On the Interaction of 3,4-Dibenzoylfuroxan with Hydroxylamine

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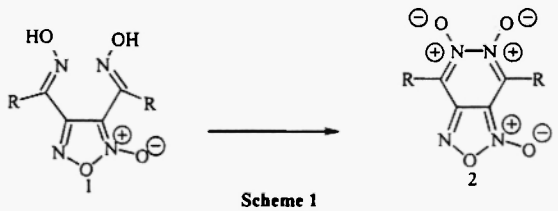
Abstract: Dibenzoylfuroxan **3** (R = Ph) reacts with hydroxylamine in a ring transformation to give a 4,5-dioximino-3-phenyl-1,2-oxazole **6**. The structure of **6** has been confirmed by an X-ray structure determination. Some density functional theoretical (DFT) calculations for **6** and related compounds are reported.

Introduction

Recently in connection with the intense search of compounds capable of generating nitrogen oxide, NO, in the organism, a definite interest has been shown in N,N'-dioxides of the pyridazine series containing furazan or furoxan moieties (1a). N,N'-Dioxides of the pyridazine series in themselves and methods of their synthesis have been studied insufficiently. They can be obtained either via oxidation of pyridazine derivatives or by a rather unusual closing of pyridazine-N,N'-dioxide cycle on interaction of the oximes of diacetyl- and dibenzoylfurazans (-furoxans) with oxidizers like $KMnO_4$, N_2O_4 or HNO_3 (1,2). In order to synthesize 4,7-diphenylpyridazino[4,5-*d*]-1,2,5-oxadiazol-1,5,6-trioxide **2** (R = Ph) and its furazan analog, we tried to reproduce the synthesis of the dioxime of 3,4-dibenzoylfuroxan **1** (R = Ph) (Scheme 1).



Scheme 1

Several methods of its synthesis are known, *i.e.*, from the corresponding hydroxamic acid chloride (3), via dimerization of α-hydroximinophenylacetonitriloxide (4), or through oximation of dibenzoylfuroxan (5), although in an early publication it was stated that both isomers of dibenzoylfuroxan cannot be oximated (6). All these methods produce a high-melting isomer of **1** (R = Ph). The other group of methods include basic hydrolysis of the diacetate formed upon

the interaction of acetic anhydride with 4-phenylfuroxan (7) or with α-hydroximinophenylacetonitriloxide (4) as well as the interaction of the diacetyl derivative of phenylchloroglyoxime with sodium carbonate (3b) which produce a low-melting isomer of 1 (R = Ph).

Preparative Investigations

We believed the oximation of dibenzoylfuroxan to be the superior method because of the well known reactivity of aldehydes and ketones in the furoxan series (1a). Unfortunately, our attempts to reproduce this synthesis (5) failed. When conducting the oximation of dibenzoylfuroxan in ethanol in the presence of small amounts of water, a substance with mp 172-175°C was obtained. The same compound was formed when the oximation was carried out in 2-propanol, pyridine or dimethylformamide. According to both the mass spectrum (*m/z* = 205) and to ^{13}C NMR (7 signals) this compound is not a dioxime of 3,4-dibenzoylfuroxan. The structure was solved unambigously by an X-ray diffraction analysis (8), which showed that a 4,5-dioximino-3-phenyl-1,2-oxazole 6 has been formed. It is interesting to note that in the solid state 3 molecules of 6 are connected *via* linear and bifurcated hydrogen bonds (Fig.1, see Theoretical Investigations). Selected geometrical data of compound 6 are given in Table 1.

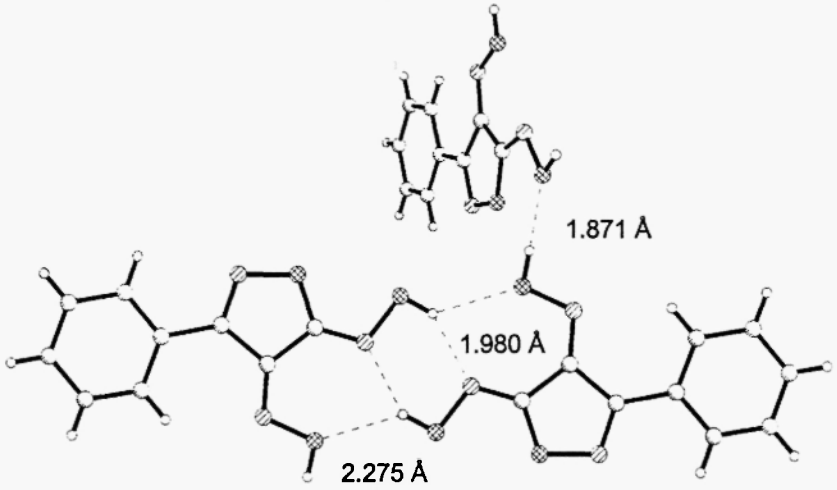
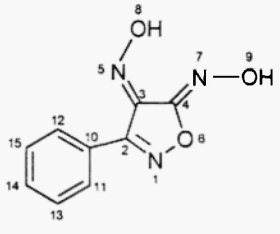


