HETEROCYCLIC BIOANTIOXIDANTS.
5.* STABILIZATION OF 3-NITRO-4-COUMARINYLTHIOLATE BY AMMONIUM COUNTERIONS

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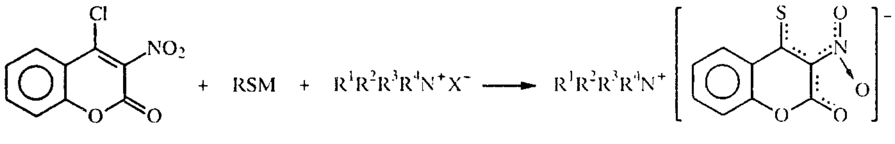
Thiolation of 3-nitro-4-chlorocoumarin in the presence of a substituted or unsubstituted ammonium ion can be used to isolate 3-nitro-4-coumarinylthiolates, which are stabilized by the corresponding ammonium cation, while 3-nitro-4-mercaptocoumarin or its potassium or sodium salts decompose during the reaction. Ammonium 3-nitro-4-coumarinylthiolates are decomposed by acids, and the unsubstituted ammonium salt is S-alkylated in the reaction with benzyl chloride.

In the course of synthesizing sulfur-containing coumarin reductones we attempted to introduce a mercapto group by reacting 3-nitro-4-chlorocoumarin (I) with organic and inorganic thiolating agents [2]. However, instead of the 3-nitro-4-mercaptocoumarin (II) that was anticipated, we obtained as reaction products 3-nitro-4-hydroxycoumarin (III), bis(3-nitro-4-coumarinyl)sulfide (IV) and an unidentified labile colored product V.

Further investigation into the 3-nitro-4-chlorocoumarin thiolation reaction has revealed that by introducing ammonium ions into the mixture the reaction can be stopped at the mercapto group addition stage. We have demonstrated this using as an example the synthesis and isolation of 14 compounds having the general formula VI.

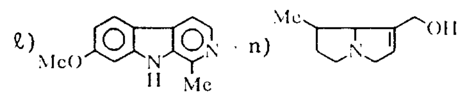


I

VI a-n

VIa-f, *l*, n) R^1 = H; a-f) R^2 = H; a, b, f) R^3 = H; a) R^4 = H; c) R^3 = Me; g, j) R^1 = R^2 = R^3 = Me; g) R^4 = Me; k, m) R^1 = R^2 = R^3 = Et; h) R^1 = R^2 = R^3 = R^4 = $CH_3(CH_2)_3$; m) R^4 = $(CH_2)_8CH_3$; i) R^1 = $(CH_2)_{15}CH_3$; j) R^4 = Ph; b, c, k) R^4 = CH_2Ph; f) R^4 = $C(S)NH_2$; d) $R^3R^4N{=}N{=}C(NH_2)_2$; e) $N{=}C(NH_2)NHN{=}CMe_2$

i) $R^2R^3R^4N$ = Py.



RSM = $Na_2S_2O_3$, Na_2S, NaHS

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*For communication 4, see [1].

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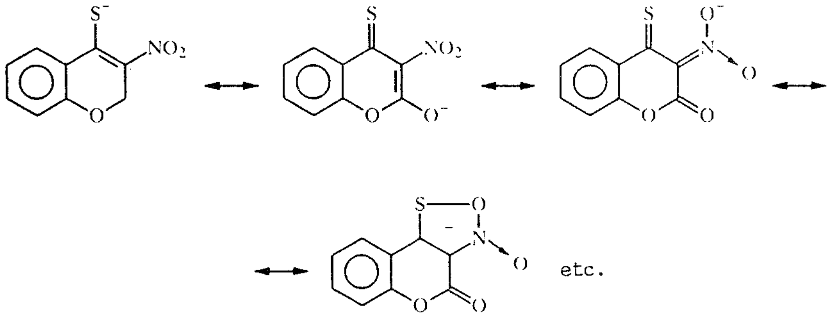
It is clear that the stabilizing effect is exhibited by any ammonium group $R^1R^2R^3R^4N^+$, where R^1, R^2, R^3, and R^4 are H, alkyl, aryl or aralkyl and the nitrogen atom can form part of the imino group or the nonaromatic heterocyclic ring. Thus, the only difference between the counterions in the shape of the H^+, Na^+, and K^+ cations on the one hand and similar strong acids in the form of the ammonium cations on the other, is the coordination saturation of the latter, which prevents the formation of chelate structures with the resonance stabilized 3-nitro-4-coumarinylthiolate counterion (VII).



