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Ring Transformation of 2-Furylcarbamates to 5-Hydroxy-3-pyrrolin-2-ones.
Effects of Substitution in the Benzene Ring on the N-Carbo-
benzyloxy-5-hydroxy-5-phenyl-3-pyrroline-2-one—
cis- γ -Ketoamide Equilibrium

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In the ring transformation of 2-furylcarbamates (2) to 5-hydroxy-3-pyrrolin-2-ones (3) by irradiation in the presence of oxygen, there is an equilibrium between N-carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrrolin-2-one (3-A) and *cis*- γ -ketoamide (3-B); this equilibrium was studied by nuclear magnetic resonance spectroscopy. The presence of electron-withdrawing groups in the benzene ring selectively stabilized the hydroxypyrrolinone tautomer, while that of electron-releasing groups had the opposite effect. These results indicate that the ring-chain tautomerism depends on the electronic and/or steric factors of substituents on the benzene ring.

Keywords—2-furylcarbamate; 5-hydroxy-3-pyrrolin-2-one; γ -ketoamide; photo-oxidation; ring transformation; ring-chain tautomerism; ring-chain equilibrium

We have recently reported the ring transformation of 2-furylcarbamates to 5-hydroxypyrrolinones by autoxidation or photooxidation.¹⁾ In the course of these studies, the ring-chain tautomeric equilibrium between N-carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrrolin-2-one (3a-A) and the corresponding *cis*-benzyl N-(β -benzoylacryloyl)carbamate (3a-B) was observed by nuclear magnetic resonance (NMR) spectroscopy. The occurrence of this equilibrium seems to be due to the steric effect of the 5-phenyl group, because each compound 1 was confirmed to exist only as the cyclic form.¹⁾ It has recently been shown that the equilibrium in the 5-hydroxy-5-phenyl-3-pyrrolinone system is sensitive to the steric effect of N-substituents.²⁾ However, the electrostatic effect of substituents on the ring-chain equilibrium is not clear. We report here the effects of substituents in the benzene ring on the equilibrium between N-carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrrolin-2-ones (3-A) and the corresponding *cis*- γ -ketoamides (3-B).

R₁=R₂=Ph, R₃=H
R₁=R₂=R₃=H
R₁=CH₃, R₂=R₃=H
R₂=CH₃, R₁=R₃=H
R₃=CH₃, R₁=R₂=H

Chart 1

Benzyl N-(5-phenyl-2-furyl)carbamates (2a—k) were prepared from 2-furoic acid and various aniline derivatives by the Meerwein arylation,³⁾ followed by successive treatments with ethyl chloroformate, sodium azide and benzyl alcohol (Table I). Upon irradiation with a 400W high pressure mercury lamp under oxygen in benzene for 1 h, 2-furylcarbamates (2) gave the corresponding ring transformation products (3) (Table II) and *trans*- γ -ketoamides (4) (Table III). Moreover, upon further irradiation of the *trans*- γ -ketoamides, they were found to isomerize to cyclic forms. For example, irradiation of *trans*-benzyl N-(5-*p*-tolyl-2-furyl)carbamate (4c) in benzene for 30 min caused partial isomerization to N-carbobenzyloxy-5-hydroxy-5-*p*-tolyl-3-pyrrolin-2-one (3c), and the treatment of 3c with triethylamine, trifluoroacetic acid or 5% hydrogen chloride-methanol gave 4c quantitatively. Treatment of 3c

	R	Yield (%)		R	Yield (%)
3a	H	41	3g	<i>m</i> -Cl	36
3b	<i>p</i> -OCH ₃	42	3h	<i>m</i> -NO ₂	41
3c	<i>p</i> -CH ₃	34	3i	<i>o</i> -CH ₃	16
3d	<i>p</i> -Cl	36	3j	<i>o</i> -Cl	35
3e	<i>p</i> -NO ₂	77	3k	<i>o</i> -NO ₂	—
3f	<i>m</i> -OCH ₃	32

Chart 2

with hydrogen over Pd/C in ethanol and with sodium borohydride afforded the saturated amide (**5**)⁴ and diol (**6**), respectively, in good yields. In the case of *o*-nitrophenyl carbamate (**2k**), the corresponding cyclic form (**3k-A**) was not detected, but the formation of a small amount of *trans*- γ -ketoamide (**4k**) was confirmed. The reactivity of 2-furylcarbamates having a nitro group in the *ortho*-position of the benzene ring is now being studied.⁵

Next, the ring-chain equilibrium of 5-hydroxypyrrolinones (**3a–j**) was examined by NMR spectroscopy. In the equilibrium, the ratio of the ring form (**3-A**) to the chain form (**3-B**) in compounds **3a–j** could be confirmed by comparison of the relative intensities of the corresponding olefinic proton signals. The NMR data in Table IV show that compounds **3** have signals of α -protons at 5.99–6.15 ppm and β -protons at 6.89–7.00 ppm as doublets ($J=6$ –7 Hz) in $CDCl_3$, and of α -protons at 5.98–6.16 ppm and β -protons at 6.89–7.04 ppm as doublets ($J=6$ –6.5 Hz) in CD_3CN . These signals were assigned to the olefinic protons of the cyclic form (**3-A**) from the chemical shifts and the coupling constants. On the other hand, the signals of α -protons at 6.81–6.99 ppm and β -protons at 6.66–6.81 ppm as doublets ($J=12$ Hz)

