SYNTHESIS OF 3-NITRO-4-AMINO- AND 3,4-DIAMINOTHIOCOUMARINS*

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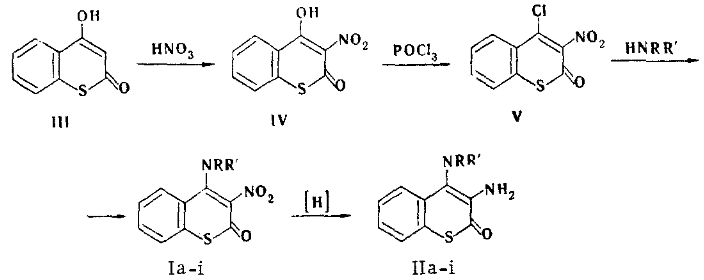
Nitration of 4-hydroxythiocoumarin gave 3-nitro-4-hydroxythiocoumarin, which was converted to 3-nitro-4-chlorothiocoumarin by the action of phosphorus oxychloride in dimethylformamide. The corresponding 3-nitro-4-aminothiocoumarins were synthesized by reaction of 3-nitro-4-chlorothiocoumarin with ammonia or amines. The 3-nitro-4-aminothiocoumarins were hydrogenated in alcohol over Raney nickel to give 3,4-diaminothiocoumarins. The β-aminovinylcarbonyl form of the 4-substituted 3-aminothiocoumarins was established on the basis of the UV, IR, and PMR spectra.

In contrast to the oxygen and nitrogen heteroanalogs – coumarin and carbostyril – little study has been devoted to the chemical properties of the heterocyclic ring of 1-thiocoumarin and substituted 1-thiocoumarins [2-4], whereas polyfunctional thiocoumarin derivatives, particularly 3-substituted 4-aminothiocoumarins, may be of particular interest as subjects for chemical and physicochemical studies.

We have synthesized a number of 3-nitro-4-amino- (Ia-i) and 3,4-diaminothiocoumarins (IIa-i):



I, II: a $R=R'=H$; b $R=H$, $R'=CH_3$; c $R=H$, $R'=C_4H_9$-*n*; d $R=H$, $R'=C_4H_9$-tert; e $R=H$, $R'=CH_2C_6H_5$; f $R=H$, $R'=C_6H_5$; g $R=R'=C_2H_5$; h $R+R'=(CH_2)_5$; i $R+R'=CH_2CH_2OCH_2CH_2$

Nitration of 4-hydroxycoumarin (III) with fuming nitric acid in a mixture of concentrated sulfuric and glacial acetic acids gave 3-nitro-4-hydroxythiocoumarin (IV), which by the action of phosphorus oxychloride in dimethylformamide (DMF) was converted to 3-nitro-4-chlorothiocoumarin (V) – the key compound for the synthesis of amino derivatives I and II. Compounds V were aminated to Ia-i by the action of excess ammonia or 2 moles of amine in absolute benzene solution. Diamines IIa-i were obtained by hydrogenation of nitro compounds Ia-i in alcohol over Raney nickel.

According to the PMR spectra, aminonitrothiocoumarins Ia-f exist in the thiocoumarin form. Thus the signal of the protons of the CH_2N group in the spectrum of Ie in solution in $(CD_3)_2SO-CDCl_3$ (1 : 2) appears at 4.4 ppm in the form of a doublet due to spin–spin coupling (SSC) ($J=6$ Hz) with the proton of the NH group, the broad signal of which is found at 8.5 ppm; when CD_3OD is added, the doublet is converted to a singlet (deuteration and exchange processes), and the signal at 8.5 ppm practically vanishes.

Dependent vibrations of the $C=O$ group are observed at 1615 cm^{-1}, i.e., in a longer-wavelength region than in the spectrum of thiocoumarin itself (1640 cm^{-1}), in the IR spectra (in chloroform) of Ig-i (Table 1), which are model compounds with a fixed amino group; in addition, there are characteristic absorption bands of double bonds of the cyclic system (1585 and 1570 cm^{-1}) and stretching vibrations of an NO_2 group (~ 1525 and ~ 1350 cm^{-1}).

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*See [1] for our preliminary communication.

