Chemistry of Heterocyclic Compounds, Vol. 40, No. 10, 2004

FORMATION OF THE PYRROLINE N-OXIDE RING BY INTERACTION OF α-ISONITROSOKETONES – DERIVATIVES OF TETRAHYDROBENZOFURAZAN AND -FUROXAN WITH ALDEHYDES AND MORPHOLINE AND SOME OF THE REACTIONS OF THESE COMPOUNDS

V. A. Samsonov

α-Isonitroso ketones, derivatives of tetrahydrobenzofurazan and furoxan, react with aldehydes (acetaldehyde and propionaldehyde) and morpholine to form derivatives of tetrahydropyrrolo[2,3-e]-2,1,3-benzoxadiazole 6-oxide. Treatment of the latter with hydrazine hydrate gave derivatives of 4,5-dihydro-1,2,5-oxadiazolo[3,4-f]cinnoline which are readily dehydrogenated with tetrachlorobenzoquinone to derivatives of 1,2,5-oxadiazolo[3,4-f]cinnoline. Reduction of tetrahydropyrrolo[2,3-e]-2,1,3-benzoxadiazole 6-oxides with sodium borohydride gave derivatives of N-hydroxyhexahydropyrrolo[2,3-e]-2,1,3-benzoxazole.

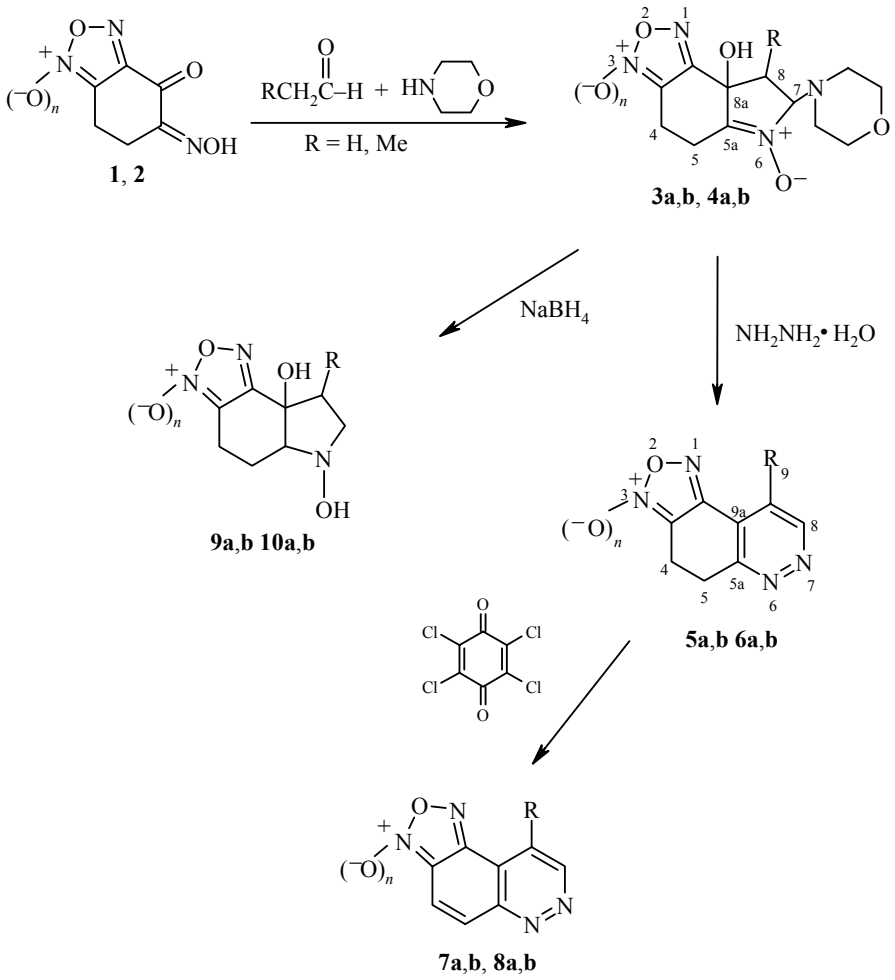
Keywords: enamines, α-isonitroso ketones, indolines, pyrroline N-oxides, 4,5,6,7-tetrahydrobenzofurazans, 4,5,6,7-tetrahydrobenzofuroxans, cinnolines.