TABLE I. Physical and Spectral Data for 2-Furylcarbamates (2)

No.	R	mp (°C)	Appearance	IR $\nu_{\max}^{\text{CHCl}_3}$, cm ⁻¹		NMR (CDCl ₃) δ			MS (<i>m/e</i>)	Formula	Analysis (%)		
				NH	C=O	C-2	C-3 ^a	C-4 ^a , C-5			C	H	N
2a	H	81–82	Colorless prisms	3400	1725	7.06(br s) 7.38(s) 5.18(s)	6.18 6.58	7.61–7.06(m)	293(M ⁺), 185, 158	C ₁₈ H ₁₅ NO ₃	73.70 (73.65)	5.15 4.93	4.78 4.77)
2b	<i>p</i> -OCH ₃	114–115	Colorless needles	3380	1715	7.36(br) 7.36(s) 5.18(s)	6.14 6.46	7.48(d, <i>J</i> =10 Hz) 6.86(d, <i>J</i> =10 Hz) 3.80(s)	323(M ⁺), 215, 188	C ₁₉ H ₁₇ NO ₄	70.57 (70.29)	5.30 5.10	4.33 4.24)
2c	<i>p</i> -CH ₃	91–92	Colorless needles	3400	1725	6.84(br s) 7.36(s) 5.15(s)	6.12 6.50	7.42(d, <i>J</i> =9 Hz) 7.10(d, <i>J</i> =9 Hz) 2.30(s)	307(M ⁺), 199, 172	C ₁₈ H ₁₇ NO ₃	74.25 (74.18)	5.58 5.34	4.56 4.52)
2d	<i>p</i> -Cl	104–105	Colorless needles	3380	1720	6.98(br s) 7.36(s) 5.16(s)	6.14 6.54	7.44(d, <i>J</i> =9 Hz) 7.26(d, <i>J</i> =9 Hz) 5.16(s)	327(M ⁺), 219, 192	C ₁₈ H ₁₄ ClNO ₃	65.95 (65.77)	4.31 4.28	4.27 4.17)
2e	<i>p</i> -NO ₂	133–134	Yellow needles	3390	1725	7.12(br s) 7.38(s) 5.22(s)	6.27 6.83	8.16(d, <i>J</i> =9 Hz) 7.60(d, <i>J</i> =9 Hz) 3.80(s)	338(M ⁺), 230, 203	C ₁₈ H ₁₄ N ₂ O ₅	63.90 (63.76)	4.17 4.01	8.28 8.11)
2f	<i>m</i> -OCH ₃	—	Colorless oil	3410	1725	6.82(br s) 7.32(s) 5.16(s)	6.12 6.54	7.18–6.64(m) 3.80(s)	323(M ⁺), 215, 188	C ₁₉ H ₁₇ NO ₄	—	—	—
3g	<i>m</i> -Cl	102–103	Colorless needles	3410	1740	7.10(br s) 7.36(s) 5.20(s)	6.16 6.58	7.56–7.08(m) 3.80(s)	327(M ⁺), 219, 192	C ₁₈ H ₁₄ ClNO ₃	65.95 (65.84)	4.31 4.28	4.27 4.07)
2h	<i>m</i> -NO ₂	126–128	Yellow needles	3440	1735	7.00(br s) 7.32(s) 5.16(s)	6.18 6.68	8.30–7.28(m) 3.80(s)	338(M ⁺), 230, 203	C ₁₈ H ₁₄ N ₂ O ₅	63.90 (63.78)	4.17 3.97	8.28 8.16)
2i	<i>o</i> -CH ₃	53–54	Colorless needles	3400	1720	6.96(br s) 7.32(s) 5.16(s)	6.14 6.42	7.60–7.08(m) 2.40(s)	307(M ⁺), 199, 173	C ₁₉ H ₁₇ NO ₃	74.25 (74.21)	5.58 5.38	4.56 4.31)
2j	<i>o</i> -Cl	59–62	Colorless scales	3410	1725	6.92(br s) 7.32(s) 5.16(s)	6.18 7.02	7.70–7.08(m) 3.80(s)	327(M ⁺), 219, 192	C ₁₈ H ₁₄ ClNO ₃	65.95 (65.79)	4.31 4.16	4.27 4.09)
2k	<i>o</i> -NO ₂	87–88	Yellow needles	3400	1725	7.62(br s) 7.28(s) 5.11(s)	6.14 6.55	7.58–7.08(m) 3.80(s)	338(M ⁺), 230, 203	C ₁₈ H ₁₄ N ₂ O ₅	63.90 (63.76)	4.17 4.03	8.28 8.15)

a) These proton signals have the usual coupling constants of the furan ring.