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TABLE 1. Frequencies of the Characteristic Absorption Bands of 3-Nitro-4-amino- (Ia-i) and 3,4-Diaminothiocoumarins (IIa-i)

Compound	ν, cm^{-1}		Compound	ν, cm^{-1}	
	NH	C=O, C=C		NH	C=O, C=C
Ia[a]	3465, 3400, 3360, 3245 (δ_{NH} 1640[b])	1588, 1565	IIa	3385, 3350, 3310, 3230 (δ_{NH} 1650)[b]	1552, 1517
Ib[a]	3340	1585	IIb[f]	3450, 3350	1600, 1565, 1530
Ic[a]	3350	1586	IIc[a]	3405, 3340, 3300 (δ_{NH} 1615)[b]	1592, 1562, 1520
Ic[c]	3450	1610[d], 1597	IIc[f]	3440, 3360	1600, 1565, 1530
Id[a]	3360	1595	IId[f]	3480, 3370	1590, 1562, 1530
Id[c]	3348	1630, 1595, 1580	IIe[f]	3440, 3355	1600, 1565, 1530
Ie[a]	3360	1585	IIf[a]	3440, 3340, 3280	1596, 1588, 1562, 1530
Ie[c]	3450	1610[d], 1597	IIf[f]	3485, 3385	1600, 1565, 1530
If[a]	3340	1600, 1590	IIg[e]	3490, 3380	1600d, 1580, 1550d 1515
If[c]	3430, 3360	1630, 1597, 1580	IIh[a]	3450, 3340 (δ_{NH} 1608)[b]	1583, 1557, 1535, 1520
Ig[e]		1610, 1586, 1570	IIh[e]	3490, 3380	1600d 1580, 1550d, 1515
Ih[e]		1615, 1585, 1572	IIi[e]	3490, 3380	1600d, 1580, 1550d, 1515
Ii[e]		1620, 1590, 1582			

[a] The IR spectra of oil suspensions were recorded. [b] This band vanishes when the compound is deuterated. [c] Solution in chloroform (c 0.01 M, d 1.01 mm). [d] Shoulder. [e] Solution in chloroform (c 0.1 M, d 0.16 mm). [f] Solution in chloroform (c 0.01 M, d 0.6 mm).

TABLE 2. Data from the UV Spectra of 3-Nitro-4-amino- (I) and 3,4-Diaminothiocoumarins (II)

Compound	λ_{max}, nm	log ε
Ic	235; 261; 317	4,47; 4,09; 4,07
Ig	238; 266; 295; 353	4,40; 3,88; 3,87; 3,87
Ih	235; 265; 293; 352	4,32; 3,87; 3,84; 3,87
IIa	236; 278; 365	4,64; 3,96; 4,03
IIc	237; 257; 278; 371	4,40; 4,01; 4,00; 4,02
IId	235; 277; 373	4,54; 4,15; 4,06
IIe	237; 279; 372	4,51; 4,07; 4,06
IIg	227; 273; 364	4,47; 3,99; 3,97
IIh	225; 274; 366	4,55; 4,03; 3,99

The IR spectra of mineral oil suspensions of Ib-f, which have a secondary amino group, are characterized by the following absorption frequencies: 3350 (ν_{NH}), ~1590 (broad intense band, dependent vibrations of the carbonyl group and ring double bonds), ~1530 and ~1350 cm^{-1} (NO_2 group). The transition to solutions in chloroform in the case of Ic, e is accompanied by an increase in the frequency of the vibrations of the secondary amino group (3450 cm^{-1}) and partial resolution of the broad band in the region of the vibrations of the double bonds of the system (1597 and shoulder at 1610 cm^{-1}). In analogy with the spectra of 4-amino-3-nitrocoumarins [5], the band at 3450 cm^{-1} should be assigned to vibrations of a free amino group. In the case of Id, f passing to solutions in chloroform does not have a special effect on the absorption and form of the bands corresponding to the vibrations of the NH group (an additional band at 3430 cm^{-1} from the vibrations of a free amino group appears in the spectrum of thiocoumarin If) but does give rise to substantial changes in the region of absorption of the double bonds of the system: Bands are observed at 1630 (dependent vibrations of the C=O group) and ~1595 cm^{-1} (ring double bonds). The absence of vibrations of a free NH group in the spectrum of a solution of Id is probably determined by the great advantageousness of intramolecular hydrogen bonds between the NH and NO_2 groups due to repulsion of the bulky substituent attached to the amino group in the 4 position away from the nitro group [5].

Instead of the one long-wave absorption maximum at 317 nm observed in the spectra of I that contain a secondary amino group, the UV spectra of I (Table 2) with a tertiary amino group contain two maxima at 295 and 353 nm; this is evidently associated with the change in the electronic interaction of the amino and nitro groups with one another and with the π-electron system of the thiocoumarin ring.

