduction of coumarin IIIb with a methoxy group in the 4 position. 4-Hydroxy-

3-nitrocoumarin (IIIa) is ionized under the reduction conditions (in a weakly alkaline medium), and the O^- substituent gives rise to an electropositive effect and transformation of the type observed for 4-amino-substituted coumarins IIa-j.

In contrast to nitrogen and oxygen atoms, chlorine and sulfur atoms are capable of expanding their valence shells, and they can therefore stabilize the radical particle in the form of bridged intermediate XIV. Since opening of the three-membered ring in it in the case of attack by hydrogen takes place with the formation of only 4-substituted coumarins IX and X, the 3 position can be considered to be the preferred site of addition of the mercapto group.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Perkin—Elmer 580 spectrometer. The PMR spectra were obtained with a Varian T-60 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. Thin-layer chromatography was carried out on standard Silufol UV-254 plates in a benzene—ethyl acetate (38:3) or benzene—ethyl acetate (2:1) system, as well as in a benzene—acetone (3:1) system (for analysis of the more polar products). The melting points of the known coumarins Va, b, e-j, VIa, VIII, and IX were in agreement with the literature data [3, 4, 12-14].

The results of elementary analysis were in agreement with the calculated values.

3-Amino-4-diethylaminocoumarin (Vj). A. A mixture of 11.84 g (45.1 mmole) of 3-nitro-4-diethylaminocoumarin (IIj) with 80 ml of dioxane and 230 ml of water containing 2.2 g of Raney nickel catalyst was heated to 60°C, after which 18.8 g (180.4 mmole) of sodium hypophosphite monohydrate was added in small portions with stirring in the course of 2 h to the reaction mixture while not allowing the temperature to increase above 70°C. The mixture was then stirred for another 40 min, after which it was cooled, mixed with 100 ml of chloroform, and separated from the catalyst. The substance extracted by the chloroform was washed with water and dried with sodium sulfate. The residue obtained after separation of the drying agent and the solvent was passed through a chromatographic column packed with silica gel (elution with benzene with an increasing amount of chloroform) and dissolved in absolute alcohol. The hydrochloride of coumarin Vj was isolated by passing hydrogen chloride through the solution. The yield was 9.63 g (80%).

B. The yield of coumarin Vj hydrochloride was 60-70% when the reaction was carried out with formic acid or its salts in the presence of 10% Pd/C by the method in [10] (isolation by method A).

General Method for the Reduction of 3-Nitro-4-heterosubstituted Coumarins I-IV with Sodium Hydrosulfite. A reaction mixture consisting of 20 mmole of 3-nitro-4-heterosubstituted coumarin I-IV and 80 mmole of sodium hydrosulfite was stirred for 10 min to 4 h (monitoring by TLC) at 18-20°C in an organic solvent [methanol, ethanol, dioxane, dimethylformamide (0-30 ml, usually ≈25 ml)]—water (100 ml) medium containing 100 mmole of a weak base (sodium acetate, sodium bicarbonate, ammonia, pyridine). The amine (Va-i, VIa) that precipitated after dilution of the reaction mixture with excess water was separated by filtration, washed with water, and air dried. Coumarin IX was isolated after acidification of the reaction mixture to pH 2. The compounds obtained generally did not require additional purification.

3-Amino-4-methoxycoumarin (VIb) and 4-Methoxycoumarin (VIII). A reaction mixture consisting of 0.53 g (2.4 mmole) of 3-nitro-4-methoxycoumarin (IIIb), 1.67 g (9.6 mmole) of sodium hydrosulfite, and 1.62 g (12.0 mmole) of sodium acetate trihydrate in a mixture of 5 ml of methanol and 20 ml of water was stirred for 1 h in a nitrogen atmosphere at 18-20°C. The resulting precipitate of aminocoumarin VIb, which, according to TLC in benzene—ethyl acetate (38:3) and benzene—acetone (2:1) systems, contained admixed coumarin VIII, was separated and washed with water. The filtrate obtained after isolation of the product was diluted with excess water, which made it possible to isolate 0.08 g of pure coumarin VIb. The crude product was purified with a column packed with silica gel (elution with benzene containing an increasing amount of chloroform) and yielded an additional 0.08 g of coumarin VIb.

When sodium acetate was replaced by sodium bicarbonate with retention of the remaining reaction conditions, workup gave 4-methoxycoumarin (VIII) (28%) as the chief product and aminocoumarin VIb as an impurity. PMR spectrum of VIII, δ, ppm ($CDCl_3$): 4.00 (s, 3H, OCH_3), 5.70 [s, 1H, $C_{(3)}H$], 7.1-7.8 (m, 4H, Ar).