in CD_3CN , and of α - and β -protons at 6.75–6.98 ppm as singlets or doublets ($J=12$ Hz) in CDCl_3 , were assigned to those of the chain form (**3-B**). In the case of *cis*- γ -ketoamides (**3a–d-B**), these structures are also characterized by lowfield-shifted aromatic protons adjacent to the carbonyl group at 7.78–7.87 ppm in CDCl_3 and 7.76–7.85 ppm in CD_3CN . For example, the NMR spectrum of the *p*-methyl compound **3c** in CD_3CN shows a singlet at 2.32, and doublets at 6.02 ($J=6.5$ Hz) and 7.02 ($J=6.5$ Hz) ppm for the methyl and olefinic protons of the cyclic form (**A**), respectively, and a singlet at 2.38, and doublets at 6.73 ($J=12$ Hz), 6.96 ($J=12$ Hz) and 7.76 ($J=8$ Hz) ppm for the methyl, olefinic and C-2', 6' protons of the *cis*- γ -ketoamide (**B**), respectively (Fig. 1). Thus, the NMR data in Table IV show that compounds **3a–j**, except for **3e** and **3h**, exist as both forms in CDCl_3 or CD_3CN . The *p*- and *m*-nitro compounds **3e** and **3h** were concluded to exist as only the cyclic form (**A**) in these solvents (Table V). As a result, electron-withdrawing groups on the phenyl moiety should selectively stabilize the corresponding cyclic form (**A**), leading to a shift in the equilibrium away from the chain form (**B**). In contrast, the presence of electron-releasing groups should shift the equilibrium toward the chain form (**B**). Moreover, Fig. 2 illustrates that the amount of the cyclic form (%) of *p*- and *m*-substituted compounds **3b–h** shows a linear correlation with the Hammett constants (δ). Thus, it is clear that the amounts of cyclic forms are proportional to the substitution constants (δ).

TABLE II. Physical and Spectral Data for Ring Transformation Products (3)

No.	R	mp (°C)	Appearance	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm ⁻¹		MS (<i>m/e</i>)	Formula	Analysis (%)		
				OH, NH	C=O			Calcd (Found)	C	H
3a	H	113—115	Colorless needles	3480 3370	1773 1738 1695	310(M ⁺ + 1), 291, 248, 203, 185, 160, 151	C ₁₈ H ₁₅ NO ₄	69.89 (69.73)	4.89 4.78	4.53 4.42)
3b	<i>p</i> -OCH ₃	110—112	Colorless needles	3490 3370	1770 1740 1690	339(M ⁺), 295, 231, 190, 161, 151	C ₁₉ H ₁₇ NO ₅	67.25 (67.13)	5.05 4.98	4.13 4.05)
3c	<i>p</i> -CH ₃	98—102	Colorless needles	3490 3370	1775 1740 1690	324(M ⁺ + 1), 305, 279, 217, 199, 174, 151	C ₁₉ H ₁₇ NO ₄	70.57 (70.49)	5.30 5.21	4.33 4.19)
3d	<i>p</i> -Cl	105—110	Colorless needles	3500 3400	1775 1740 1695	344(M ⁺ + 1), 325, 237, 219, 194, 151	C ₁₈ H ₁₇ ClNO ₄	62.88 (62.73)	4.11 4.02	4.08 3.96)
3e	<i>p</i> -NO ₂	156—157	Yellow prisms	3480	1770 1740 1695	354(M ⁺), 293, 248, 230, 205, 188, 151	C ₁₈ H ₁₇ N ₂ O ₆	61.01 (60.81)	3.98 3.79	7.91 7.74)
3f	<i>m</i> -OCH ₃	104—107	Colorless needles	3500 3410	1775 1740 1690	339(M ⁺), 321, 279, 233, 215, 190, 161, 151	C ₁₉ H ₁₇ NO ₅	67.25 (67.09)	5.05 4.96	4.13 4.04)
3g	<i>m</i> -Cl	108—112	Colorless prisms	3480 3380	1775 1740 1690	344(M ⁺ + 1), 325, 282, 239, 221, 195, 165, 151	C ₁₈ H ₁₄ ClNO ₄	62.88 (62.66)	4.11 3.97	4.08 3.89)
3h	<i>m</i> -NO ₂	139—141	Yellow needles	3520	1775 1750 1710	353(M ⁺ - 1), 336, 292, 257, 205, 177, 151	C ₁₈ H ₁₄ N ₂ O ₆	61.01 (60.99)	3.98 3.85	7.91 7.84)
3i	<i>o</i> -CH ₃	113—118	Colorless prisms	3490 3380	1770 1745 1695	323(M ⁺), 305, 232, 215, 177, 172, 151	C ₁₉ H ₁₇ NO ₄	70.57 (70.42)	5.30 5.21	4.33 4.22)
3j	<i>o</i> -Cl	55—57	Colorless needles	3490 3400	1775 1745 1695	345(M ⁺ + 2), 325, 237, 219, 194, 151	C ₁₈ H ₁₄ ClNO ₄	62.88 (62.79)	4.11 4.01	4.08 3.97)

