FORMATION OF 4,7-DIOXO-5-ACETAMIDO-4,7-DIHYDROBENZOFURAZAN FROM 4-OXO-5-HYDROXIMINO-4,5,6,7-TETRAHYDROBENZOFURAZAN AND -FUROXAN AND INVESTIGATION OF ITS REACTION WITH AMINES

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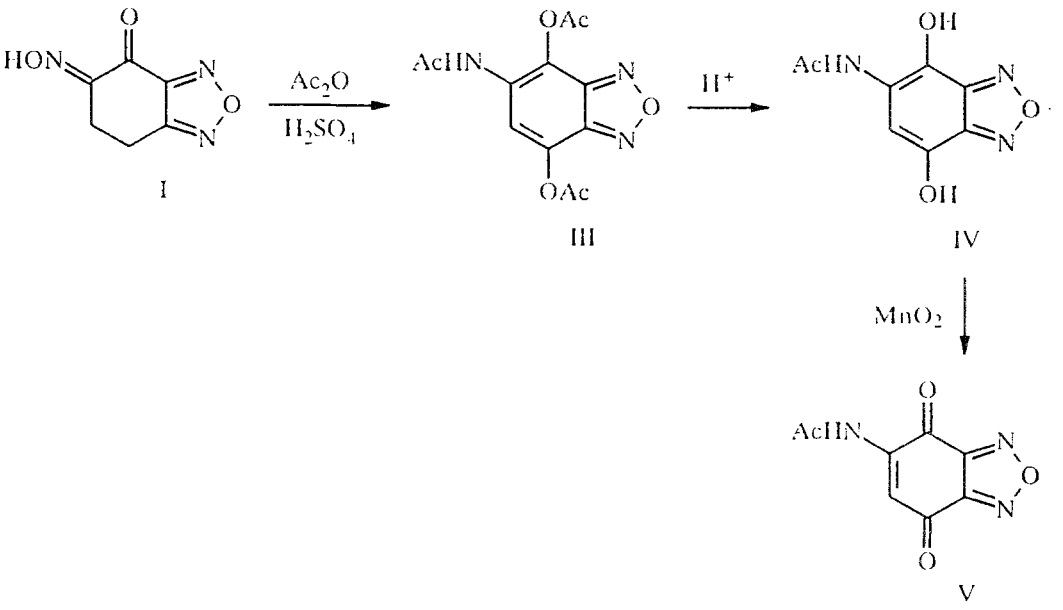
The reaction of 4-oxo-5-hydroximino-4,5,6,7-tetrahydrobenzofurazan and 4-oxo-5-hydroximino-4,5,6,7-tetrahydrobenzofuroxan with acetic anhydride in the presence of an acid gives 4,7-diacetoxy-5-acetamidobenzofurazan and 2,3-diacetoximino-5-acetamido-1,4-benzoquinone, respectively, which were used to obtain 4,7-dioxo-5-acetamido-4,7-dihydrobenzofurazan. The synthesized quinone reacts with amines to give the corresponding aminoquinones; when 4,7-dioxo-5-acetamido-6-anilino-4,7-dihydrobenzofurazan is heated, it is readily converted to 5-phenyl-6-methyl-4,8-dioxo-1H-imidazo[4,5-f]benzofurazan.

In a study of the chemical properties of the previously described 4-oxo-5-hydroximino-4,5,6,7-tetrahydrobenzofurazan (I) and 4-oxo-5-hydroximino-4,5,6,7-tetrahydrobenzofuroxan (II) [1] we observed that the reaction of I with acetic anhydride in the presence of sulfuric acid unexpectedly leads to an aromatic derivative of benzofurazan — 4,7-diacetoxy-5-acetamidobenzofurazan (III). The acidic hydrolysis of III gives 4,7-dihydroxy derivative IV, the oxidation of which with manganese dioxide leads smoothly to 4,7-dioxo-5-acetamido-4,7-dihydrobenzofurazan (V).