TABLE 3. 4-Amino-3-nitrothiocoumarins (Ia-i)

Compound	mp, °C	Found, %		Empirical formula	Calc., %		R_f	Yield, %
		N	S		N	S		
Ia	268—269[a,b]	12,7	14,4	$C_9H_6N_2O_3S$	12,6	14,4	0,14	91
Ib	251—252[a,c]	11,6	13,4	$C_{10}H_8N_2O_3S$	11,9	13,6	0,17	56
Ic	164—164,5[d]	10,0	11,6	$C_{13}H_{14}N_2O_3S$	10,0	11,5	0,55	98
Id	144,5—145,5[e]	10,0	11,7	$C_{13}H_{14}N_2O_3S$	10,0	11,5	0,80	90
Ie	190,5—191[c]	9,0	10,4	$C_{16}H_{12}N_2O_3S$	9,0	10,3	0,44	88
If	218—219[a,f]	9,5	10,8	$C_{15}H_{10}N_2O_3S$	9,4	10,7	0,26	97
Ig	125—126[g]	10,0	11,6	$C_{13}H_{14}N_2O_3S$	10,1	11,5	0,90	94
Ih	166,5—167[g]	9,5	11,2	$C_{14}H_{14}N_2O_3S$	9,6	11,0	0,70	94
Ii	211—212[d]	9,5	11,0	$C_{13}H_{12}N_2O_4S$	9,6	11,0	0,71	82

[a] With decomposition. [b] From dioxane. [c] From alcohol. [d] From benzene. [e] From benzene–hexane (1 : 1). [f] From n-butanol. [g] From cyclohexane.

TABLE 4. 3,4-Diaminothiocoumarins (IIa-i)

Compound	mp, °C	Found, %		Empirical formula	Calc., %		R_f	Yield, %
		N	S		N	S		
IIa	237—237,5[a]	14,6	16,3	$C_9H_8N_2OS$	14,6	16,7	0,20	70
IIb	272—273[b]	13,5	15,4	$C_{10}H_{10}N_2OS$	13,6	15,5	0,21	75
IIc	106,5—107,5[c]	11,2	12,9	$C_{13}H_{16}N_2OS$	11,3	12,9	0,60	95
IId	186—187[c]	11,6	12,9	$C_{13}H_{16}N_2OS$	11,3	12,9	0,80	76
IIe	136—138[c]	9,9	11,3	$C_{16}H_{14}N_2OS$	9,9	11,4	0,55	87
IIf	201—203[d]	10,4	12,0	$C_{15}H_{12}N_2OS$	10,4	11,9	0,56	74
IIg	96—97[d]	11,1	12,8	$C_{13}H_{16}N_2OS$	11,3	12,9	0,76	65
IIh	144—145[c]	10,4	12,5	$C_{14}H_{16}N_2OS$	10,8	12,3	0,79	83
IIi	183—184[d]	10,6	12,2	$C_{13}H_{14}N_2O_2S$	10,7	12,2	0,59	61

[a] Purified by reprecipitation from dimethylformamide by the addition of water. [b] From alcohol. [c] From 70% alcohol. [d] From 80% alcohol.

The 3-NH_2 group in diaminothiocoumarins IIa-i has basic character, as a consequence of which they form salts with mineral acids. The PMR spectrum of IIe [in $(CD_3)_2SO$] is characterized by a doublet signal of the protons of the CH_2N group at 4.4 ppm ($J = 7$ Hz; SSC with the NH proton) and a triplet signal of the NH proton at δ 5.6 ppm ($J = 7$ Hz); the indicated SSC is confirmed by deuteration of a sample of the compound. Thus IIa-f exist in the thiocoumarin form. The protons of the 3-NH_2 group give a narrow singlet at 5 ppm; this constitutes evidence for rather rapid exchange of these two magnetically nonequivalent protons.

