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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-Carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrroline-2-one—— *cis*-γ-Ketoamide Equilibrium

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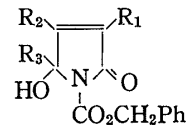
In the ring transformation of 2-furylcarbamates (**2**) to 5-hydroxy-3-pyrrolin-2-ones (**3**) by irradiation in the presence of oxygen, there is an equilibrium between N-carbobenzyloxy-5-hydroxy-5-phenyl-3-pyrrolin-2-one (**3-A**) and *cis*-γ-ketoamide (**3-B**); this equilibrium was studied by nuclear 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; photooxidation; 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**).

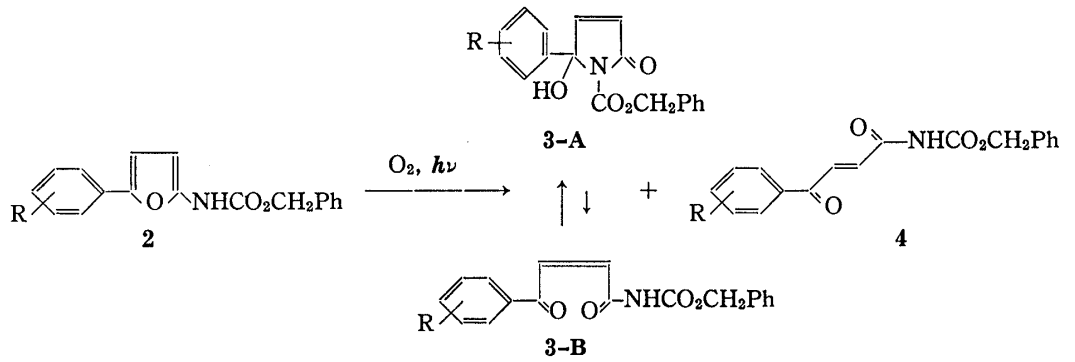


1

$R_1=R_2=Ph$, $R_3=H$
$R_1=R_2=R_3=H$
$R_1=CH_3$, $R_2=R_3=H$
$R_2=CH_3$, $R_1=R_3=H$
$R_3=CH_3$, $R_1=R_2=H$

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**	*m*-Cl	36
3b	*p*-OCH_3	42	**3h**	*m*-NO_2	41
3c	*p*-CH_3	34	**3i**	*o*-CH_3	16
3d	*p*-Cl	36	**3j**	*o*-Cl	35
3e	*p*-NO_2	77	**3k**	*o*-NO_2	—
3f	*m*-OCH_3	32			