TABLE III. Physical and Spectral Data for *trans*- γ -Ketoamides (4)^{a)}

No.	R	mp (°C)	Appearance	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm ⁻¹ <div>NH C=O</div>	NMR (CDCl ₃) δ^b			Formula	Analysis (%)		
					C- α , C- β	<div><div><div></div><div>R</div><div></div></div></div>	-NHCO ₂ CH ₂ Ph		Calcd (Found)	C	H
4a	H	154—156	Colorless needles	3390 1775 1690 1665	8.02 (d, J = 16 Hz) 7.68 (d, J = 16 Hz)	8.10—7.44(m)	8.26 (br s) 5.18 (s) 7.36	C ₁₈ H ₁₅ NO ₄	69.89 (69.69)	4.89 4.65	4.53 4.41
4b	<i>p</i> -OCH ₃	161—162	Colorless needles	3380 1745 1690 1650	7.98 (d, J = 16 Hz) 7.64 (d, J = 16 Hz)	7.96 (d, J = 8 Hz) 6.92 (d, J = 8 Hz) 3.86(s)	8.00 (br) 5.20 (s) 7.38 (s)	C ₁₉ H ₁₇ NO ₅	67.25 (67.09)	5.05 4.87	4.13 4.01
4c	<i>p</i> -CH ₃	180—181	Colorless needles	3370 1750 1680 1655	7.98 (d, J = 16 Hz) 7.66 (d, J = 16 Hz)	7.89 (d, J = 8 Hz) 7.24 (d, J = 8 Hz) 2.41(s)	7.98 (br) 5.18 (s) 7.35 (s)	C ₁₉ H ₁₇ NO ₄	70.57 (70.43)	5.30 5.19	4.33 4.19
4d	<i>p</i> -Cl	186—187	Colorless needles	3380 1760 1690 1660	7.93 (d, J = 16 Hz) 7.68 (d, J = 16 Hz)	7.89 (d, J = 9 Hz) 7.42 (d, J = 9 Hz)	7.80 (br) 5.18 (s) 7.36 (s)	C ₁₈ H ₁₇ ClNO ₄	62.88 (62.71)	4.11 4.02	4.08 3.89
4e	<i>p</i> -NO ₂	172—174	Colorless needles	3360 1740 1685 1660	7.93 (d, J = 16 Hz) 7.61 (d, J = 16 Hz)	8.42 (d, J = 9 Hz) 8.28 (d, J = 9 Hz)	10.00 (br) 5.21 (s) 7.39 (s)	C ₁₈ H ₁₄ N ₂ O ₆	61.01 (60.92)	3.98 3.87	7.91 7.85
4f	<i>m</i> -OCH ₃	124—126	Colorless needles	3370 1745 1690 1650	7.90 (d, J = 16 Hz) 7.66 (d, J = 16 Hz)	7.52—7.08(m) 3.82(s)	7.45 (br) 5.16 (s) 7.34 (s)	C ₁₉ H ₁₇ NO ₅	67.25 (67.07)	5.05 5.01	4.13 4.01
4g	<i>m</i> -Cl	141—142	Colorless needles	3360 1745 1680 1655	7.85 (d, J = 16 Hz) 7.63 (d, J = 16 Hz)	7.96—7.00(m)	8.04 (br s) 5.16 (s) 7.32 (s)	C ₁₈ H ₁₄ ClNO ₄	62.88 (62.71)	4.11 4.03	4.08 3.97
4h	<i>m</i> -NO ₂	160—163	Colorless needles	3360 1745 1685 1663	7.99 (d, J = 16 Hz) 7.63 (d, J = 16 Hz)	8.84—7.20(m)	10.03 (br) 5.23 (s) 7.43 (s)	C ₁₈ H ₁₄ N ₂ O ₆	61.01 (60.87)	3.98 3.78	7.91 7.77
4i	<i>o</i> -CH ₃	73—75	Colorless needles	3370 1745 1680 1650	7.70 (d, J = 16 Hz) 7.52 (d, J = 16 Hz)	7.42—7.16(m)	7.74 (br) 5.17 (s) 7.38 (s)	C ₁₉ H ₁₇ NO ₄	70.57 (70.43)	5.30 5.34	4.33 4.25
4j	<i>o</i> -Cl	129—131	Colorless needles	3370 1745 1685 1660	7.55 (s)	7.50—7.20(m)	8.03 (br s) 5.16 (s) 7.34 (s)	C ₁₈ H ₁₄ ClNO ₄	62.88 (62.75)	4.11 4.03	4.08 3.99
4k	<i>o</i> -NO ₂	155—156	Yellow needles	3390 1795 1750 1675	7.32 (s)	8.20—7.26(m)	7.90 (br s) 5.10 (s) 7.32 (s)	C ₁₈ H ₁₄ N ₂ O ₆	61.01 (60.83)	3.98 3.82	7.91 7.78

a) 4a—k were obtained in 5—10% yields.

b) 4e and 4h were measured in acetone-*d*₆.