5-Hydroximino-4-oxo-4,5,6,7-tetrahydrobenzofurazan (**1**) and 5-hydroximino-4-oxo-4,5,6,7-tetrahydrobenzofuroxan (**2**) react easily with both ketones and amines and with enamines to give derivatives of pyrroline N-oxide [1]. In a continuation of the study of this reaction, we have investigated the reaction of the α-isonitroso ketones **1** and **2** with aldehydes (acetaldehyde and propionaldehyde) and morpholine. The reaction gave high yields of the pyrroline N-oxides **3a,b** and **4a,b** (Table 1) which are colorless crystalline compounds, soluble in ethanol and water. The presence in the ^{1}H NMR spectra of compounds **3** and **4** of doubled sets of signals permits the conclusion that compounds **3a,b** and **4a,b**, are mixtures of diastereomeric products (Tables 2 and 3), just as in the case of pyrroline N-oxides derived from ketones [1]. In the case of compounds **3a** and **4a,b** the ratio of isomers is approximately 1:1, whereas for compound **3b** the ratio is 1:10. It should be noted that since the compounds are mixtures of isomers and the molecules of the compounds are not planar (see [1]), the ^{1}H NMR spectra of these compounds are complex and not very informative. The ^{13}C NMR spectra are considerably more informative (Table 3).

As is the case with pyrroline N-oxides obtained from ketones [2,3], compounds **3a,b** and **4a,b** reacted with hydrazine hydrate to give the corresponding derivatives of dihydrocinnoline **5a,b** and **6a,b**, which are easily dehydrogenated with tetrachlorobenzoquinone to the derivatives of cinnoline **7a,b** and **8a,b**. Treatment of compounds **3a,b** and **4a,b** with sodium borohydride to give derivatives of N-hydrocinnoline **9a,b** and **10a,b**. It must be noted that, according to their ^{1}H and ^{13}C NMR spectra, compounds **9a** and **10a,b** are individual isomers

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Novosibirsk 630090; e-mail: Samson@nioch.nsc.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, 1558-1563. October, 2004. Original article submitted February 15, 2002.

although the starting materials were mixtures of diastereomers, while compound **9b** is a mixture of two stereoisomers in the ratio 1:4, although the starting material was a relatively pure isomer. Evidently the reduction of the nitrone group with elimination of morpholine occurs stereoselectively as we noted previously [3].



1, **3**, **5**, **7**, **9** $n = 0$; **2**, **4**, **6**, **8**, **10** $n = 1$; **3-10 a** R = H, **b** R = Me

TABLE 1. Characteristics of Compounds **3-10**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	UV spectrum, λ_{max} (log ε)	Yield, %
		C	H	N			
1	2	3	4	5	6	7	8
3a	$C_{12}H_{16}N_4O_4$	51.30 / 51.42	5.70 / 5.75	20.00 / 19.99	146-149 (dec.)	252 (3.98)	70
3b	$C_{13}H_{18}N_4O_4$	53.10 / 53.05	6.20 / 6.16	19.12 / 19.04	185-187 (dec.)	252 (3.90)	73
4a	$C_{12}H_{16}N_4O_5$	48.60 / 48.64	5.42 / 5.44	18.90 / 18.91	169-171 (dec.)	268 (3.95)	82
4b	$C_{13}H_{18}N_4O_5$	50.30 / 50.31	5.85 / 5.85	18.10 / 18.06	192-195 (dec.)	270 (3.97)	70

