SYNTHESIS OF 4H-[1]BENZOPYRANO[3,4-c][1,2,5]THYADIAZOL-4-ONE AND ITS REACTIONS WITH SOME NUCLEOPHILIC AND ELECTROPHILIC AGENTS

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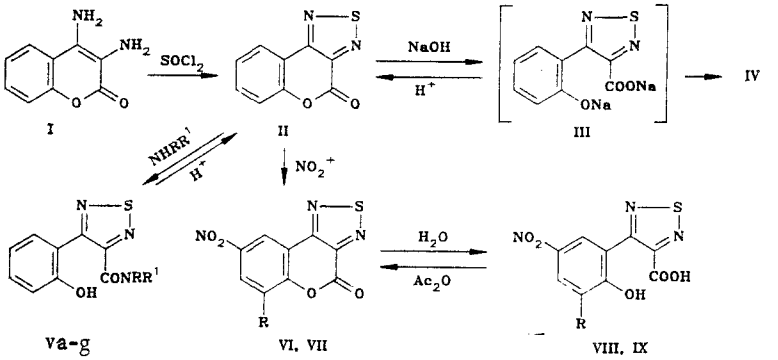
UDC 547.814.04'794.3:542.
958.1:543.422.25

The reaction of 3,4-diaminocoumarin with thionyl chloride gave 4H-[1]benzopyrano[3,4-c][1,2,5]thiadiazol-4-one (II), which was cleaved by the action of nucleophilic agents to the corresponding 4-(2-hydroxyphenyl)-1,2,5-thiadiazole-3-carboxylic acid derivatives. The nitration of II leads to the 8-nitro or 6,8-dinitro derivative; the latter was isolated in the form of 4-(2-hydroxy-3,5-dinitrophenyl)-1,2,5-thiadiazole-3-carboxylic acid.

In a continuation of our research on the synthesis of condensed systems on the basis of 3,4-diaminocoumarins [1, 2] we have accomplished the synthesis* of 4H-[1]benzopyrano[3,4-c]-[1,2,5]thiadiazol-4-one (II) by the reaction of 3,4-diaminocoumarin (I) with thionyl chloride and studied the chemical properties of this new heterocyclic system.

The IR spectrum of II (KBr pellet) contains an intense band at 1750 cm^{-1}, which is characteristic for the vibrations of the C=O group of the coumarin ring [4] (Table 1); a multiplet of a 9-H proton at 8.00 ppm and multiplet signals of protons with close chemical shifts at 7.63 (7H), 7.40 (6H), and 7.37 ppm (8H) are observed in the PMR spectrum at weak field. The assignment of the signals was made on the basis of a comparison with the PMR spectrum of coumarin [5] taking into account the spin–spin coupling constants (SSCC).

Coumarin II dissolves readily in cold dilute alkali with the formation of a yellow-green solution of sodium 4-(2-hydroxyphenyl)-1,2,5-thiadiazole-3-carboxylate (III), from which, in contrast to 4-(2-hydroxyphenyl)furazan-3-carboxylic acid [6], the free acid cannot be isolated – a precipitate of starting lactone II forms slowly from it on acidification of the alkaline solution. However, if salt III is treated with dimethyl sulfate, 4-(2-methoxyphenyl)-1,2,5-thiadiazole-3-carboxylic acid (IV) can be isolated upon acidification. The action of ammonia, amines, or hydrazine hydrate on II gives the corresponding amides (Va-f) or hydrazide (Vg) of the acid (Table 2), which undergo cyclization to coumarin II on treatment with hydrochloric acid. The ease of opening of the pyrone ring in II under the influence of nucleophilic reagents as compared with coumarin, for the cleavage of which, as is well known, more severe conditions are required, is due to the electron-acceptor effect of the thiadiazole ring, which increases the electrophilicity of the carbonyl center.