3-Amino-4-(benzylthio)coumarin (VIIa) and 4-(Benzylthio)coumarin (Xa). A 0.5-g (1.6 mmole) sample of 3-nitro-4-(benzylthio)coumarin (IVa) [1] was reduced with 1.14 g (6.4 mmole) of sodium hydrosulfite in a mixture of 5 ml of DMF, 10 ml of water, and 1 ml of 25% ammonium hydroxide [monitoring by TLC in a benzene—ethyl acetate (19:1) system]. The precipitate was separated, and the filtrate was diluted with water to give 0.06 g of pure 4-(benzylthio)coumarin (Xa). Recrystallization of the crude product from dioxane gave 0.12 g of 3-amino-4-(benzylthio)coumarin (VIIa), and the mother liquor yielded an additional 0.12 g of coumarin Xa. PMR spectrum of Xa, δ, ppm ($CDCl_3$): 4.21 (s, 2H, CH_2), 6.19 [s, 1H, $C_{(3)}H$], 7.1-7.8 (m, 8H, Ar).

When the reaction was carried out in aqueous 20% ethanol, 42% of the starting 3-nitrocoumarin IVa was not reduced.

3-Amino-4-(o-carboxyphenylthio)coumarin (VIIb), 4-(o-Carboxyphenylthio)coumarin (Xb), and 3-Mercapto-4-(o-carboxyphenylthio)coumarin (XI). A 1.68-g (4.55 mmole) sample of 3-nitro-4-(o-carboxyphenylthio)coumarin (IVb) was reduced with 3.34 g (18.2 mmole) of sodium hydrosulfite in 42.5 ml of 1.5% ammonium hydroxide in the course of 1 h at 18-20°C. The resulting solution was filtered and, by gradually decreasing the pH to 1-2, separated into fractions enriched in the individual products [monitoring by TLC in a benzene—acetone (2:1) system]. For final purification the products were recrystallized from methanol and water. This procedure gave 0.33 g of coumarin VIIb (sesquihydrate), 0.34 g of coumarin Xb, and 0.30 g of coumarin XI (hydrate). PMR spectrum of coumarin Xb, δ, ppm (CF_3COOH): 5.90 [s, 1H, $C_{(3)}H$], 6.9-7.8 (m, 8H, Ar).

LITERATURE CITED

1. É. A. Parfenov and L. D. Smirnov, *Khim. Geterotsikl. Soedin.*, No. 11, 1476 (1991).
2. É. A. Parfenov and L. D. Smirnov, *Khim. Geterotsikl. Soedin.*, No. 8, 1032 (1991).
3. V. L. Savel'ev, O. S. Artamonova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, No. 3, 316 (1976).
4. V. L. Savel'ev, O. S. Artamonova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, No. 8, 1147 (1972).
5. R. S. Verma and G. W. Kabalka, *Chem. Lett.*, 243 (1985).
6. T. Saton, Y. Suzuki, S. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Lett.*, 4555 (1969).
7. J. A. Cowan, *Tetrahedron Lett.*, **27**, 1205 (1986).
8. A. Nose and T. Kudo, *Chem. Pharm. Bull.*, **36**, 1529 (1988).
9. K. Nanjo and M. Sekiya, *Chem. Pharm. Bull.*, **27**, 198 (1979).
10. I. D. Entwistle, A. E. Jackson, R. A. W. Johnstone, and R. P. Telford, *J. Chem. Soc., Perkin Trans. 1*, 443 (1977).
11. D. Monti, P. Gramatica, G. Speranza, and P. Manitto, *Tetrahedron Lett.*, **24**, 417 (1983).
12. V. L. Savel'ev, A. V. Makarov, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, No. 6, 845 (1983).
13. I. M. Heilbron and D. N. Hill, *J. Chem. Soc.*, 1707 (1927).
14. D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).
15. M. E. Perel'son, Yu. N. Sheinker, and L. A. Savina, *Spectra and Structures of Coumarins, Chromones, and Xanthones* [Russian translation], Meditsina, Moscow (1975), p. 91.
16. O. Lowis-Andre and G. Gelbard, *Bull. Chim. France*, 565 (1986).
17. N. Ono and A. Kaji, *Synthesis*, 693 (1986).
18. N. Kornblum and J. Widmer, *J. Am. Chem. Soc.*, **100**, 7086 (1978).
19. N. Kornblum, *Angew. Chem.*, **87**, 797 (1975).
20. D. O. Lambeth and G. Palmer, *J. Biol. Chem.*, **248**, 6095 (1973).
21. M. Wayman and W. J. Lem, *Canad. J. Chem.*, **48**, 782 (1970).