A New, Convenient Synthesis of 3-Amino-4-hydroxy-2-oxo-1,2-dihydroquinoline Derivatives via 5-(2-Acylaminophenyl)-4-methoxycarbonyl-1,3-oxazoles[1]

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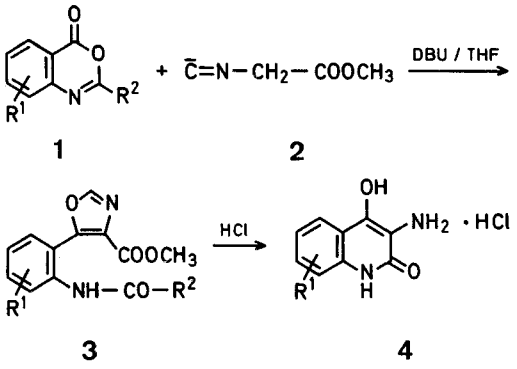
2-Oxo-1,2-dihydroquinoline (carbostyril) derivatives are pharmaceutically interesting compounds and a number of synthetic methods have been reported. However, only one method for the preparation of 3-amino-4-hydroxy-2-oxo-1,2-dihydroquinolines is known, namely the diazocoupling reaction of 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline, followed by reduction to the amino derivatives[2].

In the course of our studies on the synthesis of amino acids and related compounds using isocyano compounds,

we previously reported a synthesis of 3-amino-4-hydroxycoumarin derivatives by the reaction of methyl isocyanoacetate and acetylsalicyclic acid derivatives[3]. The reaction has now been extended to the synthesis of 3-amino-4-hydroxy-2-oxo-1,2-dihydroquinoline derivatives using 4-oxo-4*H*-3,1-benzoxazines (**1**) in place of the acetylsalicyclic acid derivatives.



1 **2** **3** **4**

The reaction of methyl isocyanoacetate (**2**) with the benzoxazine **1** was carried out in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in tetrahydrofuran at room temperature to give 5-(2-acylaminophenyl)-4-methoxycarbonyl-1,3-oxazoles **3** in good yields as listed in Table 1. The structure of the resultant products **3** was confirmed by spectral and analytical data (see Table 1). Subsequently, hydrolysis of the 1,3-oxazoles **3** with methanolic hydrochloric acid at 50–55° afforded the desired 3-amino-4-hydroxy-2-oxo-1,2-dihydroquinolines **4** in high yields (see Table 2). The reaction probably proceeds via the cleavage of the oxazole ring and the subsequent intramolecular cyclization.

The I.R. spectra of the 2-oxo-1,2-dihydroquinolines **4** showed the characteristic absorptions of the amide group at ~1670 cm^{-1} and of the C=C double bond at ~1625 cm^{-1}. Furthermore, the structure of the compounds **4** was supported by the microanalyses and the mass spectral data. These results are summarized in Table 2.

Preparation of 5-(2-Acylaminophenyl)-4-methoxycarbonyl-1,3-oxazoles (3); Typical Procedures:

2-Methyl-4-oxo-4*H*-3,1-benzoxazine (1, $R^1 = H$, $R^2 = CH_3$; 2.42 g, 0.015 mol) dissolved in tetrahydrofuran (20 ml) was added dropwise to a stirred mixture of methyl isocyanoacetate (**2**; 1.49 g, 0.015 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.28 g, 0.015 mol) in tetrahydrofuran (20 ml) at 25–28°. Stirring was continued for 18 h at room temperature, the reaction mixture was neutralized with 20% acetic acid under cooling, water (50 ml) was added to the mixture, and then the solvent was removed under reduced pressure. The resultant residue was extracted with ethyl acetate, the extract was washed with saturated sodium chloride solution, dried with sodium sulfate, and evaporated in vacuo. The resultant crystals were recrystallized from ethyl acetate to afford *5-(2-acetylaminophenyl)-4-methoxycarbonyl-1,3-oxazole* (**3a**) as colorless prisms; yield: 3.01 g (77%); m.p. 148–149°.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 9.55$ (broad, 1H, NH), 8.52 (s, 1H, oxazole-CH), 7.00–7.80 (m, $4H_{arom}$), 3.68 (s, 3H, $COOCH_3$), 1.90 ppm (s, 3H, $COCH_3$).

