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Influence of conditions and *N*-substituent on the reactions of 6-methoxy-3-methyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one with hydrazines

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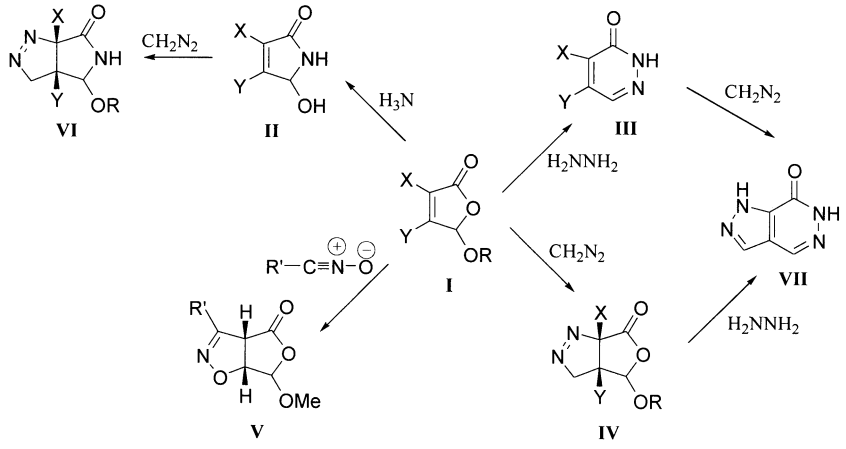
Abstract—The reactions of the title compound with hydrazines are studied to shed light on the course of the reaction of γ-alkoxyfuran-2(5*H*)-ones with these binucleophiles. At room temperature, both unsubstituted hydrazine and phenylhydrazine in ethanol, or hydrazine and its methylderivative in ethanol–acetic acid, afforded good yields of 5-amino-, 5-phenylamino-, and 5-methylamino-6-hydroxy-3-methyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-ones. Only the methylhydrazine, in ethanol at room temperature, gave a derivative of the isoxazolo[4,5-*d*]pyridazin-4(3a*H*)-one system. No pyridazinone derivative is obtained from phenylhydrazine.

1. Introduction

Previous papers from our research group had dealt with the conversion of 5-alkoxyfuran-2(5*H*)-ones of type I into several nitrogen-containing heterocyclic systems (II–V) by condensation[1–3] or cycloaddition[4–6] reactions (Scheme 1). Additionally cycloaddition of diazomethane to pyrrolinones II had lead to pyrrolopyrazolones[7] VI. Pyrazolo[3,4-*d*]pyridazinones VII had been obtained by cycloaddition of diazomethane to pyridazinones[8,9] III, as well as by reaction of furopyrazolines[5] IV with hydrazine.

Other authors have demonstrated that 5-alkoxy-3,4-dihydrofuran-2(5*H*)-ones derivatives are synthetic intermediates suitable for the elaboration of 4,5-dihydropyridazin-3(2*H*)-ones[10] by reaction with hydrazine.

In contrast with our previous results[3,5] and with those published by Meakins[10] on the behaviour of γ-alkoxy-γ-lactones with hydrazine, the reactions of this binucleophile with 5-methoxy-5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-furan-2(5*H*)-one[11] do not afford the pyridazinone derivative as the main reaction product. The reaction of fused



Scheme 1.

Keywords: hydrazines; pyrrolo[3,4-*d*]isoxazol-4-ones; furanones; isoxazolo[4,5-*d*]pyridazin-4(3a*H*)-ones.
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γ-alkoxyfuranones with hydrazines has only been studied by Fišera, who reported the formation of the corresponding 7-hydroxy-3-phenyl-5,6,7,7a-tetrahydroisoxazolo[3,4-*d*]-pyridazin-4(3a*H*)-ones from 5-ethoxy-3-phenyl-6,6a-dihydrofuro[3,4-*d*]ixosazol-4(3a*H*)-one.[12]

The different results obtained and the scarce antecedents described on the reactions of hydrazines with γ-alkoxy-γ-lactones, as well as the possibility of obtaining physiologically interesting molecules as tetrahydro- or dihydroisoxazolo[4,5-*d*]pyridazin-3(3a*H*)-ones, prompted us to investigate the behaviour of furoisoxazolone **1** towards hydrazines. In the present paper we report the results obtained, under different conditions, in the reactions of hydrazines with furoisoxazolones **1**–**2**. The reactions have been explored with hydrazine and its methyl- and phenyl derivatives in order to get some information on the influence of the hydrazine substituent on the course of the reaction.

2. Results and discussion

The reaction of **1** with hydrazine hydrate, at room temperature in ethanol, proceeded readily affording the 5-amino-6-hydroxy-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (**3a**) as the sole product in high yield (Table 1). The same result was obtained when acetonitrile or a 9:1 mixture of ethanol–acetic acid was used as the solvent. However, under the reaction conditions used by Fišera and Meankis (100°C in H_2O/AcOH as the solvent) a 67:33 mixture of **3a** and *Z*-**4a** was obtained.

Separation of compounds **3a** and **4a** by flash chromatography was unsuccessful. Only a mixture of *Z* and *E* oximes $\mathbf{4a_1}$ and $\mathbf{4a_{1'}}$ could be isolated by chromatography.

