SYNTHESIS OF 1,2,3,4,5,6,7,8-OCTAHYDRO-9-ETHOXY-10-HYDROXY-1-ANTHRACENONE[OEHA]

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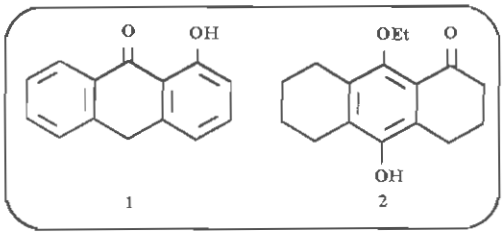
ABSTRACT: *Anthralin and some of its derivatives have implied antipsoriatic effect in clinical and pharmaceutical studies. Anthralin is synthesised by different strategies. In this work we report the synthesis of "OEHA" as a precursor of another biological active compound.*

KEY WORDS: *Anthralin, Antipsoriatic activity, 1-Hydroxy-9-anthrone, Octahydro-9-ethoxy-10-hydroxy-1-anthracenone.*

INTRODUCTION

Anthralin (1,8-dihydroxy-9-anthrone) was used for antipsoriatic threapy in 1916 for the first time [1]. Antipsoriatic activities of some anthrones have been studies by many researchers [2]. It is proved that special arrengments of functional groups are necessary in order to indicate antipsoriatic effect. These arrangments are attained in 1-hydroxy-9-anthrone (**1**). The presence of hydrogen bonding between centeral carbonyl group at C_9 and hydroxyl group at C_1 and methylene at C_{10} are the least requirements. These make the lipophilic and hydrophilic parts in these biological active molecules.

We have synthesised [OEHA] (**2**) as a precursor for preparation of another anthrone derivative, i.e., **1**. Anthrone **1** is also synthesised by direct functional transformations in very good yield [3c]. The work reported here is based on cyclization method.



1 2

EXPERIMENTAL

5,8-Diethoxy-1-tetralone(7)

A solution of 4-(2,5-diethoxyphenyl) butanoic acid (**6**) (0.504 g, 2 mmol) in an excess of polyphosphoric acid (about 20 mL) was prepared in a 50 mL round bottom flask and stirred with a glass rod at 90-95 °C (water bath). Stirring was continued for 15 minutes, giving a light brown-red glass solution. The mixture was poured into a mixture of water and ice (50 mL and 50 g respectively) and then extracted

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with ether (4×20 mL). The combined ether extracts were washed with saturated sodium hydrogen carbonate (5×20 mL) and then washed with ether (3×10 mL), acidified with concentrated hydrochloric acid and cooled to give a yellow oily material, which did not solidify over night. It was extracted with ether (3×20 mL), the extract was washed with water until the washings were neutral, the ether layer was dried with sodium sulphate and evaporated. The residue was a semisolid (0.35 g, %75). The semisolid product was crystallized from a mixture of water-methanol or *n*-heptane (10:1). The yellow needle crystals was obtained, m.p. 77-9 °C. It had $\bar{\nu}_{max}$ (KBr) 3050 (m), 3000-2800 (s), 1680 (s), 1300-1000 (s) cm^{-1}. δ(80 MHz, $CDCl_3$), 1.3(t, 6H), 2(m, 2H), 2.6(t, 2H), 2.8(t, 2H), 4(m, 4H), 6.8(dd, 2H).

4-[4-(3-Carboxypropyl)-2,5-diethoxyphenyl]-4-oxobutanoic acid (8)

A solution of 4-(2,5-diethoxyphenyl) butanoic acid (**6**), (5.04 g, 0.02 mol) in mixture (3:7) of dry nitrobenzene and tetrachlorethane (50 mL) was prepared in a 250 mL three-necked round bottom flask. Aluminium chloride (2.93 g, 0.022 mol) dissolved in the solvent mixture (20 mL) was added to the vigorously magnetically stirred solution over 30 minutes. Powdered succinic anhydride (3 g, 0.03 mol) was added and then a second portion of aluminium chloride (10 g, 0.075 mol) dissolved in the solvent mixture (30 mL) was added to the reaction mixture dropwise at 0-5 °C temperature. The reaction was exothermic. The mixture was then stirred for 12 hours at 0-5 °C temperature. The reaction mixture was poured slowly with stirring into a mixture of aqueous 20% hydrochloric acid (350 mL) and ice (about 250 g). The reaction mixture was extracted with ether (1×150 mL and 3×30 mL). The combined ether extracts were then washed with water (3×20 mL), and extracted with saturated sodium hydrogen carbonate (1×80 mL and 5×30 mL). The bicarbonate extract was washed with ether (3×20 mL) and finally acidified with concentrated hydrochloric acid at ice bath temperature. The red-brown solid product was crystallized from a mixture of methanol-water (3:7) to give colourless long flat needle crystals (4.22 g, %60), m.p. 154-6 °C. It had $\bar{\nu}_{max}$ (KBr) 3200-2600 (s, broad), 1715 (s), 1660 (s), 1300-1000 (s) cm^{-1}. δ(80 MHz, DMSO), 1.3 (t, 6H), 1.8(m, 2H), 2.2(t, 2H), 2.6(m, 4H), 3.3(m, 4H), 4.2(m, 4H), 6.9(s, 1H), 7.1(s, 1H).