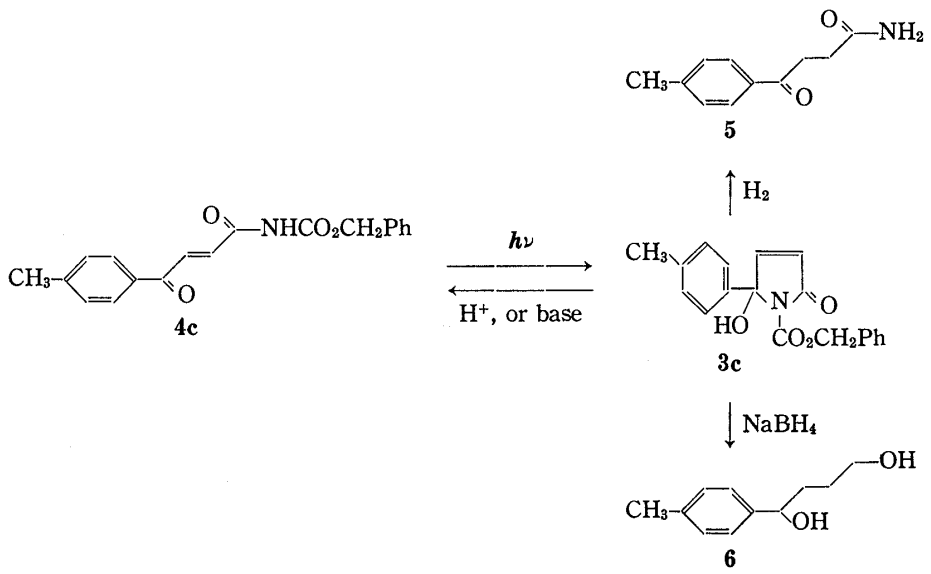


Chart 2

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 $\nu_{max}^{CHCl_3}$ cm^{-1} NH	IR C=O	NMR ($CDCl_3$) δ C-2	NMR C-3[a], C-4[a]	NMR C-5	MS (m/e)	Formula	Analysis (%) Calcd (Found) 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	*p*-OCH_3	114—115	Colorless needles	3380	1715	7.36(br) 7.36(s) 5.18(s)	6.14 6.46	7.48 (d, J=10 Hz) 6.86 (d, J=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	*p*-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, J=9 Hz) 7.10 (d, J=9 Hz) 2.30(s)	307(M^+), 199, 172	$C_{19}H_{17}NO_3$	74.25 (74.18	5.58 5.34	4.56 4.52)
2d	*p*-Cl	104—105	Colorless needles	3380	1720	6.98(br s) 7.36(s) 5.16(s)	6.14 6.54	7.44 (d, J=9 Hz) 7.26 (d, J=9 Hz)	327(M^+), 219, 192	$C_{18}H_{14}ClNO_3$	65.95 (65.77	4.31 4.28	4.27 4.17)
2e	*p*-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, J=9 Hz) 7.60 (d, J=9 Hz)	338(M^+), 230, 203	$C_{18}H_{14}N_2O_5$	63.90 (63.76	4.17 4.01	8.28 8.11)
2f	*m*-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	*m*-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)	327(M^+), 219, 192	$C_{18}H_{14}ClNO_3$	65.95 (65.84	4.31 4.28	4.27 4.07)
2h	*m*-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)	338(M^+), 230, 203	$C_{18}H_{14}N_2O_5$	63.90 (63.78	4.17 3.97	8.28 8.16)
2i	*o*-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	*o*-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)	327(M^+), 219, 192	$C_{18}H_{14}ClNO_3$	65.95 (65.79	4.31 4.16	4.27 4.09)
2k	*o*-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)	338(M^+), 230, 203	$C_{18}H_{14}N_2O_5$	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 $\nu_{max}^{CHCl_3}$ cm^{-1} OH, NH	IR C=O	MS (*m/e*)	Formula	Analysis (%) Calcd (Found) C	H	N
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	*p*-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	*p*-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	*p*-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	*p*-NO_2	156—157	Yellow prisms	3480	1770 1740 1695	354(M^+), 293, 248, 230, 205, 188, 151	$C_{18}H_{17}N_2O_6$	61.01 (60.81	3.98 3.79	7.91 7.74)
3f	*m*-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	*m*-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	*m*-NO_2	139—141	Yellow needles	3520	1775 1750 1710	353(M^+−1), 336, 292, 257, 205, 177, 151	$C_{18}H_{14}N_2O_6$	61.01 (60.99	3.98 3.85	7.91 7.84)
3i	*o*-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	*o*-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 $\nu_{max}^{CHCl_3}$ cm^{-1} NH	IR C=O	NMR ($CDCl_3$) δ[b) C-α, C-β	NMR R–	NMR –NHCO$_2$CH$_2$Ph	Formula	Analysis (%) Calcd (Found) C	H	N
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	*p*-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	*p*-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	*p*-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	*p*-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)	$C_{18}H_{14}N_2O_6$	61.01 (60.92	3.98 3.87	7.91 7.85)
4f	*m*-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	*m*-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	*m*-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)	$C_{18}H_{14}N_2O_6$	61.01 (60.87	3.98 3.78	7.91 7.77)
4i	*o*-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	*o*-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	*o*-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)	$C_{18}H_{14}N_2O_6$	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_3CN 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	*p*-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	*p*-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)			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	*p*-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	*p*-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	*m*-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	*m*-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	*m*-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	*o*-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	*o*-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 CH_2 (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_3CN	
		A%	B%	A%	B%
3a	H	81	19	68	32
3b	*p*-OCH_3	50	50	31	69
3c	*p*-CH_3	67	33	63	37
3d	*p*-Cl	88	12	87	13
3e	*p*-NO_2	100	0	100	0
3f	*m*-OCH_3	87	13	73	27
3g	*m*-Cl	92	8	84	16
3h	*m*-NO_2	100	0	100	0
3i	*o*-CH_3	20	80	26	74
3j	*o*-Cl	89	11	89	11