V a R=R¹=H; b R=H, R¹=*n*-Bu; c R=R¹=*n*-Bu; d R—R¹=$(CH_2)_4$; e R—R¹=$(CH_2)_5$; f R—R¹=$(CH_2)_2O(CH_2)_2$; g R=H, R¹=NH_2; VI, VIII R=H; VII, IX R=NO_2

*See [3] for our preliminary communication.

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow 125315. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 977-981, July, 1988. Original article submitted December 22, 1986.

0009-3122/88/2407-0805$12.50

TABLE 1. Frequencies of the Absorption Bands of the Carbonyl Groups in the IR Spectra

Compound	λ_{max}, cm^{-1}			Compound	λ_{max}, cm^{-1}		
	KBr pellets	in d_6-DMSO	in acetonitrile		KBr pellets	in d_6-DMSO	in acetonitrile
II	1750—1740	1771	1769	VII	1786	1794	1798
IV	1712	1720	1745	VIII	1702	1718	1741
VI	1771	1781	1780	IX	1712	1718	1741

The nitration of II with an equimolar amount of a nitrating mixture gave the 8-nitro derivative (VI), while the use of excess nitrating agent leads to the formation of dinitro derivative VII. The introduction of nitro groups increases the sensitivity of the pyrone ring to nucleophilic attack. Thus cleavage of the mononitro derivative 4-(2-hydroxy-5-nitrophenyl)-1,2,5-thiadiazole-3-carboxylic acid (VIII) occurs in the case of refluxing in water, whereas dinitro compound VII is unstable even under the reaction conditions, as a result of which acid IX was isolated. The reverse cyclization of acids VIII and IX to coumarins VI and VII is observed when they are refluxed in acetic anhydride. However, the activity of the carbonyl group of VII is so high that it is converted to acid IX when it is allowed to stand in solution in concentrated H_2SO_4 or upon brief refluxing in concentrated HCl.

Data from the PMR spectrum of VI constitute evidence that the nitro group enters the 7 or 8 position. On the basis of a comparison of the calculated and experimental [7] values of the chemical shifts with those that we obtained we established that the nitro group in VI occupies the 8 position. Thus the doublets at 8.70 and 7.68 ppm in the PMR spectrum of this compound were assigned to the 9-H and 6-H protons, while the doublet of doublets at 8.40 ppm was assigned to the 7-H proton (J_{67} = 9.0, J_{79} = 3.0 Hz). The evaluation of the chemical shifts for VII taking into account the contribution of two nitro groups shows that the signals with shifts 8.93 and 9.03 ppm (J = 3.0 Hz) correspond to the 9-H and 7-H protons. Two new doublet signals at 8.30 and 8.60 ppm (J = 3.0 Hz), the integral intensities of which gradually increase, appear in this spectrum with the passage of time. After a few hours, the spectrum obtained is completely similar to the spectrum of acid IX; this constitutes evidence for opening of the lactone ring of coumarin VII under the conditions of recording of the spectrum. The course of this transformation in solution in DMSO can also be followed by means of the IR spectrum: the band at 1794 cm^{-1} vanishes with time, and a band at 1718 cm^{-1}, the intensity of which gradually increases, appears.

Compounds VI and VIII or VII and IX can be readily identified from the frequencies of the carbonyl bands of the IR spectra (KBr pellets): an absorption band at 1771 and 1786 cm^{-1} is observed for the coumarin ring of VI and VII, respectively, while a band at 1702 and 1716 cm^{-1}, respectively, is observed for acids VIII and IX. The introduction of a nitro group into the aromatic ring of II gives rise to a successive shift of the frequency of the coumarin carbonyl group to the shorter-wave region [1769 (II), 1780 (VI), 1798 cm^{-1} (VII) in solution in acetonitrile]; this is due to an increase in the strength of the C=O bond under the influence of the electronic effects of the introduced nitro groups. At the same time, the introduction of nitro groups into the benzene ring of VIII and IX does not affect the frequency of the carboxy carbonyl group (1740 and 1741 cm^{-1}, respectively) as compared with 1745 cm^{-1} for model compound IV (in solution in acetonitrile, in which both the intermolecular and possible intramolecular bonds are virtually cleaved).

