Synthesis of Novel Derivatives of 2-Phenylquinoline-4-carboxylic Acid

M.-G. A. Shvekhgeimer and N. N. Kondrashova

Presented by Academician N.K. Kochetkov December 6, 2001

Received December 21, 2001

Among the compounds of a quinoline series, quinoline-4-carboxylic acid derivatives attract the attention of researchers due to their close structural resemblance to alkaloids.

The most general and simple method for preparing quinoline-4-carboxylic acids is the Pfitzinger reaction: the condensation of compounds of an isatin series with ketones of the general formula $R^1CH_2COR^2$ in the presence of NaOH or KOH [1, 2]:



It follows from the literature data that both acetophenone and a wide variety of its derivatives were involved in the reaction with numerous compounds of isatin series. Before our work, however, no information on the use of 4-aminoacetophenone (1) in the Pfitzinger reaction was available. At the same time, the reaction of ketone 1 with isatin and its derivatives opens the way to the preparation of 2-(4-aminophenyl)quinoline-4-carboxylic acids, initial compounds for the synthesis of numerous derivatives of 2-phenylquinoline-4-carboxylic acid.

We studied the reaction of ketone **1** with isatin, 5-bromoisatin, and 5-nitroisatin in the presence of

potassium hydroxide in water and an aqueous alcohol medium and found that the yields of 2-(4-aminophenyl)quinoline-4-carboxylic acids (2) are higher (72– 86%) when the reaction is run in an aqueous alcohol medium. According to spectral data, the resulting compounds exist as bipolar ions 2:



The diazotization of compound 2 was found to readily occur under standard conditions to produce diazonium salts 3. Diazonium salts 3 were involved *in situ* into the coupling reaction with the derivatives of 1-aryl-3-methylpyrazol-5-one (4) to form coupling products (5), usually in high yield.



Kosygin State Textile University, Moscow, ul. Malaya Kaluzhskaya 1, Moscow, 117918 Russia R = H, Br, NO₂; Ar = C₆H₅-, 4-CH₃C₆H₄-, 4-HO₃SC₆H₄-.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrophotometer (as pressed KBr pellets). UV spectra were recorded on a Uvidek-610 spectrophotometer in a 1% aqueous solution of sodium hydroxide. ¹H NMR spectra were recorded on Bruker AC-300 or WM-250 spectrometers in DMSO-d₆–CCl₄ solutions.

2-(4-Aminophenyl)quinoline-4-carboxylic acid (2) ($\mathbf{R} = \mathbf{H}$). A mixture of 10.37 g (0.075 mol) of isatin, 9.45 g (0.07 mol) of ketone 1, and a solution of 11.2 g (0.2 mol) of potassium hydroxide in 80 mL of alcohol and 2 mL of water was heated under reflux with stirring until compound 1 was exhausted (monitoring with the use of thin layer chromatography), which required 20-24 h. The hot reaction mixture was filtered, 100 mL of water was added to the filtrate, and hydrochloric acid (1:1) was added with stirring to pH 6–6.5. The mixture was stirred for 15 min and filtered. The precipitate was washed on the filter with water $(3 \times 25 \text{ mL})$, alcohol $(2 \times 5 \text{ mL})$, and ether $(2 \times 10 \text{ mL})$. The yield was 15.89 g (85.9%); mp 174–176°C (DMF–H₂O). IR (KBr, v, cm⁻¹): 1544 and 1496 (C=C arom.), 3202 (C–H arom.), 816 (1,4-disubstituted benzene ring), 2802 and 588 (NH_3^+) , 1536 and 1400 (COO⁻). UV (λ_{max} , nm (log ϵ)):

227.2 (4.26), 282.4 (4.17), 345.6 (4.01). ¹H NMR (300 MHz, DMSO-d₆-CCl₄, δ , ppm): 6.72 (d, 2H, C_αH), 8.01 (d, 2H, C_βH), 8.32 (s, 1H, C₃H), 8.03 (d, 1H, C₅H), 7.72 (m, 1H, C₆H), 7.52 (m, 1H, C₇H), 8.69 (d, 1H, C₈H).