TABLE IV. NMR Spectral Data for Ring Transformation Products (3)^{a)}

No.	R	in CDCl ₃ δ				in CD ₃ CN δ			
		A		B		A		B	
		C- α C- β	CH ₃	C- α C- β	CH ₃ C-2', 6'	C- α C- β	CH ₃	C- α C- β	CH ₃ C-2', 6'
3a	H	6.05 (d, $J=6$ Hz)	—	6.98 (s)	—	6.02 (d, $J=6$ Hz)	—	6.95 (d, $J=12$ Hz)	—
		7.00 (d, $J=6$ Hz)	—	—	7.87 (d, $J=8$ Hz)	7.01 (d, $J=6$ Hz)	—	6.73 (d, $J=12$ Hz)	7.84 (d, $J=8$ Hz)
3b	<i>p</i> -OCH ₃	6.00 (d, $J=6$ Hz)	3.76 (s)	6.92 (s)	3.82 (s)	5.98 (d, $J=6$ Hz)	3.75 (s)	6.93 (d, $J=12$ Hz)	3.83 (s)
		6.96 (d, $J=6$ Hz)	—	—	7.85 (d, $J=9$ Hz)	6.89 (d, $J=6$ Hz)	—	6.67 (d, $J=12$ Hz)	7.82 (d, $J=8$ Hz)
3c	<i>p</i> -CH ₃	6.02 (d, $J=7$ Hz)	2.33 (s)	^{b)}	2.38 (s)	6.02 (d, $J=6.5$ Hz)	2.32 (s)	6.96 (d, $J=12$ Hz)	2.38 (s)
		6.90 (d, $J=7$ Hz)	—	^{b)}	7.79 (d, $J=8$ Hz)	7.02 (d, $J=6.5$ Hz)	—	6.73 (d, $J=12$ Hz)	7.76 (d, $J=8$ Hz)
3d	<i>p</i> -Cl	6.02 (d, $J=6$ Hz)	—	^{b)}	—	6.07 (d, $J=6$ Hz)	—	6.96 (d, $J=12$ Hz)	—
		6.92 (d, $J=6$ Hz)	—	—	7.78 (d, $J=8$ Hz)	7.03 (d, $J=6$ Hz)	—	6.79 (d, $J=12$ Hz)	7.85 (d, $J=8.5$ Hz)
3e	<i>p</i> -NO ₂	6.12 (d, $J=6$ Hz)	—	—	—	6.12 (d, $J=6$ Hz)	—	—	—
		6.96 (d, $J=6$ Hz)	—	—	—	7.02 (d, $J=6$ Hz)	—	—	—
3f	<i>m</i> -OCH ₃	5.99 (d, $J=7$ Hz)	3.70 (s)	^{b)}	3.77 (s)	6.00 (d, $J=6$ Hz)	3.69 (s)	6.99 (d, $J=12$ Hz)	3.76 (s)
		6.94 (d, $J=7$ Hz)	—	—	—	6.99 (d, $J=6$ Hz)	—	6.81 (d, $J=12$ Hz)	—
3g	<i>m</i> -Cl	6.00 (d, $J=6$ Hz)	—	^{b)}	—	6.04 (d, $J=6$ Hz)	—	6.81 (d, $J=12$ Hz)	—
		6.89 (d, $J=6$ Hz)	—	—	—	6.99 (d, $J=6$ Hz)	—	6.75 (d, $J=12$ Hz)	—
3h	<i>m</i> -NO ₂	6.11 (d, $J=7$ Hz)	—	—	—	6.13 (d, $J=6$ Hz)	—	—	—
		6.97 (d, $J=7$ Hz)	—	—	—	7.04 (d, $J=6$ Hz)	—	—	—
3i	<i>o</i> -CH ₃	6.11 (d, $J=6$ Hz)	2.30 (s)	6.90 (s)	2.56 (s)	6.08 (d, $J=6$ Hz)	2.22 (s)	6.91 (d, $J=12$ Hz)	2.51 (s)
		^{b)}	—	—	—	6.99 (d, $J=6$ Hz)	—	6.66 (d, $J=12$ Hz)	—
3j	<i>o</i> -Cl	6.15 (d, $J=7$ Hz)	—	6.75 (d, $J=12$ Hz)	—	6.16 (d, $J=6$ Hz)	—	6.86 (d, $J=12$ Hz)	—
		6.90 (d, $J=7$ Hz)	—	6.92 (d, $J=12$ Hz)	—	6.90 (d, $J=6$ Hz)	—	6.66 (d, $J=12$ Hz)	—

a) The ring/chain ratios of 3 could be determined by comparing the relative intensities of the NH (about 8.3 ppm), OH (about 4.7 ppm), or CH₂ (about 5.2 ppm) signals. All samples were measured immediately after preparation.

b) These signals were overlapping with aromatic protons.

TABLE V. Ring/Chain Ratios of 3

No.	R	CDCl ₃		CD ₃ CN	
		A %	B %	A %	B %
3a	H	81	19	68	32
3b	<i>p</i> -OCH ₃	50	50	31	69
3c	<i>p</i> -CH ₃	67	33	63	37
3d	<i>p</i> -Cl	88	12	87	13
3e	<i>p</i> -NO ₂	100	0	100	0
3f	<i>m</i> -OCH ₃	87	13	73	27
3g	<i>m</i> -Cl	92	8	84	16
3h	<i>m</i> -NO ₂	100	0	100	0
3i	<i>o</i> -CH ₃	20	80	26	74
3j	<i>o</i> -Cl	89	11	89	11

Fig. 2. Correlation of the Amount of the Cyclic Form (3-A) with Hammett's Constants

- (a) *p*-substituted phenyl derivatives
 ○ — CDCl₃, × — CD₃CN.
 (b) *m*-substituted phenyl derivatives
 ○ — CDCl₃, × — CD₃CN.

Fig. 1. NMR Spectrum of 3c in CD₃CN

Chart 3

The solvent dependency of the equilibrium of **3c** is also clearly demonstrated by the NMR spectra in CDCl_3 , acetone- d_6 , CD_3CN and $\text{DMSO}-d_6$ at room temperature. The amount of the cyclic form (**A**) is 67% in CDCl_3 , 64% in acetone- d_6 , 63% in CD_3CN and 59% in $\text{DMSO}-d_6$, *i.e.*, an increase of solvent polarity decreased the ratio of cyclic form (**A**). This observation was expected, because the cyclic form (**A**) would be stabilized by intramolecular hydrogen bonding in solvents of lower polarity.

