A Novel Synthesis of 3-Halo-2-phenylquinoline-4-carboxylic Acids

Luca F. Raveglia,* Giuseppe A. M. Giardina, Mario Grugni,
Roberto Rigolio and Carlo Farina

Department of Chemistry, SmithKline Beecham S.p.A., Via Zambeletti, 20021-Baranzate (Milano), Italy

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The 3-chloro and 3-bromo-2-phenylquinoline-4-carboxylic acids were obtained in good yields through a novel procedure, entailing the synthesis of the 3-amino intermediate and the subsequent replacement of the amino group with chlorine or bromine, according to the Sandmeyer reaction.

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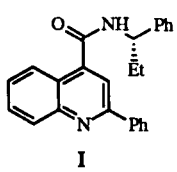
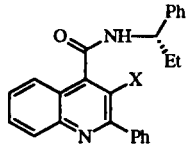
As a result of our structure-activity relationships study within a novel series of selective, non peptide, neurokinin-3 (NK-3) receptor antagonists based on the quinoline structure **I** (Chart 1) [1], the position 3 of the quinoline ring was identified as a key position for optimal binding affinity. In fact, the affinity increased about 4-fold with the introduction, at this position, of a small alkyl chain (**II**, X = Me, Et, *n*-Pr) and 7-18-fold with the incorporation of an electron-donating group (**II**, X = OH, OMe, NH_2). Thus, we decided to study the effects of electron-withdrawing groups, such as fluorine, chlorine or bromine.

Chart 1



I



II (X = Me, Et, *n*-Pr, OH, OMe, NH_2)

The synthesis of derivatives of formula **II** required the preparation of the corresponding carboxylic acid intermediates **2**, which can usually be obtained using the Pfitzinger reaction [2] of isatin (**1**) with the appropriate phenyl ketones in potassium hydroxide/ethanol at 60-80° (Scheme 1). However, when applied to 3-halo-2-phenylquinoline-4-carboxylic acids, this reaction was suitable only for the synthesis of the 3-fluoro derivative **2** (X = F) (44% yield), while 3-chloro and 3-bromo-2-phenylquinoline-4-carboxylic acids could not be obtained by this procedure because of the extreme reactivity of α-chloro and α-bromoacetophenone in the presence of potassium hydroxide [3].

Two modifications of the above reaction, which, in principle, should allow us to reach the target, are reported in the literature. The first involves the condensation between isatin and α-chloro or α-bromoacetophenone using 2-methoxyethanol as a solvent and a catalytic amount (1%) of potassium hydroxide [3]. The second method entails the reaction, under phase-transfer conditions, between isatin and α-bromoacetophenone in benzene and aqueous 50% potassium hydroxide, at 60-70°, using tetraethylammonium bromide as a phase-transfer catalyst [4]. However, in our hands, both these reactions were unsuccessful, giving only complex mixtures of by-products.

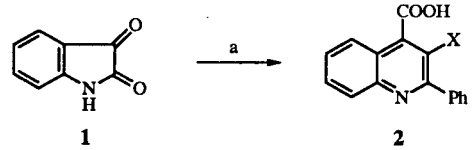
A third approach described in the literature [5] is the bromination of 2-phenylquinoline-4-carboxylic acid (**3**) at position 3 *via* the corresponding oxymercury derivative, as illustrated in Scheme 2. We repeated, without characterising the organomercury intermediates, the synthetic procedure described in ref [5]. Accordingly, 2-phenylquinoline-4-carboxylic acid (**3**) and mercury(II) acetate were refluxed in acetic acid for 3 hours; the acetoxymercury derivative was then converted into the oxymercury derivative by treatment with sodium carbonate and carbon dioxide in aqueous ethanol. The latter compound was, in turn, converted into the supposed 3-bromo derivative **4** by reaction with bromine and sodium bromide in water. Unfortunately, also in this case we were not able to repeat the literature

Chart 1

I

II (X = Me, Et, *n*-Pr, OH, OMe, NH_2)

Scheme 1 [a]



