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RECYCLIZATION OF 2-IMINO-2H-1-BENZOPYRANS UNDER THE INFLUENCE OF NUCLEOPHILIC REAGENTS. 2.* REACTION OF 2-IMINOCOUMARIN-3-CARBOXAMIDES WITH *o*-AMINOBENZENESULFONAMIDE

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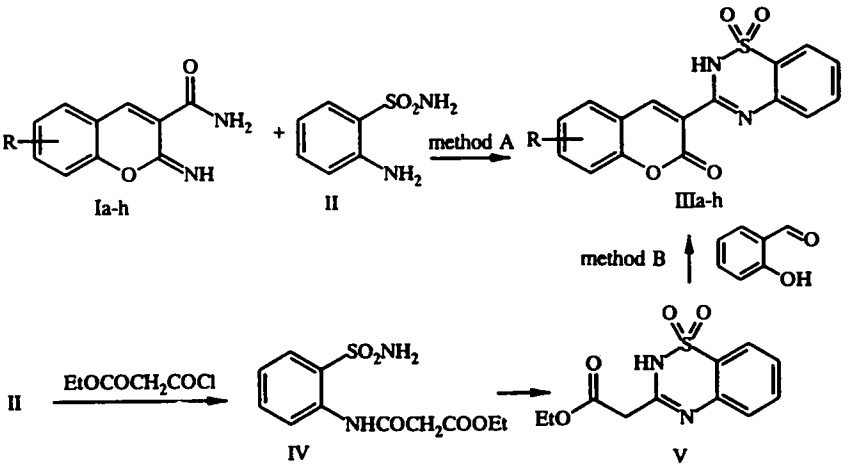
2-Iminocoumarin-3-carboxamides recyclized into 3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazinyl-3)coumarins under the influence of o-aminobenzenesulfonamide. An alternative method of synthesis is discussed. Proposed mechanisms for the recyclization are discussed.

In the preceding paper [1] we described the recyclization of 2-iminocoumarin-3-carboxamides into $N_{(1)}$-benzoylamidrazones of coumarin-3-carboxylic acids under the influence of N-nucleophiles, arenecarboxylic acid hydrazides. This recyclization process was successfully used for the effective synthesis of 3-hetarylcoumarins with 1,3,4-oxadi-, thiadi-, and triazole nuclei. In a continuation of this investigation we have studied the interaction of 2-iminocoumarin-3-carboxamides with *o*-aminobenzenesulfonamide.

Scheme 1



I,III a R = H; b 7-OH; c 6-OMe; d 6-Br; e 6-Cl; f 5,6-benzo; g 7-NEt_2 h 6-hexyl, 7-OH

When the reaction of 2-iminocoumarin-3-carboxamides Ia-h with *o*-aminobenzenesulfonamide (II) was investigated we observed the formation of a heavy precipitate when the reagents were boiled for 30-40 min in glacial acetic acid (method A).

*For part 1, see [1].

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TABLE 1. Characteristics of 3-(1,1-Dioxo-2H-benzo-1,2,4-thiadiazinyl-3)coumarins IIIa-h