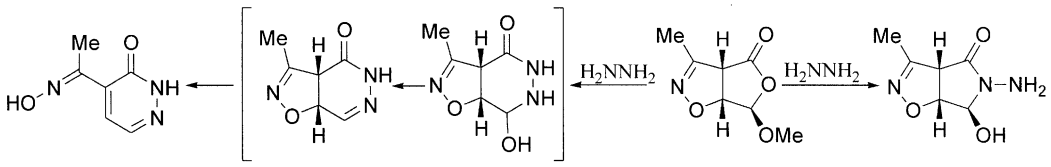
The structures of the compounds **3a** and **4a** were established on the basis of their spectral and analytical data. Further confirmation of bicyclic structure of **3a** was obtained from a chemical correlation. Thus **3a**, upon treatment with nitrous acid, afforded the pyrrolinone **7** (Scheme 2), which was obtained as the sole product by ammonolysis of **1**.

Several results of these reactions are noteworthy. First, the reactions of **1** with hydrazine hydrate never led to the isoxazolopyridazinone derivatives, in contrast with the formation of 7-hydroxy-3-phenyl-5,6,7,7a-tetrahydroisoxaxolo[4,5-*d*]-pyridazin-4(3a*H*)-one reported by Fišera from 6-ethoxy-3-phenyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one, under ***C*** conditions. The pyridazinone derivatives **5a** or **6a** are not detected under the experimental conditions used by us, however the oxime **4a** is probably formed from **6a** by cleavage of the isoxazole ring. Similar ring opening has been reported for the cycloadduct of arylnitrile oxides and indol.[13,14] Finally, the aminopyrrolinone **3a** was the only reaction product, under both ***A*** and ***B*** conditions, whereas under ***A*** conditions, Maeba[11] reported the isolation of the corresponding pyridazinone derivative (26%) together with *N*-aminopyrrolinone (71%).

The reactions of furoisoxazolone **1** with methylhydrazine afforded compounds **3b**, **4b**, and **5b** (Table 2). As it can be deduced from the Table 2, the nature of the obtained compounds and their ratio in the crude reaction mixture depend on the experimental conditions.

The hydroxypyridazinone **5b** was isolated by filtration after

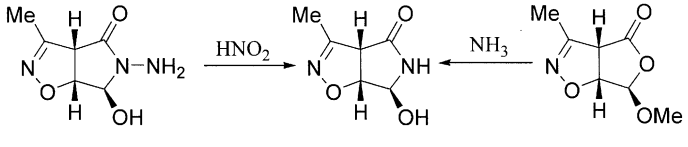
Table 1. Reactions of **1** with hydrazine



4a **6a** **5a** **1** **3a**

	Reaction conditions				Products (ratio)[a], [Yield, %][b]
	1/NH_2NH_2	Solvent	Temperature	Time (h)	
A	1/1.2	EtOH	rt	0.5	**3a** (100), [86]
A′	1/1.2	MeCN	rt	0.5	**3a** (100), [86]
B	1/1.2	EtOH/AcOH (9:1)	rt	18	**3a** (100), [78]
C	1/2	H_2O/AcOH (9:7)	reflux	1.5	**3a** (67), **4a** (33); [69][c]

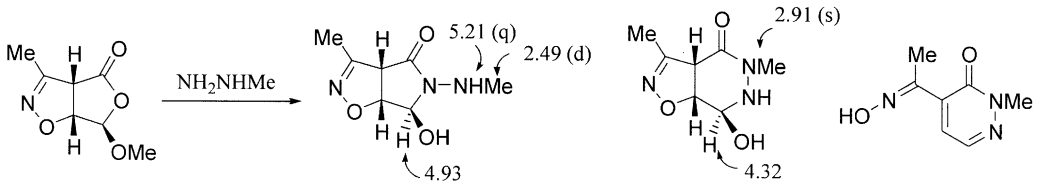
[a] Determined by ^{1}H NMR.
[b] Isolated yield, non optimized.
[c] Combined yield.



3a **7** **1**

Scheme 2.

Table 2. Reactions of **1** with methylhydrazine



1 **3b** **5b** **4b**

	Reaction conditions				Products (ratio)[a], [Yield, %][b]
	1/NH_2NHMe	Solvent	Temperature	Time (h)	
A	1/1.2	EtOH	rt	1	**3b** (29) [27], **5b** (71) [53]
B	1/1.2	EtOH/AcOH (9:1)	rt	24	**3b** (100), [78]
C	1/2	H_2O/AcOH (9:7)	reflux	0.5	**4b** (100), [60]

[a] Determined by ^1H NMR.
[b] Isolated yield, non optimized.

addition of ethyl acetate to the crude reaction mixture. However, purification by column chromatography (ethyl acetate-hexane) was not successful, due to the transformation of **5b** into the compounds **6b**, and *Z*- and *E*-oximes **4b**.

The structure of the compounds **3b** and **5b** obtained under ***A*** condition, was unequivocally determined by their spectral data and thermal transformation. The minor compound **3b**, shows spectral data similar to those of compound **3a**, except for the signals at δ 5.21 (NH, q) and 2.49 (N-Me, d), corresponding to the methylamino group, which corroborates the structure of *N*-methylaminopyrrolinone.

The spectroscopic differences between the compounds **3b** and **5b**, such as the frequency of the carbonyl band in the IR spectra (1705 and 1665 cm^{-1} for **3b** and **5b**, respectively) and the chemical shifts of carbon atoms of the C=O and CH(OH)N groups (166.8 and 86.0 ppm for **3b** and 163.5 and 83.2 ppm 4.32 for **5b**), allow the unequivocal assignment of structure **5b**.

The formation of the tetrahydroisoxazolo[4,5-*d*]pyridazinone derivative **5b**, under the ***A*** condition, and the 4-(*N*-hydroxyethanimidoyl)pyridazin-3(2*H*)-one (**4b**), under ***C*** condition, contrast with the results reported by Fišera,[12] since this author obtained the tetrahydroisoxazolo[4,5-*d*]-pyridazinone derivative when using the ***C*** conditions.