Fig. 1.

Perspective drawing of molecular arrangement in the crystal structure of 4,5-dioximino-3-phenyl-1,2-oxazole 6

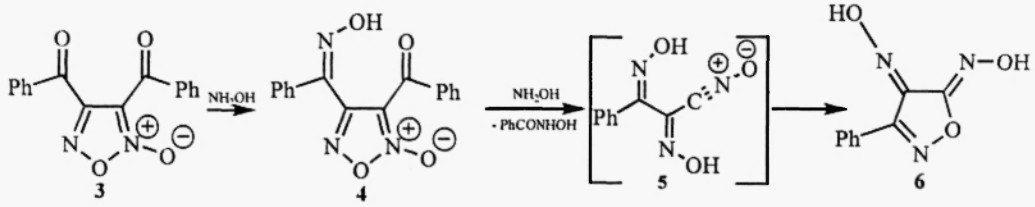
Table 1: Selected geometrical data (bond lengths in Å) for compound 6 [X-ray data and calculated values (DFT)[a]]



Bond	exp.	DFT [a]	Bond	Exp.	DFT [a]
1-2	1.295	1.294	3-5	1.287	1.285
1-6	1.439	1.415	4-6	1.356	1.367
2-3	1.464	1.472	4-7	1.276	1.280
2-10	1.472	1.473	5-8	1.379	1.376
3-4	1.453	1.465	7-9	1.401	1.390

B3LYP/6-311+G*; [b] ω(1-2-10-11): 0.7 [0] (20.9 [0]).

The appearence of this product can be rationalized easily (Scheme 2). In the first reaction the monoxime 4 may be formed. After nucleophilic attack of hydroxylamine on the carbonyl group at 4-position with subsequent elimination of benzoylhydroxamic acid and concomitant opening of the furoxan ring, compound 5 undergoes an intramolecular cyclization forming the oxazole derivative 6. Ring opening reactions of furoxans with subsequent formation of a 1,2-oxazole derivative are not forbidden (1).



Scheme 2

Theoretical Investigations

As has been pointed out in the preceeding section the structure of 6 was confirmed by a X-ray structure determination.

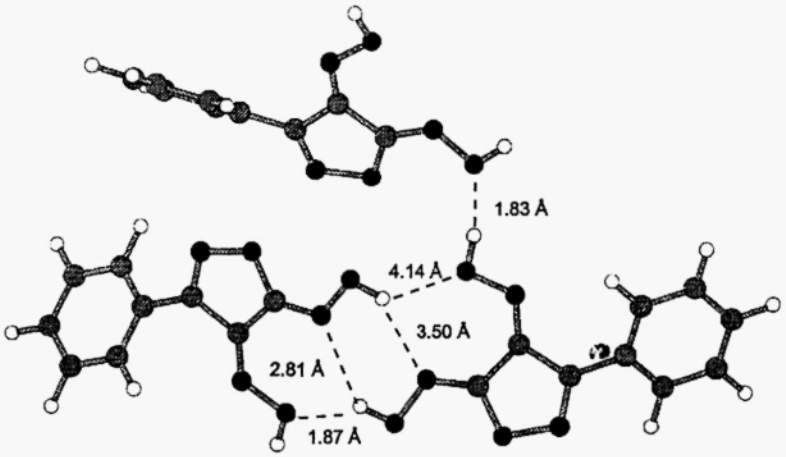
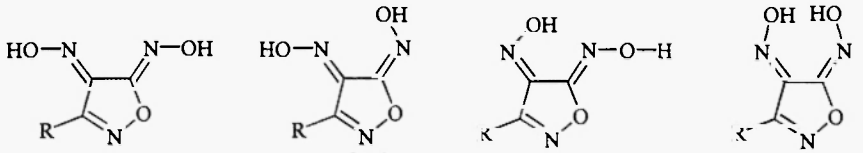


Fig.2

Intramolecular hydrogen bonds in the structure of 4,5-dioximino-3-phenyl-1,2-oxazole 6, calculated on the PM3 level

Preliminary investigations have shown that semiempirical calculations on the PM3 level for a cluster of 3 molecules of 6 show linear hydrogen bonds (Fig. 2), although for obvious reasons the exact geometry differs from the X-ray structure determination..