I III IV V

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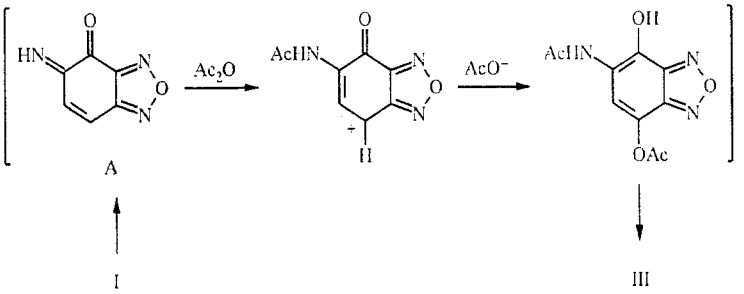
TABLE 1. Characteristics of the Synthesized Compounds

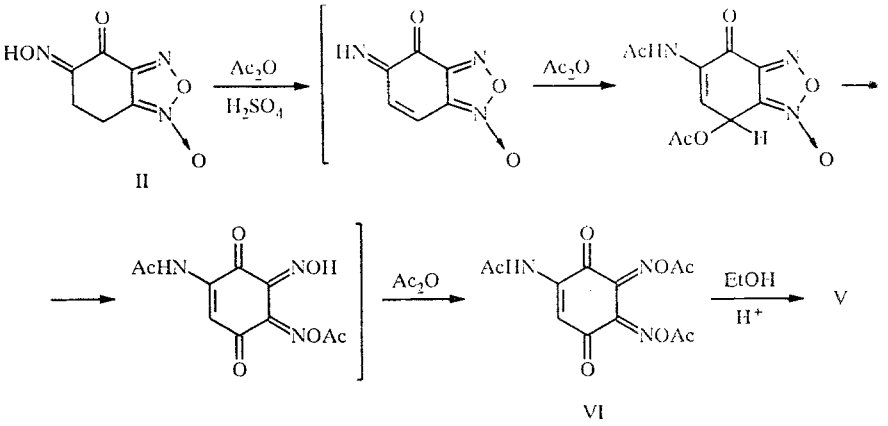
Compound	Empirical formula	mp,* °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Yield, %
III	$C_{12}H_{11}N_3O_6$	178...180	240 (4,17); 294 (3,30); 352 (3,30)	1710, 1760, 1790, 3340	95
IV	$C_8H_7N_3O_4$	209...212	212 (4,03); 240 (3,83); 280 (3,60); 360 (3,60)	1680	75
V	$C_8H_5N_3O_4$	152...154	217 (4,26); 285 (3,91); 355 (3,86)	1710, 3410	80
VI	$C_{12}H_{11}N_3O_7$	192...194 (dec.)	207 (3,82); 272 (4,00); 338 (2,92)	1670, 1700, 1790, 1810, 3300	77
VIIa	$C_{12}H_{12}N_4O_5$	183...185	212 (4,12); 370 (3,90); 495 (3,70)	1660, 1705, 3300	70
VIIb	$C_{13}H_{13}N_4O_4$	206...210	215 (4,22); 380 (4,02); 500 (3,80)	1670, 1700, 3310	57
VIIc	$C_{12}H_{14}N_4O_4$	138...140	212 (4,19); 390 (3,86); 450 (3,70)	1670, 1710, 3250, 3310	40
VII d	$C_{14}H_{10}N_4O_4$	181...183	210 (4,25); 350 (4,04); 490 (3,78)	1680, 1700, 3250, 3330	70
VIIe	$C_8H_6N_4O_4$	212...215	212 (4,11); 335 (3,80), 450 (3,60)	1650, 1710, 3250, 3300, 3410	37
VIII	$C_6H_3N_3O_3$	192...194	210 (4,19); 325 (3,98); 440 (3,78)	1710, 3300, 3420	79
IX	$C_{14}H_8N_4O_3$	235...238	210 (4,32); 350 (3,83)	1700	86

*The compounds were recrystallized: III from acetic acid, IV, V, VIIa, b, d, e, and IX from alcohol, VI from acetic anhydride, and VIII from ethyl acetate—hexane (1:1).

The scheme of the formation of III from isonitroso ketone I apparently includes in the first step aromatization to give the corresponding quinoneimine (A) (see [2]), which then reacts with acetic anhydride via a reaction of the Thiele—Winter type [3].



