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SYNTHESIS OF A 9-AZA ANALOGUE OF ELEUTHEROL

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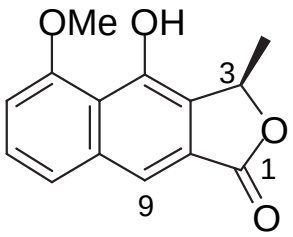
Abstract – A 9-aza analogue of the natural product eleutherol was synthesized by intramolecular acylation of a dihydrokynurenic acid.

INTRODUCTION

Eleutherol (**1**) was first isolated in the early 1950's from the tubers of *Eleutherine bulbosa*.[1] Since then it has been obtained from *Eleutherine subaphylla*,[2] *Eleutherine palmifolia*,[3] medicinal plants found in Vietnam and Indonesia respectively, and from the rhizome of *Eleutherine americana*.[4] Eleutherol has a wide range of pharmacological activity. It has been shown to inhibit tyrosinase activity as well as melanin formation *in vitro*, is a coronary vasodilator and has been used in the treatment of heart diseases such as angina pectoris.[5, 6]



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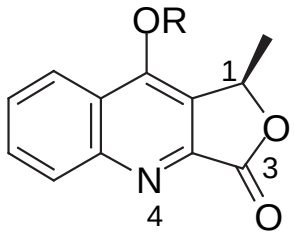
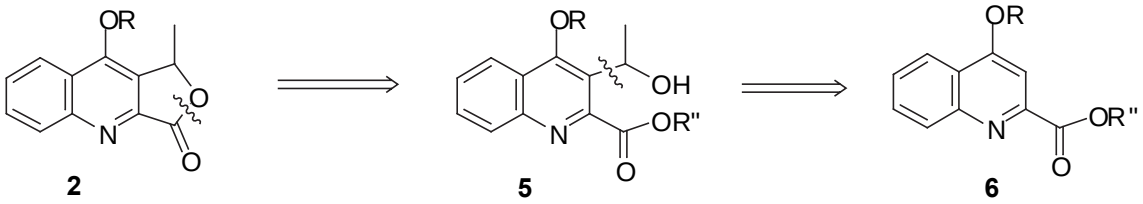


2a R = Ac

We explored synthesis of compounds of type **2** (nitrogen analogues of eleutherol), with a view to investigating their biological properties, and now report the synthesis of compound **2a**, a 9-aza-5-demethoxyeleutherol.

RESULTS AND DISCUSSION

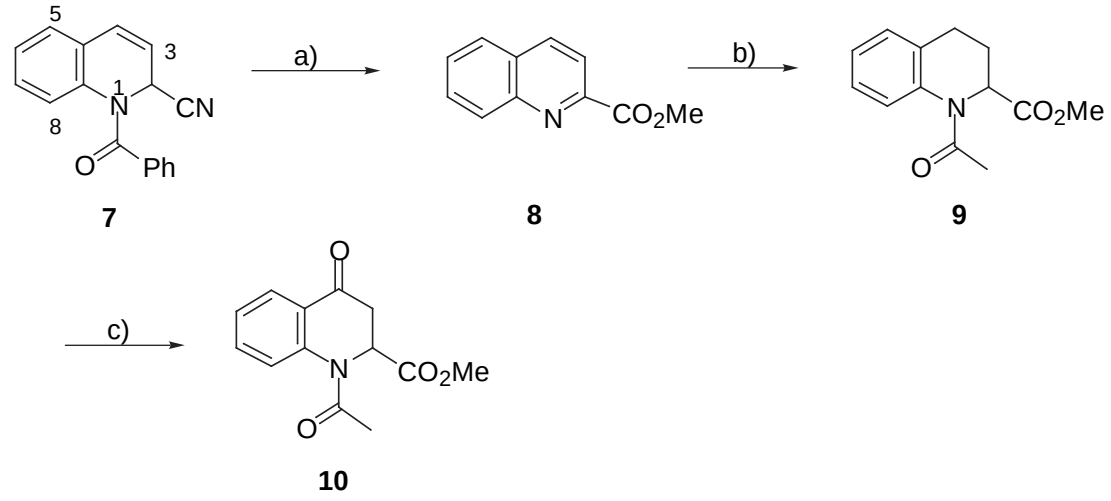
Retrosynthetic analysis showed the sequence outlined in Scheme 1 to be a likely route. This pathway involved introducing the lactone unto a quinoline backbone, and raised the possibility of using readily available and inexpensive starting materials to achieve the target.