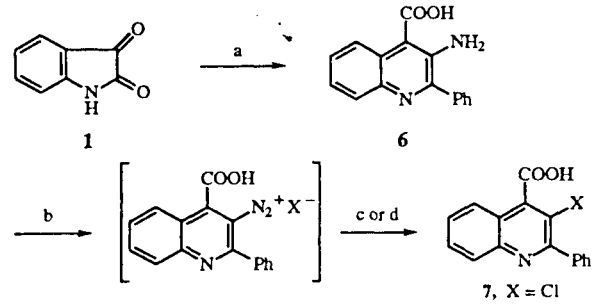
1 **2**

[a] Reagents and conditions: a = $PhCOCH_2X$, KOH, EtOH, 80°, 3-4 hours

findings since the only compound isolated in 61% yield was proven to be 2-(2-bromophenyl)quinoline-4-carboxylic acid (**5**) and not **4**, as unequivocally demonstrated by nmr data which revealed the presence of one hydrogen in position 3 at 8.0 ppm as a singlet. Probably the mercuriation occurs at the *ortho* position of the 2-phenyl ring and not at position 3 of the quinoline nucleus.

Finally, the desired compounds were obtained in satisfactory yields using a previously unreported procedure which entailed the synthesis of the 3-amino derivative and the replacement of the amino group with chlorine or bromine, according to the Sandmeyer reaction illustrated in Scheme 3.

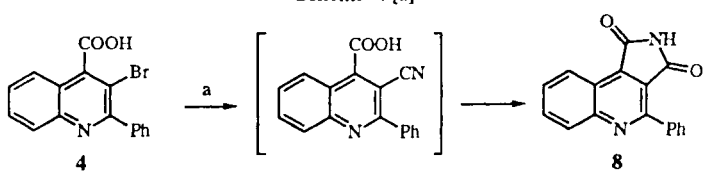
Scheme 3 [a]



[a] Reagents and conditions: a = $PhCOCH_2NH_2$•HCl, NaOH, H_2O/EtOH, 85°, 3 hours; b = $NaNO_2$, HX, H_2O, 0°, 10 minutes; c = CuCl, 37% HCl, r.t., 1 hour, 70°, 1 hour; d = CuBr, 48% HBr, r.t., 15 minutes, 80°, 1 hour.

3-Amino-2-phenylquinoline-4-carboxylic acid (**6**) was obtained in 68% yield through the classic Pfitzinger reaction between isatin (**1**) and α-aminoacetophenone hydrochloride in aqueous sodium hydroxide at 85°. The amino group was then converted into the diazonium salts with sodium nitrite and hydrochloric or hydrobromic acid and then treated with cuprous chloride or bromide to give **7** and **4** in 71 and 58% yield, respectively. To evaluate the possibility to use these halogen derivatives for the introduction, at position 3 of the quinoline nucleus, of other functional groups, compound **4** was treated with cuprous cyanide in *N,N*-dimethylformamide at reflux (Scheme 4). However, the 3-cyano derivative could not be isolated since, under the reaction conditions, it cyclised directly into imide **8**. This was somewhat unexpected, since these types of cyclisations generally entail the use of a strong acidic medium such as boiling polyphosphoric acid [6] or sulphuric acid [7]. In any case, this result confirms the high reactivity of the bromine at position 3 and the possible employment of compounds **4** or **7** as useful synthons for further functionalisation of the quinoline nucleus.

Scheme 4 [a]



[a] Reagents and conditions: a = CuCN, DMF, reflux, 6 hours.

EXPERIMENTAL

Melting points were determined with a Büchi 530 hot stage apparatus and are uncorrected. Proton nmr spectra were recorded on a Bruker ARX 300 spectrometer at 303K unless otherwise indicated. Chemical shifts were recorded in parts per million (δ units) downfield from tetramethylsilane; nmr spectral data are reported as a list. Infrared spectra were recorded in potassium bromide with a Perkin-Elmer 1420 spectrophotometer; mass spectra were obtained on a Finnegan MAT TSQ-700 spectrometer. Silica gel used for flash column chromatography was Kiesgel 60 (230-400 mesh) (E. Merck AG, Darmstadt, Germany). Microanalyses were performed at Redox SNC, Milan, Italy.

3-Fluoro-2-phenylquinoline-4-carboxylic Acid (**2**, X = F).