TABLE 1 (continued)

1	2	3	4	5	6	7	8
5a	$C_8H_6N_4O$	55.15 55.17	3.45 3.47	32.20 32.17	108-110	246 (3.90), 254 (3.88), 277 (3.77)	75
5b	$C_9H_8N_4O$	57.40 57.44	4.40 4.29	30.00 29.77	155-158	255 (4.02)	82
6a	$C_8H_6N_4O_2$	50.50 50.53	3.20 3.18	29.50 29.47	123-125	237 (4.12), 278 (3.79)	75
6b	$C_9H_8N_4O_2$	52.95 52.94	4.00 3.95	27.50 27.44	148-150	240 (4.14)	80
7a	$C_8H_4N_4O$	55.90 55.82	2.34 2.34	32.60 32.55	139-141	243 (4.32), 274 (3.90), 285 (3.74)	65
7b	$C_9H_6N_4O$	58.10 58.06	3.25 3.25	30.10 30.10	156-157	240 (4.30), 274 (3.60), 312 (3.30)	70
8a	$C_8H_4N_4O_2$	51.00 51.07	2.14 2.14	29.82 29.78	155-157	271 (4.30), 330 (3.94)	68
8b	$C_9H_6N_4O_2$	53.42 53.46	3.00 2.99	27.68 27.72	167-169	254 (4.24), 269 (4.08), 330 (3.94)	62
9a	$C_8H_{11}N_3O_3$	48.68 48.72	5.60 5.62	21.35 21.31	128-130	—	73
9b	$C_9H_{13}N_3O_3$	51.20 51.17	6.20 6.20	19.90 19.90	122-125	—	72
10a	$C_8H_{11}N_3O_4$	45.10 45.07	5.20 5.20	19.75 19.71	105-107	267 (3.84)	68
10b	$C_9H_{13}N_3O_4$	47.60 47.57	5.80 5.77	18.50 18.49	118-120	270 (3.70)	65

* Compounds **3a,b** and **4a,b** were recrystallized from ethanol, compounds **5a,b**-**8a,b** from ethyl acetate, and compounds **9a,b** and **10a,b** from a 1:1 mixture of ethyl acetate and hexane.

TABLE 2. ^{1}H NMR Spectra of Compounds **3**-**10**

Com-pound*	Chemical shifts, δ, ppm (*J*, Hz)*[2]
1	2
3a	2.20-2.75 (4H, m, $2CH_2$); 2.75-3.20 (4H, m, $2CH_2$); 3.20-3.35 (2H, m, CH_2); 3.38-3.75 (4H, m, $2CH_2$); 4.70-4.85; 5.15-5.30 (1H, m, $C_{(7)}H$); 6.70, 6.82 (1H, s, OH)
3b	1.17, 1.29 (3H, d, *J* = 7, CH_3); 2.49-2.80 (6H, m, $3CH_2$); 2.80-3.10 (1H, m, CH); 3.10-3.25 (2H, m, CH_2); 3.40-3.25 (4H, m, $2CH_2$ morpholine); 4.60-4.75 (1H, m, $C_{(7)}H$); 6.38, 6.70 (1H, s, OH)
4a	2.15-2.90 (6H, m, $3CH_2$); 2.90-3.35 (4H, m, $2CH_2$); 3.45-3.60 (4H, m, $2CH_2$ morpholine); 4.65-4.75, 5.15-5.25 (1H, m, $C_{(7)}H$); 6.76, 6.90 (1H, s, OH)
4b	1.24, 1.27 (3H, d, *J* = 7, CH_3); 2.48-2.60 (2H, m, CH_2); 2.60-2.90 (4H, m, $2CH_2$); 3.00-3.20 (1H, m, CH); 3.28-3.35 (2H, m, CH_2); 3.50-3.58 (4H, m, $2CH_2$ morpholine); 4.32-4.34, 4.60-4.75 (1H, m, $C_{(7)}H$); 6.44, 6.85 (1H, s, OH)
5a	3.40-3.60 (4H, m, $C_{(4,5)}H_2$); 9.04 (1H, d, *J* = 5, $C_{(9)}H$); 9.28 (1H, d, *J* = 5, $C_{(8)}H$)
5b	2.62 (3H, s, CH_3); 3.30-3.32 (2H, m, $C_{(4)}H_2$); 3.42-3.44 (2H, m, $C_{(5)}H_2$); 9.24 (1H, s, $C_{(8)}H$)
6a	3.10-3.20 (2H, m, $C_{(4)}H_2$); 3.52-3.62 (2H, m, $C_{(5)}H_2$); 8.06 (1H, d, *J* = 5, $C_{(9)}H$); 9.22 (1H, d, *J* = 5, $C_{(8)}H$)
6b	2.67 (3H, s, CH_3); 3.05-3.16 (2H, m, $C_{(4)}H_2$); 3.47-3.56 (2H, m, $C_{(5)}H_2$); 9.17 (1H, s, $C_{(8)}H$)