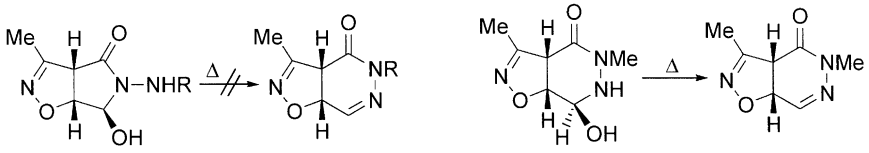
The comparison of the compounds obtained from **1** with hydrazine and methylhydrazine, under the ***A*–*C*** conditions, makes evident the influence of the substituent of the hydrazine and the reaction conditions on the product obtained. Thus, in the reaction with hydrazine the NH analogous of **5b** was not obtained, and under the ***C*** conditions **4a** appears as the minor component along with **3a**, whereas with methylhydrazine the oxime **4b** is obtained as the sole product.

When the aminopyrrolinones **3a**,**b** were reflused for 1 h, in ethanol, more than 90% of the starting material was recovered, and only traces of the oximes **4a**,**b** were detected in the crude mixtures (^1H NMR). This result indicates the high thermal stability of **3**, which contrasts with the easy transformation of the monocyclic aminopyrrolinone into the corresponding pyridazinone reported by Maeba,[11] as well as the dehydration of **5b** to **6b** (Scheme 3).

The results obtained from the reactions of **1** with phenylhydrazine, as well as the experimental conditions employed, are shown in Table 3.

The structure of isomers **8** and **9** is supported by analytical and spectral data. The frequency of the carbonyl band in the IR spectra, at 1690 and 1710 cm^{-1} for **8** and **9,** respectively, and the NMR data shown in Table 3 were of interest to assign both structures. Additionally the transformation of hydrazone **8** into bicyclic compound **9** proved the proposed structures.

The results shown in Table 3, and the fact that the hydrazide **8** was obtained along with the starting furanone **1** in the reaction in ethanol/acetic acid, using a 1/1.2 ratio of **1**: phenylhydrazine, indicate that in the presence of acetic acid the condensation with two molecules of nucleophile is favoured.

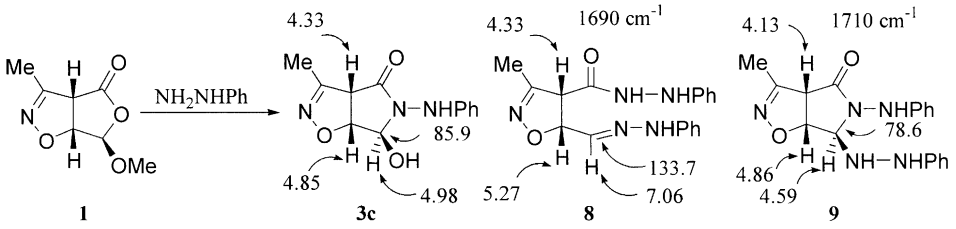


3a: R=H
3b: R=Me

5b **6b**

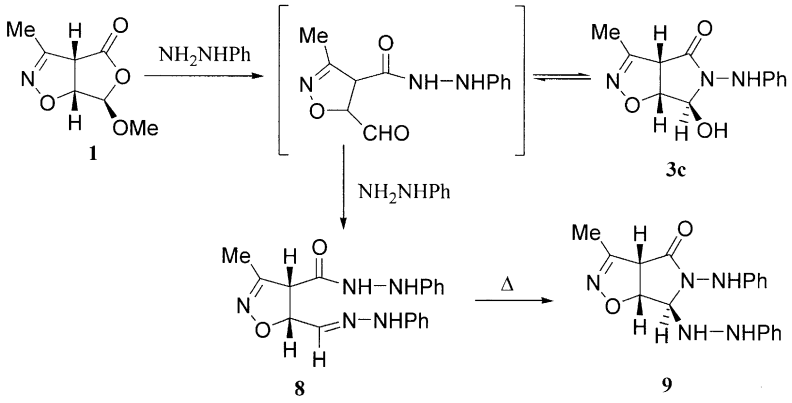
Scheme 3.

Table 3. Reactions of **1** with phenylhydrazine



	Reaction Conditions				Products (Yield, %)[a]
	1/NH_2NHMe	Solvent	Temperature	Time (h)	
A	1/1.2	EtOH	rt	26	**8** (10), **3c** (70)
B	1/2.3	EtOH/AcOH (9:1)	rt	2	**8** (91)
C	1/2.2	H_2O/AcOH (6:8)	reflux	1.5	**3c**, **9** (90)[b]

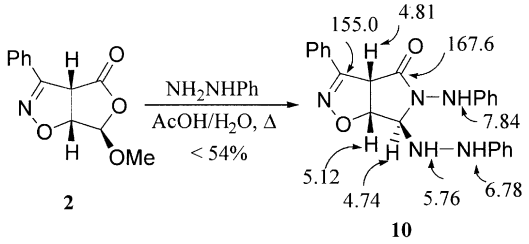
[a] Isolated yields.
[b] In a 4:6 ratio **3c**/**9**.



Scheme 4.

The formation of the product obtained from the reaction of **1** with phenylhydrazine can be explained as shown in Scheme 4. The transformation of hydrazide **8** into isomer **9** has been carried out, in a 93% yield, by reflux in ethanol/acetic acid (8:1) for 24 h.