A mixture of isatin (1.25 g, 8.5 mmoles), ethanol (20 ml) and 85% potassium hydroxide (1.57 g, 10.0 mmoles) was stirred at room temperature for 30 minutes. α-Fluoroacetophenone [8] (1.38 g, 10.0 mmoles), dissolved in ethanol (5 ml), was added and the reaction was stirred at room temperature for 1 hour and at 60° for 30 minutes. The solvent was evaporated to dryness *in vacuo* and the residue was dissolved in water and washed with ether. The aqueous layer was acidified with 37% hydrochloric acid and the precipitate was collected by suction filtration, washed with water and dried in a ventilated oven at 80° to yield 1.0 g (44%) of the title compound, mp 247-249°; ir (potassium bromide): ν 3610-3300, 3040, 2680-2120, 2100-1800, 1730, 1600 cm^{-1}; 300 MHz ^1H nmr (DMSO-d_6): δ 14.30 (s br, 1H), 8.17 (d, 1H), 8.04-7.97 (m, 3H), 7.85 (dd, 1H), 7.76 (dd, 1H), 7.62-7.56 (m, 3H); ms: (EI, source 190°, 70 eV, 200 μA) m/z 267 (M^+), 221.

Anal. Calcd. for $C_{16}H_{10}FNO_2$: C, 71.91; H, 3.77; N, 5.24; F, 7.11. Found: C, 71.80; H, 3.75; N, 5.05; F, 7.15.

3-Amino-2-phenylquinoline-4-carboxylic Acid (**6**) [9].

A mixture of isatin (5.0 g, 34.0 mmoles), water (66 ml) and sodium hydroxide (7.5 g, 187.5 mmoles) was heated to 85°. α-Aminoacetophenone hydrochloride (8.0 g, 46.7 mmoles), dissolved in a mixture of ethanol (74 ml), water (74 ml) and tetrahydrofuran (15 ml), was added dropwise during 2 hours, then the reaction was refluxed for 1 hour. The organic solvents were evaporated *in vacuo*, the solid was filtered off and the filtrate was acidified to *p*H = 4 with acetic acid. The yellow precipitate was collected by suction filtration, washed with water and dried in a ventilated oven at 80° to yield 6.1 g (68%) of the title compound, mp 214-215° (lit [10] mp 223-224°); ir (potassium bromide): ν 3430, 3335, 3060, 1630-1570 cm^{-1}; 300 MHz ^1H nmr (DMSO-d_6): δ 8.41 (dd, 1H), 7.82 (dd, 1H), 7.68 (dd, 2H), 7.60-7.52 (m, 3H), 7.48 (ddd, 1H), 7.40 (ddd, 1H); ms: (EI, source 190°, 70 eV, 200 μA) m/z 264 (M^+), 218.

3-Chloro-2-phenylquinoline-4-carboxylic Acid (**7**).

The 3-amino-2-phenylquinoline-4-carboxylic acid (**6**) (1.0 g, 3.8 mmoles) was dissolved in 37% hydrochloric acid (15 ml)

and water (10 ml) by gentle warming on a water bath. The solution was cooled to 0° and sodium nitrite (0.41 g, 6.0 mmoles), dissolved in water (2.5 ml), was added dropwise during 10 minutes, maintaining the temperature between 0 and 5°. Stirring was continued at 0° for 10 minutes, then the reaction mixture was added to an ice-cooled solution of cuprous chloride (0.38 g, 3.8 mmoles) in 37% hydrochloric acid (2.1 ml), under magnetic stirring. The temperature was allowed to rise to 25°; after 1 hour the reaction mixture was heated at 70° for 1 hour. The precipitate was collected by suction filtration, washed with water and dried in a ventilated oven at 80° to yield 0.76 g (71%) of the title compound as a yellow solid, mp 249-251°; ir (potassium bromide): ν 3700-3300, 3060, 3040, 2600-2160, 2140-1800, 1720; 1580 cm^{-1}; 300 MHz ^1H nmr (DMSO-d_6): δ 13.78 (s br, 1H), 8.13 (d, 1H), 7.90 (ddd, 1H), 7.87-7.78 (m, 2H), 7.78-7.72 (m, 2H), 7.58-7.52 (m, 3H); ms: (EI, source 190°, 70 eV, 200 μA) m/z 283 (M^+), 248, 239, 204.

Anal. Calcd. for $C_{16}H_{10}ClNO_2$: C, 67.73; H, 3.55; N, 4.94; Cl, 12.50. Found: C, 67.45; H, 3.58; N, 5.00; Cl, 12.61.

3-Bromo-2-phenylquinoline-4-carboxylic Acid (**4**).

