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FORMATION OF DERIVATIVES OF BENZOFURAN, INDOLE, AND CINNOLINE IN THE REACTION OF 7-(N-MORPHOLINYL)-7-METHYL-8*a*-HYDROXY-4,5,8,8*a*-TETRAHYDRO-7H-PYRROLO[3,2-*e*]-2,1,3-BENZOXADIAZOLE 6-OXIDE WITH NUCLEOPHILIC REAGENTS

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7-(N-Morpholinyl)-7-methyl-8a-hydroxy-4,5,8,8a-tetrahydro-7H-pyrrolo[3,2-e]-2,1,3-benzoxadiazole 6-oxide behaves as the synthetic equivalent of a 1,4-dicarbonyl compound in reactions with amines, dioxime, and hydrazine to give derivatives of benzofuran, indole, 1,4-dioxime, and pyridazine. This compound also undergoes reactions characteristic for nitrones, adding water and a hydride ion.

In a study of the properties of α-isonitrosoketones, we found that these compounds readily react with enamines or carbonyl compounds and amines to give a pyrroline N-oxide ring. Both alicyclic α-isonitrosoketones, such as 4-oxo-5-hydroximino-4,5,6,7-tetrahydro-2,1,3-benzoxadiazole, its N-oxide, and 2,6-diisonitrosocyclohexanone, and acyclic compounds such as ω-isonitrosoacetophenone undergo this reaction [1, 2].

In the presence of acids, pyrroline N-oxides are capable of forming derivatives of pyrrole and indole, including 1-hydroxyindoles, which have not been readily available reagents [1]. Pyrroline N-oxides behave as synthetic equivalents of

TABLE 1. Physical Indices of Products

Compound	Chemical formula	Found, % / Calculated			mp, °C	UV spectrum (ethanol) λ, nm (log ε)	Yield, %
		C	H	N			
III	$C_9H_6N_2O_2$	62.0 62,1	3.5 3,5	16.1 16,1	117...120 CCl_4*	235(4,45); 242(4,40); 355(3,84)	22
IVa	$C_{10}H_9N_3O$	64.2 64,2	4.9 4,9	22.5 22,5	176...178 hexane*	247(4,13); 308(3,79); 375(3,53)	17
IVb	$C_{15}H_{11}N_3O$	72.2 72,3	4.5 4,5	16.9 16,9	121...123 hexane*	240(4,30); 312(3,70); 380(3,45)	12
V	$C_9H_{12}N_4O_4$	45.1 45,0	5.0 5,0	23.3 23,3	139...141 ethanol*	220(3,72)	82
VI	$C_9H_8N_4O$	57.3 57,4	4.2 4,3	29.7 29,8	143...145 ethanol*	250(4,25); 255(4,20); 286(4,01)	95
VII	$C_9H_{11}N_3O_4$	48.1 48,0	4.9 4,9	18.6 18,7	192...195 dec. ethanol*	220(3,80)	35
VIII	$C_9H_{13}N_3O_3$	51.2 51,2	6.2 6,2	20.0 19,9	117...119 ethyl acetate–hexane, 1 : 1*	220(3,70)	70

*Crystallization solvent.

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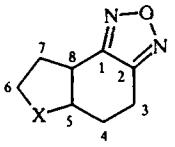
TABLE 2. PMR Spectra of Products,* δ, ppm, Coupling Constants (J), Hz

Compound	CH_3	CH=CH or CH_2–CH_2	=CH (1H, S)	COH (1H,S)	Signals of other protons
III	2,41	7,41 (2H, s)	6,70	—	
IVa	2,35	7,22 (1H, d, J = 9, 5-H), 7,30 (1H, d, J = 9, 4-H)	6,62	—	3,62 (3H, s, NCH_3)
IVb	2,28	7,25 (1H, d. J = 9, 5-H), 7,40 (1H, d, J = 9, 4-H)	6,86	—	7,40...7,50(2H,m, H Ph), 7,55...7,75(3H,m, H Ph)
V	1,80	2,52...2,80 (2H, m, CH_2), 2,80...3,30 (4H,m, $2CH_2$)	—	5,28	9,50 (1H, s, =NOH), 10,35 (1H, s, =NOH)
VI	2,72	3,30...3,51 (4H,m, $2CH_2$)	7,90		
VII*2	1,84 1,92	1,93...3,15 (6H,m, CH_2)	—	3,53 and 6,24 6,91 and7,06	
VIII	0,96 d, (J = 6)	1,50...1,80 (2H,m, CH_2), 1,90...2,20 (1H,m, CH), 2,30...2,50 (1H,m, CH), 2,60...3,00 (4H,m, CH_2)	—	6,12	7,98 (1H, s, NOH)