Bis-dioximes of type 6 can exist as four geometric isomers: *anti* 8, *amphi1* 9, *amphi2* 10 and *syn* 11 (Scheme 3).



8a, b **9a, b** **10a, b** **11a, b**

a: R = H; b: R = Ph

Scheme 3

In order to get insight into details of the structure of compound 6 both semiempirical (AM1) (9,10) and DFT calculations (11, 12) have been undertaken. For R = H isomer **8a** (Scheme 3) is the most stable one; **11a** is the least stable isomer (Table 2). The same sequence is obtained with DFT calculations (B3LYP/6-31G*, B3LYP/6-311+G*) (12). For R = Ph both on the AM1 and the DFT level isomer **10b** (*amphi2*) is calculated to be the most stable compound. This is in agreement with the experimental geometry.

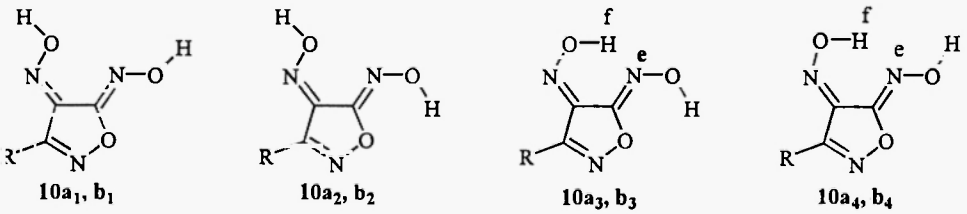
The AM1 and DFT sequences differ slightly for the other isomers, but in line with the expectations the DFT calculations reveal that **11b** (*syn*) is the least stable compound in this series.

Table 2: Enthalpies of formation (ΔH_f^0)[a] and energies (E)[b] of dioximes 8a,b-11a,b

Compound	AM1	DFT [c]	Compound	AM1	DFT [c]
8a	41.63	-505.84978	**8b**	70.24	-736.90221
9a	42.23	-505.84809	**9b**	73.24	-736.90314
10a	41.78	-505.84779	**10b**	68.66	-736.90972
11a	45.32	-505.84112	**11b**	72.19	-736.90157

[a] AM1 values in kcal/mol; [b] B3LYP/6-31G* values, in hartrees; [c] B3LYP/6-311+G* gives the following energies: **8a**: -505.99428; **9a**: -505.99180; **10a**: -505.99089; **11a**: -505.98429

Table 3: Heats of formation (ΔH_f^0) [a] and energies (E) [b] of dioximes $10a_1$–$10a_4$ and $10b_1$–$10b_4$



$10a_1$, b_1 **$10a_2$, b_2** **$10a_3$, b_3** **$10a_4$, b_4**

a: R = H; b: R = Ph

Compound	AM1	DFT [c, d]	Compound	AM1	DFT [c, d]
$10a_1$	41.24	-505.85069 (2.1)	**$10b_1$**	68.17	-736.91241 (3.1)
$10a_2$	41.78	-505.84779 (4.0)	**$10b_2$**	68.66	-736.90972 (4.8)
$10a_3$	41.65	-505.85121 (1.8)	**$10b_3$**	68.50	-736.91479 (1.6)
$10a_4$	41.67	-505.85408 (0.0)	**$10b_4$**	68.59	-736.91732 (0.0)

[a] AM1 values in kcal/mol; [b] B3LYP/6-31G* values, in hartrees; [c] Relative values in parenthesis; [d] $10a_3$ ($10b_3$): r_{fe} = 1.920 Å (1.869 Å), $10a_4$ ($10b_4$): r_{fe} = 1.896 Å (1.849 Å).