VII

Compounds VIa-n shown in Table 1 were obtained by reacting 3-nitro-4-chlorocoumarin (I) with sodium sulfide or sodium thiosulfate in DMF (or better still in ethyl alcohol, which reduces separation losses) at 18-20°C in the presence of an equivalent amount of the appropriate ammonium ion. If sodium hydrosulfide is used as the thiolating agent, an organic base may be introduced into the reaction mixture instead of the stabilizing ammonium ion. The solubility of the resultant compounds VIa-n is governed by the nature of the ammonium cation.

The IR spectra of salts VIa-n displayed significant differences from the spectrum of 3-nitro-4-S-benzylcoumarin (VIII), a compound in which the single and double bonds are of the fixed type. For example, the $\nu C{=}O$ band in compounds VIa-n was shifted 18-43 cm^{-1} toward the low-frequency region, and the νNO_{2asym} band was displaced 16-30 cm^{-1} in the same direction. These differences suggest that there is considerable delocalization of the negative charge in the 3-nitro-4-coumarinylthiolate anion (VII).

It was useful to compare the spectral characteristics of ammonium salts VIa-n (Table 1) and the sodium salt of 3-nitro-4-hydroxycoumarin (IX). In the IR spectrum of the latter compound the carbonyl absorption vibration band was shifted 43 cm^{-1} toward the low-frequency region (the maximum value for ammonium salts VIa-n), while the νNO_{2asym} band, on the other hand, was displaced 38 cm^{-1} upfield relative to the spectrum of compound VIII. These spectral divergences suggest that the thiolate radical in structures VIa-n and the alcoholate radical in compound IX react with their counterion in different ways.

The above conclusion was confirmed by a comparison of UV spectra.* In terms of the position of its extreme points (λ_{max}, nm: 204, 242, 329; λ_{min}, nm: 230, 287) the sodium salt of 3-nitro-4-hydroxycoumarin (IX) was the same as 3-nitro-4-hydroxycoumarin (III), while the spectral characteristics of the tetrabutylammonium salt of 3-nitro-4-coumarinylthiolate (VIh) differed considerably in this respect (λ_{max}, nm: 213, 282, 335; λ_{min}, nm: 205, 260, 347).

The PMR spectrum of compound VIh corroborated the structure of the ammonium salt. It contained a broad multiplet from the aromatic protons of the coumarin moiety, while the cation was characterized by a triplet from the methylene group located by the nitrogen atom and a multiplet from the propyl radical protons.

The chemical behavior of the salts with general formula VI was in line with the outlined structural interpretation.

VIII

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*The authors would like to express their gratitude to V. G. Vinokurov and V. S. Troitskaya for recording the UV spectra.

TABLE 1. Characteristics of the 3-Nitro-4-coumarinylthiolate Ammonium Salts VIa-n