TABLE 2 (continued)

1	2
7a	8.14 (1H, d, J = 10, $C_{(4)}H$); 8.25 (1H, d, J = 10, $C_{(5)}H$); 8.65 (1H, d, J = 6, $C_{(9)}H$); 9.63 (1H, d, J = 6, $C_{(8)}H$)
7b	2.97 (3H, s, CH_3); 8.11 (1H, d, J = 9, $C_{(4)}H$); 8.17 (1H, d, J = 9, $C_{(5)}H$); 9.49 (1H, s, $C_{(8)}H$)
8a	8.03 (1H, d, J = 10, $C_{(4)}H$); 8.12 (1H, d, J = 10, $C_{(5)}H$); 8.40 (1H, d, J = 5, $C_{(9)}H$); 9.51 (1H, d, J = 5, $C_{(8)}H$)
8b	2.80 (3H, s, CH_3); 7.63 (1H, d, J = 9, $C_{(4)}H$); 7.85 (1H, d, J = 9, $C_{(5)}H$); 9.45 (1H, s, $C_{(8)}H$)
9a	1.70-2.35 (4H, m, $C_{(4,5)}H_2$); 2.70-2.95 (4H, m, $C_{(7,8)}H_2$); 3.00-3.20 (1H, m, $C_{(5a)}H$); 6.14 (1H, s, OH); 8.02 (1H, s, –NOH)
9b	0.91, 1.11 (3H, d, J = 7, CH_3); 1.60-2.45 (4H, m, $C_{(4,5)}H_2$); 2.50-2.53 (1H, m, CH); 2.53-3.20 (2H, m, CH_2); 3.30-3.50 (1H, m, $C_{(5a)}H$); 5.88, 6.05 (1H, s, OH); 7.97, 8.00 (1H, s, –NOH)
10a	1.80-2.42 (4H, m, $C_{(4,5)}H_2$); 2.40-2.60 (2H, m, $C_{(8)}H_2$);2.80-3.10 (2H, m, $C_{(7)}H_2$); 3.15-3.25 (1H, m, $C_{(5a)}H$); 5.24 (1H, s, OH); 7.35 (1H, s, -NOH)
10b	1.19 (3H, d, J = 7, CH_3); 1.80-2.60 (6H, m, $C_{(4,5,7)}H_2$); 3,04 (1H, t, J = 3, $C_{(5a)}H$); 3.38 (1H, dd, J_1 = 8, J_2 = 9, $C_{(8)}H$); 4.90 (1H, s, OH); 7.40 (1H, s, –NOH)

* Compounds **3a**, **4a,b** – two isomers, 1:1; compound **3b** – two isomers, 1:10; compound **9b** – two isomers 1:4.

