

## **AN EFFICIENT SYNTHESIS OF $\beta$ -(3-QUINOLINYL)- $\alpha$ -ALANINE**

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### **ABSTRACT:**

*A convenient synthesis for  $\beta$ -(3-quinolinyl)- $\alpha$ -alanine (**4**) is presented. Condensation of 2-chloro-3-chloromethylquinoline (**5**) with diethyl acetamidomalonate (**2**) gave high yield of diethyl 2-acetyl-amino-2-(2-chloro-3-quinolinylmethyl)-propanedionate (**6**), which was dehalogenated in the presence of ammonium formate and palladium/charcoal. Diethyl 2-acetamido-2-(3-quinolinylmethyl)-malonate (**3**) was easily converted to the amino acid. The condensation reaction between **2** and **6** is also useful for the construction of (1H)-2,3-dihydropyrrolo[2,3-b]quinoline-2,2-bis(carboxylic acid) and pyrrolo[2,3-b]quinoline-2-carboxylic acid derivatives.*

**KEYWORDS:** reductive dehalogenation; unnatural amino acid;  $\beta$ -(3-quinolinyl)- $\alpha$ -alanine; pyrrolo[2,3-b]quinoline-2-carboxylic acid skeleton

### **RESUMO:**

*Uma síntese eficaz para  $\beta$ -(3-quinolinil)- $\alpha$ -alanina (**4**) é apresentada. A condensação de 2-cloro-3-clorometilquinolina (**5**) com dietilacetamido malonato (**2**) levou a um rendimento alto de dietil 2-acetilamino-2-(2-cloro-3-quinolinilmetil)-propanodionato (**6**), que foi sujeito à dehalogenação na presença de Pd/C. O dietil 2-acetamido-2-(3-quinolinilmetil)-malonato (**3**) foi facilmente convertido no amino ácido. A reação de condensação entre **2** e **6** é também útil para a síntese de (1H)-2,3-dihidropirol[2,3-b]quinolina-2,2-bis(ácido carboxílico) e derivados de pirol[2,3-b]quinolina-2-ácido carboxílico.*

**PALAVRAS CHAVES:** dehalogenação redutiva; amino ácido não-natural;  $\beta$ -(3-quinolinil)- $\alpha$ -alanina; esqueleto de pirol[2,3-b]quinolina-2-ácido carboxílico

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## INTRODUCTION

The use of 3-(3-quinolinyl)-alanine (**4**), a rare unnatural amino acid is limited due to difficulties in access. Folkers *et al.* prepared the title compound in the synthesis of highly active peptides as Luteinising Hormone Releasing Hormone (LHRH) antagonists, as drug carriers and also of peptides with activity on central nerve system.<sup>1-4</sup> In other reports the influence on tryptophan biosynthesis or chorismate mutase has been studied.<sup>5-7</sup> It has also been applied as a replacement of tryptophan in structure-activity studies of brain/gut peptide like Acetyl-cholecystokinin-heptapeptide (Ac-CCK-7) analogues.<sup>8, 9</sup>

