

On the Mechanism of a Novel 3(2*H*)-Furanone-2(5*H*)-Furanone Rearrangement

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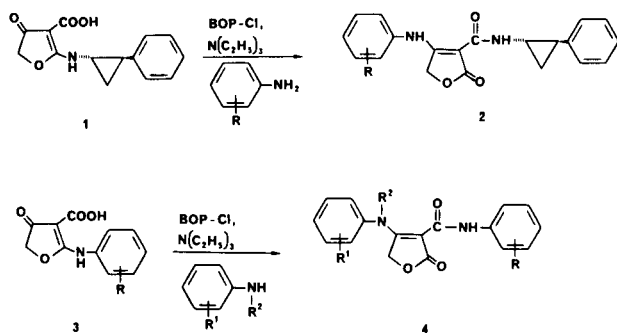
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The isolation of a stable intermediate product and the mechanism of a novel 3(2*H*)-furanone-2(5*H*)-furanone rearrangement that led to the facile preparation of a new class of γ -lactone amides **2** and **4** are discussed.

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In a recent communication, we reported a novel 3(2*H*)-furanone-2(5*H*)-furanone rearrangement involving the 2-(substituted amino)-4,5-dihydro-4-oxo-3-furancarboxylic acids **1** and **3** [1]. When treated with 1 equivalent of *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (BOP-Cl) [2] and an appropriately substituted aromatic amine (1 equivalent), in the presence of triethylamine, the 3(2*H*)-furanones **1** and **3** readily underwent rearrangement to the corresponding 5(2*H*)-furanones **2** and **4** (Scheme I).

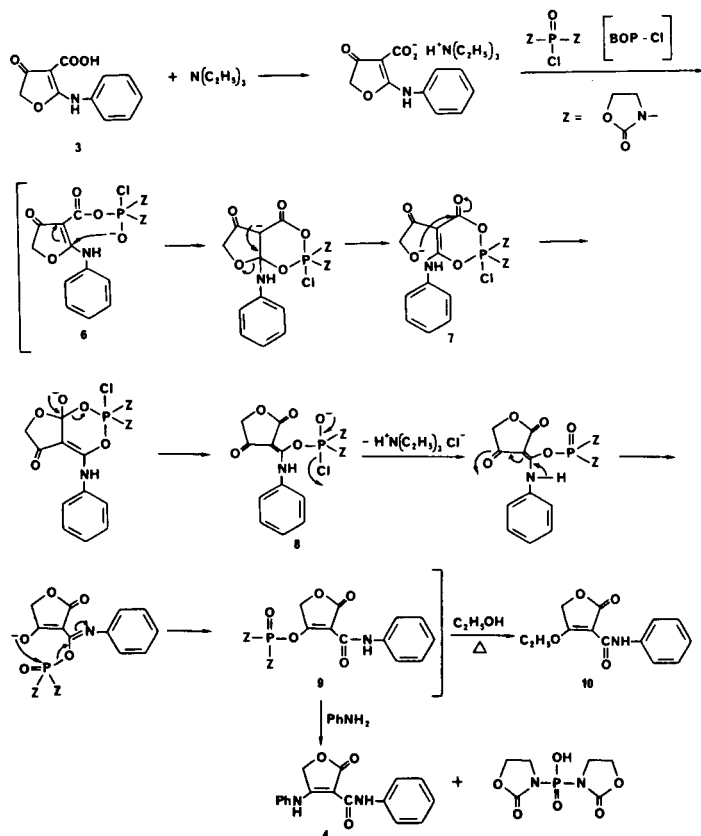
Scheme I



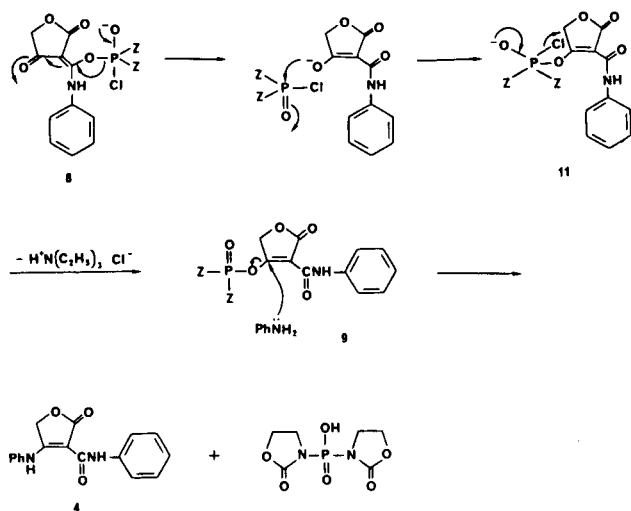
The mechanism of this novel rearrangement appears to be a complex one. It is assumed that the first step involves an activation of the carboxyl group of acids **1** and **3** by BOP-Cl through an initial nucleophilic attack on the phosphorus atom by the carboxyl anion [2] to form adduct **6** (Scheme II). In order to learn more about the rearrangement, we attempted and were able to isolate one stable intermediate product. Thus, by using ethanol as a trapping agent, we obtained *N*-phenyl-4-ethoxy-2,5-dihydro-2-oxo-3-furancarboxamide (**10**) as a stable crystalline material. Compound **10** was formed most likely through a displacement of the *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic group of the intermediate γ -lactone **9** by ethanol. Two acceptable pathways that rationalize the generation of compound **10** are postulated and depicted in Schemes II and III. Both mechanisms evolve around the formation of a 4*H*-1,3,2-dioxaphosphorin intermediate **7** from adduct **6**