The products obtained by us from **1** with hydrazines differ notably from those reported by Fišera from the 6-ethoxy-3-phenyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one under the same reaction conditions, since Fišera with the three hydrazines obtained 7-hydroxy-3-phenyl-5,6,7,7a-tetrahydroisoxazolo[4,5-*d*]pyridazin-4(3a*H*)-ones, whereas under their reaction conditions we could not detected this system. To check whether the phenyl group at C-3 is the responsible for the different results obtained by us and Fišera, we carried out the reaction of the 6-methoxy-3-phenyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one **2** with phenylhydrazine at 100°C in H_2O/AcOH as the solvent. The reaction mixture afforded a solid product, which was filtered following the procedure reported by Fišera, although the structure assigned by us to the isolated product is **10** (Scheme 5). The structure **10** was determined on the basis of microanalysis, mass spectrum (M^+ of *m*/*z* 399 and M^+-PhNHNH as the base peak) and NMR spectra. Besides the signals indicated in Scheme 5, there are also signals between 7.83–6.54 ppm (H) and 150.5–112.0 ppm (C) corresponding to the aromatic rings.



Scheme 5.

3. Conclusion

The results reported in this paper reveal that the adduct type formed with hydrazines and furoisoxazolone **1** depend of the hydrazine and/or the reaction conditions. Thus, hydrazine affords 5-amino-3a,5,6,6a-tetrahydro-*4H*-pyrrolo[3,4-*d*]isoxazol-4-one as the only or major product under all used conditions. However, the sole or major product obtained with methyl- and phenylhydrazines depends on the reaction conditions (see Tables 2 and 3). Only the methylhydrazine at room temperature in ethanol affords the isoxazol[4,5-*d*]pyridazin-4(3a*H*)-one system. It

is noteworthy that no pyridazinone derivatives were detected with phenylhydrazine.

On the other hand, from the comparison of the results reported by Fišera from 6-ethoxy-3-phenyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one and those obtained by us from corresponding 5-methoxy derivative, it could be deduced that the substituent at C-6 of the starting material also plays an important role in the course of the reaction of 6-alkoxy-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one with hydrazines.

4. Experimental

M.p.s are uncorrected. Microanalysis were performed with a Perkin Elmer 2400 CHN analyzer. IR spectra were recorded on Perkin Elmer model 681 grating spectrophotometer, ν values given in cm^{-1}. ^1H and ^{13}C NMR spectra were determined with Bruker AC-200, in $CDCl_3$ solution, unless otherwise stated. Chemical shifts were reported in ppm (δ) downfield from Me_4Si. Silica gel Merck 60 (230–400 mesh) was used for flash column chromatography.

4.1. Reactions of 6-methoxy-3-methyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one (1) with hydrazine hydrate

To a stirred solution of **1** (0.342 g, 2 mmol) in ethanol or acetonitrile (17.3 mL), was added hydrazine hydrate (0.119 g, 2.38 mmol). After stirring for 30 min at room temperature the precipitated compound **3a** was filtered off (0.294 g, 1.72 mmol). Yield 86%.

To a stirred solution of **1** (0.342 g, 2 mmol) in a 9:1 mixture of ethanol–acetic acid (18 mL), was added hydrazine hydrate (0.119 g, 2.38 mmol). After stirring for 18 h at room temperature the solvent was removed in vacuo, the residue was taken up in ethyl acetate and washed with a saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give **3a** (0.267 g, 1.56 mmol) in a 78% yield.

A mixture of **1** (0.1 g, 0.58 mmol), acetic acid (0.46 mL), water (0.35 mL), and hydrazine hydrate (0.06 g, 1.2 mmol) was refluxed for 1.5 h. After cooling the reaction mixture, it was neutralized with a saturated sodium bicarbonate solution, and the mixture was extracted several times with ethyl acetate. The organic layer was dried ($MgSO_4$) and the solvent removed. ^1H NMR analysis showed the presence of **3a** and **4a** in a 2:1 ratio, combined yield 69%. Separation of compounds **3a** and **4a** by flash chromatography was unsuccessful. Only a mixture of *Z* and *E* oximes $\mathbf{4a_1}$ and $\mathbf{4a_{1'}}$ could be isolated by chromatography.

4.1.1. 5-Amino-6-hydroxy-3-methyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (3a). M.p. 197–198°C. IR (Nujol): 3260–3160; 1710; 1600. ^1H NMR: 6.71 (d, 1H, OH, $J_{OH,6}$=6.8); 4.84 (d, 1H, H_6, $J_{6,OH}$=6.8); 4.69 (d, 1H, H_{6a}, $J_{6a,3a}$=9.2); 4.56 (s, 2H, NH_2); 4.16 (d, 1H, H_{3a}, $J_{3a,6a}$=9.2); 1.98 (s, 3H, Me). ^{13}C NMR: 166.1 (C=O); 153.1 (C=N); 87.8 (C_6); 83.5 (C_{6a}); 56.7 (C_{3a}); 11.5 (Me). MS, *m/z*: 171 (M^+, 34); 153 (18); 123 (7); 111 (10); 97 (24); 84 (78); 71 (100); 60 (90). Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.40; H, 5.28; N, 24.25.

4.1.2. 4-[(1Z) and (1E)-*N*-Hydroxyethanimidoyl]pyridazin-3(2*H*)-one ($\mathbf{4a_1}$+$\mathbf{4a_{1'}}$). ^1H NMR: ($\mathbf{4a_1}$): 12.28 (s, 1H, NH or OH); 11.60 (s, 1H, OH or NH); 7.87 (d, 1H, H_6, $J_{6,5}$=3.9); 7.35 (d, 1H, H_5, *J*=3.9); 1.98 (s, 3H, Me). ($\mathbf{4a_{1'}}$): 12.28 (s, 1H, NH or OH); 10.85 (s, 1H, OH or NH); 7.87 (d, 1H, H_6, $J_{6,5}$=4.0); 7.30 (d, 1H, H_5, *J*=4.0); 2.09 (s, 3H, Me). ^{13}C NMR: 160.4, 152.1, 137.3, 136.5, 129.1, 13.3.