The IR spectra of IIb-f (in chloroform) contain two bands at 3440-3485 cm^{-1} (a narrow band, probably ν4-NH and ν_{as}3-NH_2) and 3350-3385 cm^{-1} (ν_s3-NH_2); in the spectra of IIg-i the stretching vibrations of the 3-NH_2 group show up in the form of narrow bands at 3490 and 3380 cm^{-1}. The frequency of the stretching vibrations of the carbonyl group (~1600 cm^{-1}) of diaminothiocoumarins IIb-i is reduced by ~40 and 10-15 cm^{-1}, respectively, as compared with the frequency for unsubstituted thiocoumarin and Ib-i. This phenomenon can be explained by conjugation of the carbonyl and 4-amino groups and by the formation of intramolecular hydrogen bonds between the C = O and 3-NH_2 groups. It is apparent from a comparison of the UV spectra of II that a hypsochromic shift of the long-wave absorption maximum is characteristic for IIg-i.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds (c $5 \cdot 10^{-5}$-$1 \cdot 10^{-4}$ M) were recorded with a Perkin–Elmer 402 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin–Elmer 457 spectrometer. The PMR spectra of the compounds on the δ scale were recorded with a Varian T-60 spectrometer. The course of the reactions and the degree of purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on activity IV Al_2O_3 with elution by chloroform (see Tables 3 and 4) or benzene and also on Silufol.

4-Hydroxythiocoumarin (III). This compound, with mp 210°C (from o-chlorobenzene), was synthesized by the method in [6]. IR spectrum: 1620 (C = O); 1580, 1550, and 1520 cm^{-1} (C = C bonds of the thiocoumarin ring).

3-Nitro-4-hydroxythiocoumarin (IV). A mixture of 1.06 g (16.5 mmole) of fuming nitric acid (sp. gr. 1.508) and 1.74 g (16.5 mmole) of concentrated H_2SO_4 was added dropwise with stirring to a suspension of 2.67 g

(15 mmole) of III in 40 ml of glacial acetic acid, and the mixture was stirred for 3 h. The resulting precipitate was removed by filtration and washed with cold water. Compound IV, with mp 142-143°C [dec., from benzene–cyclohexane (3:1)], was obtained in 94% yield. Found: N 6.3; S 14.2%. $C_9H_5NO_4S$. Calculated: N 6.3; S 14.4%. According to [4], IV has mp 139°C. IR spectrum: 1650 (C=O); 1580 (C=C); 1515 and 1390 cm^{-1} (NO_2).

3-Nitro-4-chlorothiocoumarin (V). A mixture of 7.3 g (0.1 mole) of absolute DMF and 15.3 g (0.1 mole) of phosphorus oxychloride was stirred for 30 min, after which a solution of 22.3 g (0.1 mole) of IV in 200 ml of DMF was added dropwise with stirring, and the mixture was stirred for 2 h. It was then diluted with cold water, and the precipitate was removed by filtration and washed with water. Compound V, with mp 176-177°C (from alcohol), was obtained in 93% yield. Found: Cl 14.4; N 6.0; S 13.2%. $C_9H_4ClNO_3S$. Calculated: Cl 14.7; N 5.8; S 13.3%. IR spectrum: 1640 (C=O), 1580 (C=C); 1540 and 1360 cm^{-1} (NO_2).

4-Amino-3-nitrothiocoumarins (Ia-i). A) A stream of dry ammonia was passed through a solution of 3.63 g (15 mmole) of V in 120 ml of absolute benzene for 30 min, after which the mixture was allowed to stand for 5 h. The resulting precipitate was removed by filtration and washed with water to give Ia.

B) A 0.02-mole sample of the corresponding amine was added dropwise with stirring to a solution of 2.42 g (0.01 mole) of V in 90 ml of absolute benzene, and the mixture was stirred at 20°C for 4-7 h. The resulting precipitate was removed by filtration, washed successively with benzene, 5% hydorochloric acid, and water, and dried to give Ib, c, e, i; the benzene-soluble Id, g, h were isolated from the benzene solutions after washing with 5% hydrochloric acid and water.

C) A solution of 3.63 g (15 mmole) of V and 3.07 g (33 mole) of aniline in 120 ml of absolute benzene was refluxed for 4 h, after which the precipitate was removed by filtration, washed successively with benzene, 5% hydrochloric acid, and water, and dried to give If. The data for I are presented in Table 3.

3,4-Diaminothiocoumarins (IIa-i). A suspension of 5 mmole of thiocoumarins Ia-i in 100 ml of alcohol was hydrogenated under the usual conditions over Raney nickel until hydrogen absorption ceased. In the case of IIa, b the precipitate was removed by filtration and dissolved in DMF; the catalyst was removed by filtration, and the products were precipitated by the addition of water (additional amounts of the products were obtained by evaporation of the alcohol filtrate). In the remaining cases the mixtures were filtered, and the precipitate was washed on the filter several times with alcohol and chloroform or acetone (for IIf); the combined solutions were evaporated, and the residue was crystallized from aqueous alcohol [in the case of IIi after trituration with ether–petroleum ether (1:1)] to give pure IIc-i. The data for IIa-i are presented in Table 4.

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