EXPERIMENTAL

The IR spectra of KBr pellets and solutions of the compounds in acetonitrile and d_6-DMSO were recorded with a Perkin-Elmer-580 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO were obtained with a Varian HA-100 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were recorded with a Varian MAT-112 spectrometer with a system for direct introduction of the samples into the ion source at 100-120°C and an ionizing voltage of 70 eV. The course of the reactions and the purity of the products were monitored by means of TLC on Silufol UV-254 plates in hexane—ethyl acetate (2:1) with development with UV light.

Starting diamine I was obtained by reduction of 3-nitro-4-aminocoumarin (X) with sodium hydrosulfite in an aqueous alcohol medium instead of by the previously described hydrogenation

TABLE 2. Characteristics of the Synthesized Amines Va-g

Compound	bp.,* °C	IR spectrum, cm^{-1} (KBr pellets)	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
Va	119—121	3307, 3280, 1659	49,0	3,2	19,3	14,3	$C_9H_7N_3O_2S$	48,9	3,2	19,0	14,5	81
Vb	83—85	3281, 3200, 1654	56,3	5,5	15,2	11,3	$C_{13}H_{15}N_3O_2S$	56,3	5,5	15,2	11,6	61
Vc	89—91	3118, 1625	61,0	6,9	12,6	9,5	$C_{17}H_{23}N_3O_2S$	61,2	7,0	12,6	9,6	84
Vd	167—169	3133, 1625	56,5	4,8	15,0	11,6	$C_{13}H_{13}N_3O_2S$	56,7	4,8	15,3	11,6	86
Ve	134—135	3138, 1620	58,0	5,2	14,6	10,9	$C_{14}H_{15}N_3O_2S$	58,1	5,2	14,5	11,1	90
Vf	180—183	3140, 1627	53,6	4,5	14,4	11,1	$C_{13}H_{13}N_3O_3S$	53,6	4,5	14,4	11,0	89
Vg	140—142	3337, 3288, 3182, 1685, 1670	45,7	3,5	23,6	13,3	$C_9H_8N_4O_2S$	45,8	3,4	23,7	13,6	93

*The compounds were recrystallized: Va, d, f from benzene, Vb, e from ethyl acetate—petroleum ether, Vc from benzene—hexane, and Vg from 2-propanol.

method [8]. Compound X was synthesized by a modified method [9] by reaction of 3-nitro-4-chlorocoumarin with aqueous ammonia in solution in dioxane.

3-Nitro-4-aminocoumarin (X). An 18-ml (0.25 mole) sample of concentrated ammonium hydroxide was added dropwise with stirring to a solution of 22.5 g (0.1 mole) of 3-nitro-4-chlorocoumarin [9] in 350 ml of dioxane, and the mixture was stirred for 2 h at room temperature. The resulting precipitate was removed by filtration, washed with water, and dried to give 19.2 g (93%) of X with mp 272-274°C (mp 271-273°C [9]).

3,4-Diaminocoumarin (I). A solution of 70 g (0.4 mole) of sodium hydrosulfite in 300 ml of water was added with stirring to a suspension of 20.6 g (0.1 mole) of X in 200 ml of alcohol, after which the mixture was stirred for 1 h at 60°C until the starting compound vanished. It was then cooled and diluted with water, and the resulting precipitate was removed by filtration, washed with water, and dried to give 13 g (74%) of a product with mp 203-205°C (dec.) (mp 201-205°C (dec.) [8]).