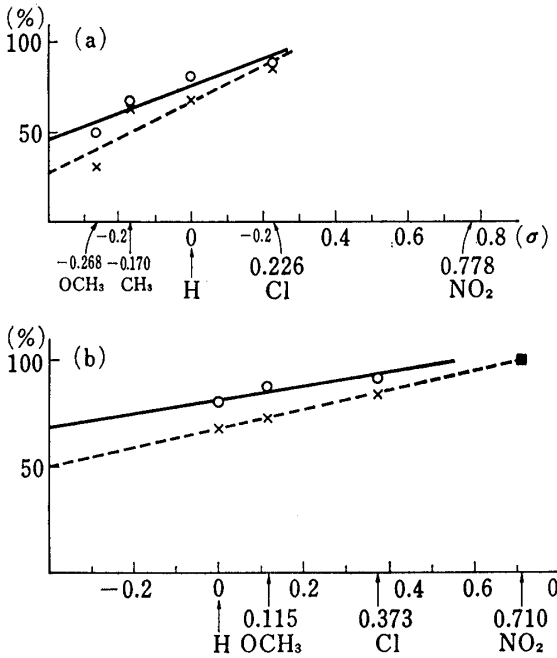
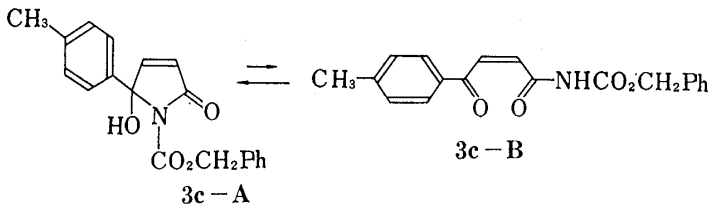


Fig. 2. Correlation of the Amount of the Cyclic Form (3-A) with Hammett's Constants

(a) *p*-substituted phenyl derivatives
○—— $CDCl_3$, ×----- CD_3CN.
(b) *m*-substituted phenyl derivatives
○—— $CDCl_3$, ×----- CD_3CN.



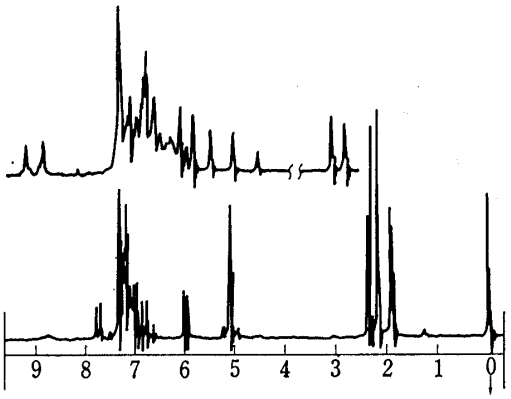


Fig. 1. NMR Spectrum of **3c** in CD_3CN

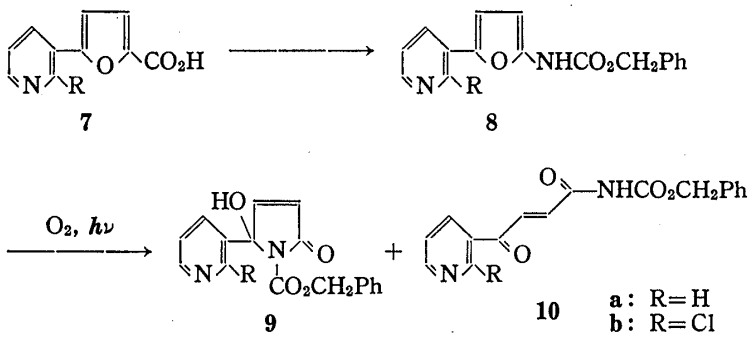


Chart 3

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 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 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.