*[2] ^{1}H NMR spectra of compounds **5a,b** , **6a,b** , **7a,b** , **9b** and **10b** were recorded in $(CD_3)_2CO$, compounds **3a,b**, **4a,b**, **8a,b**, **9a** and **10a** were recorded in $(CD_3)_2SO$.

TABLE 3. ^{13}C NMR Spectra of Compounds **3-10**

Com-pound*	Chemical shifts, δ, ppm*[2]
1	2
3a	16.39, 16.51, 17.18, 17.28 ($C_{(4)}$ and $C_{(5)}$); 35.52, 35.65 ($C_{(8)}$); 47.37, 48.02, 66.50 (CH_2 morpholine); 69.27, 69.95 ($C_{(8a)}$); 90.50, 91.71 ($C_{(7)}$); 141.23, 141.36 ($C_{(5a)}$); 151.72, 151.77, 155.23, 156.40 (C=N)
3b*[3]	9.72 (CH_3), 16.45 ($C_{(4)}$); 17.27 ($C_{(5)}$); 47.99, 66.72 (CH_2 morpholine); 38.70 ($C_{(8)}$); 69.69 ($C_{(8a)}$); 95.18 ($C_{(7)}$); 141.29 ($C_{(5a)}$); 151.65, 154.81 (C=N)
4a	14.99, 15.20, 17.00 ($C_{(4)}$ and $C_{(5)}$); 34.54, 39.28 ($C_{(8)}$); 47.42, 47.94, 66.46, 66.51 (CH_2 morpholine); 70.07, 70.81 ($C_{(8a)}$); 90.53, 91.66 ($C_{(7)}$); 111.94, 111.99 (C=N–O); 140.47 ($C_{(5a)}$); 158.83, 159.92 (C=N)
4b	9.91, 16.28 (CH_3); 14.92, 15.22, 16.99, 17.43 ($C_{(4,5)}$); 38.16, 41.66 ($C_{(8)}$); 48.02, 48.34, 66.49, 66.71 (CH_2 morpholine); 70.36, 73.96 ($C_{(8a)}$); 95.30, 98.03 ($C_{(7)}$); 111.81, 112.70 (C=N–O); 140.56, 141.02 ($C_{(5a)}$); 157.45, 158.70 (C=N)
5a	18.29 ($C_{(4)}$); 28.74 ($C_{(5)}$); 121.76 ($C_{(9)}$); 122.36 ($C_{(9a)}$); 151.79 ($C_{(8)}$); 149.00, 153.32 (C=N); 158.95 ($C_{(5a)}$)
5b	17.20 ($C_{(4)}$); 17.49 (CH_3); 27.80 ($C_{(5)}$); 120.81 ($C_{(9a)}$); 134.74 ($C_{(9)}$); 149.09, 153.10 (C=N); 153.10 ($C_{(8)}$); 157.49 ($C_{(5a)}$)
6a	17.59 ($C_{(4)}$); 28.13($C_{(5)}$); 111.30 (C=N–O); 120.10 ($C_{(9)}$); 123.30 ($C_{(9a)}$); 151.76 ($C_{(8)}$); 152.59, 158.76 ($C_{(5a)}$, C=N)
6b	17.61 ($C_{(4)}$); 18.06 (CH_3); 28.53 ($C_{(5)}$); 154.08 ($C_{(8)}$); 111.81 (C=N–O); 122.19 ($C_{(9a)}$); 134.98 ($C_{(9)}$); 153.61, 158.05 ($C_{(5a)}$, C=N)
7a	119.50 ($C_{(4)}$); 119.72 ($C_{(9a)}$); 121.72 ($C_{(9)}$); 135.40 ($C_{(5)}$); 147.77, 148.39 (C=N); 150.68 ($C_{(8)}$); 152.63 ($C_{(5a)}$)
7b	18.74 (CH_3); 119.36 ($C_{(4)}$); 119.36 ($C_{(9a)}$); 135.77 ($C_{(5)}$); 136.13 ($C_{(9)}$); 148.06, 149.62 (C=N); 152.16 ($C_{(5a)}$); 152.40 ($C_{(8)}$)
8a	108.14 (C=N–O); 117.32 ($C_{(9a)}$); 119.01 ($C_{(9)}$); 120.86 ($C_{(4)}$); 134.33 ($C_{(5)}$); 150.10, 151.12 ($C_{(5a)}$, C=N); 159.96 ($C_{(8)}$)