*Spectra of III and IV taken in $CDCl_3$, spectra of V, VII, and VIII in $(CD_3)_2CO$, while the spectra of IX and X were taken in $(CD_3)_2SO$.

*2Spectrum of a mixture of two diastereomers given.

TABLE 3. ^{13}C NMR Spectra of Products*



Compound	Carbon chemical shifts, δ, ppm*2								
	CH_3	1	2	3	4	5	6	7	8
III	13,7	144,2	148,2	120,3	110,1	153,3	156,7	103,2	112,7
IVa	12,3	144,2	148,3	119,7	106,6	135,7	133,2	102,9	109,4
IVb	13,0	145,1	149,5	122,2	108,1	137,4	135,4	104,1	110,6
V	14,8	157,0	158,0	19,2	18,4	152,7	154,2	44,9	70,7
VI	22,0	150,0	153,5	28,5	18,5	160,5	156,6	121,8	123,3
VII*3	20,7	154,9	156,2	25,9	16,5	95,7	151,4	33,2	63,1
	21,7	153,4	155,9	24,5	16,5	94,4	151,5	36,5	61,9
VIII	18,8	158,5	151,4	14,7	19,8	72,8	60,5	44,1	68,4

*Spectra of III and IV taken in $CDCl_3$, spectra of V, VII, and VIII in $(CD_3)_2CO$, and of IX and X in $(CD_3)_2SO$.

*2Other carbon atoms: IVa) 30.1 (NCH_3), IVb) 137.7 (arom C), 130.7, 130.0, 128.8 (arom CH).

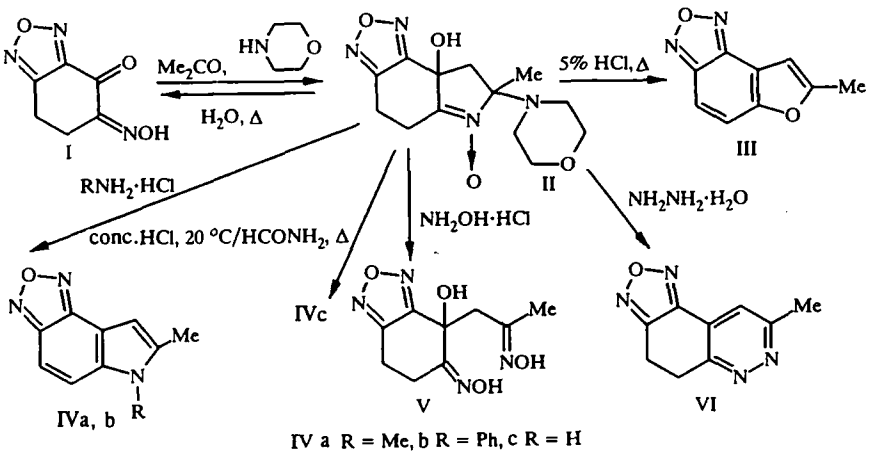
*3Spectrum of a mixture of two diastereomers given. The assignments for $C_{(1)}$ and $C_{(2)}$, $C_{(3)}$ and $C_{(4)}$, and $C_{(5)}$ and $C_{(6)}$ may be reversed.

1,4-dicarbonyl compounds in reactions with nucleophilic reagents [2]. In the present work, we continued our study of the properties of these compounds in the case of 7-(N-morpholinyl)-7-methyl-8*a*-hydroxy-4,5,8,8*a*-tetrahydro-7H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole 6-oxide (II), which is a derivative of pyrroline N-oxide, previously obtained from 4-oxo-5-hydroximino-4,5,6,7-tetrahydro-2,1,3-benzoxadiazole (I) [1].