For $C_{16}H_{12}N_2O_2$ anal. calcd. (%): C, 72.71; H, 4.58; N, 10.60.

Found (%): C, 73.07; H, 4.21; N, 10.37.

2-(4-Aminophenyl)-6-bromoquinoline-4-carboxylic acid (2) (R = Br) was obtained similarly to compound **2** (R = H). The yield was 85%; mp 288–290°C (from DMF–H₂O). IR (KBr, v, cm⁻¹): 1592 and 1472 (C=C arom.), 3208 (C–H arom.), 825 (1,4-disubstituted benzene ring), 2802 and 1592 (NH₃⁺), 1582 and 1402 (COO⁻). UV (λ_{max} , nm (logε)): 232.0 (4.46), 265.6 (4.22), 293.6 (4.25), 353.6 (4.14). ¹H NMR (300 MHz, DMSO-d₆-CCl₄, δ , ppm): 7.14 (d, 2H, C_αH), 8.23 (d, 2H, C_βH), 8.46 (s, 1H, C₃H), 8.89 (s, 1H, C₅H), 7.93 (d, 1H, C₇H), 8.07 (d, 1H, C₈H).

For $C_{16}H_{11}BrN_2O_2$ anal. calcd. (%): C, 55.99; H, 3.23; N, 8.16.

Found (%): C, 55.67; H, 3.19; N, 7.79.

2-(4-Aminophenyl)-6-nitroquinoline-4-carboxylic acid (2) ($\mathbf{R} = \mathbf{NO}_2$) was obtained similarly to compound 2 ($\mathbf{R} = \mathbf{H}$, \mathbf{Br}) with the difference that the reaction mixture after refluxing was not filtered but diluted with 100 mL of water and treated as described above. The yield was 72.1%; decomposition temperature >300°C (from DMF). IR (KBr, v, cm⁻¹): 1592 and 1472 (C=C arom.), 3208 (C–H arom.), 825 (1,4-disubstituted ben-

DOKLADY CHEMISTRY Vol. 383 Nos. 1-3 2002

zene ring), 2802 and 1592 (NH₃⁺), 1582 and 1402 (COO⁻), 1560 and 1352 (NO₂). UV (λ_{max} , nm (log ϵ)): 228.0 (4.25), 272.8 (4.22), 368.0 (4.09). ¹H NMR (300 MHz, DMSO-d₆-CCl₄, δ , ppm): 6.74 (d, 2H, C_{\alpha}H), 8.09 (d, 2H, C_{\beta}H), 8.46 (s, 1H, C₃H), 8.85 (s, 1H, C_{\stringermatrix}H), 7.86 (d, 1H, C_{\stringermatrix}H), 8.66 (d, 1H, C_{\stringermatrix}H).

For $C_{16}H_{11}N_3O_4$ anal. calcd. (%): C, 62.13; H, 3.58; N, 13.58.

Found (%): C, 61.62; H, 3.74; N, 13.17.