Compound	Empirical formula	mp, °C	IR spectra, ν, cm^{-1}				Yield, %
			NH, OH	C=O	C=C, Ar	NO_2	
VIa	$C_9H_8N_2O_4S$	> 150 (decomp.)	3394, 3300, 3255, 3220	1712	1630, 1609, 1541	1373, 1304	62
VIb	$C_{16}H_{14}N_2O_4S$	127...128 (decomp.)	3200...2800	1677, 1668	1602, 1520	1380, 1311	86
VIc	$C_{17}H_{16}N_2O_4S$	132...133	2975, 2953, 2772	1686	1602, 1585, 1522	1370, 1298	63
VId	$C_{10}H_{10}N_4O_4S$	170 (decomp.)	3430, 3330, 3188	1652	1600, 1518	1358, 1310	97
VIe	$C_{13}H_{15}N_5O_4S$	165...166 (decomp.)	3436	1684, 1652	1600, 1506, 1488	1372, 1302	77
VIf	$C_{10}H_{10}N_4O_4S_2$	> 120 (decomp.)	3440, 3272	1718, 1702	1604, 1510	1374, 1352	49
VIg	$C_{13}H_{16}N_2O_4S$	208...209	3034, 2923	1700, 1684	1605, 1585, 1520	1377, 1296	65
VIh	$C_{25}H_{40}N_2O_4S$	114...115	2967, 2880	1702, 1670	1603, 1522	1379, 1300	57
VIi	$C_{30}H_{42}N_2O_4S$	93...94	3060, 2920, 2851	1676, 1668	1605, 1585, 1577, 1485	1379, 1295	91
VIj	$C_{18}H_{18}N_2O_4S$	136...137 (decomp.)	3040, 3020	1700, 1663	1601, 1584, 1518	1372, 1300	64
VIk	$C_{22}H_{26}N_2O_4S$	102...103	2964, 2926, 2875, 2856	1698, 1689	1605, 1583, 1522	1378, 1294	89
VIl	$C_{22}H_{17}N_3O_5S$	172 (decomp.)	3300...2500	1700, 1668	1626, 1600, 1518	1368, 1298	99
VIm	$C_{24}H_{38}N_2O_4S$	Oil	2953, 2927, 2857	1698, 1680	1604, 1585, 1524	1376, 1293	92
VIn	$C_{17}H_{18}N_2O_6S$	Oil	3300...2600	1696, 1678	1603, 1582	1375, 1296	95

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*Compound VIa was crystallized from an alcohol–ether mixture; compounds VIb, c and *l* were crystallized from alcohol; VId from chloroform–hexane; VIe from chloroform–acetone; VIf from acetone–ether; VIg from alcohol–hexane; VIh from isopropyl alcohol; VIi-k from alcohol–water.

Thus, on reacting with benzyl chloride, ammonium thiolate VIa exhibited nucleophilic character, as was seen by the formation of the well-known 3-nitro-4-S-benzylcoumarin (VIII) [3].

On treatment with mineral acids all the ammonium thiolates VIa-n formed a colored product V, which could not be identified because of its lability. This transformation was in line with our previous unsuccessful attempts to synthesize 3-nitro-4-mercaptocoumarin (II) by thiolating 3-nitro-4-chlorocoumarin (I) [2].

EXPERIMENTAL

IR spectra of solid samples were taken on a Perkin–Elmer 580 and Specord 60 M in KBr tablets, with those of the liquid samples being recorded in thin films. UV spectra were registered on a Specord UV-VIS, $1 \cdot 10^{-4}$ M solutions being prepared in 50% ethyl alcohol, with cuvette thickness of 0.5 cm. PMR spectra were recorded in carbon tetrachloride solution on a Varian T60 spectrometer, internal standard HMDS. TLC was performed on standard Silufol UV 254 plates, with development in UV light. Silica gel L 40/100 (Chemapol) was used for column chromatography.

Elemental analysis data relating to C, H, N, and S contents was in line with calculated values for the synthesized compounds.

Tetrabutylammonium 3-Nitro-4-coumarinylthiolate (VIh). A mixture of 0.5 g (2.22 mmoles) of 3-nitro-4-chlorocoumarin (I), 0.55 g (2.22 mmoles) of sodium thiosulfate pentahydrate and 0.82 g (2.22 mmoles) of tetrabutylammonium iodide was stirred in 5 ml of DMF, the thiosulfate dissolving completely after 15 min. After dilution with 15 ml of water the resultant orange precipitate was separated off, washed with water and dried in air. Yield 0.59 g. PMR spectrum (δ, ppm): 7.04-8.82 (4H, m, Ar), 3.15 (8H, t, $4NCH_2$), 0.66-2.04 (28H, m, $4CH_2CH_2CH_3$).