TABLE 3 (continued)

1	2
8b	17.95 (CH_3); 111.40 (C=N–O); 115.62 ($C_{(4)}$); 118.60 ($C_{(9a)}$); 131.30 ($C_{(5)}$); 134.45 ($C_{(9)}$); 150.35, 151.18 ($C_{(5a)}$, C=N); 151.48 ($C_{(8)}$)
9a	14.56 ($C_{(4)}$); 19.23 ($C_{(5)}$); 35.61 ($C_{(8)}$); 54.40 ($C_{(7)}$); 69.70 ($C_{(5a)}$); 72.23 ($C_{(8a)}$); 151.39, 157.98 (C=N)
9b	12.01, 16.79 (CH_3); 14.65, 14.90 ($C_{(5)}$); 19.65, 20.65 ($C_{(4)}$); 38.77, 40.62 ($C_{(8)}$); 61.69, 62.98 ($C_{(7)}$); 70.74, 73.64 ($C_{(8a)}$); 72.82, 73.24 ($C_{(5a)}$); 151.5, 152.4, 154.4, 156.1 (C=N)
10a	14.48 ($C_{(5)}$); 18.25 ($C_{(4)}$); 34.49 ($C_{(8)}$); 54.20 ($C_{(7)}$); 70.55 ($C_{(8a)}$); 71.72 ($C_{(5a)}$); 111.94 (C=N–O); 161.68 (C=N)
10b	12.82 (CH_3); 15.77 ($C_{(5)}$); 20.85 ($C_{(4)}$); 39.23 ($C_{(8)}$); 64.31 ($C_{(7)}$); 73.03 ($C_{(8a)}$); 73.44 ($C_{(5a)}$); 112.10 (C=N–O); 162.02 (C=N)

* Compounds **3a**, **4a,b** – two isomers, 1:1; compound **3b** – two isomers, 1:10; compound **9b** – two isomers 1:4.

*[2] ^{13}C NMR spectra of compounds **5a,b**, **6a,b**, **7a,b**, **9b** and **10b** were recorded in $(CD_3)_2CO$, compounds **3a,b**, **4a,b**, **8a,b**, **9a** and **10a** were recorded in $(CD_3)_2SO$.

*[3] The ^{13}C NMR spectrum of the predominant isomer.

EXPERIMENTAL

IR spectra of KBr discs (c = 0.25%) were recorded on a Specord M-80 spectrometer. UV spectra of ethanol solutions were recorded on a Specord UV-vis spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 Machine (200 and 50 MHz respectively); ^{13}C NMR spectra of compounds **3a** and **4a** were recorded on a Bruker AM- 400 machine (100 MHZ).

Analytical and spectroscopic characteristics of the synthesized compounds are reported in Tables 1-3.

8a-Hydroxy-7-(N-morpholinyl)-4,5,8,8a-tetrahydro-7H-pyrrolo[2,3-*e*]-2,1,3-benzoxadiazole 6-Oxide (3a), 8a-Hydroxy-8-methyl-7-(N-morpholinyl)-4,5,8,8a-tetrahydro-7H-pyrrolo[2,3-*e*]-2,1,3-benzoxadiazole 6-Oxide (3b), 8a-Hydroxy-7-(N-morpholinyl)-4,5,8,8a-tetrahydro-7H-pyrrolo[2,3-*e*]-2,1,3-benzoxadiazole 3,6-Dioxide (4a), 8a-Hydroxy-8-methyl-7-(N-morpholinyl)-4,5,8,8a-tetrahydro-7H-pyrrolo[2,3-*e*]-2,1,3-benzoxadiazole 3,6-Dioxide (4b). The corresponding aldehyde (0.015 mol) was added to a solution of the isonitroso ketone **1** or **2** (0.01 mol) in methanol (60 ml), then a solution of morpholine (0.01 mol) in methanol (10 ml) was added dropwise with stirring at 5-10°C. The reaction mixture was stirred for 3 h at 0-5°C. The precipitate was filtered off, washed with cold methanol, and dried.