via a nucleophilic attack on the double bond, followed by fission of a heterocyclic C-O bond attached to a negatively charged carbon atom [3]. Cyclization and opening of the 4*H*-1,3,2-dioxaphosphorin ring allows for the formation of a furan-2,4-dione intermediate **8**, which in turn, converts to the γ -lactone **9** (Scheme II). Alternatively, the formation of **9** may be visualized through a P-O bond cleavage of intermediate **8** to free BOP-Cl. A nucleophilic attack on the phosphorus atom of BOP-Cl then generates intermediate **11**, which following a loss of chlorine anion provides the 5(2*H*)-furanone **9** (Scheme III).

Scheme II



Scheme III



The structure of compound **10** was determined by X-ray crystallography and a thermal-ellipsoid plot of **10** is presented in Figure 1.

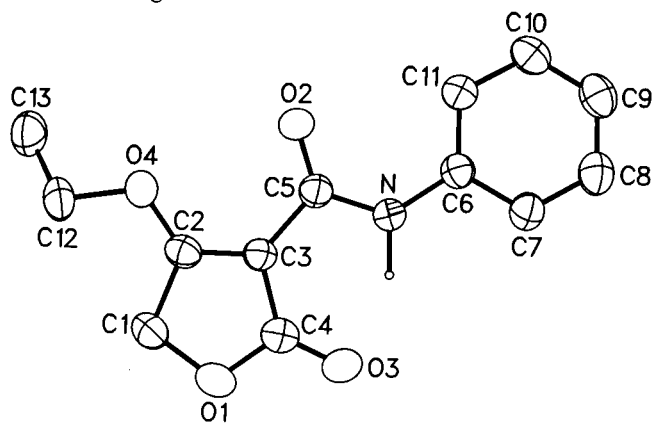


Figure 1

An ORTEP representation of the unit cell of **10** along the *a*-axis is given in Figure 2. Final positional parameters and equivalent isotropic thermal parameters are listed in Table I, and the refined displacement parameter expressions and hydrogen parameters are presented in Tables II and III, respectively.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared (ir) spectra were obtained on a Nicolet MX-1 FT spectrometer as potassium bromide discs. The proton nuclear magnetic resonance (¹H nmr) spectra were taken on a Varian EM-360A (60 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard. All spectra were consistent with the assigned structures.

N-Phenyl-4-ethoxy-2,5-dihydro-2-oxo-3-furancarboxamide (**10**).