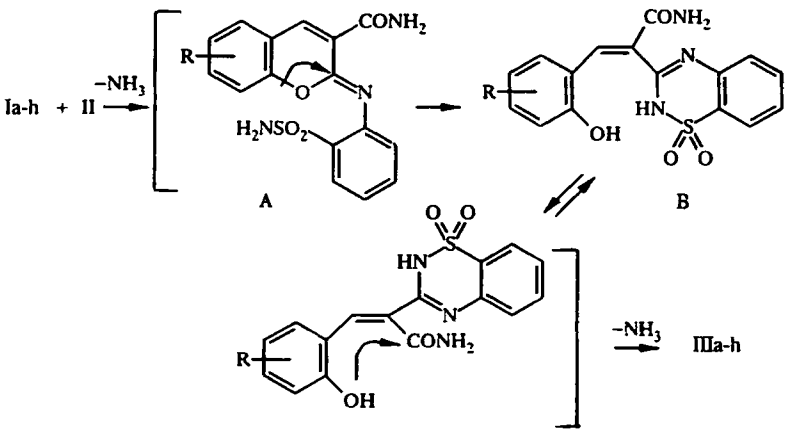
Compound	Molecular formula	(Found, %) (Calculated, %) N	S	mp, °C	IR spectra (KBr), ν, cm^{-1} (assignment)	Electronic spectra (dioxan), λ_{max}, nm (ε)	Yield, % (method)
IIIa	$C_{16}H_{10}N_2O_4S$	8,56 / 8,58	9,84 / 9,83	323...325	3153, 3113 (NH) 1717 (C=O) 1297/1175 (SO_2, as/s)	235(14500) 318(24100) 333(19200)	83 (A) 87 (B)
IIIb	$C_{16}H_{10}N_2O_5S$	8,18 / 8,18	9,38 / 9,37	>380	3166 br (NH + OH) 1705 (C=O) 1645 (C=N) 1296/1171 (SO_2, as/s)	248(11000) 367(26200)	70
IIIc	$C_{17}H_{12}N_2O_5S$	7,83 / 7,86	8,89 / 9,00	359...361	3168 (NH) 1688 (C=O) 1301/1176 (SO_2, as/s)	240(17700) 314(21100) 373(10400)	78
IIId	$C_{16}H_9BrN_2O_4S$	6,90 / 6,91	7,93 / 7,91	350...351	3151 (NH) 1706 (C=O) 1305/1176 (SO_2, as/s)	306(19300) 350(13900)	85
IIIe	$C_{16}H_9ClN_2O_4S$	7,75 / 7,76	8,90 / 8,89	353...355	3156 (NH) 1706 (C=O) 1303/1175 (SO_2, as/s)	304(19300) 350(14700)	80
IIIf	$C_{20}H_{12}N_2O_4S$	7,46 / 7,44	8,50 / 8,52	358...360	3156 (NH) 1719 (C=O) 1300/1171 (SO_2, as/s)	233(52600) 267(14800) 390(20300) 410(16700)	91
IIIg	$C_{20}H_{19}N_3O_4S$	10,59 / 10,57	8,06 / 8,07	346...348	3150 (NH) 1690 (C=O) 1660 (C=N) 1298/1172 (SO_2, as/s)	248(10600) 273(11800) 292(8100) 312(4500) 443(60900)	68
IIIh	$C_{22}H_{22}N_2O_5S$	6,55 / 6,57	7,51 / 7,52	306...308	3220, 3168 (NH + OH) 1689 (C=O) 1656 (C=N) 1304/1174 (SO_2, as/s)	251(12000) 375(26800)	72

TABLE 2. ^1H NMR Spectra of 3-(1,1-Dioxo-2H-benzo-1,2,4-thiadiazinyl-3)-coumarins IIIa-h (DMSO-D_6)

Compound	Chemical shift (δ), ppm, coupling constant (J), Hz			
	1H, s, NH	1H, s, 4-H	H_{arom}	other protons
IIIa	12,33	8,97	7,45...8,08 (8H, m)	—
IIIb	12,09	8,95	7,40...7,95 (5H, m) 6,86...6,97 (2H, m, 6-H; 8-H)	11,3 (1H, s, OH)
IIIc	12,23	8,95	7,36...8,00 (7H, m)	3,83 (3H, s, CH_3)
IIId	12,23	8,90	8,30 (1H, d, J = 1,3Hz, 5-H) 7,49...8,00 (6H, m)	—
IIIe	12,23	8,91	8,18 (1H, d, J = 1,2Hz, 5-H) 7,48...7,98 (6H, m)	—
IIIf	12,32	9,53	7,50...8,70 (10H, m)	—
IIIg	12,05	8,86	7,42...7,85 (5H, m) 6,88 (1H, dd, J = 7,8 and 1,2 Hz, 6-H) 6,70 (1H, d, J = 1,3 Hz, 8-H)	1,15 (6H, t, $N(CH_2\underline{CH_3})_2$) 3,52 (4H, q, $N(\underline{CH_2}CH_3)_2$)
IIIh	12,10	8,91	7,45...7,94 (5H, m) 6,85 (1H, d, J = 1,4 Hz, 8-H)	11,40 (1H, br. s.) 0,85...1,55 (13H, m)

Previously in a study of the reaction of 2-iminocoumarins with primary amines we established that 2-N-R-substituted iminocoumarins were formed in high yield in acetic acid [2]. It might be expected by analogy in this case that substitution would occur at the imino group to form 2-(N-[*o*-sulfamidophenyl]imino)coumarins. However, analysis of the spectroscopic data (Tables 1-3) showed that the reaction did not stop at the stage of formation of the 2-N-R-substituted iminocoumarins but proceeded further to give 3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazinyl-3)coumarins (IIIa-h) (Scheme 1). This may be explained if the reaction between the carboxamides Ia-h with o-aminobenzenesulfonamide occurred via recyclization to give the 3-hetarylcoumarins IIIa-h. Apparently a reaction of the "2-iminocoumarin + primary amine" type [2] occurs first to give 2-N-R-substituted iminocoumarins A (Scheme 2), followed by an attack by the second nucleophilic center (the nitrogen atom of the SO_2NH_2 group) at the carbon atom of the C=N bond of the intermediate A with opening of the "iminolactone" ring.

