88. A Novel Rearrangement of 2(5*H*)-Furanones

by **Robert A. Mack, Thomas R. DeCory,** and **Vassil St. Georgiev***

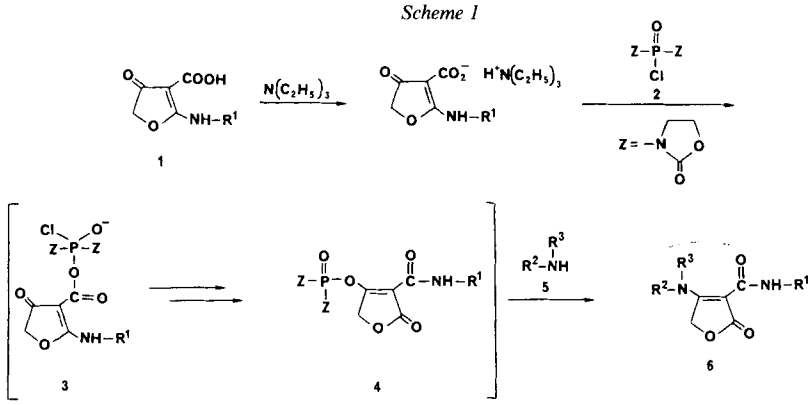
Department of Organic Chemistry, Pennwalt Corporation, Pharmaceutical Division, Rochester, New York 14623, USA

(25.II.88)

A novel rearrangement of 2(5*H*)-furanones is described. When refluxed in aq. ethanolic solution in the presence of excess KOH, the 2,5-dihydro-2-oxofuran-3-carboxamides **6** underwent a novel rearrangement to the corresponding 4,5-dihydro-4-oxo-2-(phenylamino)-3-furancarboxylic acids **1** in moderate-to-excellent yields.

Introduction. – Previously [1–5], we have reported the synthesis and biological activity of a new class of 2,5-dihydro-2-oxofuran-3-carboxamides **6** *via* a novel 3(2*H*)-furanone → 2(5*H*)-furanone rearrangement. Thus, when treated with 1 equiv. of chlorooxobis(2-oxo-1,3-oxazolidin-3-yl)phosphorus (**2**) and an aromatic amine in the presence of Et_3N, the starting 3(2*H*)-furanones **1** [6] [7] readily rearranged to the 2(5*H*)-furanones **6** presumably through the intermediacy of the P-containing adduct **3** and the intermediate **4** *(Scheme 1)* [8].

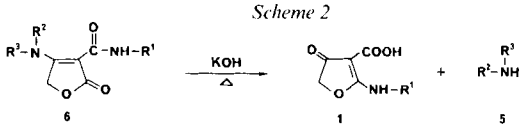
Scheme 1



When tested for antiallergic activity in the rat dermal vascular permeability assay, a number of derivatives **6** inhibited the action of mediators (serotonin, histamine, and bradykinin) on the small blood vessels [2] [3]. In addition, some compounds **6** were also found active as antiallergic agents in the rat active anaphylaxis assay [2] [3].

Chemistry. – In the present communication, we wish to report a further extension of our studies, namely, a novel rearrangement of the 2(5*H*)-furanones **6** back to 3(2*H*)-fu-