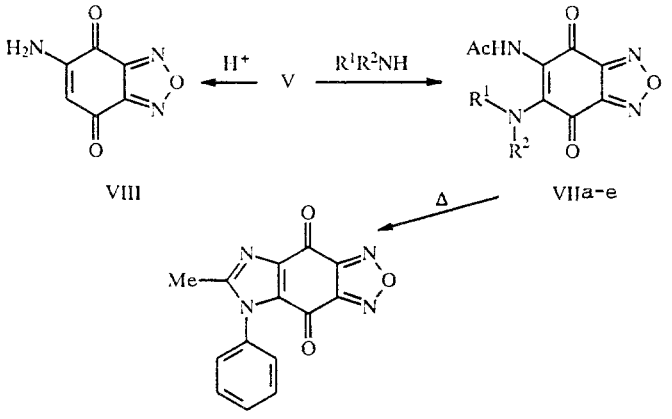
The reaction of isonitroso ketone II with acetic anhydride in the presence of sulfuric acid led to VI, in the IR spectrum of which one observes absorption bands at 1820, 1790, 1705, and 1670 cm^{-1} of stretching vibrations of four C=O groups. Absorption bands of an NH bond are present at 3310 cm^{-1}. Signals of three CH_3 groups at 2.00 ppm (6H, s, $2CH_3$) and at 2.1 ppm (3H, s, CH_3), a signal of a proton at 7.9 ppm (1H, s, =CH), and a broad singlet at 8.87 ppm (1H, s, NH) are observed in the PMR spectrum. Three signals of carbon atoms of three CH_3 groups at 20.26, 20.34, and 25.91 ppm, a signal at 124.46 ppm of the carbon atom of a =CH group, three signals of carbon atoms at 147.38, 148.51, and 149.04 ppm, and five signals of carbon atoms at 172.60, 172.95, 178.29, and 184.74 ppm, which we ascribed to C=O groups, are observed in the ^{13}C NMR spectrum. A molecular-ion peak (m/z 309) is observed in the mass spectrum of the compound. Quinone V is formed smoothly when VI is treated with alcohol. These data made it possible to assign the 2,3-diacetoximino-5-acetamido-1,4-benzoquinone structure to VI. The scheme of the formation of VI, as in the case of the formation of III, apparently includes aromatization and subsequent intramolecular oxidation—reduction with opening of the furoxan ring.



II

VI

Compound V reacts with secondary and primary amines to give the corresponding aminoquinones VIIa-d, and unsubstituted 5-amino-6-acetamidobenzofurazan VIIe is formed on reaction with hydroxylamine. When VIId is heated above its melting point, water is split out to give 5-phenyl-6-methyl-4,8-dioxoimidazo[4,5-f]benzofurazan (IX). Hydrolysis of the acetyl group to give 5-amino-4,7-dioxo-4,7-dihydrobenzofurazan (VIII) occurs when V is treated with aqueous sulfuric acid solution.



VIII

VIIa-e

IX

VII a $R^1 + R^2 = (CH_2)_2O(CH_2)_2$; b $R^1 + R^2 = (CH_2)_5$; c $R^1 = H$, $R^2 = t$-Bu; d $R^1 = H$, R = Ph; e $R^1 = R^2 = H$

The structures of the compounds are in agreement with their spectral characteristics, as well as the mass-spectral data and the results of elementary analysis.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds (concentration 0.25%) were recorded with a UR-20 spectrometer. The UV spectra of solutions in ethanol were obtained with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Varian A-56-60A spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The ^{13}C NMR spectra of solutions in d_6-DMSO were recorded with a Bruker VP-200 spectrometer. The mass spectra were obtained with a Finnigan MAT-8200 mass spectrometer with an ionizing voltage of 70 eV. The yields, melting points, and spectral data for the synthesized compounds are presented in Tables 1-3.