Under a nitrogen atmosphere, triethylamine (0.64 ml, 4.591 mmoles) in

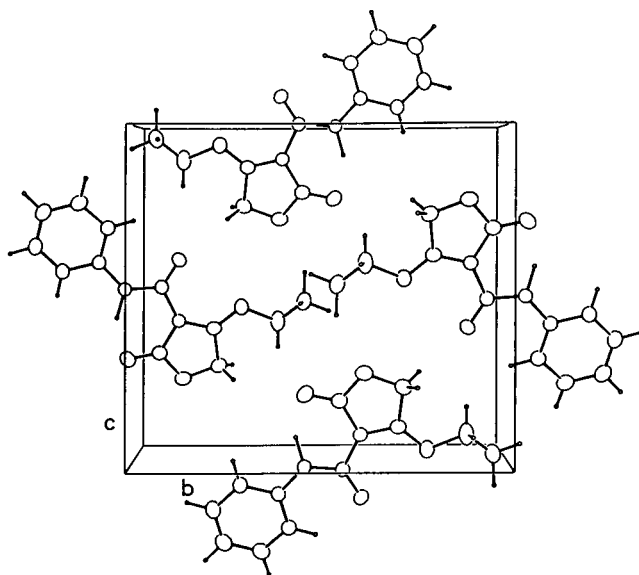


Figure 2

Table I

Refined Positional Parameters in **10**

Atom	x	y	z	B(A ²)
C(1)	0.0815(6)	0.2164(3)	0.2593(4)	6.0(1)
C(2)	0.1498(5)	0.2045(3)	0.3790(3)	4.99(9)
C(3)	0.1768(5)	0.1070(3)	0.4038(3)	4.62(9)
C(4)	0.1319(6)	0.0515(3)	0.3015(3)	5.6(1)
C(5)	0.2427(5)	0.0614(3)	0.5108(3)	4.82(9)
C(6)	0.3202(5)	-0.1083(3)	0.5884(3)	4.86(9)
C(7)	0.3082(6)	-0.2096(3)	0.5607(4)	5.9(1)
C(8)	0.3626(6)	-0.2820(3)	0.6380(4)	6.6(1)
C(9)	0.4290(6)	-0.2555(4)	0.7430(4)	6.5(1)
C(10)	0.4412(6)	-0.1556(4)	0.7709(4)	6.4(1)
C(11)	0.3869(6)	-0.0807(3)	0.6946(3)	5.7(1)
C(12)	0.1455(8)	0.3821(4)	0.4008(5)	9.1(1)
C(13)	0.2449(7)	0.4551(4)	0.4660(4)	7.9(1)
N	0.2625(4)	-0.0400(2)	0.5041(3)	5.12(8)
O(1)	0.0739(4)	0.1155(2)	0.2180(2)	6.38(7)
O(2)	0.2749(4)	0.1110(2)	0.5955(2)	6.21(7)
O(3)	0.1420(5)	-0.0376(2)	0.2820(2)	7.46(8)
O(4)	0.1803(4)	0.2810(2)	0.4473(2)	6.48(7)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter.

6 ml of methylene dichloride was added dropwise over 25 minutes to a suspension of 2-phenylamino-4,5-dihydro-4-oxo-3-furoic acid (**3**) (1.0 g, 4.562 mmoles) in 9 ml of methylene dichloride at 0°. The resulting clear solution was stirred for 15 minutes at 0°, after which BOP-Cl (96%, 1.21 g, 4.562 mmoles) was added in one portion. The reaction mixture was stirred at 0° for 45 minutes, then at ambient temperature for 2 hours. After cooling to 0°, water (20 ml) was added dropwise over a 30-minute

Table II
Refined Displacement Parameter Expressions - Beta's in **10**

Name	B(1,1)	B(2,2)	B(3,3)	B(1,2)	B(1,3)	B(2,3)
C(1)	0.0270(9)	0.0091(3)	0.0095(3)	0.003(1)	-0.004(1)	0.0023(6)
C(2)	0.0194(8)	0.0084(3)	0.0082(3)	0.0008(8)	-0.0004(8)	0.0002(5)
C(3)	0.0206(8)	0.0068(2)	0.0077(3)	-0.0002(8)	-0.0005(8)	-0.0004(5)
C(4)	0.0249(9)	0.0088(3)	0.0090(3)	-0.0008(9)	-0.0005(9)	-0.0002(6)
C(5)	0.0209(8)	0.0067(3)	0.0088(3)	-0.0001(8)	0.0000(9)	-0.0002(5)
C(6)	0.0209(8)	0.0068(3)	0.0089(3)	0.0014(8)	0.0023(9)	0.0003(5)
C(7)	0.030(1)	0.0069(3)	0.0104(4)	0.0014(9)	0.003(1)	-0.0000(6)
C(8)	0.032(1)	0.0073(3)	0.0132(4)	0.003(1)	0.007(1)	0.0018(6)
C(9)	0.026(1)	0.0094(3)	0.0127(4)	0.007(1)	0.005(1)	0.0049(6)
C(10)	0.027(1)	0.0103(4)	0.0102(4)	0.002(1)	-0.003(1)	0.0027(7)
C(11)	0.028(1)	0.0076(3)	0.0094(3)	0.0004(9)	-0.002(1)	0.0001(6)
C(12)	0.051(2)	0.0071(3)	0.0180(5)	0.010(1)	-0.022(1)	0.0007(7)
C(13)	0.045(1)	0.0076(3)	0.0149(5)	0.002(1)	0.005(1)	0.0029(7)
N	0.0284(8)	0.0063(2)	0.0079(2)	0.0001(7)	-0.0010(7)	-0.0003(4)
O(1)	0.0306(7)	0.0104(2)	0.0084(2)	0.0009(7)	-0.0046(7)	0.0005(4)
O(2)	0.0373(7)	0.0074(2)	0.0086(2)	0.0029(7)	-0.0067(7)	-0.0025(4)
O(3)	0.0430(8)	0.0090(2)	0.0108(3)	0.0002(8)	-0.0096(8)	-0.0042(4)
O(4)	0.0345(7)	0.0069(2)	0.0116(3)	0.0057(6)	-0.0091(7)	-0.0005(4)

The form of the anisotropic displacement parameter is: $\exp\{-B(1,1)h^2 + B(2,2)k^2 + B(3,3)l^2 + B(1,2)hk + B(1,3)hl + B(2,3)kl\}$.