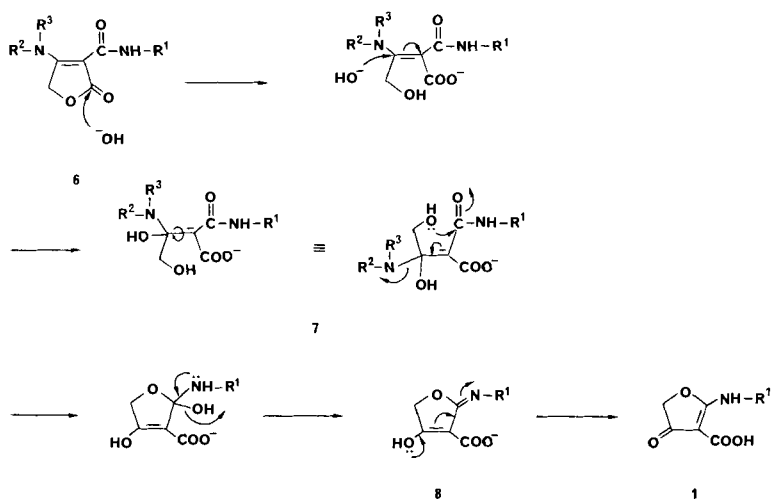
Scheme 2



Compound	R^1	R^2	R^3	NR^2R^3	Yields of **1** [%]	Yields of **5** [%]
6a	Ph	H	Ph		47	–
b	Ph	H	4-Cl–C_6H_4		42	36
c	3-NO_2–C_6H_4	H	Ph		13	–
d	2-CH_3O–C_6H_4	H	3-CF_3–C_6H_4		63	–
e	Ph	CH_3	Ph		77	–
f	4-Br–C_6H_4	H	4-CH_3O–C_6H_4		22	–
g	*trans*-2-phenylcyclopropyl	H	4-Cl–C_6H_4		57	52
h	*trans*-2-phenylcyclopropyl	H	3-CF_3–C_6H_4		68	–
i	*trans*-2-phenylcyclopropyl	H	3-NO_2–C_6H_4		57	95
j	Ph	H	$CH_3(CH_2)_{13}$		100	–
k	Ph	C_2H_5	C_2H_5		100	–
l	Ph			morpholino	83	–
m	Ph			1,2,3,4-tetrahydroquinolinyl	64	35
n	Ph			piperidinyl	90	–
o	Ph			pyrrolidinyl	78	–

ranones **1**. When refluxed in aqueous ethanolic solution in the presence of excess KOH, the 2,5-dihydro-2-oxofuran-3-carboxamides **6** underwent a reverse rearrangement giving the corresponding 4,5-dihydro-4-oxo-2-(phenylamino)-3-furancarboxylic acids **1** in moderate-to-excellent yields *(Scheme 2)*. One plausible mechanism of this novel rearrangement is depicted in *Scheme 3*. We postulate that in the presence of a strong base, an initial

Scheme 3



nucleophilic attack which led to a ring opening, is followed by another nucleophilic attack to generate the amino-alcohol intermediate **7**. Subsequent ring closure with a concomitant loss of amine, and then elimination of HO^- provided the 2-phenyliminofuran **8**. Tautomerization of **8** to the 4,5-dihydro-4-oxo-2-(phenylamino)-3-furancarboxylic acid (R^1 = Ph, **1**) completed the rearrangement. In the cases of 2(5*H*)-furanones **6b, g, i,** and **m**, we were also able to isolate the corresponding amines **5** *(Scheme 2)*. A variety of substituents on both N-atoms of the 2(5*H*)-furanones **6** were used to demonstrate the scope of the rearrangement. The highest yields of resulting 3(2*H*)-furanones **1** occurred with compounds **6** having either a 4-mono(or dialkyl)amino group or a 4-heterocyclic ring. The presence of electron-withdrawing groups in the 3-phenylcarboxamide moiety of compounds **6c** and **f** decreased significantly the yields of the corresponding 3(2*H*)-furanones **1** (13 and 22%, respectively). It appears likely that an electron-deficient aromatic ring will interfere with the formation of the 2-phenyliminofuran intermediate **8**[1]).

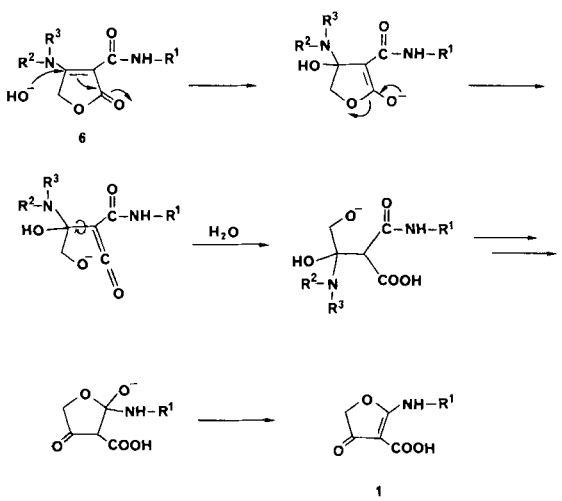
A number of previously unknown 2(5*H*)-furanones **6j-o** used in the present study, were prepared by utilizing the recently reported [1–3] 3(2*H*)-furanone → 2(5*H*)-furanone rearrangement.