Next, similar reactions were carried out to synthesize nicotine analogs. Benzyl N-[5-(3-pyridyl)-2-furyl]carbamate (**8a**) prepared from 5-(3-pyridyl)-2-furoic acid (**7a**)⁶⁾ was irradiated to give N-carbobenzyloxy-5-hydroxy-5-(3-pyridyl)-3-pyrrolin-2-one (**9a**) and *trans*-benzyl N-[β -(3-pyridoyl)acryloyl]carbamate (**10a**), both in 8% yields. However, the cyclic form (**9a**) is very unstable and isomerizes to the *trans* form (**10a**). In the case of benzyl N-[5-(2-chloro-3-pyridyl)-2-furyl]carbamate (**8b**) having a Cl substituent as an electron-withdrawing group, N-carbobenzyloxy-5-hydroxy-5-(2-chloro-3-pyridyl)-3-pyrrolin-2-one (**9b**) and a small amount of *trans*-benzyl N-[β -(2-chloro-3-pyridyl)acryloyl]carbamate (**10b**) were afforded by irradiation. It is clear that the cyclic form (**9b**) was stabilized by the presence of the Cl substituent compared with **9a**.

Finally, the electronic nature of substituents R on the benzene ring exerts a pronounced effect on the equilibrium of 5-hydroxy-5-phenyl-3-pyrrolinone—*cis*- γ -ketoamide tautomerism. Thus, the presence of electron-withdrawing groups on the benzene ring should selectively stabilize the γ -hydroxylactam structure (**A**), and that of electron-releasing groups should shift the equilibrium toward the *cis*- γ -ketoamide structure (**B**). The mechanism of the reaction may be proposed to be as follows: the endoperoxide intermediate is initially formed by the cycloaddition of molecular oxygen with 2-furylcarbamate. Next, cleavage of this intermediate with loss of an oxygen atom yields the *cis*- γ -ketoamide. Part of this is spontaneously cyclized to γ -hydroxylactam by ring-chain tautomerism, and the remainder isomerizes to *trans*- γ -ketoamide (Chart 4). Therefore, it is clear that the tautomeric equilibrium between the 5-hydroxy-5-phenyl-3-pyrrolinone system and the corresponding *cis*- γ -ketoamide depends not only on the steric effects as indicated by Zikan *et al.*²⁾ but also on the electronic effects of substituents in the benzene ring.

Chart 4

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Proton NMR spectra were recorded using a JEOL PS-100 spectrometer with tetramethylsilane as an internal standard. The infrared (IR) spectra were taken on a Jasco IR-A-1 spectrometer. Mass spectra (MS) were obtained with a Hitachi M-52 spectrometer operating at an ionization potential of 70 eV. Irradiation was carried out with a 400W high pressure mercury lamp, Riko UVL-400P, with a Pyrex filter.

5-Substituted phenyl-2-furoic acids were prepared by the reported method.³⁾ 5-(*m*-Chlorophenyl)-2-furoic acid: mp 168—170°C as colorless needles from CH₂Cl₂, yield 20%; 5-(*o*-tolyl)-2-furoic acid: mp 161—162°C as colorless needles from benzene, yield 10%; 5-(*o*-chlorophenyl)-2-furoic acid: mp 167—168°C as colorless needles from CH₂Cl₂, yield 15%. Other starting materials are described in the literature.³⁾

Benzyl N-(5-phenyl-2-furyl)carbamates (2a—k)—As an example, we describe the preparation of benzyl N-(5-phenyl-2-furyl)carbamate (2a).

A solution of ethyl chloroformate (1.3 g, 12 mmol) in tetrahydrofuran (THF) (5 ml) was added to a solution of 5-phenyl-2-furoic acid (2 g, 10.6 mmol) and triethylamine (1.2 g, 12 mmol) in THF (20 ml) at 0—10°C with stirring. After half an hour, a solution of NaN₃ (2 g) in H₂O (25 ml) was added to the reaction mixture and the whole was stirred for 1 h at room temperature. The reaction mixture was poured into ice water and extracted with ether. The organic layer was dried over MgSO₄ and the ether was removed to give 5-phenyl-2-furoyl azide (2.1 g, 93%) as colorless needles (Table VI). Next, a solution of the azide (1 g, 4.7 mmol) and benzyl alcohol (1.5 g, 14 mmol) in benzene (30 ml) was stirred under reflux for 20 h. Removal of the benzene by evaporation and washing of the residue with petroleum ether gave colorless crystals, and recrystallization from benzene-petroleum ether afforded 2a as colorless prisms (1.3 g, 94%), mp 81—82°C.

Compounds 2b—k were prepared in the same way, using the same molar ratios of the corresponding reaction components. The physical and spectral data for these compounds are listed in Table I.

TABLE VI. 5-Phenyl-2-furoyl Azides

R	mp (°C)	Appearance	IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm ⁻¹	
			N ₃	C=O
H	85—88	Colorless needles	2125	1670
<i>p</i> -OCH ₃	98	Colorless prisms	2130	1670
<i>p</i> -CH ₃	61	Colorless prisms	2125	1665
<i>p</i> -Cl	129	Colorless prisms	2130	1675
<i>p</i> -NO ₂	134	Yellow needles	2130	1675
<i>m</i> -OCH ₃	69	Colorless needles	2180	1695
<i>m</i> -Cl	114	Colorless needles	2150	1690
<i>m</i> -NO ₂	125	Yellow needles	2120	1670
<i>o</i> -CH ₃	57—58	Colorless needles	2130	1680
<i>o</i> -Cl	47	Colorless needles	2140	1675
<i>o</i> -NO ₂	87—88	Yellow needles	2120	1670

Photooxidation of 2—As an example, we describe the photooxidation of benzyl N-(5-phenyl-2-furyl)carbamate (2a); the other compounds were photooxidized in the same way, using the same amount of the furylcarbamates. Physical and spectral data for 5-hydroxypyrrolinones (3) and *trans*- γ -ketoamides (4) produced in these reactions are shown in Tables II, III and IV.