Table 1. Yields, Physical, and Analytical Data of 5-(2-Acylaminophenyl)-4-methoxycarbonyl-1,3-oxazoles (**3a–e**)

3	R^1	R^2	m.p. (solvent)	Yield [%]	I.R. (nujol) ν_{max} [cm^{-1}]	Molecular formula[a]
a	H	CH_3	148–149° (C_2H_5OAc)	77	3350, 3110, 1705, 1695, 1617, 1592	$C_{13}H_{12}N_2O_4$ (260.3)
b	5-H_3CO	CH_3	166–167° (CH_3OH)	76	3290, 3100, 1710, 1690, 1618, 1595	$C_{14}H_{14}N_2O_5$ (290.3)
c	5-H_3C	CH_3	161–162° (CH_3OH)	72	3360, 3140, 1702, 1680, 1625, 1595	$C_{14}H_{14}N_2O_4$ (274.3)
d	5-Cl	CH_3	190–191° (CH_3OH)	82	3350, 3100, 1700, 1680, 1620, 1590	$C_{13}H_{11}ClN_2O_4 \cdot 1/2H_2O$ (303.7)
e	H	C_2H_5	129–130° (C_2H_5OAc)	68	3360, 3130, 1705, 1680, 1625, 1595	$C_{14}H_{14}N_2O_4$ (274.3)

[a] All products gave satisfactory microanalyses (C ±0.31%, H ±0.19%, N ±0.26%, Cl ±0.23%).

Table 2. Yield, Physical, and Analytical Data of 3-Amino-4-hydroxy-2-oxo-1,2-dihydroquinoline Hydrochlorides (**4a–d**)

4	R^1	Yield [%]	I.R. (nujol) ν_{max} [cm^{-1}]	U.V. (methanol) λ_{max} [nm (ε)]	M.S. *m/e*	Molecular formula[a]
a	H	98[b] 91[c]	1670, 1630	217 (32500), 229 (30800), 300 (7300), 321 (10600), 333 (10600)	176 ($M^{\oplus}$ – HCl)	$C_9H_9ClN_2O_2 \cdot 3/4H_2O$ (226.2)
b	6-H_3CO	87	1663, 1630	216 (31300), 236 (37200), 305 (6900), 327 (11900), 347 (11500)	206 ($M^{\oplus}$ – HCl)	$C_{10}H_{11}ClN_2O_3 \cdot 1/4H_2O$ (247.2)
c	6-H_3C	85	1680, 1620	217 (35400), 233 (37700), 299 (8200), 325 (11800), 338 (11600)	190 ($M^{\oplus}$ – HCl)	$C_{10}H_{11}ClN_2O_2 \cdot 1/2H_2O$ (235.7)
d	6-Cl	81	1660, 1625	218 (34700), 238 (50000), 305 (9100), 330 (14100), 342 (15300)	210, 212 ($M^{\oplus}$ – HCl) (3:1)	$C_9H_8Cl_2N_2O_2$ (247.1)

[a] Water of crystallization could not be removed even on drying at 70° for 24 h under reduced pressure in compounds **4a–c**. All products gave satisfactory microanalyses (C ±0.39%, H ±0.2%, N ±0.29%).

[b] From **3a**.

[c] From **3e**.

Preparation of 3-Amino-4-hydroxy-2-oxo-1,2-dihydroquinoline Derivatives (4); Typical Procedures:

To a solution of **3a** (19.0 g, 0.073 mol) dissolved in methanol (100 ml) at 50–55°, concentrated hydrochloric acid (20 ml) was added dropwise at the same temperature with stirring. Stirring was continued for 3 h at the same temperature, during this time precipitates gradually separated from the reaction mixture. The resultant precipitates were isolated by suction under cooling and washed with a small amount of cold methanol and ether to afford *3-amino-4-hydroxy-2-oxo-1,2-dihydroquinoline hydrochloride* (**4a**) as an analytically pure compound; yield: 15.2 g (98%); m.p. >270°.

^{1}H-N.M.R. (DMSO-d_6): δ = 12.00 (broad, 1 H, NH), 7.00–8.50 ppm (m, 8 H, arom H, OH, and $NH_2 \cdot HCl$).

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