Experimental Part

General. M.p.: *Thomas-Hoover* capillary melting point apparatus; uncorrected. IR spectra (KBr): *Nicolet-MX-1-FT* spectrometer. ^{1}H-NMR spectra: *Varian-EM-360-A* (60 MHz) spectrometer; TMS as internal standard. All spectra were consistent with the assigned structures.

*Rearrangement of 2(5*H*)-Furanones to 3(2*H*)-Furanones. General Procedure.* A soln. of KOH (0.42 g, 6.525 mmol) in 8 ml of H_2O was added in one portion, at r.t., to a suspension of *2,5-dihydro-2-oxo-*N*-phenyl-4-[(*N*-phenyl-*N*-methyl)amino]-3-furancarboxamide* (**6e**; 0.40 g, 1.3 mmol) in 16 ml of EtOH. The mixture was heated at reflux for 2 h, after which a clear soln. was obtained. The solvent was removed under reduced pressure, and the solid residue was dissolved in H_2O. The aq. soln. was extracted with Et_2O, then acidified with 4N HCl (pH 1), and the

[1]) We acknowledge the pointful remark of one of the reviewers that an alternative mechanism for the 2(5*H*)-furanone → 3(2*H*)-furanone rearrangement may also be considered possible as follows:



precipitated product was collected. Recrystallization from EtOH afforded the *4,5-dihydro-4-oxo-2-(phenylamino)-3-furancarboxylic acid* (**1**; R^1 = Ph; 0.22 g, 77%), identical in all respects with an authentic sample [9].

Compound **1** (R′ = Ph) was obtained by procedures similar to that described in the above example, utilizing the following furan-3-carboxamides **6** and reflux times (yields given in *Scheme 2*).

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(phenylamino)-3-furancarboxamide* (**6a**), 19 h.

*4-[*N*-(*p*-Chlorophenyl)amino]-2,5-dihydro-2-oxo-*N*-phenyl-3-furancarboxamide* (**6b**), 21 h.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(tetradecylamino)-3-furancarboxamide* (**6j**), 2 h.

*4-(*N,N*-Diethylamino)-2,5-dihydro-2-oxo-*N*-phenyl-3-furancarboxamide* (**6k**), 1 h.

*2,5-Dihydro-4-morpholino-2-oxo-*N*-phenyl-3-furancarboxamide* (**6l**), 2 h.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(1,2,3,4-tetrahydroquinolin-1-yl)-3-furancarboxamide* (**6m**), 2 h.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(piperidin-1-yl)-3-furancarboxamide* (**7n**), 1 h.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(pyrrolidin-1-yl)-3-furancarboxamide* (**7o**), 1 h.

The following compounds **1** [1] were obtained by procedures similar to that described in the aforementioned general procedure.

*4,5-Dihydro-2-[(*m*-nitrophenyl)amino]-4-oxo-3-furancarboxylic Acid* (**1**; R^1 = 3-NO_2–C_6H_4) *from 2,5-Dihydro-*N*-(*m*-nitrophenyl)-2-oxo-4-(phenylamino)-3-furancarboxamide* (**6c**). Reflux time 27 h. Yield 13%. M.p. 215–218°C (THF/H_2O). IR: 3225, 1725, 1651, 1597, 1552, 1522, 1425, 1341, 1265, 1160, 1045, 1020, 779, 730. ^{1}H-NMR ((D$_6$)DMSO/D_2O): 8.66–9.00 (*m*, 1 arom. H); 7.40–8.10 (*m*, 3 arom. H); 5.65 (*s*, 2 H, labile; NH, C–OH); 4.65 (*s*, O–CH_2–C=O). Anal. calc. for $C_{11}H_8N_2O_6$: C 50.01, H 3.05, N 10.60; found: C 50.24, H 3.04, N 10.60.