Scheme 1

Reissert compound (**7**)[7] was utilized to install a carbomethoxy group at position 2 of the quinoline. Methanolysis of compound (**7**) and concomitant formal loss of benzaldehyde afforded methyl quinaldate (**8**) (Scheme 2). Acetylation at position 3 would be an ideal way to introduce the alcohol functionality necessary for lactone formation. The electronic nature of the quinoline system, however, does not allow this, making modification of the heterocyclic ring necessary. Using hydrogen and 10% palladium on carbon as catalyst, this ring was selectively reduced to produce the corresponding 1,2,3,4-tetrahydroquinoline which was acetylated without further purification to give **9**.

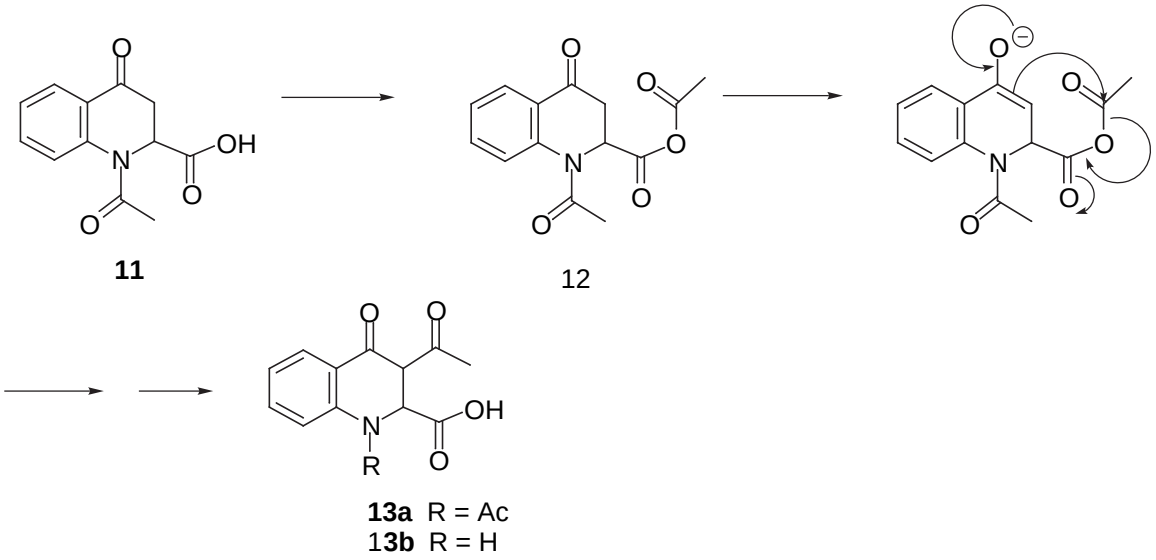
Subsequent benzylic oxidation of compound (**9**) using *tert*-butylhydroperoxide and chromium hexacarbonyl,[8] gave a mixture of starting material (30%) and ketone (**10**) (60%). Introduction of a carbonyl group at position 4 was seen as advantageous here since it should increase the susceptibility of neighbouring position 3 to acetylation.



Scheme 2 Reagents: a) MeOH, HCl, rt, 12 h, (53%); b) i) H_2, Pd-C, MeOH, rt, 55 h; ii) Ac_2O, 100°C, 3 h, 82%, 2 steps); c) $Cr(CO)_6$, *t*-BuOOH, MeCN, reflux, 40 h (60%).

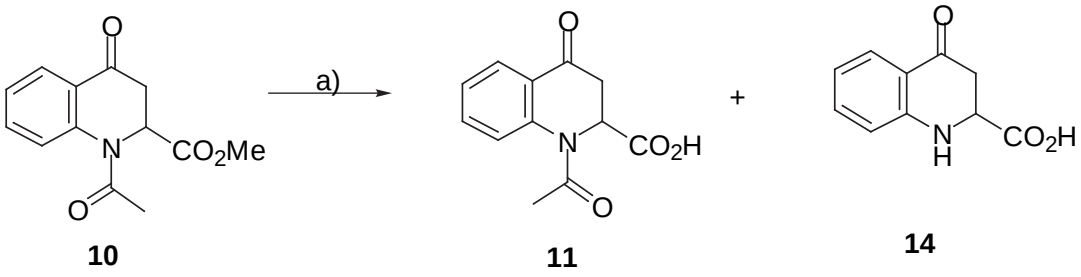
The ^{1}H-NMR spectrum of compound (**10**) proved different from that previously reported.[9] The C-2 methine proton resonated as a broad singlet at δ 6.00 while the C-3 methylene protons resonated as double doublets at δ 3.03 (J = 18.3 Hz, 6.6 Hz) and δ 3.32 (J = 18.3 Hz, 1.9 Hz). Surprisingly, attempts to acetylate position 3 of compound (**10**) using acetic anhydride and triethylamine were largely unsuccessful.