Hydrazone 5 ($\mathbf{R} = \mathbf{H}, \mathbf{Ar} = \mathbf{C}_{6}\mathbf{H}_{5}$). A. A mixture of 1.32 g (0.005 mol) of compound 2 (R = H), 25 mL ofwater and 5.4 mL of 27.5% hydrochloric acid was heated to reflux with stirring and cooled to 0°C. Then, 3.5 mL of an aqueous solution of NaNO₂ (concentration 200 g/L) was added, and the mixture was stirred at 0°C for 1 h. B. Water (4.5 mL) and a solution of 0.2 g of NaOH in 2 mL of H₂O were added to 0.86 g (0.005 mol) of 1-phenyl-3-methylpyrazol-5-one (4) $(Ar = C_6H_5)$ with stirring. The mixture was heated to 60°C, and 0.5 mL of a 10% aqueous solution of NaOH and a solution of 0.5 g of Na_2CO_3 in 6.5 mL of H_2O were added with stirring. The resulting solution was cooled to 5-8°C and added to mixture A over 10 min. During the mixing of mixtures A and B, the pH 8.5 of the medium was maintained by periodically adding a 10% aqueous NaOH solution. The reaction mixture was stirred at 5–8°C to the complete disappearance of diazonium salt, allowed to stand overnight, and acidified to pH 7 with acetic acid. The precipitate was collected by filtration, washed on the filter with water, and dried in air. The yield was 2.25 g (88.9%); mp 226-228°C. IR (KBr, v, cm⁻¹): 1548 (C=C arom.), 3216 (C-H arom.), 829 (1,4-disubstituted benzene ring), 1636 $(>C=NNH-), 1664 (>C=O). UV (\lambda_{max}, nm (log \epsilon)):$ 336.8 (4.37), 375.2 (4.41). ¹H NMR (250 MHz, δ, ppm): 2.32 (s, 3H, CH₃), 8.22 (s, 1H, C₃H), 8.06 (d, 1H, C₅H), 7.53 (m, 1H, C₆H), 7.22 (m, 1H, C₇H), 8.68 (d, 1H, C₈H), 7.94 (d, 2H, C_αH), 8.33 (d, 2H, C_βH), 7.46– 7.74 (6H, C₆H₅, NH).

For $C_{26}H_{19}N_5O_3$ anal. calcd. (%): C, 69.48; H, 4.26; N, 15.58.

Found (%): C, 69.12; H, 4.48; N, 15.17.

Other hydrazones 5 were obtained in a similar way from the corresponding compounds 2 and 4.

Hydrazone 5 (R = Br, Ar = C₆H₅). Yield, 87.0%; mp 159–161°C. IR (KBr, ν, cm⁻¹): 1552 (C=C arom.), 3216 (C–H arom.), 836 (1,4-disubstituted benzene ring), 1640 (>C=NNH–), 1664 (>C=O). UV (λ_{max} , nm (logε)): 207.2 (4.35), 221.6 (4.5), 237.2 (4.46), 354.4 (4.22), 428.8 (4.35).

For $C_{26}H_{18}BrN_5O_3$ anal. calcd. (%): C, 59.09; H, 3.43; N, 13.26.

Found (%): C, 58.68; H, 3.54; N, 12.91.

Hydrazone 5 ($\mathbf{R} = \mathbf{NO}_2$, $\mathbf{Ar} = \mathbf{C}_6\mathbf{H}_5$). Yield, 77.2%; decomposition temperature > 250°C. IR (KBr, v, cm⁻¹):

1512 (C=C arom.), 3408 (C–H arom.), 840 (1,4-disubstituted benzene ring), 1636 (>C=NNH–), 1660 (>C=O), 1544 and 1356 (NO₂). UV (λ_{max} , nm (log ϵ)): 207.2 (4.41), 220.8 (4.49), 246.4 (4.43), 374.4 (4.33), 456.0 (4.48).

For $C_{26}H_{18}N_6O_5$ anal. calcd. (%): C, 63.15; H, 3.41; N, 17.00.

Found (%): C, 63.25; H, 3.41; N, 16.52.

Hydrazone 5 (R = H, Ar = 4-CH₃C₆H₄). Yield, 87.0%; mp 156–158°C. IR (KBr, ν, cm⁻¹): 1524 (C=C arom.), 3404 (C–H arom.), 816 (1,4-disubstituted benzene ring), 1628 (>C=NNH–), 1664 (>C=O). UV (λ_{max} , nm (logε)): 330.4 (4.44), 376.0 (4.49).

For $C_{27}H_{21}N_5O_3$ anal. calcd. (%): C, 69.96; H, 4.57; N, 14.16.

Found (%): C, 69.62; H, 4.28; N, 15.81.

Hydrazone 5 (R = Br, Ar = 4-CH₃C₆H₄). Yield, 70.1%; mp 154–156°C. IR (KBr, v, cm⁻¹): 1512 (C=C arom.), 3416 (C–H arom.), 810 (1,4-disubstituted benzene ring), 1640 (>C=NNH–), 1656 (>C=O). UV (λ_{max} , nm (logɛ)): 207.2 (4.58), 238.4 (4.67), 385.6 (4.4), 433.6 (4.4).