*4,5-Dihydro-2-[(*o*-methoxyphenyl)amino]-4-oxo-3-furancarboxylic Acid* (**1**; R^1 = 2-CH_3O–C_6H_4) *from 2,5-Dihydro-*N*-(*o*-methoxyphenyl)-2-oxo-4-[*N*-(*m*-trifluoromethylphenyl)amino]-3-furancarboxamide* (**6d**). Reflux time 22 h. Yield 63%. M.p. 161–164° (i-PrOH). IR: 3280, 1740, 1650, 1558, 1460, 1430, 1292, 1255, 1024, 748. ^{1}H-NMR ($CDCl_3$): 11.36 (*s*, 1 H); 9.52 (br. *s*, 1 H); 8.40–8.02 (*m*, 1 H); 7.30–6.73 (*m*, 3 H); 4.75 (*s*, 2 H); 3.93 (*s*, 3 H). Anal. calc. for $C_{12}H_{11}NO_5$: C 57.83, H 4.45, N 5.62; found: C 57.46, H 4.36, N 5.65.

*2-[(*p*-Bromophenyl)amino]-4,5-dihydro-4-oxo-3-furancarboxylic Acid* (**1**; R^1 = 4-Br–C_6H_4) *from* N*-(*p*-bromophenyl)-2,5-dihydro-4-[*N*-(*p*-methoxyphenyl)amino]-2-oxo-3-furancarboxamide* (**6f**). Reflux time 23 h. Yield 22%. M.p. 195–197° (xylene). IR: 3225, 1750, 1660, 1600, 1549, 1483, 1439, 1395, 1348, 1280, 1235, 1175, 1060, 1030, 829. ^{1}H-NMR ($CDCl_3$/(D$_6$)DMSO): 7.10–7.80 (*q*, 4 arom. H); 5.60 (*s*, 2 H, labile; NH, C–OH); 4.70 (*s*, O–CH_2–C=O). Anal. calc. for $C_{11}H_8BrNO_4$: C 44.32, H 2.70, N 4.70; found: C 44.53, H 2.52, N 4.70.

The *4,5-dihydro-4-oxo-2-[(*trans*-2-phenylcyclopropyl)amino]-3-furancarboxylic acid* (**1**; R^1 = *trans*-2-phenylcyclopropyl) [7] was obtained by procedures similar to the aforementioned general procedure, utilizing the following furan-3-carboxamides **6** and reflux times (yields given in *Scheme 2*).

*4-[(*p*-Chlorophenyl)amino]-2,5-dihydro-2-oxo-*N*-(*trans*-2-phenylcyclopropyl)-3-furancarboxamide* (**6g**). Reflux time 3 h.

*2,5-Dihydro-2-oxo-*N*-(*trans*-2-phenylcyclopropyl)-4-[(*m*-trifluoromethylphenyl)amino]-3-furancarboxamide* (**6h**). Reflux time 7 h.