Harminium 3-Nitro-4-coumarinylthiolate (VI*l*). A mixture of 0.5 g (2.22 mmoles) of 3-nitro-4-chlorocoumarin (I), 0.18 g (2.44 mmoles) of sodium hydrosulfide hydrate and 0.47 g (2.22 mmoles) of harmine was stirred in 8 ml of ethyl alcohol for 1 h at 18-20°C. Then, after dilution with 40 ml of water, the precipitate was filtered off, washed with water, and dried in air. Yield 0.95 g.

Acetone Amidinium Hydrazone 3-Nitro-4-coumarinylthiolate (VIe). A mixture of 0.5 g of 3-nitro-4-chlorocoumarin (I), 0.62 g (2.44 mmoles) of sodium sulfide nonahydrate and 0.30 g (2.22 mmoles) of aminoguanidinium nitrate was stirred for 1 h in 8 ml of ethyl alcohol at 18-20°C. Then the mixture was diluted with 10 ml of acetone, warmed for 15 min at 40°C and cooled. When the inorganic salts had been separated from the precipitate, it was concentrated by evaporation in vacuum and placed in a chromatography column packed with silica gel. After eluting with chloroform and mixtures of chloroform and acetone (up to 1:2), the fractions containing coumarin VIe were combined, then evaporated. Yield 0.58 g.

Coumarins VIa-d, f, g, i-k, m, and n (Table 1) were obtained in a similar way from the following reagents, respectively: ammonium chloride; benzylamine, methylbenzylamine, guanidine, and thiosemicarbazide hydrochlorides; tetramethylammonium bromide; cetylpyridinium bromide; phenyltrimethylammonium benzenesulfonate; benzyltrimethylammonium chloride; n-nonyltriethylammonium tosylate; and retronecine hydrochloride.

Sodium Salt of 3-Nitro-4-hydroxycoumarin (IX). A mixture of 0.30 g (1.45 mmoles) of 3-nitro-4-hydroxycoumarin (III) and 0.12 g (1.45 mmoles) of sodium bicarbonate was stirred in 3 ml of DMF at 18-20°C until the precipitate had completely dissolved (~30 min). The reaction mixture was then diluted with 15 ml of ether. The resultant greenish substance (colorless with a green tint) was filtered off, washed with ether, and dried in air. Yield 0.31 g (94%), mp 294-296°C with decomp. IR spectrum (ν, cm^{-1}): 1677 (C=O), 1616 and 1470 (Ar and C=C), 1578 (NO_{2asym}), 1375 and 1339 (NO_{2sym}).

3-Nitro-4-S-benzylcoumarin (VIII). A mixture of 0.5 g (2.22 mmoles) of 3-nitro-4-chlorocoumarin (I), 0.62 g (2.44 mmoles) of sodium sulfide nonahydrate and 0.14 g (2.64 mmoles) of ammonium chloride was stirred in 8 ml of ethyl alcohol at 18-20°C until the formation of ammonium 3-nitro-4-coumarinylthiolate (VIa) was shown to be complete from analytical TLC in a 1:2 benzene–acetone system (~30 min). Then 0.14 ml (2.55 mmoles) of benzyl chloride was added to the reaction mixture, which was stirred for 1 h at 18-20°C and a further 20 min at 60-65°C. After the bulk of the alcohol had been driven off in vacuum, the residue was diluted with 20 ml of water, then the precipitate was filtered off and dried in air. The crude product was placed in a chromatography column packed with silica gel and eluted with chloroform. Yield 0.34 g (49%), mp 149-150°C (149.5-150°C in [3]). IR spectrum (ν, cm^{-1}): 1720 (C=O), 1605 (Ar), 1590 (C=C), 1540 and 1529 (NO_2).

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