It was postulated that intramolecular acylation of the corresponding carboxylic acid to produce compound (**13a**) (Scheme 3), should proceed more smoothly.



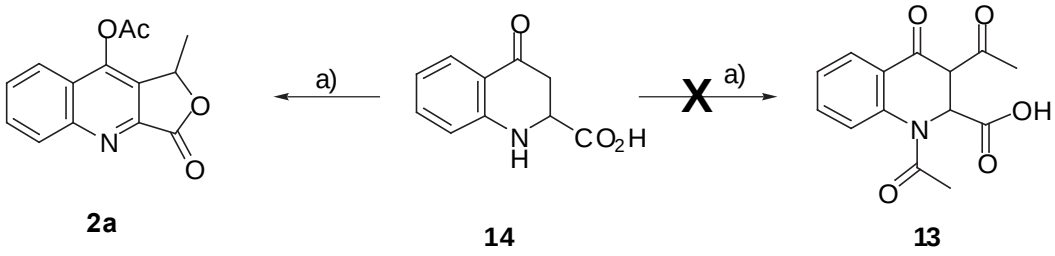
Scheme 3

Hydrolysis of the ester group of compound (**10**) was therefore attempted using K_2CO_3 in refluxing methanol. After two hours, the required carboxylic acid (**11**) was present only as the minor product. The major product was identified as dihydrokynurenic acid (**14**).[9] In fact, compound (**11**) was always the minor product even when the reaction time was as short as 30 minutes, and for reaction times greater than 3 hours only compound (**14**) was obtained.



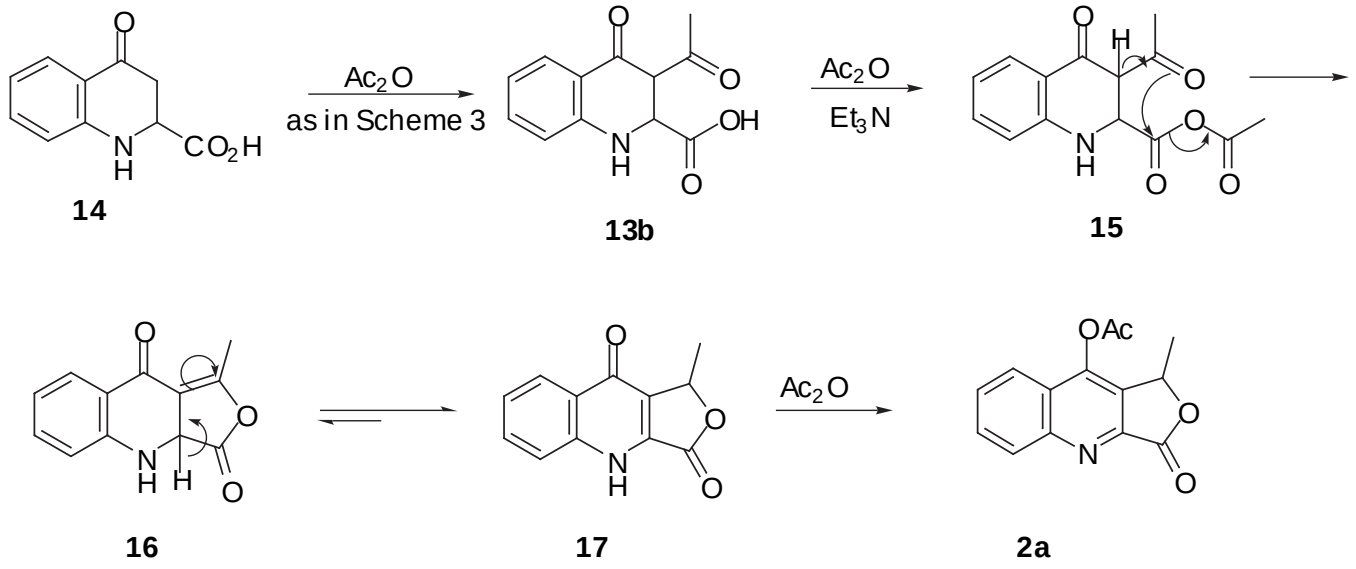
Scheme 4 Reagents: a) K_2CO_3, MeOH, reflux; 2h - **11** (8%), **14** (73%); 4 h - **11** (0%),**14** (80%).