4H-[1]Benzopyrano[3,4-c][1,2,5]thiadiazole-4-one (II). A 16-ml sample of thionyl chloride was added dropwise with stirring and cooling to a suspension of 8.8 g (0.05 mole) of diamine I in 100 ml of absolute pyridine, after which the mixture was stirred for 3 h at room temperature. It was then poured over ice, and the aqueous mixture was acidified to pH 1-2 with concentrated HCl. The precipitate was removed by filtration, washed with water, and dried to give 8.9 g (87%) of II with mp 157-158°C [2-propanol–benzene (4:1)]. Found, %: C 53.1; H 2.0; N 13.8; S 15.7. M^+ 204. $C_9H_4N_2O_2S$. Calculated, %: C 52.9; H 2.0; N 13.7; S 15.7. M 204.2.

Action of Alkali on II. A suspension of 1.02 g (5 mmole) of II in 20 ml of 5% NaOH was maintained at room temperature for 1 h until the solid material had dissolved completely. The resulting yellow-green solution of salt III was separated into two different parts. One part of the solution was acidified cautiously with concentrated HCl and allowed to stand for 3 days. The precipitate, which formed gradually, was removed by filtration, washed with water, and dried to give 0.49 g (96%) of coumarin II.

4-(2-Methoxyphenyl)-1,2,5-thiadiazole-3-carboxylic Acid (IV). An alkaline solution of salt III (the second part mentioned above) was mixed with 0.69 g (5.5 mmole) of dimethyl sulfate, the mixture was refluxed for 1.5 h, another 5 ml of 5% NaOH and 0.5 ml of dimethyl sulfate were added, and the resulting mixture was refluxed for another 1.5 h. The solution was cooled, filtered, and acidified cautiously with concentrated HCl. The resulting oily product was extracted rapidly with ether, the extract was shaken with a saturated solution of $NaHCO_3$, and the aqueous layer was separated and acidified with concentrated HCl. The resulting precipitate was removed by rapid filtration, washed with water, and dried to give 0.33 g (56%) of acid IV with mp 121-123°C (CCl_4). PMR spectrum: 7.00-7.35 (4H, m, Ar), 3.65 ppm (3H, s, OCH_3). Found, %: C 51.0; H 3.4; N 11.9; S 13.7. $C_{10}H_8N_2O_3S$. Calculated, %: C 50.8; H 3.4; N 11.9; S 13.6.

The precipitate that formed gradually from the acidic solution when it was allowed to stand for 3 days was removed by filtration, washed successively with a saturated solution of $NaHCO_3$ and water, and dried to give 0.05 g (10%) of coumarin II with mp 155-157°C.

4-(2-Hydroxyphenyl)-1,2,5-thiadiazole-3-carboxylic Acid Amides Va-f. A) A stream of dry ammonia was passed through a suspension of 1.02 g (5 mmole) of II in 50 ml of absolute benzene, and the mixture was allowed to stand at room temperature for 20 h until the starting substance had vanished. The precipitate was removed by filtration, washed successively with benzene and water, and dried. The product was crystallized from benzene to give 0.9 g of amide Va.

B) A 10-mmole sample of the corresponding amine was added dropwise with stirring to a suspension of 1.02 g (5 mmole) of II in 25 ml of absolute benzene, and the mixture was stirred for 2-3 h at room temperature until the reaction was complete. In the case of the reaction with n-butylamine and di-n-butylamine the solution was washed with 5% HCl and water, dried, and evaporated to give amides Vb, c. In the reaction with pyrrolidine and piperidine the solution was evaporated, the residue was triturated with 5% HCl, and the precipitate was removed by filtration, washed with water, and dried to give amides Vd, e. In the reaction with morpholine the precipitate was removed by filtration, washed with water, and dried to give amide Vf.

4-(2-Hydroxyphenyl)-1,2,5-thiadiazole-3-carboxylic Acid Hydrazide (Vg). A solution of 0.27 ml (5.5 mole) of hydrazine hydrate in 3 ml of absolute alcohol was added with stirring to a suspension of 1.02 g (5 mmole) of II in 10 ml of absolute alcohol, and the mixture was stirred for 2 h at room temperature. It was then evaporated, and the residue was triturated with a small amount of water, removed by filtration, and dried to give 1.1 g of hydrazide Vg.