If the hydrogen atoms of the oxime groups are taken into consideration, the number of conformers increases. Calculations for isomers **10a, b** reveal that on the AMI level the conformers **10a**$_1$ - **10a**$_4$ and **10b**$_1$ - **10b**$_4$ (Table 3) differ only slightly in their energies. DFT calculations show a decrease in the total energies when an intramolecular hydrogen bonding is possible **10a**$_3$, **10b**$_3$; **10a**$_4$, **10b**$_4$. Application of Boltzmann's law shows that at 300° K these rotamers are in equilibrium with 2.6% **10a**$_1$ (0.5% **10b**$_1$), 0.1% **10a**$_2$ (0.0% **10b**$_2$), 4.5% **10a**$_3$ (6.5% **10b**$_3$) and 92.8% **10a**$_4$ (93% **10b**$_4$). Interestingly the shortest intramolecular hydrogen bond was calculated for **10a**$_4$ (**10b**$_4$) (Table 3, footnote [d]).

Experimental

IR-spectra were recorded on a FT-IR spectrometer FT-IR-1600 (Perkin Elmer) in KBr, ^{1}H- and ^{13}C NMR spectra were obtained on a Bruker DRX500 spectrometer (TMS as internal standard). Mass spectrum was recorded on a MAT8230 instrument (Finnigan). 3,4-Dibenzoylfuroxan was synthesized according to (13).

Interaction of dibenzoylfuroxan with hydroxylamine hydrochloride:

1) in ethanol:

a) A solution of 2 g (6.8 mmol) of 3,4-dibenzoylfuroxan and 2 g (28.8 mmol) of hydroxylamine hydrochloride in 50 ml ethanol was heated to 75-80 °C for 1 h, after which the solvent was distilled off. The remaining solid was dissolved in ether, the solution was washed several times with water and twice with 2N solution of NaOH. The basic extracts were acidified with hydrochloric acid to pH 2-3, the precipitate was filtered off and dried in the air. After multiple washings with boiling chloroform compound **6** was obtained in 35% yield , mp 172-175° C. Recrystallisation from ethyl acetate yielded colorless needles which were suitable for X-ray structure determination.

IR(KBr): ν = 3289 cm^{-1} (OH), 1451, 1226, 1044, 982, 889; UV(CH_3CN): λ_{max} (lg ε) = 325 nm (2.654), 215 (sh, 2.591); ^{1}H-NMR (500 MHz, d_6-DMSO): δ = 7.53-7.61 ppm (m, 3H, H-13, H-14, H-15) 7.95 (d, 2H, H-11, H-12, J_1 = 7.19 Hz), 11.75 (s, 1H, OH), 13.98 (s, 1H, OH); ^{13}C-NMR (125 MHz, d_6-DMSO): δ = 126.09 ppm (s, C-10), 128.07 (d, C-13, C-15), 128.82 (d, C-11, C-12), 131.37 (d, C-14), 141.45 (s, C-2), 148.34 (s, C-3), 156.57 (s, C-4); MS m/z 205 (M^+); $C_9H_7N_3O_3$: Calc. 205.04874 Found 205.04860

b) A solution of 3 g (43.2 mmol) of hydroxylamine hydrochloride in minimal amount of water was added to a solution of 3 g (10.2 mmol) of 3,4-dibenzoylfuroxan in 300 ml of ethanol and was kept for 1 month, after which it was poured in 2 l of water, extracted with ether and treated as described above. Compound **6** was obtained in 40% yield (0.84 g). The mixed probe with the previous sample gave no depression of melting point.

2) in pyridine:

Five grams (71 mmol) hydroxylamine hydrochloride was added to a solution of 5 g (17 mmol) of 3,4-dibenzoylfuroxan in 50 ml of pyridine, stirred until complete solution of the hydrochloride and left for several days, after which it was poured into 500 ml of cold water. The solution was acidified with hydrochloric acid to pH 3, the precipitate was filtered off and treated as before. The product (1.5 g, 43.7%) has mp 172-175 °C. The mixed probe with compound **6** obtained in ethanol solution gave no depression of melting point.

3) in dimethylformamide:

A solution of 2 g (6.8 mmol) of 3,4-dibenzoylfuroxan and 2 g (28.8 mmol) of hydroxylamine hydrochloride in 50 ml of dimethylformamide was left for 1 month, after which it was poured into 500 ml of water and extracted with ether. The

extract was washed with 2N solution of NaOH, the basic solution was treated as before. Compound **6** was obtained in 40% yield (0.6 g), mp 172-175 ^{0}C.

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8 Space group: $P2_1/C$, cell dimensions: a = 12.567(4) Å, b = 6.2310 (10) Å, c = 12.563(5) Å; $\alpha = 90^0$, $\beta = 111.04^0$, $\gamma = 90^0$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been disposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 116485 CCDC. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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