Heating II in water leads to the starting isonitrosoketone I, while heating at reflux in 5% hydrochloric acid gives 7-methylfurano[3,2-*e*]-2,1,3-benzoxadiazole (III). Evidence for the structure of III was obtained from the analytical and spectral

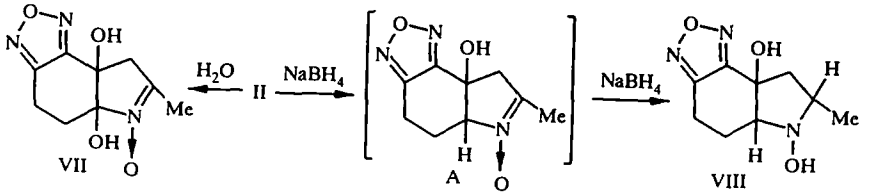
data given in Tables 1-3. The ^{13}C NMR chemical shifts of the furan ring carbon atoms in III are analogous to the shifts found for benzofuran derivatives [3]. Hydrolysis of the pyrroline N-oxide ring in II to the corresponding 1,4-diketone likely occurs initially upon heating at reflux in an acid medium. Subsequent cyclization and aromatization of this ring lead to III.

The corresponding indole derivatives IVa and IVb are formed in low yield in the reaction of pyrroline N-oxide II with the hydrochloride salts methylamine and aniline. Treatment of a methanolic solution of II with concentrated hydrochloric acid at room temperature leads to previously reported indole derivative IVc [1] in low yield. Product IVc is also formed upon heating pyrroline N-oxide II in formamide. The reaction of II with the hydrochloride salt of hydroxylamine leads to the corresponding 1,4-dioxime (V), while the reaction with hydrazine hydrate leads to 8-methyl-4,5-dihydro[1.2.5]oxadiazolo-[3,4-*f*]cinnoline (VI) in quantitative yield. In all the above reactions, pyrroline N-oxide II behaves as a synthetic equivalent of the corresponding 1,4-dicarbonyl compound.



IV a R = Me, b R = Ph, c R = H

Maintaining II at room temperature in 5% hydrochloric acid gives VII, which was identified on the basis of analytical and spectral data as 5*a*,8*a*-dihydroxy-7-methyl-4,5,5*a*,8*a*-tetrahydro-8H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole. This product was isolated as a mixture of the *cis* and *trans* diastereomers. We have already reported that II adds ammonia with the concurrent loss of morpholine, displacement of the double bond, and formation of 5*a*-amino-8*a*-hydroxy-4,5,5*a*,8*a*-tetrahydro-8H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole 6-oxide [1]. In the present case, a similar reaction is observed with water as the nucleophilic reagent. The action of sodium borohydride on II gives reduction of the nitrone group with loss of morpholine and formation of VIII. We should note that starting pyrroline N-oxide II is a mixture of two diastereomers [1]. On the other hand, the ^{13}C NMR spectrum of VIII contains only one set of signals, indicating that only one diastereomer is formed as a result of the reaction. The reduction of the nitrone group with concurrent loss of morpholine, formation of intermediate nitrone A, and subsequent addition of a hydride ion apparently proceeds with steric selectivity.



Thus, derivatives of pyrroline N-oxide readily obtained in the reaction of α-isonitrosoketones with enamines or with carbonyl compounds and amines hold interest as convenient synthetic equivalents of 1,4-dicarbonyl compounds in the synthesis of various heterocyclic compounds.

EXPERIMENTAL

The IR spectra were taken on a Specord M-80 spectrometer in KBr pellets (0.25% concentration). The UV spectra were taken on a Specord UV-VIS spectrometer for ethanol solutions. The ^{1}H and ^{13}C NMR spectra were taken on a Bruker AC-200 spectrometer. The analytical and spectral data of these products are given in Tables 1-3.

4-Oxo-5-hydroximino-4,5,6,7-tetrahydro-2,1,3-benzoxadiazole (I). A sample of 50 ml water was added to 1.47 g (0.005 mole) II. The mixture was heated at reflux for 2 h, cooled, and extracted with three 50-ml portions of ethyl acetate. The extract was dried over magnesium sulfate and filtered. The filtrate was evaporated. Chromatography of the residue on silica gel using ethyl acetate as the eluent gave 0.45 g (53%) I.

