# STUDIES ON THE REACTIONS OF 2,3-DIKETOPYRIDO[4,3,2-*de*] QUINOLINES WITH ALIPHATIC AMINES

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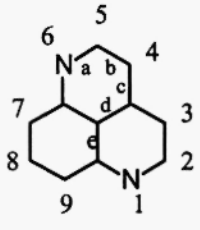
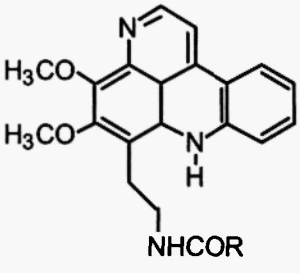
**Abstract:** A reaction of 2,3-diketopyrido[4,3,2-*de*]quinolines with different amines is described. The aminative transfer is carried out in the presence of triethylamine in tetrahydrofuran under ambient conditions.

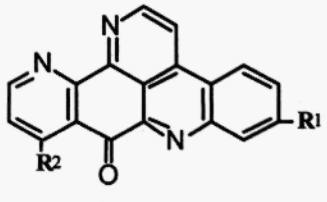
Marine organisms are a rich and valuable source of natural products. History has proven that marine organisms, especially invertebrates such as sponges, soft corals, and molluscs, produce many secondary metabolites which are unprecedented within the terrestrial biosphere. Marine natural products, as a field of scientific endeavor, has hence grown considerably. Many metabolites having been isolated from marine sources[1-2]. Some of these compounds have generated interest both as challenging problems for structure elucidation and synthesis, as well as




Pyrido[4,3,2-*de*]quinoline skeleton




R = $CH_3$, Varamines A
R = H, Varamines B

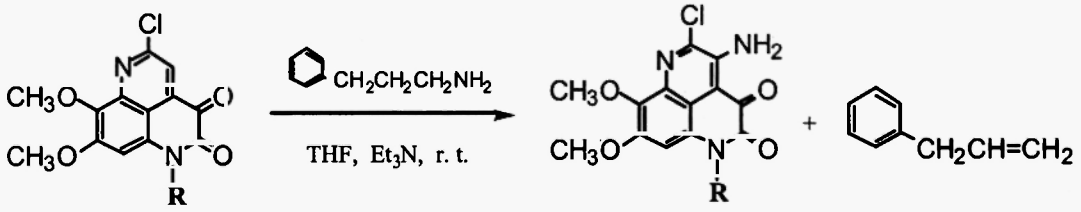



R1 = R2= H, Ascidiemin
R1 =Br, R2= H, 2-Bromoleptoclinidinone

for their biological activities[3-6]. The varamines are brilliant red pigments which were isolated from a Fijian collection of the ascidian *Lissoclinum uareau* [7], and both compounds contain the same carbon skeleton as the cystodytins[8]. Varamines A and B are cytotoxic toward L1210

murine leukemia with $IC_{50}$ values of 0.03, 0.05 μg/mL. Ascididemin[9] and 2-bromoleptoclindinone[10] from *Leptoclinides* sp. and *Didemnum* sp., respectively, were the first polycyclic aromatic metabolites to be isolated from ascidians. These compounds are cytotoxic toward leukemia cell lines *in vitro* with $IC_{50}$'s of 0.4 μg/mL, while ascididemin also causes the release of calcium in the sarcoplasmic reticulum with a potency 7 times greater than caffeine. These marine products contain a pyrrolo[4,3,2-*de*]quinoline core structure. Many of these compounds have been reported as having significant cytotoxicity. Previously, we have synthesized a series of heterocycloquinolines such as pyrrolo[4,3,2-*de*]quinolines, furo[4,3,2-*de*]quinoline and pyrido[4,3,2-*de*]quino-lines and reported the cytotoxic potency and anticancer activities of these compounds[11-15]. 1*H*-2,3-diketo-5-chloro-7,8-dimethoxypyrido[4,3,2-*de*]quinoline **1** selectively affects cell growth against non small cell lung cancer HOP-92 cell line, breast cancer MDA-MB-435, and MDA-N cells lines with $LC_{50}$ values less than 8μM and the compound can react with a series of compounds which include amino acids, amino esters and peptides which contain a primary amino group and with certain ketones.