*2,5-Dihydro-4-[(*m*-nitrophenyl)amino]-2-oxo-*N*-(*trans*-2-phenylcyclopropyl)-3-furancarboxamide* (**6i**). Reflux time 4 h. Yield 57%.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-tetradecylamino-3-furancarboxamide* (**6j**). Under N_2, a soln. of Et_3N (3.5 ml, 0.025 mol) in 20 ml of CH_2Cl_2 was added dropwise to a soln. of 2-anilino-4-oxo-3-furoic acid (5.0 g, 0.023 mol) in 40 ml of CH_2Cl_2, at 0–5° (ice-water bath). Then, **2** (5.8 g, 0.023 mol) was added in one portion, and the mixture was stirred at 0–5° for 40 min, followed by a dropwise addition (over a 6-h period) of a soln. of l-tetradecylamine (5.8 g, 0.025 mol) in 200 ml of CH_2Cl_2. The mixture was allowed to warm up to ambient temp. and was stirred for 18 h, then poured into ice-water and extracted with CH_2Cl_2. The org. extract was washed sequentially with H_2O and 5% aq. soln. of Na_2CO_3, dried over anh. $MgSO_4$ and the solvent evaporated under reduced pressure. The resulting crude product was purified by flash-chromatography over silica gel using $CHCl_3$ to provide pure **6j**. Yield 1.37 g. M.p. 84–85° (EtOH). IR: 3410, 3290, 2910, 2840, 1727, 1668, 1652, 1630, 1595, 1552, 1463, 1312, 1034, 781, 749, 710. ^{1}H-NMR ($CDCl_3$): 9.39 (br. *s*, 1 H); 8.54 (br. *s*, 1 H); 7.68–6.96 (*m*, 5 H); 4.77 (*s*, 2 H); 3.37–2.97 (*m*, 2 H); 1.88–0.72 (*m*, 27 H). Anal. calc. for $C_{25}H_{38}N_2O_3$: C 72.43, H 9.24, N 6.76; found: C 72.51, H 9.32, N 6.66.

*4-(*N,N*-Diethylamino)-2,5-dihydro-2-oxo-*N*-phenyl-3-furancarboxamide* (**6k**). Compound **6k** was prepared by a procedure similar to that described for **6j** by using Et_2NH in place of l-tetradecylamine. B.p. 195–200°/0.015 Torr. Yield 44%. IR (neat): 3260, 2970, 2930, 1705, 1665, 1585, 1540, 1440, 1310, 1250, 1080, 1045, 785, 755, 695. ^{1}H-NMR ($CDCl_3$): 10.20 (br. *s*, 1 H); 7.70–6.83 (*m*, 5 H); 4.68 (*s*, 2 H); 3.62 (br. *s*, 4 H); 1.22 (*t*, *J* = 6, 6 H). Anal. calc. for $C_{15}H_{18}N_2O_3 \cdot xH_2O$: C 64.62, H 6.69, N 10.05; found: C 64.74, H 7.06, N 10.05.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(1,2,3,4-tetrahydroquinolin-1-yl)-3-furancarboxamide* (**6m**). Under N_2, a soln. of Et_3N (14.0 ml, 0.1 mol) in 40 ml of CH_2Cl_2 was added dropwise to a soln. of 2-anilino-4-oxo-3-furoic acid (10.0 g, 0.046 mol) in 80 ml of CH_2Cl_2, at 0–5° (ice-water bath). Then, **2** (11.60 g, 0.046 mol) was added in one portion at 0–5°, and the mixture was stirred at 0–5° for 45 min, followed by the dropwise addition (over a 6-h period) of a soln. of 1,2,3,4-tetrahydroquinoline (6.4 ml, 0.051 mol) in 100 ml of CH_2Cl_2. The mixture was allowed to warm up to ambient temp. and was stirred for an additional 18 h, then poured into ice-water and extracted with CH_2Cl_2. The combined org. extract was washed sequentially with H_2O and 5% aq. soln. of Na_2CO_3, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to provide crude **6m**, which was recrystallized from EtOH. Yield 4.30 g. M.p. 155–157°. IR: 3280, 2930, 1715, 1660, 1599–1530, 1490, 1440, 1418, 1310, 1250, 1180, 1055, 1040, 785, 755, 695. ^{1}H-NMR ($CDCl_3$): 10.30 (br. *s*, 1 H); 7.80–6.82 (*m*,9 H); 4.82 (*s*, 2 H); 4.32–3.92 (*m*, 2 H); 3.05–2.59 (*m*, 2 H); 2.27–1.64 (*m*, 2 H). Anal. calc. for $C_{20}H_{18}N_2O_3$: C 71.84, H 5.43, N 8.38; found: C 71.62, H 5.52, N 8.37.

