TRANSFORMATION OF 5-(2-NITROPHENYL)-2-FURYLCARBAMATE INTO 4-HYDROXY-2-QUINOLINECARBOXAMIDE 1-OXIDE

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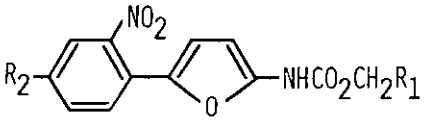
Abstract —— 5-(2-Nitrophenyl)-2-furylcarbamates 1a-d are spontaneously cyclized to 4-hydroxy-2-quinolinecarboxamide 1-oxides 2a-d in benzene at room temperature by intramolecular reaction. This reaction provides a new synthetic route to kynurenic acid derivatives.

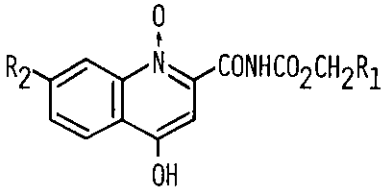
We have recently reported the ring transformation of 2-furylcarbamates to 5-hydroxypyrrolinones by autoxidation or photooxidation[1]. For example, irradiation of 5-phenyl-2-furylcarbamates having various substituents on benzene ring gave corresponding ring transformation products and *trans*-γ-ketoamides[2]. In contrast with reaction of these carbamates and molecular oxygen, we found that 5-(2-nitrophenyl)-2-furylcarbamates 1a-d easily changed to quinoline derivatives 2a-d[3]. We wish to report here this novel transformation reaction.

As a typical procedure, a solution of benzyl N-[5-(2-nitrophenyl)-2-furyl]carbamate 1a[4] (1g) in benzene (25ml) was stirred at room temperature in daylight. After several hours yellow crystals began to precipitate. The reaction was continued for 7 days to give N-benzyloxycarbonyl-4-hydroxy-2-quinolinecarboxamide 1-oxide 2a in 44% yield[5]. The IR spectrum of 2a showed characteristic peaks at 3270 (NH and OH), about 2800 (intermolecular hydrogen bond, O···HO)[6], 1755 (ester C=O), 1658 (amide C=O) and 1240 (N→O) cm^{-1}. Its NMR spectrum showed the presence of five aromatic protons [δ 8.18 (2H, m, C-5,8), 7.85 and 7.61 (each 1H, t, J=8Hz, C-6,7) and 7.00 (1H, bs, C-3, changing with D_2O to sharp singlet)], NH (δ 13.8), OH (δ 8.30) and benzyl protons [δ 7.36 (s) and 5.15 (s)], and elemental analysis was satisfied. Hydrogenolysis of 2a with hydrogen over Pd/C in ethyl

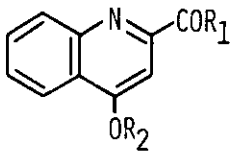
acetate gave 4-hydroxy-2-quinolinecarboxamide 3 (kynurenic acid amide), mp 295-297° [IR (KBr) 3340, 3150, 1670 cm^{-1}; UV (EtOH) 245, 290, 325, 338 and 350 nm (ε 25000, 1730, 7100, 9740 and 7320); NMR (DMSO-d_6) δ 11.68, 8.45 and about 8.10 (NH_2 and OH), 8.04 (2H, m, C-5,8, appearing with D_2O as two doublets, J=8Hz), 7.69 and 7.36 (each 1H, t, J=8Hz, C-6,7) and 6.82 (1H, bs, C-3, changing with D_2O to sharp singlet); MS *m/e* 188 (M^+), 170, 145, 143, 115, 105, 89]. Finally, the structure of 3 was identical with the compound prepared from kynurenic acid 4[7]. Similarly, 2b-d were obtained from 1b-d in 40-45% yields (Table I).



1a-d



2a-d



3; R_1=NH_2, R_2=H

4; R_1=OH, R_2=H

5; R_1=NH_2, R_2=CO_2Et

1a, 2a; R_1=Ph, R_2=H

1b, 2b; R_1=Me, R_2=H

1c, 2c; R_1=Ph, R_2=OMe

1d, 2d; R_1=Me, R_2=OMe

The formation of 2a is rationalized as the following reaction sequence[8]. The first step is the intramolecular bond formation between the oxygen atom of nitro group and the 2-position of the furan ring. Subsequent oxygen-transfer followed by recyclization forms the quinoline skelton which undergoes cleavage of oxide-bonds to give the product 2a.

The reaction described here provides a new synthetic route to kynurenic acid, a metabolic product of tryptophan and its analogues in some animals.