Recently, we have reported a novel aminative transfer reaction between 1*H*-2,3-diketo-5-chloro-7,8-dimethoxypyrido[4,3,2-*de*]quinoline **1** and a wider range of amino acids and amino esters, which includes α, β, γ, δ, ε and ω amino acid and amino esters[14, 16]. During the course of our studies regarding the reaction of 2,3-diketopyrido[4,3,2-*de*]quinoline with compounds which include acetone and amino acids, we found that the C3 and C4 positions in 2,3-diketopyrido-[4,3,2-*de*]quinolines **1** and **2** were observed to be a highly reactive positions toward nucleophilic addition[13c, 14-16]. The results prompted us to investigate this type of reactivity of these compounds



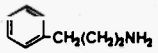
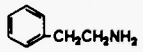
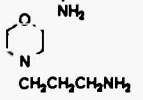
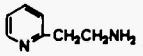
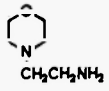
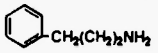
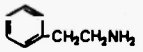
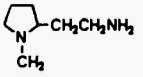
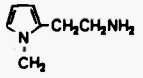
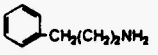
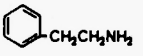
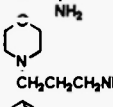
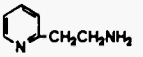
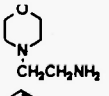
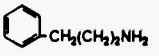
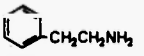
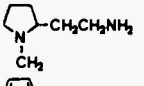
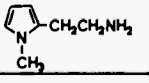

**1**. R=H
**2**. R=$CH_2COOC_2H_5$

**3**. R=H
**4**. R=$CH_2COOC_2H_5$

(1)

and which may be related to their observed cytotoxic potency. Herein we describe the reaction of 2,3-diketopyrido[4,3,2-*de*]quinolines with various amines which contain phenyl, pyridyl, morpholino, pyrrolyl and pyrrolidinyl groups. For this reaction, tetrahydrofuran was used as a solvent because solubility of both 2,3-diketopyrido[4,3,2-*de*]quinolines and amines is required for good reactivity. The results obtained with selected benzene, pyridine, morpholine, pyrrole

Table 1. Aminative transfer reaction of 2,3-diketopyrido[4,3,2-de]quinolines with various amines

| Entry [a] | Substrate | Reaction time(h) | Yield (%) [b] |
|---|---|---|---|
| 1 |  | 10 | 72 |
| 2 |  | 10 | 76 |
| 3 |  | 24 | 4.6 |
| 4 |  | 24 | 72 |
| 5 |  | 24 | 31 |
| 6 |  | 20 | 69 |
| 7 |  | 10 | 12[c] |
| 8 |  | 20 | 15[c] |
| 9 |  | 18 | 73 |
| 10 |  | 12 | 48 |
| 11 |  | 20 | 82 |
| 12 |  | 12 | 79 |
| 13 |  | 24 | 5.2 |
| 14 |  | 12 | 71 |
| 15 |  | 20 | 67 |
| 16 |  | 22 | 70 |
| 17 |  | 20 | 13 [c] |
| 18 |  | 12 | 10 [c] |
| 19 |  | 12 | 71 |
| 20 |  | 20 | 62 |

a. Entries 1-10: the reaction of compound **1** with amines; Entries 11-20: the reaction of compound **2** with amines; b. Yield of compound **3** or **4** in the reaction scheme; c. The elimination products were identified by GC-MS, GC-IR and GC analysis compared with authentic materials.