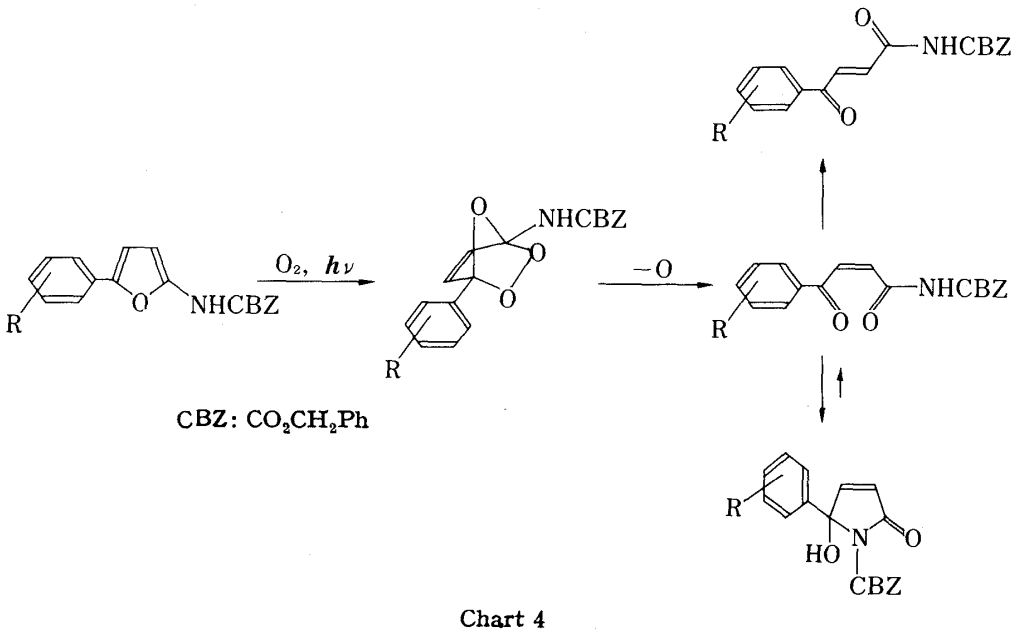


Chart 4

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 CH_2Cl_2, 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 CH_2Cl_2, 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 NaN_3 (2 g) in H_2O (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 $MgSO_4$ 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 $\nu_{max}^{CHCl_3}$ cm^{-1}	
			N_3	C=O
H	85—88	Colorless needles	2125	1670
p-OCH_3	98	Colorless prisms	2130	1670
p-CH_3	61	Colorless prisms	2125	1665
p-Cl	129	Colorless prisms	2130	1675
p-NO_2	134	Yellow needles	2130	1675
m-OCH_3	69	Colorless needles	2180	1695
m-Cl	114	Colorless needles	2150	1690
m-NO_2	125	Yellow needles	2120	1670
o-CH_3	57—58	Colorless needles	2130	1680
o-Cl	47	Colorless needles	2140	1675
o-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 $CHCl_3$: ether (9: 1). Further purification by preparative silica gel thin-layer chromatography (TLC) with $CHCl_3$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3382, 1665. NMR ($CDCl_3$) δ: 7.83 (2H, d, J= 8Hz), 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 $C_{11}H_{13}NO_2$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3382, 1667. NMR ($CDCl_3$) 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 $C_{11}H_{11}NO_2$: 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 $NaBH_4$ (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 $MgSO_4$ and the ether was removed to give **6** (0.05 g, 90%) as colorless needles, mp 36—37°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3380. NMR ($CDCl_3$) 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 $C_{11}H_{16}O_2$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3380. NMR ($CDCl_3$) 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 ν_{max}^{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 $C_{10}H_7NO_3$: 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 ν_{max}^{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 $C_{10}H_6ClNO_3$: 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 ν_{max}^{KBr} cm^{-1}: 3390, 1720. NMR ($CDCl_3$) 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 $C_{17}H_{14}N_2O_3$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3395, 1723. NMR ($CDCl_3$) 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 $C_{17}H_{13}ClN_2O_3$: 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 $CHCl_3$: MeOH (40: 1). Further purification by preparative TLC with $CHCl_3$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 1770, 1739, 1682. NMR ($CDCl_3$) 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 ν_{max}^{KBr} cm^{-1}: 3080, 1730, 1660. UV λ_{max}^{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 $C_{17}H_{14}N_2O_4$: 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1778, 1753, 1705. UV λ_{max}^{EtOH} nm: 258 (sh), 266, 273 (sh). NMR ($CDCl_3$) 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 $C_{17}H_{13}ClN_2O_4$: C, 59.22; H, 3.80; N, 8.13. Found: C, 59.32; H, 3.77; N, 8.05. **10b**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 1745, 1690, 1670. UV λ_{max}^{EtOH} nm: 235, 273 (sh). NMR ($CDCl_3$) 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 $C_{17}H_{13}ClN_2O_4$: C, 59.22; H, 3.80; N, 8.13. Found: C, 59.11; H, 3.60; N, 7.97.

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