TABLE 2. PMR and Mass Spectra of the Synthesized Compounds

Compound	δ,* ppm	m/z (I, %)**
III	2,10 (3H, s, CH_3); 2,31 (3H, s, CH_3); 2,35 (3H, s, CH_3); 8,25 (1H, s, CH); 8,75 (1H, br.s. NH)	293 (5) M^+, 209 (70), 167 (100); 43 (85)
IV	2,12 (3H, s, CH_3); 3,53 (1H, br.s OH), 6,75 (1H, s, CH); 9,82, 10,00 (2H, br.s NH, OH)	209 (30) M^+, 167 (80), 150 (30), 68 (70), 43 (100)
V	2,23 (3H, s, CH_3); 8,00 (1H, s, CH); 8,75 (1H, br.s, NH)	207 (30) M^+, 179 (20), 165 (20), 68 (10), 43 (100)
VI	2,01 (6H, s, $2CH_3$); 2,11 (3H, s, CH_3); 7,92 (1H, s, CH); 8,87 (1H, br.s NH)	309 (10) M^+, 267 (40), 225 (70)
VIIa	2,18 (3H, s, CH_3); 3,30...3,52 (4H, m, $2CH_2$), 3,58...3,85 (4H, m, $2CH_2$)	292 (50) M^+, 250 (40), 233 (25), 203 (15), 192 (60), 175 (20), 85 (30), 43 (100)
VIIb	2,21 (3H, s, CH_3), 1,67 (6H, m, $3CH_2$); 3,42 (4H, m, $2CH_2$); 8,65 (1H, s, NH)	290 (60) M^+, 248 (100), 231 (80), 203 (50), 177 (80)
VIIc	1,48 (9H, s, $3CH_3$); 2,16 (3H, s, CH_3); 6,34 (1H, s, NH); 8,51 (1H, s, NH)	278 (50) M^+, 212 (100), 205 (80), 179 (90)
VIId	1,29 (3H, s, CH_3); 6,95...7,50 (5H, m, CH); 9,35 (1H, s, NH); 9,67 (1H, s, NH)	298 (100) M^+, 280 (70), 256 (60), 239 (70), 212 (50), 104 (30), 77 (80)
VIIe	2,00 (3H, s, CH_3)	222 (20) M^+, 180 (50), 83 (10), 43 (100)
VIII	6,10 (1H, s CH); 7,10 (2H, br.s NH_2)	165 (70) M^+, 107 (60), 95 (40), 79 (50)
IX	2,30 (3H, s, CH_3); 7,55 (5H, s, CH)	280 (60) M^+, 251 (40), 225 (50)

*The PMR spectra were recorded in various solvents: III, IV, VIId, and IX in $(CD_3)_2SO$, V, VIIa-c, e in $(CD_3)_2CO$, and VI in CF_3COOH.

**The M^+ peaks and the peaks with intensities > 10% in the mass spectra are presented.

TABLE 3. Chemical Shifts (ppm) in the ^{13}C NMR Spectra of the Synthesized Compounds

Compound	CH_3	CH_2	=CH	C=C, C=N	C=O
III	20,44; 24,10		121,31	123,16; 133,38; 136,60; 144,71; 146,51	168,34; 168,71; 170,20
IV	23,40		108,95	123,30; 126,42; 138,36; 144,69; 146,88	171,12
V	24,58		117,95	144,69; 148,35; 148,41	171,39; 171,70; 176,11
VI	20,27; 20,34; 25,91		124,46	147,37; 148,51; 149,04	172,60; 172,95; 178,29; 184,75
VIIa	22,55	50,05; 66,52		125,17; 148,36; 149,10; 149,32	168,20; 170,50; 173,50
VIIb	22,48	23,48; 26,20; 51,01		124,70; 148,40; 149,10; 150,30	167,90; 170,10; 173,60
VIIc	23,19; 30,86	56,50		122,34; 148,00; 149,28; 149,65	169,55; 171,18; 174,16
VIId	21,69		124,19; 124,57; 127,40	136,76; 140,83; 148,83; 149,23	165,95; 170,00; 173,14
VIIe	23,04			117,20; 148,40; 148,90; 149,54	168,61; 169,20; 172,10
VIII			105,26	148,86; 150,02; 154,18	172,44
IX	13,64		130,20; 129,80; 126,90	134,40; 136,01; 145,28; 150,80; 151,40; 155,20	164,80; 169,30

The results of elementary analysis for the synthesized compounds are in agreement with the calculated values.

4,7-Diacetoxy-5-acetamidobenzofurazan (III). Acetic anhydride (50 ml) was added to 8 g (0.048 mole) of isonitroso ketone I, after which 2 ml of concentrated sulfuric acid was added dropwise with vigorous stirring and cooling to 0°C, and the reaction mass was allowed to stand at room temperature for 16 h. The solvent was then removed by distillation in vacuo to a volume of 20 ml, and the residue was poured into 200 ml of water. The aqueous mixture was maintained at room temperature for 3 h, and the resulting precipitate was removed by filtration, washed with water, and dried to give 13.6 g of III.