and pyrrolidine derivatives of the amines are summarized in Table 1. In a typical example, 2,3-diketopyrido[4,3,2-*de*]quinolines and 3 equivalents of the amine are mixed with triethylamine in tetrahydrofuran at room temperature for the time indicated in the Table 1. The amination reaction of 2,3-diketopyrido[4,3,2-*de*]quinoline **1** with 2-phenylethylamine proceeded in 76% yield (Table 1, entry 2). Similar reaction rates and yields of products were observed for different amines (Table 1, entries 1, 4-6, 9 and 10). For 2,3-diketopyrido[4,3,2-*de*]quinoline **2**, it reacts essentially similarly (Table 1, entries 11, 12, 14-16, 19 and 20).

The amino group reactivity and steric effects are two important factors affecting the aminative transfer reaction. Thus, with 1-aminoindan as substrate, which has approximately the same basicity as 2-phenylethylamine but is sterically more hindered, the amination product was isolated in 4.6% yield (Table 1, entry 3). Evidently, steric effects can exert a strong influence on the course of the reaction. As in the case of the amination of 2,3-diketopyrido[4,3,2-*de*]quinoline **1** with 1-aminoindan, the reaction with 2,3-diketopyrido[4,3,2-*de*]quinoline **2** using 1-aminoindan was similar, i. e., the reaction was slow and only a little of the amination product was formed (Table 1, entry 13).

The aminative transfer reaction between 2,3-diketopyrido-[4,3,2-*de*]quinolines and amines generally proceeds more readily than with amino acids. The reaction of amines required a shorter reaction time and the yield was greater. Amination at the C4 position occurs more rapidly in the case of amino acids.

A mechanism for a novel aminative transfer and elimination between 2,3-diketopyrido[4,3,2-*de*]quinolines and amines has been proposed in our previous paper[14]. The double bond between carbon (C3a) and carbon (C4) undergoes nucleophilic addition by an amino group to form a dihydro intermediate. Then this dihydro intermediate is dehydrogenated to afford the more stable aromatic system. After the elimination reaction, the final product 4-amino-2,3-diketopyrido[4,3,2-*de*]quinolines is formed.

In summary, in this communication, we have explored the novel aminative transfer and elimination reaction that occurs between 2,3-diketopyrido[4,3,2-*de*]quinolines and amines that contain phenyl, pyridyl, morpholino, pyrrolyl and pyrrolidinyl groups and have compared the reactivities of different amines. The comparable studies of the reactions between 2,3-diketopyrido[4,3,2-*de*]quinolines and peptides, nucleotides as well as nucleic acids are currently in progress.

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17. General experimental procedure for the aminative transfer reaction summarized in Table 1: A solution of 10 mg ( 0.034 mmol) of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinolines (**1**) in 10 ml of tetrahydrofuran was mixed with 12.1 mg 2-phenylethylamine, then 3 drops of triethylamine were added (Table 1, entry 2). The resulting mixture was stirred at room temperature for 10 hours. A red product formed in the solution. After removing the solvent under a reduced pressure, the residue was subjected to column chromatography on silica gel (Merck, 230-400 mesh) using a solvent mixture of ethyl acetate to hexane (4:1) and then ethyl acetate and ethyl acetate to methanol (5:1) to give the red product, 1*H*-2,3-diketo-4-amino-5-chloro-7,8-dimethoxypyrido[4,3,2-*de*]quinoline (**3**). HRMS: calcd for $C_{13}H_{10}N_3O_4Cl$ 307.0360, found 307.0355 ($M^+$, 100%); $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 11.95 (s, 1H, Ar-H), 9.58 (s, 1H, NH), 8.30 (s, 1H, NH), 7.23 (s, 1H, Ar-H), 3.91 (s, 3H, $OCH_3$), 3.87 (s, 3H, $OCH_3$); Anal. calcd for $C_{13}H_{10}N_3O_4Cl$: C, 50.75; H, 3.28; N, 13.66; Found C, 50.92; H, 3.40; N, 13.81

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