The 3-amino-2-phenylquinoline-4-carboxylic acid (**6**) (2.0 g, 7.6 mmoles) was dissolved in 48% hydrobromic acid (21 ml) by gentle warming on a water bath. The solution was cooled to 0° and sodium nitrite (0.82 g, 11.9 mmoles), dissolved in water (5 ml), was added dropwise during 10 minutes, maintaining the temperature between 0 and 5°. The reaction mixture was stirred at 0° for 10 minutes and then added to an ice-cooled solution of cuprous bromide (1.1 g, 7.7 mmoles) in 48% hydrobromic acid (2.9 ml), under magnetic stirring. The temperature was allowed to rise to 25° and after 15 minutes the reaction mixture was heated at 80° for 1 hour. The precipitate was collected by suction filtration, washed with water and dried in a ventilated oven at 80°; trituration with isopropyl ether afforded 1.44 g (58%) of the title compound as a white solid, mp 246-248°; ir (potassium bromide): ν 3600-3200, 3060, 3040, 2600-2160, 2100-1800, 1726, 1575 cm^{-1}; 300 MHz ^1H nmr (DMSO-d_6): δ 8.11 (d, 1H), 7.92 (ddd, 1H), 7.83-7.73 (m, 2H), 7.71-7.56 (m, 2H), 7.57-7.51 (m, 3H); ms: (EI, source 190°, 70 eV, 200 μA) m/z 327 (M^+), 248, 203.

Anal. Calcd. for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.25; Br, 24.35. Found: C, 58.20; H, 3.09; N, 4.20; Br, 23.98.

2-(2-Bromophenyl)quinoline-4-carboxylic Acid (**5**).

This compound was synthesised (61% yield) starting from 2-phenylquinoline-4-carboxylic acid and following, without characterising the acetoxymercury and oxymercury intermediates, the experimental procedure reported in ref [5] for the synthesis of 3-bromo-2-phenylquinoline-4-carboxylic acid. Physical and spectroscopic data for the title compound are as follows: mp 239-241° [11]; ir (potassium bromide): ν 3700-3200, 3100, 2620-2100, 2100-1800, 1725, 1595, 1570 cm^{-1}; 300 MHz ^1H nmr (DMSO-d_6): δ 8.75 (d, 1H), 8.11 (d, 1H), 8.01 (s, 1H), 7.84 (ddd, 1H), 7.80 (dd, 1H), 7.72 (ddd, 1H), 7.66 (dd, 1H), 7.56 (ddd, 1H), 7.45 (ddd, 1H); ms: (EI, source 190°, 70 eV, 200 μA) m/z 327 (M^+), 326, 283, 248, 203.

Anal. Calcd. for $C_{16}H_{10}BrNO_2$: C, 58.56; H, 3.07; N, 4.25; Br, 24.35. Found: C, 58.61; H, 3.07; N, 4.24; Br, 24.23.

1,3-Dioxo-4-phenyl-2*H*-pyrrolo[3,4-*c*]quinoline (**8**).

A mixture of 3-bromo-2-phenylquinoline-4-carboxylic acid (**4**) (5.0 g, 13.1 mmoles), cuprous cyanide (1.8 g, 19.6 mmoles) and *N,N*-dimethylformamide (40 ml) was refluxed for 6 hours. Tetrahydrofuran (200 ml) was added, the mixture was stirred at room temperature for 1 hour and the insoluble material was filtered off. The filtrate was evaporated to dryness *in vacuo* and purified by flash column chromatography on 230-400 mesh silica gel (toluene:isopropyl ether = 9:1) to yield 1.7 g (47%) of the title compound, mp 290-292° (lit. [12], mp 284° dec.; ir (potassium bromide): ν 3195, 3070, 1772, 1714, 1622, 1590 cm^{-1}; 300 MHz ^1H nmr (DMSO-d_6): δ 11.58 (s br, 1H), 8.82 (dd, 1H), 8.22 (dd, 1H), 8.01 (ddd, 1H), 7.98-7.92 (m, 2H), 7.86 (ddd, 1H), 7.56-7.52 (m, 3H); ms: (EI, source 190°, 70 eV, 200 μA) m/z 274 (M^+), 245, 218.

Anal. Calcd. for $C_{17}H_{10}N_2O_2$: C, 74.45; H, 3.68; N, 10.21. Found: C, 74.32; H, 3.70; N, 10.15.

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