Scheme 2



Reaction of the recyclization type then occurs [1]: in consequence of *cis-trans* isomerization of intermediate B intramolecular reaction of the phenolic hydroxy group with the carbamide group leads to closing of the coumarin ring to give products IIIa-h.

For complete proof of the structure of the reaction products we carried out an alternative synthesis of 3-(1,1-dioxo-2H-benzo-1,2,4-thiadiazinyl-3)coumarin IIIa (Scheme 1, method B), which includes the following steps: preparation of the ethyl ester of the 2-aminosulfonylanilide of malonic acid (IV), its cyclization into ethyl 1,1-dioxo-2H-benzo-1,2,4-thiadiazinyl-3-acetate (V), and Knoevenagel condensation of salicyl aldehyde with the benzothiadiazine V. Compound IIIa was prepared in good overall yield by this method which, however, is complicated by the requirement to use ethoxymalonyl chloride.

It follows from the spectroscopic results (Tables 1-3) that the ν_{NH} band at about 3150 cm^{-1} in the IR spectra of the benzothiadiazines IIIa-h is broadened, and eroded significantly for the hydroxyl compounds IIIb and IIIh because of the superposition of the ν_{OH} band. The lactone $\nu_{C=O}$ appears as a strong band (except for compounds IIIb, IIIg, and IIIh with donor substituents in position 7 of the coumarin system) at 1719-1688 cm^{-1}. A $\nu_{C=N}$ band appears at 1645-1660 cm^{-1} for compounds IIIb, IIIg, and IIIh of about the same intensity as the $\nu_{C=O}$ band. Asymmetric and symmetric vibrations ν_{SO_2} (1305-1296 and 1176-1171 cm^{-1} respectively) were observed for all compounds IIIa-h.

The electronic spectra of the benzothiadiazines IIIa-h show a system of electronic transitions characteristic of 3-hetarylcoumarins [1]. The benzothiadiazine IIIa has two strongly overlapping bands ($\Delta\lambda_{max}$ 15 nm) of approximately equal intensity in the 270-390 nm region (Table 1). These bands behave differently when substituents are introduced into the coumarin ring. For example, introduction of a substituent at position 6 (compounds IIIc, d, and e) causes a bathochromic shift of 17-40 nm and a 1.5-2 fold decrease in intensity of the first band A (λ_{max} 333 nm), while the second band (λ_{max} 318 nm) remained in place (compound IIIc) or underwent a hypsochromic shift B (compounds IIId and e) without a noticeable change in intensity. The result of these shifts causes the long wave region of the spectra of compounds IIIc, d, and e to show a more marked two band structure. When a substituent was placed at position 7 (IIIb, f-h) an opposite response was observed: band B was noticeably shifted to longer wavelength (λ_{max} 373-443 nm) with an increase in intensity. Band A scarcely changed in wavelength but decreased in intensity and was observed as a shoulder on the short wavelength side of band B, so the spectra of compounds IIIb, e-h appear to be single banded in the lone wavelength region.

The ^1H NMR spectra of the benzothiadiazines IIIa-h (Table 2) include a broad signal for the NH proton at 12.05-12.32 ppm. The signals of the aromatic protons appear as a complex multiplet of the overlapping benzothiadiazine ABCD system and

TABLE 3. Mass Spectra of 3-(1,1-Dioxo-2H-benzo-1,2,4-thiadiazinyl-3)coumarins IIIa-h

Compound	m/z (I_{rel}, %)
IIIa	326(100), 262(59), 234(22), 205(9), 172(25), 155(73), 143(7), 138(10), 117(10), 103(6), 91(79)
IIIb	342(84), 278(63), 250(21), 217(13), 207(7), 188(47), 173(60), 155(100), 149(16), 139(20)
IIIc	356(56), 292(36), 249(6), 235(10), 207(17), 201(48), 185(13), 173(52), 167(27), 155(43), 149(100)
IIId	407(6), 406(31), 405(6), 404(31), 342(22), 340(21), 314(7), 312(7), 155(65), 143(8), 138(10), 114(15), 102(16), 91(100)
IIIe	362(15), 361(7), 360(41), 298(13), 297(6), 296(31), 268(11), 205(6), 177(6), 155(64), 138(10), 114(12), 91(100)
IIIf	377(24), 376(100), 312(45), 284(32), 255(13), 223(43), 221(60), 193(50), 164(22), 155(26), 142(29), 139(29), 128(29), 91(60)
IIIg	397(53), 382(100), 376(23), 354(8), 312(13), 284(8), 221(15), 193(13), 155(16), 91(39)
IIIh	427(25), 426(100), 363(14), 362(60), 356(15), 355(63), 327(7), 291(21), 272(28), 263(9), 201(9), 200(46), 193(6)

the corresponding ABCD, ABC, or AB system of the coumarin unit at 6.85-8.30 ppm (an additional doublet is observed in this region for the 5,6-benzo derivative IIIh). The singlet for the proton at position 4 of coumarin appears at 8.86-9.53 ppm. The mass spectra (Table 3) are characterized by an intense molecular ion peak and fragmentation ion peaks which confirm the structures of the compounds synthesized.