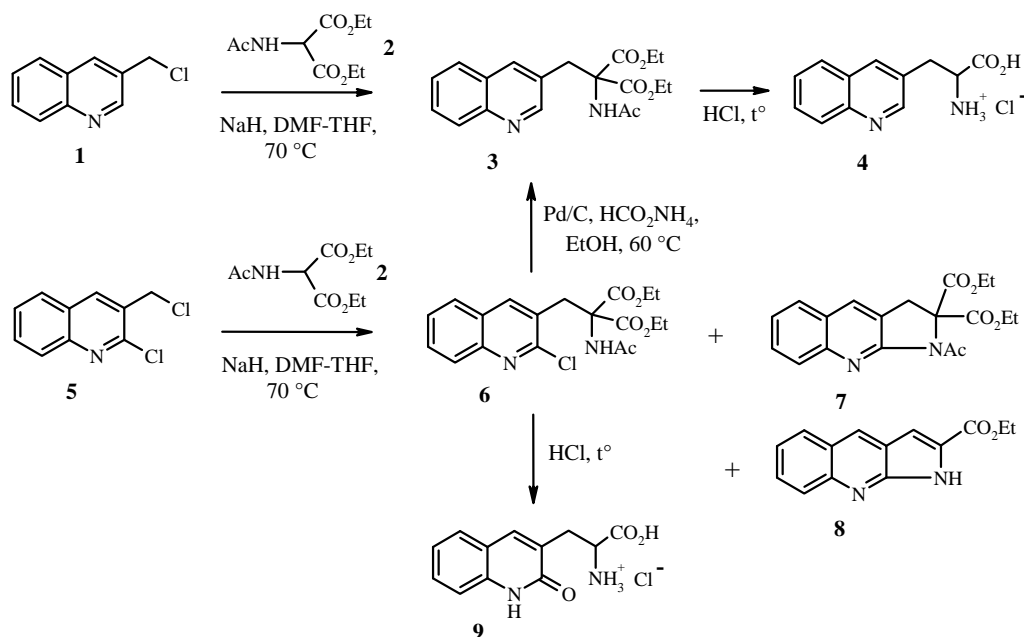
The amino acid was first prepared by Dyer and Yokoyama.<sup>10</sup> Improvements were achieved by using the azlactone approach,<sup>11</sup> which is still useful for preparing enantiopure **4**.<sup>12</sup> Condensation of 3-chloromethylquinoline (**1**) with diethyl acetamidomalonate (**2**) leads to diethyl 2-acetylamino-2-(3-quinolinylmethyl)-propanedionate (**3**).<sup>4, 13</sup> Enantioselective synthesis of **4** or its derivatives was achieved,<sup>8, 9</sup> adapting the Evans oxazolidine auxiliary method. Other enantioselective approaches to derivatives of **4** make use of enzymatic resolution,<sup>11, 13</sup> or asymmetric catalytic hydrogenation of the corresponding enamines.<sup>12, 14</sup> All these approaches suffer from limited availability of 3-substituted quinolinyl derivatives needed as precursors.

In the synthesis of **4** mentioned above,<sup>4, 13</sup> difficulties in separation of **2** and **3** were noticed because of similar polarities. The condensation product **3** on crystallization was always accompanied by unreacted **2**. A high-purity **3** could be produced only by multiple crystallization and careful chromatographic purification.

## RESULTS AND DISCUSSION

The synthesis of **4** presented here combines the acetamidomalonate process with reductive dehalogenation of 2-chloro-3-quinoline derivatives. The condensation of **2** and 3-chloromethyl-2-chloroquinoline (**5**) proceeded smoothly in DMF as solvent and sodium hydride as base.<sup>15</sup> Sufficient pure product **6** was isolated after one crystallization; separation of **2** and diethyl 2-acetylamino-2-(2-chloro-3-quinolinylmethyl)-propanedionate (**6**), contained in the mother liquors, is simplified by greater differences in polarity as compared to the original setup.<sup>4, 13</sup> **6** was obtained in reproducible yields greater than 85 %.<sup>16</sup>

Initially, efforts to condense **5** with **2** in the presence of sodium ethylate and ethanol as solvent not only resulted in incomplete reaction and markedly lower yield of the desired product, but also gave side products arising from intramolecular cyclization, such as diethyl N-acetyl-(1*H*)-2,3-dihydropyrrolo[2,3-*b*]quinoline-2,2-biscarboxylate (**7**) and ethyl pyrrolo[2,3-*b*]quinoline-2-carboxylate (**8**). Slight modifications of the reaction conditions gave access to **8** in higher yield.

Scheme: Synthetic pathway to  $\beta$ -(3-quinoliny)- $\alpha$ -alanine

**5** as precursor could easily be obtained by a procedure first developed by Meth-Cohn *et al.*<sup>17–19</sup> or by side-chain chlorination of 2-chloro-3-methylquinoline.<sup>20</sup> Calvin *et al.* have presented a procedure for preparation of **5** from 3-chloro-N-phenylpropanamide.<sup>21</sup>

**6** was dehalogenated using ammonium formate and palladium/charcoal in refluxing ethanol to produce **3** in near quantitative yield. Treatment of **3** with refluxing 25 % HCl gave **4**-HCl after removal of excess HCl in vacuum. **4** was liberated by adding ammonium hydroxide solution to a cooled solution of **4**-HCl in water. The N-Boc- and N-Fmoc derivatives of **4** were prepared by standard procedures.