A solution of 2a (0.5 g, 1.7 mmol) in benzene (200 ml) was irradiated in the presence of oxygen at room temperature for 1 h. After removal of the solvent, the residue was chromatographed on silica gel with CHCl₃: ether (9:1). Further purification by preparative silica gel thin-layer chromatography (TLC) with CHCl₃: ether (9:1) afforded N-carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrrolin-2-one (3a) as colorless needles (0.21 g, 40%), mp 113—115°C, and *trans*-benzyl N-(β -benzoylacryloyl)carbamate (4a) as colorless needles (0.04 g, 8%) mp 154—156°C.

β -*p*-Toluoylpropionamide (5)—A solution of N-carbobenzyloxy-5-hydroxy-5-*p*-tolyl-3-pyrrolin-2-one (3c) (0.1 g) in EtOH (10 ml) containing 5% Pd/C was hydrogenated at room temperature. The reaction mixture was filtered and the solvent was evaporated off to give (5) as colorless needles (0.05 g, 85%) mp 166—169°C, (lit.,⁴⁾ mp 171—173°C). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3500, 3382, 1665. NMR (CDCl₃) δ : 7.83 (2H, d, *J* = 8 Hz), 7.21 (2H, d, *J* = 8 Hz), 5.70 (2H, b), 3.31 (2H, t, *J* = 6 Hz), 2.63 (2H, t, *J* = 6 Hz), 2.40 (3H, s). Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.95; H, 6.77; N, 7.31.

Similarly, N-carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrrolin-2-one (**3a**) (0.1 g) afforded β -benzoylpropionamide as colorless needles (0.05 g, 87%) mp 119–121°C, (lit.,⁴) mp 122–123°C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3500, 3382, 1667. NMR (CDCl₃) δ : 7.95 (2H, m), 7.48 (3H, m), 5.90 (2H, b), 3.33 (2H, t, $J=6$ Hz), 2.64 (2H, t, $J=6$ Hz). Anal. Calcd for C₁₁H₁₁NO₂: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.71; H, 6.21; N, 7.79.

1-*p*-Tolyl-1,4-butanediol (6)—A solution of **3c** (0.1 g, 0.3 mmol) in MeOH (4 ml) was treated with NaBH₄ (0.1 g, 2.6 mmol) at room temperature with stirring. The reaction mixture was poured into ice water and extracted with ether. The organic layer was dried over MgSO₄ and the ether was removed to give **6** (0.05 g, 90%) as colorless needles, mp 36–37°C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3580, 3380. NMR (CDCl₃) δ : 7.22 (2H, d, $J=8$ Hz), 7.11 (2H, d, $J=8$ Hz), 4.65 (1H, t, $J=6$ Hz), 3.61 (2H, t, $J=6$ Hz), 2.47 (2H, b), 2.32 (3H, s), 1.74 (4H, m). MS m/e : 180 (M⁺), 163, 145, 121, 119. Anal. Calcd for C₁₁H₁₆O₂: C, 73.30; H, 8.95. Found: C, 73.25; H, 8.89.

Similarly, N-carbobenzyloxy-5-hydroxy-5-*p*-methoxyphenyl-3-pyrrolin-2-one (**3b**) afforded 1-*p*-methoxyphenyl-1,4-butanediol as colorless needles (87%), mp 59–60°C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3600, 3380. NMR (CDCl₃) δ : 7.21 (2H, d, $J=8$ Hz), 6.81 (2H, d, $J=8$ Hz), 4.60 (1H, t, $J=6$ Hz), 3.75 (3H, s), 3.59 (2H, t, $J=6$ Hz), 2.70 (2H, b), 1.71 (4H, m). MS m/e : 190 (M⁺), 179, 137, 121, 109.

5-(3-Pyridyl)-2-furoic Acid (7a)—**7a** was prepared as colorless needles, mp 226–229°C, by the method of Bailey *et al.*⁶ IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3360, 1690. NMR (DMSO-*d*₆) δ : 8.96 (1H, bs), 8.50 (1H, bd, $J=4$ Hz), 8.10 (1H, d, $J=8$ Hz), 7.46 (1H, dd, $J=4, 8$ Hz), 7.31 (1H, d, $J=4$ Hz), 7.22 (1H, d, $J=4$ Hz). Anal. Calcd for C₁₀H₇NO₃: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.39; H, 3.70; N, 7.29.

5-(2-Chloro-3-pyridyl)-2-furoic Acid (7b)—The procedure described above was employed. **7b** was obtained as colorless needles, mp 251–252°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400, 1690. NMR (DMSO-*d*₆) δ : 8.41 (1H, dd, $J=2, 5$ Hz), 8.26 (1H, dd, $J=2, 8$ Hz), 7.56 (1H, dd, $J=5, 8$ Hz), 7.36 (1H, d, $J=4$ Hz), 7.29 (1H, d, $J=4$ Hz). Anal. Calcd for C₁₀H₆ClNO₃: C, 53.71; H, 2.70; N, 6.26. Found: C, 53.63; H, 2.76; N, 6.33.