EXPERIMENTAL

IR spectra of the compounds synthesized in KBr disks were recorded with a Specord M-80 spectrometer. Electronic spectra of ethanol solutions were recorded with a Specord M-40 spectrometer. ^{1}H NMR Spectra of DMSO-D_6 solutions with TMS as internal standard were obtained with a Bruker WP-200 machine. Mass spectra were obtained with a Finnigan MAT-4615B machine with ballistic heating of the samples and an ionizing voltage of 70 eV.

General Method for the Synthesis of the 2-Iminocoumarin-3-carboxamides Ia-h. Equimolar amounts (0.01 mol) of the corresponding salicyl aldehydes and cyanoacetamide were dissolved in the minimal amount of ethanol and some drops of piperidine were added. The solution was stirred intensively. The precipitate was filtered off, dried, and crystallized from a suitable solvent.

General Method for the Preparation of 3-(1,1-dioxo-2H-1,2,4-thiadiazinyl-3)coumarins IIIa-h. Equimolar amounts (0.01 mol) of the 2-iminocoumarin-3-carboxamides Ia-h and *o*-aminobenzenesulfonamide II in glacial acetic acid (10-20 ml) were boiled for 15-30 min. The precipitate was filtered off, washed with ethanol, dried, and recrystallized from a suitable solvent.

Ethyl Ester of the 2-Sulfonylmalonic Acid (IV, $C_{11}H_{14}N_2O_2S$). Ethoxymalonyl chloride (1.66 ml, 0.011 mol) was added to a cooled and stirred mixture of *o*-aminobenzenesulfonamide II (1.72 g, 0.01 mol) and triethylamine (1.4 ml, 0.01 mol) in acetone (15 ml) and the mixture was kept at room temperature for 5-7 h. Water (100 ml) was added and the precipitated ester was filtered off, washed with water, and dried. Yield 2.4 g (78%), mp 142-144°C (from ethanol). ^{1}H NMR Spectrum (DMSO-D_6): 9.56 (1H, s, NH), 7.98 (1H, d, J = 8.0 Hz, H-3), 7.86 (1H, d.d., J = 7.8 and 1.6 Hz, H-6), 7.59 (1H, t.d., J = 7.6 and 1.6 Hz, H-5), 7.56 (2H, s, SO_2NH_2), 7.32 (1H, t.d., J = 7.6 and 1.2 Hz, H-4), 4.14 (2H, q, J = 7.2 Hz, OCH_2), 3.61 (2H, s, CH_2), 1.21 ppm (3H, t, J = 7.2 Hz, CH_3). Mass spectrum, *m/z* (*I*, %): 286 (14, M^+), 206 (100), 182 (12), 172 (97), 155 (73), 132 (12), 91 (32). Calculated: 286.31.

Ethyl Ester of the Acetic Acid (V, $C_{11}H_{12}N_2O_4S$). Ester IV (2.86 g, 0.01 mol) and a 10% aqueous Na_2CO_3 solution (20 ml) were stirred until solution was complete (about 30 min). The solution was brought to pH 3-4 with HCl. The precipitated benzothiadiazine V was filtered off, washed with water and dried. Yield 2.0 g (75%), mp 158-160°C (from ethanol). ^{1}H NMR Spectrum (DMSO-D_6): 12.3 (1H, s, NH), 7.82 (1H, d.d., J = 8.0 and 1.2 Hz, H-8), 7.69 (1H, t.d., J = 8.0 and 1.6 Hz, H-6), 7.46 (1H, t.d., J = 8.0 and 1.2 Hz, H-7), 7.32 (1H, d, J = 8.0 Hz, H-5), 4.15 (2H, q, J = 7.2 Hz,

OCH_2), 3.70 (2H, s, CH_2), 1.20 ppm (3H, t, J = 7.2 Hz, CH_3). Mass spectrum, m/z (I, %): 268 (100 M^+), 251 (5), 237 (22), 222 (95), 196 (36), 155 (99), 91 (93). Calculated: 268.29.

REFERENCES

1. S. N. Kovalenko, V. A. Zubkov, V. P. Chernykh, and S. M. Ivkov, Khim. Geterotsikl. Soedin., No. 2, 186 (1996).
2. V. A. Zubkov, S. N. Kovalenko, V. P. Chernykh and S. M. Ivkov, Khim. Geterotsikl. Soedin., No. 6, 760 (1994).