Data for compounds Va-g are presented in Table 2.

Cyclization of V. A 0.1-g sample of Va, Ve, or Vg was dissolved in 5 ml of concentrated HCl, and the solution was maintained at room temperature for 1, 20, and 2 h, respectively. The resulting precipitate was removed by filtration, washed with water, and dried. Coumarin II was obtained in 75-90% yields.

8-Nitro-4H-[1]benzopyrano[3,4-c][1,2,5]thiadiazol-4-one (VI). A) A mixture of 1.15 ml (27 mmole) of HNO_3 (d 1.5) and 10 ml of concentrated H_2SO_4 was added dropwise with stirring at 0-5°C to a solution of 5.1 g (25 mmole) of II in 20 ml of concentrated H_2SO_4, after which the mixture was stirred for 3 h at 20°C and poured into ice water. The resulting precipitate was removed by filtration, washed with water, dried, and crystallized from glacial acetic acid to give 5.2 g (84%) of VI with mp 192-194°C. Found, %: C 43.3; H 1.3; N 16.9; S 12.7. M^+ 249. $C_9H_3N_3O_4S$. Calculated, %: C 43.4; H 1.2; N 16.9; S 12.9. M 249.2.

B) A mixture of 0.53 g (2 mmole) of acid VIII (see below) and 2 ml of acetic anhydride was refluxed for 0.5 h, after which the solution was cooled, and the resulting precipitate was removed by filtration, washed with water, and dried to give 0.42 g (84%) of coumarin VI.

4-(2-Hydroxy-5-nitrophenyl)-1,2,5-thiadiazole-3-carboxylic Acid (VIII). A) A 1.25-g (5 mmole) sample of VI was dissolved in 20 ml of 5% NaOH, and the solution was allowed to stand for 1 h at 20°C. It was acidified with 10% HCl, and the resulting precipitate was removed by filtration, washed with a large amount of water, and dried to give 1.31 g (98%) of acid VIII with mp 185°C (dec.; water). PMR spectrum: 8.15 (1H, d, 6-H), 8.10 (1H, dd, 4-H), 7.00 (1H, d, 3-H) (J_{34} = 9.0, J_{46} = 3.0 Hz). Found, %: C 40.3; H 1.9; N 15.7; S 12.1. $C_9H_5N_3O_5S$. Calculated, %: C 40.5; H 1.9; N 15.7; S 12.0.

B) A suspension of 0.5 g (2 mmole) of coumarin VI in 30 ml of distilled water was refluxed until a solution formed (~1 h), after which the solution was refluxed for another hour and allowed to stand overnight. The resulting precipitate was removed by filtration and dried to give 0.42 g (78.6%) of acid VIII.

4-(2-hydroxy-3,5-dinitrophenyl)-1,2,5-thiadiazole-3-carboxylic Acid (IX). A mixture of 3.2 ml (75 mmole) of HNO_3 (d 1.5) and 10 ml of concentrated H_2SO_4 was added dropwise with stirring at 0-5°C to a solution of 5.1 g (25 mmole) of II in 20 ml of concentrated H_2SO_4, and the mixture was allowed to stand for 48 h at room temperature. It was then poured carefully over ice, and the resulting precipitate was removed by filtration, washed with a small amount of cold water, dried, and crystallized from benzene to give 5.8 g (74%) of acid IX with mp 155-156°C. Found, %: C 34.7; H 1.3; N 18.0; S 10.5. $C_9H_4N_4O_7S$. Calculated, %: C 34.6; H 1.3; N 17.9; S 10.3.