For $C_{27}H_{20}BrN_5O_3$ anal. calcd. (%): C, 59.78; H, 3.72; N, 12.91.

Found (%): C, 59.31; H, 3.46; N, 12.56.

Hydrazone 5 (R = NO₂, Ar = 4-CH₃C₆H₄). Yield, 78.7%; decomposition temperature >250°C. IR (KBr, ν, cm⁻¹): 1544 (C=C arom.), 3392 (C–H arom.), 816 (1,4-disubstituted benzene ring), 1642 (>C=NNH–), 1558 (>C=O), 1544 and 1356 (NO₂). UV (λ_{max} , nm (logε)): 206.4 (4.39), 246.4 (4.44), 272.8 (4.3), 380.0 (4.26), 449.6 (4.36).

For $C_{27}H_{20}N_6O_5$ anal. calcd. (%): C, 63.77; H, 3.96; N, 16.53.

Found (%): C, 64.13; H, 3.78; N, 16.14.

Hydrazone 5 ($\mathbf{R} = \mathbf{H}$, $\mathbf{Ar} = 4$ -HO₃SC₆H₄). Yield, 96.2%; decomposition temperature >280°C. IR (KBr,

v, cm⁻¹): 1483 (C=C arom.), 3412 (C–H arom.), 818 (1,4-disubstituted benzene ring), 1662 (>C=NNH–), 1554 (>C=O), 1384 and 1165 (SO₃H). UV (λ_{max} , nm (log ϵ)): 214.2 (4.29), 236.8 (4.26), 336.0 (4.02), 383.2 (4.20), 424.0 (4.27).

For $C_{26}H_{19}N_5O_5S$ anal. calcd. (%): C, 60.81; H, 3.73; N, 13.64.

Found (%): C, 61.27; H, 3.64; N, 13.21.

Hydrazone 5 (R = Br, Ar = 4-HO₃SC₆H₄). Yield, 82.2%; decomposition temperature >280°C. IR (KBr, ν, cm⁻¹): 1552 (C=C arom.), 3380 (C–H arom.), 832 (1,4-disubstituted benzene ring), 1572 (>C=NNH–), 1596 (>C=O), 1356 and 1176 (SO₃H). UV (λ_{max} , nm (logε)): 202.4 (4.29), 219.2 (4.35), 231.2 (4.31), 253.6 (4.20), 296.8 (4.04), 360.8 (4.07), 443.0 (3.96).

For $C_{26}H_{18}BrN_5O_5S$ anal. calcd. (%): C, 52.71; H, 3.06; N, 11.82.

Found (%): C, 52.38; H, 3.16; N, 12.21.

Hydrazone 5 (R = NO₂, Ar = 4-HO₃SC₆H₄). Yield, 38.3%; decomposition temperature >280°C. IR (KBr, ν, cm⁻¹): 1544 (C=C arom.), 3408 (C–H arom.), 840 (1,4-disubstituted benzene ring), 1545 (>C=NNH–), 1600 (>C=O), 1500 and 1352 (NO₂), 1336 and 1180 (SO₃H). UV (λ_{max} , nm (logε)): 203.2 (4.37), 218.4 (4.44), 252.8 (4.33), 280.0 (4.26), 440.8 (4.32).

For $C_{26}H_{18}N_6O_7S$ anal. calcd. (%): C, 55.91; H, 3.25; N, 15.05.

Found (%): C, 56.31; H, 3.46; N, 14.68.

REFERENCES

- 1. *Heterocyclic Compounds*, Elderfield, R., Ed., New York, 1952, vol. 4. Translated under the title *Geterotsiklicheskie soedineniya*, Moscow: Inostrannaya Literatura, 1955, vol. 4.
- Zhungietu, G.I. and Rekhter, M.A., *Izatin i ego proizvod-nye* (Isatin and Its Derivatives), Chisinau: Shtiintsa, 1977, pp. 68–78.