*2,5-Dihydro-4-morpholino-2-oxo-*N*-phenyl-3-furancarboxamide* (**6l**). Derivative **6l** was synthesized by a procedure similar to that described for the preparation of **6m** by using morpholine in place of 1,2,3,4-tetrahydroquinoline. Yield 27%. M.p. 205–206.5° (EtOH). IR: 3340, 2950, 2910, 2850, 1710, 1660, 1590, 1535, 1435, 1310, 1298, 1233, 1245, 1222, 1110, 1045, 1035, 1005, 880, 780, 763, 692. ^{1}H-NMR ($CDCl_3$): 10.40 (br. *s*, 1 H); 7.70–6.82 (*m*, 5 H); 4.90 (*s*, 2 H); 4.02–3.03 (*m*, 8 H). Anal. calc. for $C_{15}H_{16}N_2O_4$: C 62.71, H 5.26, N 9.75; found: C 62.59, H 5.76, N 9.74.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(piperidin-1-yl)-3-furancarboxamide* (**6n**). Compound **6n** was obtained by a procedure similar to that described for **6m** by substituting piperidine for 1,2,3,4-tetrahydroquinoline. Yield 24%. M.p. 157–158° (EtOH). IR: 3260, 2930, 1695, 1652, 1595, 1575, 1530, 1495, 1440, 1292, 1238, 1181, 1069, 1040, 780, 750, 719, 695. ^{1}H-NMR ($CDCl_3$): 10.22 (br. *s*, 1 H); 7.69–6.81 (*m*, 5 H); 4.62 (*s*, 2 H); 3.62 (br. *m*, 4 H); 1.70 (br. *s*, 6 H). Anal. calc. for $C_{16}H_{18}N_2O_3$: C 67.12, H 6.34, N 9.78; found: C 67.08, H 6.47, N 9.77.

*2,5-Dihydro-2-oxo-*N*-phenyl-4-(pyrrolidin-1-yl)-3-furancarboxamide* (**6o**). Derivative **6o** was prepared by a procedure similar to that described for **6m** by replacing the 1,2,3,4-tetrahydroquinoline with pyrrolidine. Yield 14%. M.p. 200–201° (EtOH). IR: 3260, 3220, 2970, 2945, 2860, 1696, 1580, 1540, 1435, 1305, 1240, 1080, 1040, 789, 769. ^{1}H-NMR ($CDCl_3$): 10.70 (br. *s*, 1 H); 7.72–6.87 (*m*, 5 H); 4.62 (*s*, 2 H); 4.23–3.87 (*m*, 2 H); 3.50–3.13 (*m*, 2 H); 2.23–1.72 (*m*, 4 H). Anal. calc. for $C_{15}H_{16}N_2O_3$: C 66.16, H 5.92, N 10.29; found: C 66.14, H 5.97, N 10.27.

REFERENCES

[1] R. A. Mack, V. St. Georgiev, *J. Org. Chem.* **1987,** *52,* 477.
[2] V. St. Georgiev, R. A. Mack, D. J. Walter, L. A. Radov, J. E. Baer, *Helv. Chim. Acta* **1987,** *70,* 1526.
[3] R. A. Mack, V. St. Georgiev, T. R. DeCory, L. A. Radov, *Eur. J. Med. Chem.* **1987,** *22,* 521.
[4] P. J. Carroll, R. A. Mack, V. St. Georgiev, *Acta Crystallogr., Sect. C* **1988,** *44,* 294.
[5] W. J. Kuipers, R. A. Mack, V. St. Georgiev, *Magn. Reson. Chem.* **1988,** *26,* 89.
[6] V. St. Georgiev, R. A. Mack, C. R. Kinsolving, U.S. Patent 4,614,810, 1986.
[7] V. St. Georgiev, R. A. Mack, C. R. Kinsolving, *Heterocycles* **1986,** *24,* 3195.
[8] R. A. Mack, P. J. Carroll, V. St. Georgiev, *J. Heterocycl. Chem.* **1988,** *25,* in press.
[9] L. Capuano, W. Fischer, *Chem. Ber.* **1976,** *109,* 212.