4.2. Desamination of 3a and amonolysis of 1

4.2.1. 6-Hydroxy-3-methyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (7). A solution of sodium nitrite (0.074 g, 1.07 mmol) in water (1.14 mL) was added dropwise into a stirred cooled solution (0°C) of **3a** (0.130 g, 0.76 mmol) in 6N hydrochloric acid (0.76 mL). The temperature was kept below 5°C during the addition. After stirring for additional 3 h, the solution was neutralized with a saturated solution of sodium bicarbonate to pH~7, and then extracted several times with ethyl acetate. The organic solution was dried over anhydrous magnesium sulfate, and evaporated to give **7** in 65% yield.

To an ice-cooled solution of concentrated ammonium hydroxyde (2.5 mL) was added 0.171 g (1 mmol) of 6-methoxy-3-methyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one (**1a**). After stirring for 3 h, the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure to give 0.117 g (0.75 mmol, 75%) of pyrrolinone **7** as a white solid, which was recrystallized from ethyl acetate, m.p. 160–161°C. IR (Nujol): 3350–3225; 1710; 1680. ^1H NMR: 8.75 (bs, 1H, NH); 6.32 (d, 1H, OH, $J_{OH,6}$=7.5); 4.94 (d, 1H, H_6, *J*=7.5); 4.77 (d, 1H, H_{6a}, $J_{6a,3a}$=8.8); 4.05 (d, 1H, H_{6a}, *J*=8.8), 1.96 (s, 3H, Me).^{13}C NMR: 171.1 (C=O); 153.4 (C=N); 88.0 (C_6); 83.2 (C_{6a}); 57.9 (C_{3a}); 11.5 (Me). MS, *m/z*: 156 (M^+, 31); 139 (4); 115 (5); 97 (7); 87 (29); 84 (100); 71 (64); 59 (30); 57 (17). Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.53; H, 5.15; N, 18.10.

4.2.2. Reactions of 6-methoxy-3-methyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one (1) with methylhydrazine. To a stirred solution of **1** (0.342 g, 2 mmol) in ethanol (17.3 mL) was added methylhydrazine (0.110 g, 2.38 mmol). After stirring for 60 min at room temperature the solvent was removed in vacuo. The analysis by ^1H NMR of the residue showed the presence of compounds **5b** and **3b** in a 2.4:1 ratio. The crude mixture was tritured with ethyl acetate, and the compound **5b** was collected by filtration as a white solid (0.196 g, 53%). The filtrate was concentrated to dryness and the residue was chromatographied to afford **3b** (0.100 g, 27%). Column chromatograpy (1:1 hexane–ethyl acetate) of the crude reaction mixture gave compounds **4b** (E), **4b** (Z), **6b** and **3b** in a decreasing order of elution.

To a stirred solution of **1** (0.342 g, 2 mmol) in a 9:1 mixture of ethanol–acetic acid (18 mL) was added methylhydrazine (0.110 g, 2.38 mmol). After stirring for 24 h at room

temperature, the solvent was removed under reduced pressure and the residue chromatographed on silica gel (1:1 hexane–ethyl acetate) to give **3b**. Yield 78%.

A mixture of **1** (0.1 g, 0.58 mmol), acetic acid (0.46 mL), water (0.35 mL), and methylhydrazine (0.055 g, 1.2 mmol) was refluxed for 30 min. The reaction mixture was allowed to warm up to room temperature, neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate (3×10 mL), dried ($MgSO_4$), and concentrated to dryness to give *Z*-**4b** (60%).

4.2.3. 7-Hydroxy-3,5-dimethyl-5,6,7,7a-tetrahydroisoxazolo[4,5-*d*]pyridazin-4(3a*H*)-one (5b). M.p. 126–127°C. I.R (KBr): 3260; 1665, 1635. ^{1}H NMR: 6.23 (d, 1H, NH or OH, J=3.7); 5.99 (d, 1H, OH or NH, J=3.1), 4.61 (dd, 1H, H_{7a}, $J_{7a,7}$=2.6, $J_{7a,3a}$=10.9); 4.32 (ddd, 1H, H_7, J=2.6, $J_{7,NH}$=3.7, $J_{7,OH}$=3.1); 4.01 (d, 1H, H_{3a}, J=10.9) 2.91 (s, 3H, N-Me); 1.9 (s, 3H, C-Me). ^{13}C NMR: 163.5 (C=O); 153.6 (C=N); 83.2 (C_7); 77.6 (C_{7a}); 54.9 (C_{3a}); 37.7 (N-Me); 12.0 (C-Me). MS, *m*/*z*: 185 (M^+, 24); 167 (22); 110 (42); 95 (22); 84 (100); 74 (72); 71 (64); 69 (24); 57 (36); 55 (38). Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45,53; H, 6.07; N, 22.50.