We proceeded with the acylation of dihydrokynurenic acid (**14**) with a view to obtaining both *N* and *C* acetylation products (Scheme 5). Serendipitously, treatment of **14** with acetic anhydride/ triethylamine did not yield compound (**13a**), but produced the eleutherol analogue **2a** in 70% yield.



Scheme 5 Reagents: a) Ac_2O, Et_3N, 90°C, 2 h then rt, 12 h (70%)

A likely mechanism for this unexpected transformation is shown in Scheme 6. Of significance is the isomerization of the C = C double bond of **16** to give the more stable 4-quinolone (**17**).



14 **13b** **15**

16 **17** **2a**

Scheme 6

Compound (**2a**) has thus been synthesized in five steps and 13% overall yield starting with readily available starting material. In preparing other like compounds for structure-activity relationship studies we will also assess the generality of the above sequence.

EXPERIMENTAL

General

All melting points are uncorrected. IR spectra were obtained on a Perkin Elmer 735B model or a Perkin Elmer 1600 FT-IR spectrometer and are for KBr discs. Unless otherwise stated, NMR spectra were run on a Bruker 200 MHz or 500 MHz spectrometer and were determined in $CDCl_3$ solution. Resonances are reported in δ units downfield from TMS; *J* values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK. All chromatography was carried out using silica as support.

Methyl quinaldate (8)

Reissert compound (**7**)[7] (10.0 g, 38.4 mmol) was added to dry MeOH (150 mL) in a 250 mL three necked flask. Dry HCl gas was bubbled into the suspension with constant stirring for 6 h. During this time all the solid dissolved and the solution became quite warm. The solution was allowed to cool to rt then the solvent was removed *in vacuo*. The residue was neutralized with saturated aqueous $NaHCO_3$ solution. The resulting greenish yellow suspension was extracted with Et_2O (3 x 30 mL). The combined extracts were washed with water (3 x 10 mL) then dried over sodium sulfate. The crude product was purified by

column chromatography (hexane: EtOAc – 3:1) to give a brown solid. Recrystallization from MeOH gave a white crystalline solid (3.8 g, 53%): mp 79-80°C (MeOH) (lit.,[10] mp 79°C); IR ν_{max}/ cm^{-1} 3065, 2925, 1717; δ_H 3.92 (3H, s, $-OCH_3$), 7.45 (1H, t, *J* 8.5, H-6), 7.61 (1H, t, *J* 8.5, H-7), 7.66 (1H, d, *J* 8.5, H-5), 7.99 (1H, d, *J* 8.5, H-3), 8.09 (1H, d, *J* 8.5, H-4), 8.15 (1H, d, *J* 8.5, H-8); δ_C 53.0, 120.9, 127.4, 128.5, 129.2, 130.2, 130.5, 137.2, 147.3, 147.7, 165.7.

Methyl 1-acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (9)

Methyl quinaldate (**8**) (2.50 g, 13.3 mmol) was dissolved in MeOH (60 mL) and 10% Pd/C (500 mg) was added to the solution. The mixture was hydrogenated using a Parr Hydrogenator at 20 psi for 52 h. The solution was filtered through celite then concentrated *in vacuo*. Without further purification the crude tetrahydroquinoline was dissolved in acetic anhydride (15 mL) and the solution was heated at 90°C for 3 h. The mixture was allowed to cool to rt, neutralized with saturated aqueous $NaHCO_3$ solution then extracted with EtOAc (3 x 20 mL). The combined organic extract was washed with water (3 x 10 mL) then dried over anhydrous sodium sulfate. After removing the solvent the crude product was purified by column chromatography (hexane: EtOAc - 2:1) to give compound **9** (2.55 g, 82%) as a clear oil which solidified on standing: mp102-104°C (MeOH) (lit.,[11] mp 102-103°C); IR ν_{max}/ cm^{-1} 3468, 1748, 1653; δ_H 1.74 (1H, m, H-4_a), 2.24 (3H, s, $-CH_3$), 2.47-2.74 (3H, m, H-$3_{a\ and\ b}$, H-4_b), 3.68 (3H, s, $-OCH_3$), 5.18 (1H, t, *J* 8.5, H-2), 7.15-7.28 (4H, m, H-5,6,7,8); δ_C 22.8, 26.4, 28.8, 52.2, 55.1, 125.1, 125.7, 126.9, 127.4, 170.4, 172.2.