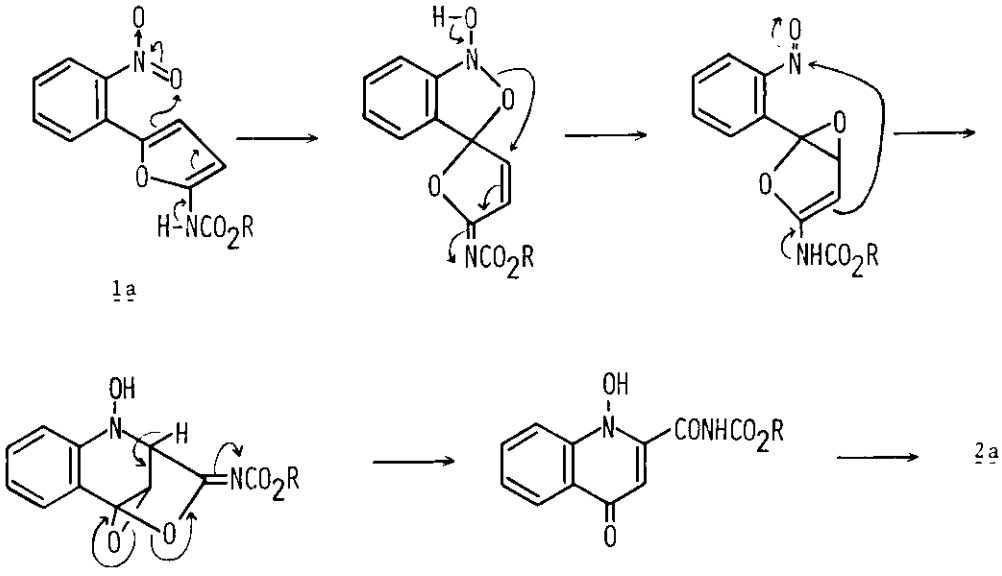


Table I. Physical and Spectral Data of 2a-d

No.	mp (°C) Appearance	IR ν_{max}^{KBr} cm^{-1}	NMR (DMSO-d_6) δ
2a	205-207 Yellow needles	3270, 2800, 1755, 1658, 1240	13.8 (b, NH), 8.30 (b, OH), 8.18 (m, C-5,8), 7.85 and 7.61 (each t, J=8Hz, C-6,7), 7.00 (bs, C-3), 7.36 and 5.15 (benzyl)
2b	213-214 Yellow needles	3250, 2800, 1755, 1660, 1250	13.6 (b, NH), 8.30 (b, OH), 8.20 (m, C-5,8), 7.88 and 7.64 (each t, J=8Hz, C-6,7), 7.00 (bs, C-3), 4.16 and 1.26 (ethyl)
2c	210-211 Yellow needles	3250, 2800, 1755, 1650, 1245	8.02 (d, J=9Hz, C-5), 7.67 (bs, C-8), 7.25 (dd, J=2, 9Hz, C-6), 7.04 (bs, C-3), 7.34 and 5.15 (benzyl), 3.90 (methyl)
2d	211-213 Yellow needles	3245, 2800, 1760, 1660, 1250	7.93 (d, J=9Hz, C-5), 7.57 (bs, C-8), 7.17 (dd, J=2, 9Hz, C-6), 6.95 (bs, C-3), 4.16 and 1.25 (ethyl), 3.88 (methyl)

References and Notes

1. K. Yakushijin, M. Kozuka and H. Furukawa, Chem. Pharm. Bull., 1980, 28, 2178; K. Yakushijin, M. Kozuka, Y. Ito, R. Suzuki and H. Furukawa, Heterocycles, 1980, 14, 1073.
2. K. Yakushijin, M. Kozuka and H. Furukawa, 13th Congress of Heterocyclic Chemistry, Shizuoka, Abstract pp. 241 (1980). Irradiation with 400w high pressure mercury lamp of 1a with oxygen in benzene for 1 hour gave a small amount of *trans*-γ-ketoamide, no cyclic products being detected. In the cases of *o*-nitro derivatives, hydroxypyrrolinones cannot exist as stable species due to steric reason.
3. Other 5-phenyl-2-furylcarbamates lacking *ortho*-nitro group are stable in benzene at room temperature, and similar reactions were not observed.
4. 1a-d were prepared from the Meerwein arylation of *o*-nitroanilines with 2-furoic acid, followed by the treatment of ethyl chloroformate, sodium azide and corresponding alcohols.
5. 45-50% of starting material 1a is recovered from the filtrate.
6. M. Ionescu, A. R. Katrizky and B. Ternai, Tetrahedron, 1966, 22, 3227.
7. 3 was obtained by treatment of 4 with ethyl chloroformate and ammonium hydroxide, and the hydrolysis of the resulting 5 with sodium carbonate. 5; mp 142-144° as colorless needles, IR (KBr) 3420, 3180, 1750, 1680 cm^{-1}, and NMR (DMSO-d_6) δ 8.33-7.68 (7H, m, aromatic-H and NH_2), 4.39 and 1.40 (5H, ethyl).
8. W. M. Horspool, "Aspects of Organic Photochemistry", Academic Press, New York, p. 259 (1976).

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