4.2.4. 6-Hydroxy-3-methyl-5-(methylamino)-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (3b). It was recrystallized from dichloromethane, m.p. 144–145°C. IR (Nujol): 3260; 1705–1685; 1625. ^{1}H NMR ($CDCl_3$): 5.26 (s, 1H, H_6); 4.94 (d, 1H, H_{6a}, $J_{6a,3a}$=9.5); 4.01 (dd, 1H, H_{3a}, $J_{3a,6a}$=9.5, $J_{3a,Me}$=0.9); 2.68 (s, 3H, N-Me); 2.15 (d, 3H, C-Me, $J_{Me,3a}$=0.86). ^{1}H NMR (DMSO): 6.75 (d, 1H, OH, $J_{OH,6}$=7.1), 5.21 (q, 1H, NH, $J_{NH,Me}$=5.7), 4.93 (d, 1H, H_6, $J_{6,OH}$=7.1), 4.70 (d, 1H, H_{6a}, $J_{6a,3a}$=9.2), 4.19 (d, 1H, H_{3a}, $J_{3a,6a}$=9.2), 2.49 (d, 3H, NMe, $J_{Me,NH}$=5.7), 1.99 (S, 3H, Me). ^{13}C NMR ($CDCl_3$): 166.8 (C=O); 152.5 (C=N); 86.0 (C_6); 83.0 (C_{6a}); 56.9 (C_{3a}); 37.4 (N-Me); 11.7 (C-Me). MS, *m*/*z*: 185 (M^+, 39); 168 (5); 139 (13); 111 (13); 84 (100); 71 (32); 74 (40). Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 45.40; H, 5.99; N, 22.69. Found: C, 45.45; H, 5.82; N, 22.67.

4.2.5. 4-[(1*E*)-(*N*-Hydroxyethanimidoyl)-2-methylpyridazin-3(2*H*)-one (4b). It was recrystallized from cyclohexane m.p. 132–133°C. IR (Nujol): 3310; 1640; 1600. ^{1}H NMR ($CDCl_3$): 7.81 (d, 1H, H_6, $J_{6,5}$=4.1); 7.24 (d, 1H, H_5, J=4.1); 3.84 (s, 3H, N-Me); 2.20 (s, 3H, C-Me). ^{1}H NMR (DMSO): 10.82 (s, 1H, OH); 7.91 (d, 1H, H_6, $J_{6,5}$=4.0); 7.32 (d, 1H, H_5, $J_{5,6}$=4.0); 3.66 (s, 3H, N-Me); 2.01 (s, 3H, C-Me). ^{13}C NMR (DMSO): 157.6 (C=O); 148.5 (C=N-OH); 136.1 (C_6); 135.5 (C_4); 130.3 (C_5); 40.2 (N-Me); 19.4 (C-Me). MS, *m*/*z*: 167 (M^+, 16); 150 (100); 109 (3); 55 (8).

4.2.6. 4-[(1*Z*)-(*N*-Hydroxyethanimidoyl)-2-methylpyridazin-3(2*H*)-one (4b). IR (Nujol): 3225 (OH); 1645 (C=O); 1595. ^{1}H NMR ($CDCl_3$): 7.79 (d, 1H, H_6, $J_{6,5}$=4.5); 7.29 (d, 1H, H_5, $J_{5,6}$=4.5); 3.83 (s, 3H, N-Me); 2.28 (s, 3H, C-Me). ^{1}H NMR (DMSO): 11.56 (s, 1H, OH); 7.89 (d, 1H; H_6, $J_{6,5}$=4.2); 7.37 (d, 1H, H_5, $J_{5,6}$=4.2); 3.67 (s, 3H, N-Me); 2.06 (s, 3H, C-Me). ^{13}C NMR ($CDCl_3$): 159.4 (C=O); 152.4 (C=N); 135.9 (C_6); 135.2 (C_4); 128.1 (C_5); 40.9 (N-Me); 12.6 (C-Me). MS, *m*/*z*: 167 (M^+, 10); 150 (7); 149 (14); 139 (19); 137 (21); 123 (29); 111 (65); 97 (85); 83 (81); 71 (79); 69 (88); 57 (100); 55 (72).

4.2.7. 3,5-Dimethyl-5,7a-dihydroisoxazolo[4,5-*d*]pyridazin-4(3a*H*)-one (6b). IR (Nujol): 1670. ^{1}H-NMR ($CDCl_3$): 7.07 (d, 1H, H_7, $J_{7,7a}$=2.1); 5.23 (dd, 1H, H_{7a}, J=2.1, $J_{7a,3a}$=12.4); 4.16 (dc, 1H, H_{3a}, J=12.4, $J_{3a,Me}$=1.1); 3.39 (s, 3H, N-Me); 2,13 (d, 3H, C-Me, J=1.1).^{13}C NMR ($CDCl_3$): 157.2 (C=O); 152.8 (C=N); 138.3 (C_7); 74.5 (C_{7a}); 53.1 (C_{3a}); 37.2 (N-Me); 11.8 (C-Me). MS, *m*/*z*: 167 (M^+, 20); 150 (100); 110 (17); 95 (7); 84 (17); 82 (25); 74 (15); 71 (14); 55 (17). Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50,49; H, 5.62; N, 24.97.

4.3. Thermal treatment of hydroxypyridazinone 5b and hydroxypyrrolinones 3a,b.

A solution of 7-hydroxy-3,5-dimethyl-5,6,7,7a-tetrahydroisoxazolo[4,5-*d*]pyridazin-4(3a*H*)-one (**5b**). (1 mmol) in ethyl acetate (6 mL) was refluxed for 24 h. After removing of the solvent, dihydroisoxazolo[4,5-*d*]pyridazin-4(3a*H*)-one **6b** was obtained in quantitative yield.

A solution of aminopyrrolinone **3a** or **3b** (1 mmol) in ethanol (6 mL) was refluxed for 1 h and the solvent removed. ^{1}H-NMR analysis showed the presence of the starting material and the corresponding (*N*-hydroxyethanimidoyl)pyridazin-3(2*H*)-one in a 90:10 ratio.