7-Methylfurano[3,2-*e*]-2,1,3-benzoxadiazole (III). A mixture of 2.94 g (0.01 mole) II and 100 ml 5% hydrochloric acid was heated to reflux and distilled. About 80 ml distillate was collected (the product was steam distilled) and extracted with three 50-ml portions of ether. The extract was dried over $MgSO_4$ and filtered. The filtrate was evaporated. The residue was suspended in hexane and filtered to give 0.38 g III.

6,7-Dimethyl-6H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole (IVa). A sample of 1.0 g (0.015 mole) methylamine hydrochloride was added to 1.47 g (0.005 mole) II in 100 ml methanol. The mixture was maintained for 72 h at room temperature and then evaporated. A sample of 100 ml water was added and the mixture was extracted with three 50-ml portions of ether. The ethereal extract was dried over magnesium sulfate and filtered. The filtrate was evaporated. Chromatography of the residue on silica gel using 1:3 ethyl acetate–hexane as the eluent gave 0.32 g IVa.

6-Phenyl-7-methyl-6H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole (IVb) was synthesized analogously using aniline hydrochloride.

7-Methyl-6H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole (IVc). A. A sample of 3 ml conc. hydrochloric acid was added to a solution of 1.47 g (0.005 mole) II in 100 ml methanol. The mixture was maintained at room temperature for 72 h and then evaporated. Chromatography of the residue on silica gel using 1:3 ethyl acetate–hexane as the eluent gave 0.14 g (15%) IVc.

B. A solution of 1.47 g (0.005 mole) II in 15 ml formamide was heated to 110°C and maintained for 1 h. The reaction mixture was then poured into 200 ml water and extracted with three 50-ml portions of ethyl acetate. The extract was washed with three 100-ml portions of saturated aqueous sodium chloride, dried over magnesium sulfate, and filtered. The filtrate was evaporated. The residue was suspended in hexane and filtered to give 0.38 g (41%) IVc.

4-Hydroxy-4-(2-hydroximinopropyl)-5-hydroximino-4,5,6,7-tetrahydro-2,1,3-benzoxadiazole (V). A sample of 0.7 g (0.01 mole) hydroxylamine hydrochloride was added to a solution of 1.47 g (0.005 mole) II in 50 ml methanol and the mixture was maintained for 48 h at room temperature. The solvent was distilled off. Chromatography of the residue on silica gel with 1:1 ethyl acetate–hexane as the eluent gave 1.0 g V.

8-Methyl-4,5-dihydro[1.2.5]oxadiazolo[3,4-*f*]cinnoline (VI). A sample of 2 ml (0.04 mole) hydrazine hydrate and 5 ml acetic acid were added to a suspension of 1.47 g (0.005 mole) II in 50 ml water. The mixture was heated at reflux for 10 min and cooled. The precipitate formed was filtered off, washed with water, and dried to give 1.80 g VI.

5*a*,8*a*-Dihydroxy-7-methyl-4,5,5*a*,8*a*-tetrahydro-8H-pyrrolo[3,2-*e*]-2,1,3-benzoxadiazole (VII). A sample of 50 ml 5% hydrochloric acid was added to 1.47 g (0.005 mole) II. The mixture was maintained for 24 h at room temperature and then extracted with four 50-ml portions of ethyl acetate. The extract was dried over magnesium sulfate and filtered. The filtrate was evaporated. Chromatography of the residue on silica gel with 3:1 ethyl acetate–hexane as the eluent gave 0.4 g VII.

6,8*a*-Dihydroxy-7-methyl-4,5,6,7,8,8*a*-hexahydropyrrolo[3,2-*e*]-2,1,3-benzoxadiazole (VIII). A sample of 0.38 g (0.01 mole) sodium borohydride was added to a solution of 1.47 g (0.005 mole) II in 50 ml ethanol. The mixture was maintained at room temperature for 48 h and extracted with three 50-ml portions of ethyl acetate. The extract was dried over magnesium sulfate and filtered. The filtrate was evaporated. The residue was triturated with hexane and filtered to give 0.74 g VIII.

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