When **6** was subjected to decarboxylation in refluxing HCl, complete conversion to 2-amino-3-(2(1*H*)-quinolinone-3-yl)-propanoic acid (**9**) was achieved, which is closely related to the 4-substituted quinolinone anti-ulcer drug “Rebamipide”.<sup>22–24</sup>

## EXPERIMENTAL

<sup>1</sup>H NMR and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded on Bruker AM-400 instrument. Chemical shifts are in ppm relative to tetramethylsilane as internal standard at 0.0 ppm (<sup>1</sup>H NMR) or relative to shifts of deuterated solvents (<sup>13</sup>C NMR) according to literature values (CDCl<sub>3</sub> middle resonance at 77.0 ppm). Melting points of organic compounds were determined on Büchi B-540 apparatus.

**Compound 3:** mp. 124–125 °C (from EtOAc-hexanes). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ): 8.60 (1H, d), 8.03 (1H, dd), 7.83 (1H, d), 7.65–7.75 (2H, m), 7.55 (1H, m), 6.60 (1H, s, NH), 4.35 (4H, q, *J* = 7.5 Hz), 3.89 (2H, s), 2.10 (3H, s), 1.35 (6H, t, *J* = 7.5 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>,  $\delta$ ): 169.7, 167.4, 152.1, 147.6, 136.8, 129.6, 129.5, 128.5, 128.0, 127.6, 127.1, 67.4, 63.2, 35.5, 23.3, 14.3.

**Compound 6:** mp. 152-153 °C (from EtOAc-hexanes).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 8.00 (1H, d), 7.90 (1H, s), 7.75 (2H, dd), 7.55 (1H, dd), 6.62 (1H, s, NH), 4.45-4.25 (4H, m), 4.00 (2H, s), 2.05, (3H, s), 1.30 (6H, t).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 169.8, 167.5, 151.4, 147.0, 140.8, 130.7, 128.3, 127.8, 127.4, 127.3, 127.2, 66.4, 63.0, 35.2, 23.1, 14.1.

**Compound 7:** yellow oil.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.90 (1H, d), 7.83 (1H, s), 7.68 (1H, d), 7.60 (1H, dd), 7.40 (1H, dd), 4.25 (4H, q), 3.70 (2H, s), 2.98, (3H, s), 1.30 (6H, t).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 170.8, 168.2, 154.2, 146.8, 132.5, 129.6, 128.3, 127.6, 125.7, 125.4, 122.7, 72.2, 62.7, 36.1, 25.8, 14.2.

**Compound 8:** mp. 173-174 °C (from EtOAc).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 10.63 (1H, s, NH), 8.55 (1H, s), 8.20 (1H, m), 7.95 (1H, m), 7.70 (1H, m), 7.45 (1H, m), 7.35 (1H, s), 4.45 (2H, q), 1.35 (3H, t).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 161.6, 150.4, 147.3, 132.1, 131.1, 129.2, 128.8, 128.2, 125.2, 123.6, 121.6, 106.9, 61.7, 14.4.

**Compound 9-hydrochloride:** 270-272 °C decomp.  $^1\text{H}$  NMR (400 MHz,  $\text{dms}-d_6$ ,  $\delta$ ): 11.95 (1H, s), 8.50 (3H, br. s, NH), 7.85 (1H, s), 7.60 (1H, m), 5.50 (1H, m), 7.40 (1H, m), 7.15 (1H, m), 4.25 (1H, m), 3.0 - 3.1 (2H, m).  $^{13}\text{C}$  NMR (100 MHz,  $\text{dms}-d_6$ ,  $\delta$ ): 170.8, 163.0, 140.3, 139.0, 130.6, 128.2, 127.8, 122.6, 119.9, 115.5, 51.6, 32.7.

The results of elemental analysis of the new synthesized compounds **3**, **6**, **8** were in agreement with calculated values.

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