4.4. Reactions of 6-methoxy-3-methyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one (1a) with phenylhydrazine

To a solution of **1a** (0.171 g, 1 mmol) in ethanol (8 mL) was added phenylhydrazine (0.129 g, 1.19 mmol). After stirring for 26 h at room temperature the white solid **8** was filtered off (10%) and the solvent of filtrate was removed. The crude product obtained from filtrate was chromatographed on silica gel (1:2 ethyl acetate–hexane) to afford pure pyrrolinone **3c** in 70% yield (0.294 g).

To a stirred solution of **1** (0.342 g, 2 mmol) in a 9:1 mixture of ethanol–acetic acid (18 mL) was added phenylhydrazine (0.496 g, 4.6 mmol). After stirring for 2 h at room temperature, the compound **8** was obtained by filtration in 91% yield.

A mixture of **1** (0.1 g, 0.58 mmol), 0.60 mL water, 0.79 mL acetic acid and phenylhydrazine (0.224 g, 2.26 mmol) was refluxed for 1.5 h. After cooling the reaction mixture was neutralized with saturated sodium bicarbonate solution, and the mixture was extracted several times with ethyl acetate. The organic layer was dried ($MgSO_4$) and the solvent removed. ^{1}H NMR analysis showed the presence of **3c** and **9** in a 1:1.5 ratio, combined yield 90%.

4.4.1. 3-Methyl-*N*′-phenyl-5-(phenylhydrazono)methyl-4,5-dihydroisoxazole-4-carbohydrazide (8). M.p. 189-190°C. IR (Nujol): 3320-3305, 3245 (NH); 1690 (C=O); 1600; 1592. ^{1}H NMR (DMSO): 10.32 (s, 1H, NH); 10.10 (s, 1H, NH); 7.89 (s, 1H, NH); 7.21 (t, 2H, H_{arom}, J=7.8); 7.06 (d, 1H, CH=N, J=8.0); 6.96 (d, 2H, H_{arom}, J=7.8); 6.88 (t, 2H, H_{arom}, J=7.7); 6.75 (t, 1H, H_{arom}, J=7.1); 6.58

(m, 3H, H_{arom}); 5.27 (dd, 1H, H_5, J=8.0, $J_{5,4}$=11.5); 4.33 (d, 1H, H_4, $J_{5.,4}$=11.5); 1.89 (s, 3H, Me). ^{13}C NMR (DMSO): 166.2 (C=O); 154.4 (C=N); 148.7, 145.26 (C_{arom}); 133.7 (CH=N); 129.4, 128.9, 119.1, 118.8, 112.2, 111.9 (C_{arom}); 82.2 (C_5); 58.3 (C_4); 12.1 (Me). MS, *m/z*: 337 (M^+, 17); 230 (100); 173 (77); 119 (10); 107 (16); 92 (99); 77 (28). Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76. Found: C, 64.00; H, 6.00; N, 20.66.

4.4.2. 5-Phenylamino-6-hydroxy-3-methyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (3c). M.p. 131–132°C. IR (Nujol): 3295 (NH); 1710 (C=O); 1605. ^{1}H NMR ($CDCl_3$): 7.22 (m, 2H, H_{arom}); 6.93 (m, 1H, H_{arom}); 6.64 (m, 2H, H_{arom}); 5.31 (s, 1H, H_6); 4.97 (d, 1H, H_{6a}, $J_{6a,3a}$=9.3); 4.02 (m, 1H, H_{3a}); 2.12 (d, 3H, Me, $J_{Me,3a}$=0.9). ^{1}H NMR (DMSO): 8.19 (s, 1H, NH or OH); 7.14 (m, 2H, H_{arom}); 7.01 (d, 1H, NH or OH, $J_{NH\text{-}OH,6}$=7.0); 6.73 (m, 1H, H_{arom}); 6.58 (d, 2H, H_{arom}, J=7.8); 4.98 (d, 1H, H_6, $J_{6,OH}$=7.0); 4.85 (d, 1H, H_{6a}, $J_{6a,3a}$=9.1); 4.33 (d, 1H, H_{3a}, $J_{3a,6a}$=9.1); 2.02 (s, 3H, Me). ^{13}C NMR (DMSO): 167.0 (C=O); 153.3 (C=N); 147.3, 129.1, 119.4, 112.2 (C_{arom}); 85.9 (C_6); 83.6 (C_{6a}); 56.2 (C_{3a}); 11.5 (Me). MS, *m/z*: 248 (M^++1, 12); 247 (M^+, 72); 229 (32); 173 (15); 171 (19); 136 (28); 118 (28); 107 (100); 92 (65); 83 (26); 77 (83); 71 (29); 69 (24); 65 (58); 57 (29); 51 (22). Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.50; H, 5.58; N, 16.57.

4.4.3. 5-Phenylamino-3-methyl-6-(2-phenylhydrazino)-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (9). M.p. 222–223°C. IR (Nujol): 3315, 3290 (NH); 1705 (C=O), 1605. ^{1}H NMR (DMSO): 7.84 (s, 1H, NH); 7.15 (m, 4H, H_{arom}); 6.88 (d, 2H, H_{arom}, J=7.7); 6.77 (m, 1H, H_{arom}); 6.73 (d, 1H, NH, J=2.5); 6.67 (m, 1H, H_{arom}); 6.55 (m, 2H, H_{arom}); 5.67 (dd, 1H, NH, $J_{NH,6}$=2.8, $J_{NH,NH}$=2.5); 4.86 (d, 1H, H_{6a}, $J_{6a,3a}$=9.2); 4.59 (d, 1H, H_6, $J_{6,NH}$=2.8); 4.13 (d, 1H, H_{3a}, $J_{3a,6a}$=9.2); 1.99 (s, 3H, Me). ^{13}C NMR (DMSO): 167.7 (C=O); 153.6 (C=N); 150.4, 146.9, 129.4, 129.0, 119.6, 118.5, 112.9, 111.9 (C_{arom}); 81.7 (C_{6a}); 78.2 (C_6); 56.8 (C_{3a}); 11.5 (Me). MS, *m/z*: 337 (M^+, 3); 230 (22); 173 (25); 145 (2); 134 (2); 119 (5); 107 (8); 92 (100); 77(18); 65 (22); 51 (4). Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76. Found: C, 64.30; H, 6.00; N, 20.55.