Benzyl N-[5-(3-Pyridyl)-2-furyl]carbamate (8a)—The procedure described above for **2** was employed. **8a** was obtained from **7a** as colorless needles in good yield, mp 74–75°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3390, 1720. NMR (CDCl₃) δ : 11.66 (1H, b), 9.01 (1H, d, $J=2$ Hz), 8.14 (1H, dd, $J=2, 4$ Hz), 7.66 (1H, dt, $J=2, 8$ Hz), 7.34 (5H, s), 7.10 (1H, dd, $J=4, 8$ Hz), 6.62 (1H, d, $J=4$ Hz), 6.18 (1H, d, $J=4$ Hz), 5.21 (2H, s). MS m/e : 294 (M⁺), 250, 250, 186, 159, 130. Anal. Calcd for C₁₇H₁₄N₂O₃: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.29; H, 4.72; N, 9.48.

Benzyl N-[5-(2-Chloro-3-pyridyl)-2-furyl]carbamate (8b)—The procedure described above was employed. **8b** was obtained from **7b** as colorless needles in good yield, mp 109–110°C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3395, 1723. NMR (CDCl₃) δ : 8.16 (1H, dd, $J=2, 5$ Hz), 7.92 (1H, dd, $J=2, 8$ Hz), 7.34 (5H, s), 7.18 (1H, d, $J=4$ Hz), 7.18 (1H, dd, $J=5, 8$ Hz), 6.22 (1H, d, $J=4$ Hz), 5.18 (2H, s). MS m/e : 328 (M⁺), 284, 220, 193, 157. Anal. Calcd for C₁₇H₁₃ClN₂O₃: C, 62.11; H, 3.99; N, 8.52. Found: C, 62.23; H, 3.92; N, 8.44.

Photooxidation of 8a—A solution of **8a** (0.5 g, 1.7 mmol) in benzene (200 ml) was irradiated in the presence of oxygen at room temperature for 70 min. After removal of the solvent, the residue was chromatographed on silica gel with CHCl₃: MeOH (40: 1). Further purification by preparative TLC with CHCl₃: MeOH (40: 1) afforded N-carbobenzyloxy-5-hydroxy-5-(3-pyridyl)-3-pyrrolin-2-one (**9a**) as a colorless oil (0.04 g, 8%) and *trans*-benzyl N-[β -(3-pyridoyl)acryloyl]carbamate (**10a**) as colorless needles (0.04 g, 8%) mp 188–189°C. The cyclic form (**9a**) is unstable and changes to the *trans* form (**10a**). **9a**: IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3470, 1770, 1739, 1682. NMR (CDCl₃) δ : 8.62 (1H, d, $J=2$ Hz), 7.74 (1H, d, $J=4$ Hz), 7.60 (1H, dt, $J=2, 8$ Hz), 7.23 (5H, s), 6.97 (1H, d, $J=6$ Hz), 6.07 (1H, d, $J=6$ Hz), 5.23 (1H, d, $J=12$ Hz), 5.09 (1H, d, $J=12$ Hz). MS m/e : 310 (M⁺), 256, 218, 161, 151. **10a**: IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3080, 1730, 1660. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 245, 277 (sh). NMR (DMSO-*d*₆) δ : 11.22 (1H, bs), 9.16 (1H, s), 8.82 (1H, d, $J=4$ Hz), 8.36 (1H, d, $J=8$ Hz), 7.86 (1H, d, $J=16$ Hz), 7.60 (1H, dd, $J=4, 8$ Hz), 7.42 (5H, s), 7.28 (1H, d, $J=16$ Hz), 5.20 (2H, s). MS m/e : 310 (M⁺), 249, 239, 204, 161. Anal. Calcd for C₁₇H₁₄N₂O₄: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.66; H, 4.35; N, 8.87.

Photooxidation of 8b—The procedure described above was employed. N-Carbobenzyloxy-5-hydroxy-5-(2-chloro-3-pyridyl)-3-pyrrolin-2-one (**9b**), colorless prisms (20%), mp 77–80°C, and *trans*-benzyl N-[β -(2-chloro-3-pyridoyl)acryloyl]carbamate (**10b**), colorless needles (3%), mp 155–157°C, were obtained from the photooxidation of **8b**. **9b**: IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3480, 1778, 1753, 1705. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 258 (sh), 266, 273 (sh). NMR (CDCl₃) δ : 8.25 (2H, m), 7.25 (6H, m), 6.90 (1H, d, $J=6$ Hz), 6.25 (1H, d, $J=6$ Hz), 5.53 (1H, bs), 5.26 (1H, d, $J=12$ Hz), 5.10 (1H, d, $J=12$ Hz). MS m/e : 344 (M⁺), 238, 195, 151, 140. Anal. Calcd for C₁₇H₁₃ClN₂O₄: C, 59.22; H, 3.80; N, 8.13. Found: C, 59.32; H, 3.77; N, 8.05. **10b**: IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3360, 1745, 1690, 1670. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 235, 273 (sh). NMR (CDCl₃) δ : 8.50 (1H, dd, $J=2, 4$ Hz), 7.86 (1H, dt, $J=2, 8$ Hz), 7.62 (2H, s), 7.34 (6H, m), 5.16 (2H, s). MS m/e : 344 (M⁺), 238, 195, 151, 140. Anal. Calcd for C₁₇H₁₃ClN₂O₄: C, 59.22; H, 3.80; N, 8.13. Found: C, 59.11; H, 3.60; N, 7.97.

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