Table III
Hydrogen Parameters in **10**

Atom	x	y	z	B(A ²)
H(1)	0.1637	0.2591	0.2193	6.0
H(1')	-0.0314	0.2508	0.2550	6.0
H(7)	0.2609	-0.2275	0.4855	6.0
H(8)	0.3559	-0.3518	0.6163	6.0
H(9)	0.4663	-0.3053	0.8002	6.0
H(10)	0.4870	-0.1350	0.8448	6.0
H(11)	0.3971	-0.0095	0.7168	6.0
H(12)	0.1722	0.3832	0.3226	6.0
H(12')	0.0162	0.3948	0.4018	6.0
H(13)	0.2070	0.4570	0.5546	6.0
H(13')	0.2208	0.5240	0.4351	6.0
H(13'')	0.3695	0.4455	0.4628	6.0

period while keeping the temperature at 0-5°. Then, the reaction mixture was acidified (pH 1) with 2 N hydrochloric acid, filtered and the two layers separated. The aqueous phase was extracted with methylene dichloride, and the combined organic extract was washed sequentially with water and aqueous solution of sodium bicarbonate. The organic extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual yellow solid was refluxed in ethanol for 1 hour.

Upon cooling orange crystals separated. The latter were purified by separation on the Chromatotron centrifugal chromatography system using chloroform-methanol (9:1) as eluent. The main isolate was recrystallized from ethanol to provide compound **10** as yellow crystals (50 mg), mp 200-202° dec; ir (potassium bromide): 3280, 3250, 1735, 1723, 1679, 1618, 1599 and 1553 cm⁻¹; nmr (deuteriochloroform-dimethyl sulfoxide-d₆): ppm 1.52 (t, 3H, J = 7 Hz), 4.48 (q, 2H, J = 7 Hz), 5.13 (s, 2H), 7.08-7.78 (m, 5H), 9.88 (bs, 1H).

X-Ray Crystallography Study.

C₁₃H₁₃NO₄, M_r = 247.25, monoclinic P2₁/c, a = 7.504(1), b = 13.318(2), c = 11.920(3) Å, β = 93.12(2)°, V = 1189.4 Å³, Z = 4, D_x = 1.381 g cm⁻³, λ (Cu-Kα) = 1.54184 Å, μ = 8.21 cm⁻¹, F(000) = 520, T = 297 K, final R = 0.066 for 1405 unique observed reflections. Clear colorless crystal (0.36 × 0.20 × 0.15 mm); Enraf-Nonius CAD4 diffractometer with graphite-monochromated Cu-Kα radiation. Lattice parameters from 22 reflections with 42 < 2θ < 57°. 2553 reflections measured using ω-2θ scan technique within ranges 6 ≤ 2θ ≤ 140°, 0 ≤ h ≤ 9, -16 ≤ k ≤ 0, -14 ≤ l ≤ 14. Intensities of three standard reflections (221, 130, 122) recorded every 2500 s of x-ray exposure showed no significant decay. 1405 unique observed reflections [I > 3σ(I)], R_{int} = 3.1%. Data corrected for Lorentz and polarization effects, not absorption. Structure solved by MULTAN 11/82 [4] in the space group P2₁/c, which revealed 16 of the 18 non-H atoms (the ethoxy C-atoms were found on the subsequent Fourier map calculated based on this fragment from MULTAN). Hydrogen atoms found from subsequent difference Fourier syntheses. Refinement by full-matrix least squares to minimize w(F_o - F_c)² led to R = 0.066 and wR = 0.063 for 163 variables with w = 1/σ²(F_o) and S = 6.87. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were not refined, but were included in the structure factor calculations with constant isotropic temperature factors of 6.0 Å². Maximum

least squares shift to esd ratio 0.03 in final refinement cycle. Largest residual electron density in final Fourier $0.23 \text{ e}\text{\AA}^{-3}$.

Atomic scattering factors from Cromer and Waber [5]; anomalous dispersion terms from Ibers and Hamilton [6]. All computer programs from Enraf-Nonius SDP package [7].

The plane defined by N, C(5), C(3), C(2), and O(2) is planar within 0.0 Å. The shortening of the N-C(5) bond, 1.363(3) Å, relative to N-C(6), 1.407(3) Å indicates substantial electron delocalization through the N-C(5)-C(3)-C(2)-O(2) π -system.

The amide hydrogen apparently participates in intramolecular hydrogen bonding with O(3): H(N)⋯O(3), 1.79 Å, N⋯O(3), 2.754(4) Å. The N, C(5), C(3), C(2), O(2), C(4), O(3) moiety is planar within 0.03 Å. There is no evidence of intramolecular hydrogen bonding.

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