4.5. Thermal cyclization of 4,5-dihydroisoxazole-4-carbohydrazide (8) to 4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (9)

A solution of the hydrazide **8** (0.168 g, 0.5 mmol) in ethanol–acetic acid (8:1, 8 mL) was refluxed for 24 h. After removing of the solvent 5-phenylamino-3-methyl-6-(2-phenylhydrazino)-3a,5,6,6a-tetrahydro-*4H*-pyrrolo[3,4-*d*]-isoxazol-4-one(**9**) was obtained. It was recrystallized from ethyl acetate, 93% yield.

4.6. Reactions of 6-methoxy-3-phenyl-6,6a-dihydrofuro[3,4-*d*]isoxazol-4(3a*H*)-one (2) with phenylhydrazine

A mixture of **2** (0.057 g, 0.24 mmol), 0.14 mL water, 0.19 mL acetic acid and phenylhydrazine (0.058 g, 0.54 mmol) was refluxed for 1.5 h. After cooling the reaction mixture in an ice-salt bath, the compound **10** was filtered off as a white solid. Yield 54%.

4.6.1. 5-Phenylamino-6-(2-phenylhydrazino)-3-phenyl-3a,5,6,6a-tetrahydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-one (10). M.p. 224–225°C. IR (Nujol): 3315, 3300, 3290 (NH); 1695 (C=O); 1605 (C=N). ^{1}H NMR (DMSO): 7.84 (s, 1H, NH); 7.83 (m, 2H, H_{arom}); 7.41 (m, 3H, H_{arom}); 7.12 (m, 4H, H_{arom}); 6.91 (m, 2H, H_{arom}); 6.78 (d, 1H, NH, $J_{NH,NH}$=2.6); 6.71 (m, 2H, H_{arom}); 6.54 (m, 2H, H_{arom}); 5.76 (dd, 1H, NH, $J_{NH,6}$=2.7, $J_{NH,NH}$=2.6); 5.12 (d, 1H, H_{6a}, $J_{6a,3a}$=9.2); 4.81 (d, 1H, H_{3a}, $J_{3a,6a}$=9.2); 4.74 (d, 1H, H_6, $J_{6,NH}$=2.7). ^{13}C NMR (DMSO): 167.6 (C=O); 155.0 (C_3); 150.5, 147.0, 130.5, 129.4, 129.0, 128.8, 128.1, 128.0, 119.7, 118.7, 113.2, 112.0 (C_{arom}); 83.9 (CH); 77.7 (CH); 53.7 (C_{3a}). MS, *m/z*: 399 (M^+, 11); 292 (100); 173 (92); 144(13); 107 (10); 92 (93); 77 (26); 65 (19). Anal. Calcd for $C_{23}H_{21}N_5O_2$: C, 69.16; H, 5.30; N, 17.53. Found: C, 68.99; H, 5.32; N, 17.35.

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References

1. Fariña, F.; Martín, M. V.; Paredes, M. C. *Synthesis* **1973**, 167–168.
2. Fariña, F.; Martín, M. V.; Ortega, M. C.; Paredes, M. C.; Tito, A. *Heterocycles* **1984**, *22*, 1733–1739.
3. Escobar, C.; Fariña, F. Span. Pat. 454136 1977.
4. Fariña, F.; Martín, M. R.; Martín, M. V.; Martinez, A. *Heterocycles* **1994**, *38*, 1307–1316.
5. Fariña, F.; Martín, M. V.; Sanchez, F. *Heterocycles* **1986**, *24*, 2587–2592.
6. Garcia, J. L.; Fraile, A.; Martin, M. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1943–1950.
7. Fariña, F.; Martín, M. V.; Paredes, M. C.; Tito, A. *J. Heterocyclic Chem.* **1987**, *24*, 1269–1274.
8. Fariña, F.; Martín, M. V.; Sánchez, F.; Paredes, M. C.; Tito, A. *Heterocycles* **1982**, *18*, 175–178.
9. Fariña, F.; Martín, M. V.; Romañach, M.; Sánchez, F. *Heterocycles* **1988**, *27*, 1431–1436.
10. Breukelmann, S. P.; Meakins, G. D.; Roe, A. M. *J. Chem. Soc., Perkin Trans 1* **1985**, 1627–1656.
11. Maeba, I.; Suzuki, M.; Hara, O.; Takeuchi, T.; Iijima, T.; Furukawa, H. J. *Org. Chem.* **1987**, *52*, 4521–4526.
12. Fišera, L.; Oravec, P. *Collection Czechoslovak Chem. Commun.* **1987**, *52*, 1315–1324.
13. Caramella, P.; Corisco, A. C.; Corsario, A.; Del Monte, D.; Albini, F. M. *Tetrahedron* **1982**, *38*, 173–182.
14. Bruché, L.; Zecchi, G. J. *Org. Chem.* **1983**, *48*, 2772–2773.