Methyl 1-acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxylate (10)

Methyl 1-acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (**9**) (500 mg, 2.14 mmol), chromium hexacarbonyl (230 mg, 1.0 mmol), which was crushed to a powder, and *tert*-butyl hydroperoxide (70 wt. % in water, 3 mL) was added to a 50 mL round bottomed flask containing acetonitrile (15 mL). The mixture was heated at reflux for 48 h, then allowed to cool to rt, and filtered, and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (hexane: EtOAc - 3:1) to give compound (**10**) as a white crystalline solid (320 mg, 60%): mp120-122°C (MeOH) (lit.,[9] mp 146-7°C); IR ν_{max}/ cm^{-1} 3746, 2958, 1743, 1669; δ_H 2.39 (3H, s, $-CH_3$), 3.03 (1H, dd, *J* 18.3 and 6.6, H-3_a), 3.32 (1H, dd, *J* 18.3 and 1.9, H-3_b), 3.60 (3H, s, $-OCH_3$), 6.00 (1H, bs, H-2), 7.25-7.42 (2H, m, H-5, 6), 7.60 (1H, t, *J* 8.5, H-7), 7.98 (1H, dd, *J* 7.8 and 2.1, H-8); δ_C 22.7, 40.7, 52.9, 54.5, 124.5, 125.5, 125.9, 127.8, 134.6, 142.0, 169.4, 170.1, 191.6. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66%. Found C, 62.93; H, 5.36; N, 5.58%.

4-Oxo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (14)

Methyl 1-acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxylate (**10**) (500 mg, 2.02 mmol) was added to a 50 mL round bottomed flask containing MeOH (15 mL). Potassium carbonate (560 mg, 4.05 mmol) was then added and the mixture heated at reflux for 4 h. The solvent was removed under vacuum then water (5 mL) was added to the residue. Dilute hydrochloric acid was added dropwise until all effervescence had ceased. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic extract was dried over anhydrous sodium sulfate and the solvent removed *in vacuo* leaving a yellow residue. The residue was triturated with CH_2Cl_2 to give **14** as a yellow solid (310 mg, 80%): mp 180-183°C (lit.,[9] mp 183-184°C); IR ν_{max}/ cm^{-1} 3363, 1728, 1604; δ_H 2.91 (2H, m, H-$3_{a\ and\ b}$), 4.31 (1H, dd, *J* 7.7 and 6.1, H-2), 6.68 (1H, dt, *J* 1.5 and 8.0, H-6), 6.86 (1H, d, *J* 8.5, H-5), 7.32 (1H, dt, *J* 1.5 and 8.0, H-7), 7.68 (1H, dd, *J* 8.0 and 1.5, H-8); δ_C 40.8, 55.6, 117.5, 118.6, 119.4, 127.8, 136.9, 153.3, 174.7, 194.8.

9-Acetoxy-1-methylfuro[3,4-*b*]quinolin-3(1*H*)-one (2a)

To a solution of 4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**14**) (200 mg, 1.04 mmol) in acetic anhydride (5 mL) was added triethylamine (1 mL). The mixture was heated at 90°C for 2 h, allowed to cool to rt and was stirred for a further 12 h. The mixture was then poured into water (10 mL) and saturated aqueous $NaHCO_3$ added until no further effervescence was observed. EtOAc (3 x 5 mL) was used to extract the mixture and the combined extract was dried over sodium sulfate and the solvent removed *in vacuo*. The crude product was purified by column chromatography (EtOAc: $CHCl_2$ – 1:3) to give **2b** as a white solid (198 mg, 70%); mp 164-166°C (MeOH); ν_{max}/ cm^{-1} 3534, 2930, 1772; δ_H 1.67 (3H, d, J = 6.7 Hz, -CH_3), 2.57 (3H, s, -CH_3), 5.76 (1H, q, *J* 6.7, H-1),7.76 (1H, dt, *J* 1.5 and 8.5, H-7), 7.89 (1H, dt, *J* 1.5 and 8.5, H-6), 8.06 (1H, d, *J* 8.5, H-8), 8.42 (1H, d, *J* 8.5, H-5); δ_C 19.1, 20.7, 75.5, 121.4, 123.3, 129.2, 129.7, 131.2, 131.4, 146.3, 149.4, 151.8, 166.8, 167.3. Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44%. Found C, 65.38; H, 4.40; N, 5.43%.

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