6,8-Dinitro-4H-[1]benzopyrano[3,4-c][1,2,5]thiadiazole-4-one (VII). A mixture of 0.62 g (2 mmole) of acid IX and 2 ml of acetic anhydride was refluxed for 0.5 h, after which the solution was cooled, and the resulting precipitate was removed by filtration, washed with hexane, and dried to give 0.45 g (77%) of coumarin VII with mp 210-211°C (absolute benzene). Found, %: C 37.0; H 0.69; N 19.1; S 10.5. M^+ 294. $C_9H_2N_4O_6S$. Calculated, %: C 36.7; H 0.68; N 19.0; S 10.9. M 294.2.

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HALOGEN-CONTAINING SPIRO COMPOUNDS BASED ON A 4-VINYLOXYETHYL-1,4-PERHYDROTHIAZINE 1-OXIDE

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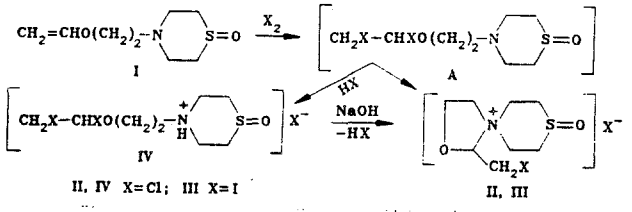
UDC 547.869.2.04:542.
944.1:543.422.25

Depending on the nature of the halogen and the polarity of the solvent, the chlorination and iodination of 4-vinyloxyethyl-1,4-perhydrothiazine 1-oxide leads to new heterocyclic tertiary or quaternary ammonium salts, including halogen-containing spiro compounds.

It is known that the halogenation of vinyl ethers and their analogs is complicated by side processes involving heterocyclization [1] and polymerization [2, p. 138], which are sometimes accompanied by explosions [3].

For the first time we have accomplished [4, p. 118] the chlorination and iodination of 4-vinyloxyethyl-1,4-perhydrothiazine 1-oxide (I), which is readily obtained on the basis of the new accessible divinyl sulfoxide [5; 6, p. 141].



Spiro bicyclic ammonium salt II was obtained in 70-75% yields in the chlorination of thiazine oxide I in benzene (10-20°C) and dichloroethane and CCl_4 (−30 to +20°C). The corresponding quaternary ammonium salt III was isolated in quantitative yield in the iodination of perhydrothiazine oxide I in both polar (methanol, ethanol) and nonpolar (CCl_4, benzene) solvents. The synthesis of salts II and III is possible by halocyclization of the initially formed intermediate A with participation of the nitrogen atom and the highly active halogen in the α position with respect to the oxygen atom of the halo ether group. Hydrochloride IV was obtained in 57% yield in the chlorination of thiazine oxide I in methanol (20-25°C). Simultaneously with chlorination at the multiple carbon–carbon bond of thiazine oxide I, the hydrogen chloride formed as a result of side processes, despite drying of the chlorine used, enters into the reaction.

The compositions and structures of the synthesized compounds are confirmed by the results of elementary analysis, IR spectroscopy, and mass spectrometry. The reaction of IV with triethylamine leads to the formation of triethylamine hydrochloride.

The multiplicity of the signals in the ^{13}C NMR spectrum of IV makes it possible to unambiguously identify the signal of the $\underline{C}HCl$ methylidyne carbon (62.95 ppm). The shift of the $O\underline{C}H_2$ carbon atom is 58.18 ppm, while the shift of the $N^+\underline{C}H_2$ (acyclic) carbon atom is 47.4 ppm. The assignment of the signals of the perhydrothiazine oxide ring in IV can be made on the basis of the shifts of the α-carbon atoms of 1-methylpiperidine (57.2 ppm) and thiocyclohexane 1-oxide (48.2 ppm) [7] taking into account the effect of protonation of the nitrogen atom, which gives rise to a shift to strong field of the resonance signals of the α-carbon

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 982-984, July, 1988. Original article submitted March 3, 1987; revision submitted October 30, 1987.

 0009-3122/88/2407-0810$12.50