4,7-Dihydroxy-5-acetamidobenzofurazan (IV). A 2.93-g (0.01 mole) sample of III was added in portions to 15 ml of concentrated sulfuric acid, and the reaction mass was stirred until a homogeneous solution formed. The solution was poured into 40 ml of water, the aqueous mixture was cooled to 0°C, and the precipitate was removed by filtration to give 1.60 g of IV.

4,7-Dioxo-5-acetamido-4,7-dihydrobenzofurazan (V). Manganese dioxide (1 g) was added to a solution of 0.21 g (0.1 mmole) of IV in 10 ml of acetone, and the mixture was stirred for 1 h. The manganese dioxide was removed by filtration, and the filtrate was evaporated to give 0.18 g of quinone V.

2,3-Diacetoximino-5-acetamido-1,4-benzoquinone (VI). Acetic anhydride (50 ml) was added to 9.2 g (0.05 mole) of isonitroso ketone II, and 2 ml of concentrated sulfuric acid was then added with cooling to 0°C to the resulting mixture. The mixture was allowed to stand for 8 h at room temperature, after which it was cooled to 0°C and allowed to stand for 1 h. The precipitate was removed by filtration to give 11.7 g of VI.

4,7-Dioxo-5-acetamido-4,7-dihydrobenzofurazan (V). A 1.68-g (5.45 mmole) sample of VI was dissolved in 50 ml of ethanol, and the mixture was allowed to stand for 24 h at room temperature. The solution was evaporated, and the residue was chromatographed on silica gel by elution with ethyl acetate—hexane (1:1) to give 0.62 g (55%) of quinone V.

4,7-Dioxo-5-acetamido-6-morpholino-4,7-dihydrobenzofurazan (VIIa). A 0.15-ml (1.56 mmole) sample of morpholine was added to a solution of 0.3 g (1.45 mmole) of quinone V in 30 ml of chloroform, and the mixture was allowed to stand for 2 h at room temperature. The solvent was removed by distillation, and the residue was chromatographed on silica gel by elution with ethyl acetate—hexane (1:1) to give 0.3 g of VIIa.

A similar procedure was used to obtain **4,7-dioxo-5-acetamido-6-piperidino-4,7-dihydrobenzofurazan (VIIb)**, **4,7-dioxo-5-acetamido-6-tert-butylamino-4,7-dihydrobenzofurazan (VIIc)**, and **4,7-dioxo-5-acetamido-6-anilino-4,7-dihydrobenzofurazan (VIId)**.

4,7-Dioxo-5-acetamido-6-amino-4,7-dihydrobenzofurazan (VIIe). A 1.81-g (8.05 mmole) sample of quinone V was added to a solution of hydroxylamine prepared from 2.11 g (30.4 mmole) of hydroxylamine hydrochloride and 1.21 g (30.4 mmole) of sodium hydroxide in 80 ml of methanol, and the mixture was allowed to stand at room temperature for 4 h. The solvent was removed by distillation, and the residue was chromatographed on silica gel by elution with ethyl acetate—hexane (1:1) to give 0.72 g of VIIe.

5-Phenyl-6-methyl-4,8-dioxoimidazo[4,5-f]benzofurazan (IX). A 2.98-g (0.01 mole) sample of VIIc was maintained for 1 h in a bath at 190°C. It was then cooled, and the residue was recrystallized from methanol to give 2.4 g of IX.

4,7-Dioxo-5-amino-4,7-dihydrobenzofurazan (VIII). A 2.07-g (0.01 mole) sample of V was added to 10 ml of concentrated sulfuric acid, and the resulting solution was poured into 10 ml of water. The aqueous mixture was maintained at room temperature for 30 min, after which it was extracted with ethyl acetate (3 × 50 ml). The extract was washed with saturated sodium chloride solution, dried with magnesium sulfate, and evaporated. The residue was chromatographed on silica gel by elution with ethyl acetate—hexane (1:1) to give 1.3 g of VIII.

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