4,5-Dihydro-1,2,5-oxadiazolo[3,4-*f*]cinnoline (5a), 9-Methyl-4,5-dihydro-1,2,5-oxadiazolo[3,4-*f*]-cinnoline (5b), 4,5-Dihydro-1,2,5-oxadiazolo[3,4-*f*]cinnoline 3-Oxide (6a), 9-Methyl-4,5-dihydro-1,2,5-oxadiazolo[3,4-*f*]cinnoline 3-Oxide (6b). Hydrazine hydrate (0.4 mol) and acetic acid (15 ml) were added to a suspension of pyrroline N-oxide **3a,b** or **4a,b** (0.1 mol) in water (150 ml). The reaction mixture was boiled for 20 min. The solvents were removed under reduced pressure, water (20 ml) was added to the residue which was cooled. The residue was filtered off, washed with ice water, and dried.

1,2,5-Oxadiazolo[3,4-*f*]cinnoline (7a), 9-Methyl-1,2,5-oxadiazolo[3,4-*f*]cinnoline (7b), 1,2,5-Oxadiazolo[3,4-*f*]cinnoline 3-Oxide (8a), 9-Methyl-1,2,5-oxadiazolo[3,4-*f*]cinnoline 3-Oxide (8b). Chloranil (0.055 mol) was added to a solution of dihydrocinnoline **5a,b** or **6a,b** (0.05 mol) in toluene (50 ml) and the reaction mixture was boiled for 3 h. The solvent was removed under reduced pressure and the residue was chromatographed on Al_2O_3 with 1:1 ethyl acetate–hexane as eluent.

6,8a-Dihydroxy-4,5,6,7,8,8a-hexahydropyrrolo[2,3-*e*]-2,1,3-benzoxadiazole (9a), 6,8a-Dihydroxy-8-methyl-4,5,6,7,8,8a-hexahydropyrrolo[2,3-*e*]-2,1,3-benzoxadiazole (9b), 6,8a-Dihydroxy-4,5,6,7,8,8a-hexahydropyrrolo[2,3-*e*]-2,1,3-benzoxadiazole 3-Oxide (10a), 6,8a-Dihydroxy-8-methyl-4,5,6,7,8,8a-hexahydropyrrolo[2,3-*e*]-2,1,3-benzoxadiazole 3-Oxide (10b). $NaBH_4$ (0.01 mol) was added to pyrroline N-oxide **3a,b** or **4a,b** (0.005 mol) in ethanol (50 ml). The mixture was stirred for 48 h at room temperature and then evaporated. Water (50 ml) was added to the residue which was then extracted with ethyl acetate (3 × 50 ml). The extract was dried over $MgSO_4$ and evaporated. The residue was triturated with hexane.

REFERENCES

1. V. A. Samsonov, L. B. Volodarskii, I. Yu. Bagryanskaya, Yu. V. Gatilov, and K. E. Lakman, *Khim. Geterotsikl. Soedin.,* 199 (1994).
2. V. A. Samsonov, L. B. Volodarskii, I. Yu. Bagryanskaya, and Yu. V. Gatilov, *Khim. Geterotsikl. Soedin.,* 1055 (1996).
3. V. A. Samsonov and L. B. Volodarskii, *Khim. Geterotsikl. Soedin.,* 303 (1998).