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SYNTHESIS OF NEW DERIVATIVES OF 4-QUINOLINECARBOXYLIC ACID

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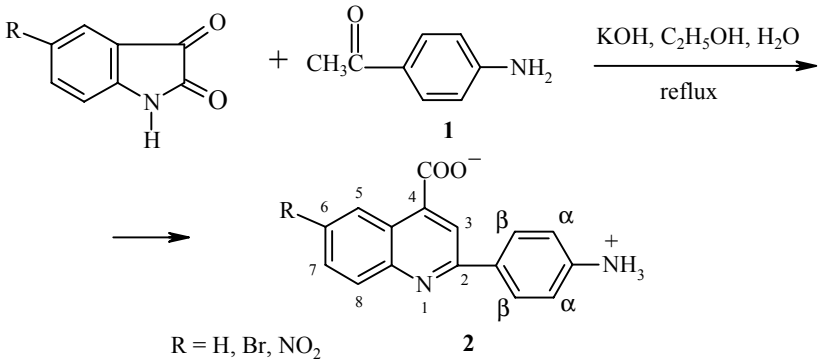
The Pfitzinger reaction is the most efficient and simplest method for the synthesis of 4-quinolinecarboxylic acid derivatives [1, 2]. Many isatin derivatives as well as acetophenone and its various derivatives have been used in this reaction. However, the use of 4-aminoacetophenone (**1**) in this reaction has not yet been studied. The use of aminoacetophenone **1** in the Pfitzinger reaction would open a path for the preparation of derivatives of 2-(4-aminophenyl)-4-quinolinecarboxylic acid, which hold interest as promising synthons.

We have studied the reaction of aminoacetophenone **1** with isatin, 5-bromoisatin, and 5-nitroisatin in aqueous ethanol in the presence of potassium hydroxide. 2-(4-Aminophenyl)-4-quinolinecarboxylic acids, which exist as internal salts **2**, were obtained in 72-86% yield.



2-(4-Aminophenyl-4-quinolinecarboxylic Acid (2, R = H). Mixture of isatin (10.37 g, 0.075 mol), aminoacetophenone **1** (9.45 g, 0.07 mol), and solution of potassium hydroxide (11.2 g, 0.2 mol) in ethanol (80 ml) and water (2 ml) was heated at reflux with stirring until starting **1** completely disappeared (20-24 h) as indicated by periodic monitoring by thin-layer chromatography. The reaction mixture was filtered hot and water (100 ml) was added to the filtrate. Then, the solution was acidified by adding of 1:1 concentrated hydrochloric acid–water to pH 6.0-6.5. The precipitate was filtered and washed with three 25 ml water portions, two 5 ml ethanol portions, and two 10 ml ether portions to give 15.89 g (86%) of compound **2**, which was recrystallized from DMSO–water; mp 174-176°C. IR spectrum (KBr pellet), ν, cm^{-1}: 1595 and 1456 (C=C, arom); 3200 (C–H, arom); 816 (1,4-disubstituted benzene ring); 2803 and 1590 (NH_3^+); 1540 and 1408 (CO_2^-). UV spectrum,

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λ_{max}, nm (log ε): 221.6 (2.01), 282.0 (1.85), 344.8 (1.68). ^{1}H NMR spectrum (300 MHz, DMSO-d_6–CCl_4), δ, ppm: 6.72 (2H, d, α-H); 8.01 (2H, d, β-H); 8.32 (1H, s, 3-H); 8.03 (1H, d, 5-H); 7.72 (1H, t, 6-H); 7.52 (1H, t, 7-H); 8.69 (1H, d, 8-H). Found, %: C 73.07, H 4.21; N 10.37. $C_{16}H_{12}N_2O_2$. Calculated, %: C 72.71; H 4.58; N 10.60.

Other compounds **2** were prepared from acetophenone **1** and corresponding isatin derivatives in the similar way.

2-(4-Aminophenyl)-6-bromo-4-quinolinecarboxylic Acid (2, R = Br) was obtained in 85% yield; mp 288-290°C (DMSO–water). IR spectrum (KBr pellet), ν, cm^{-1}: 1544 and 1496 (C=C, arom); 3202 (C–H, arom); 816 (1,4-disubstituted benzene ring); 2802 and 1580 (NH_3^+); 1536 and 1400 (CO_2^-). UV spectrum, λ_{max}, nm (log ε): 230.8 (1.94), 266.8 (1.68), 293.2 (1.72), 354.0 (1.60). ^{1}H NMR spectrum (300 MHz, DMSO-d_6–CCl_4), δ, ppm: 7.14 (2H, d, α-H); 8.23 (2H, d, β-H); 8.46 (1H, s, 3-H); 8.89 (1H, s, 5-H); 7.93 (1H, d, 7-H); 8.07 (1H, d, 8-H). Found, %: C 55.67; H 3.19; N 7.79. $C_{16}H_{11}BrN_2O_2$. Calculated, %: C 55.99; H 3.23; N 8.16.

2-(4-Aminophenyl)-6-nitro-4-quinolinecarboxylic Acid (2, R = NO_2). The reaction mixture after termination of heating at reflux was not filtered but rather diluted by adding water (100 ml) and treated as described for acid **2** (R = H). The product yield was 72%; dec. >300°C (DMSO). IR spectrum (KBr pellet), ν, cm^{-1}: 1592 and 1472 (C=C, arom); 3208 (C–H, arom); 825 (1,4-disubstituted benzene ring); 2802 and 1592 (NH_3^+); 1582 and 1402 (CO_2^-); 1560 and 1352 (NO_2). UV spectrum, λ_{max}, nm (log ε): 217.6 (1.83), 280.0 (1.72), 352.4 (1.55), 414.8 (1.39). Found, %: C 61.62; H 3.74; N 13.17. $C_{16}H_{11}N_3O_4$. Calculated, %: C 62.13; H 3.58; N 13.58.

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