2,5-Diethoxyphenyl-1,4-benzenedibutanoic acid (9)

A mixture of 4-[4-(3-carboxypropyl)- 2,5- diethoxyphenyl]-4-oxobutanoic acid (**8**) (3.52 g, 0.01 mol), %85 hydrazine hydrate (5.5 mL), diethylene glycol (100 mL) and solid potassium hydroxide (6.72 g, 0.12 mol) was prepared in a dry 250 mL two-necked flask at 60 °C (water bath) until all the potassium hydroxide had dissolved. The reaction mixture then heated with a free flame at reflux (140 °C) for two hours. The condenser was then set for distillation and heating was continued at about 185 °C until about 10 mL of solvent had distilled. The apparatus was reset for reflux, heated with a free flame at reflux temperature (190 °C) for four hours and then cooled and poured into %20 hydrochloric acid (200 mL), giving a green solid; m.p. 155-65 °C. The solid product was crystallized from chloroform or mixture of water-methanol to give light white needle crystals (3.04 g, %90), m.p. 172-3 °C. It had $\bar{\nu}_{max}$ (KBr) 3150-2500 (s, broad), 1710 (s), 1300-1000 (s) cm^{-1}. δ(80 MHz, DMSO), 1.3(t, 6H), 2.6(m, 4H), 2.2(t, 2H), 1.7(m, 2H), 3.5(m, 2H), 3.9 (q, 4H), 6.7(s, 2H).

4-(5-Ethoxy-8-hydroxy-1-tetralon-7-yl) butanoic acid (10)

A solution of 2,5-diethoxyphenyl-1,4-benzenedibutanoic acid (**9**) (1 g, 3 mmol) in an excess of polyphosphoric acid (about 20 mL) was prepared in a 50 mL round bottom flask and stirred with a glass rod at 90-95 °C (water bath). Stirring was continued for 15 minutes, giving a light brown-red glass solution. The mixture was poured into a mixture of water and ice (50 mL and 50 g respectively) and then extracted with ether (4×20 mL). The combined ether extracts were washed with saturated sodium hydrogen carbonate (5×20 mL) and then washed with ether (3×10 mL), acidified with concentrated hydrochloric acid and cooled to give a yellow oily material, which did not solidify over night. It was extracted with ether (3×20 mL), the extract was washed with water until the washings were neutral. The ether layer was dried

with sodium sulphate and evaporated. The residue was a semisolid (0.7 g, %75). The semisolid product was crystallized from a mixture of water-methanol or *n*-heptane (10:1). The yellow needle crystals was obtained, m.p. 124-6 °C. It had $\bar{\nu}_{max}$ (KBr) 3600-2400 (s, broad), 1710 (s), 1640 (s), 1590 (s), 1300-1000 (s) cm^{-1}. δ(80 MHz, $CDCl_3$), 1.2(t, 3H), 1.8-3(m, 12H), 3.9 (q, 2H), 6.8(s, 1H), 10(s, 1H), 12.2(s, 1H).

4-(1,8 Dihydroxy-5-ethoxytetralin-7-yl) butanoic acid (11, R, S)

A solution of 4-(5-ethoxy-8-hydroxy-1-tetralone-7-yl) (**10**) (0.85 g, 25 mmol) in water (15 mL) was prepared in a 50 mL round bottomed flask and then sodium borohydride (0.38 g, 10 mmol) was added. The solution became colourless in one minute. Stirring was continued for four and a half hours. The reaction mixture was then poured into 20% hydrochloric acid (20 mL) and extracted with ether (3×20 mL). The combined ether extracts were washed with water (3×15 mL) and dried with sodium sulphate. The ether was evaporated to give a liquid, (0.65 g, %75). It had $\bar{\nu}_{max}$ (film) 3600-2400 (s, broad), 3300 (s), 2960 (s), 1715 (s), 1300-1000 (s) cm^{-1} δ(80 MHz, $CDCl_3$), 1.2 (t, 3H), 1.8(m, 4H), 2.8(m, 4H), 2.6(m, 4H), 3.8(q, 2H), 6.5(dd, 1H), 6.7(s, 1H), 8.3(s, 1H).

4-(1-hydroxy-4-ethoxytetralin-2-yl) butanoic acid (13)

A mixture of 4-(5-ethoxy)-8-hydroxy-1-tetralon-7-yl butanoic acid (**10**) (3.2 g, 0.01 mol), %85 hydrazine hydrate (2 mL, 0.1 mol), diethylene glycol (100 mL) and solid potassium hydroxide (8 g, 0.12 mol) was prepared in a dry 250 mL two-necked flask equipped with reflux condenser and thermometer and stirred magnetically at 60 °C (water bath) until all the potassium hydroxide had dissolved. The reaction mixture then heated with a free flame at reflux (140 °C) for two hours. The condenser was then set for distillation and heating was continued at about 185 °C until about 10 mL of solvent had distilled. The apparatus was reset for reflux, heated with a free flame at reflux temperature (190 °C) for four hours, and then cooled and poured into %20 hydrochloric acid (200 mL), giving a green solid; m.p. 155-65 °C. The solid product was crystallized from chloroform or mixture of water-ethanol to give light pink long flat crystals (2.5 g, %90), m.p. 103.5-105.5 °C. It had $\bar{\nu}_{max}$ (KBr) 3380 (s), 3300-2400 (s, broad), 1715 (s), 1300-1000 (s) cm^{-1}. δ(80 MHz, $CDCl_3$), 1.3(t, 3H), 1.8(m, 6H), 2.7(m, 8H), (q, 2H), 6.5(s, 1H), 8(s, 1H).

1,2,3,4,5,6,7,8-octahydro-9-ethoxy-10-hydroxy-1-antracenone (2)

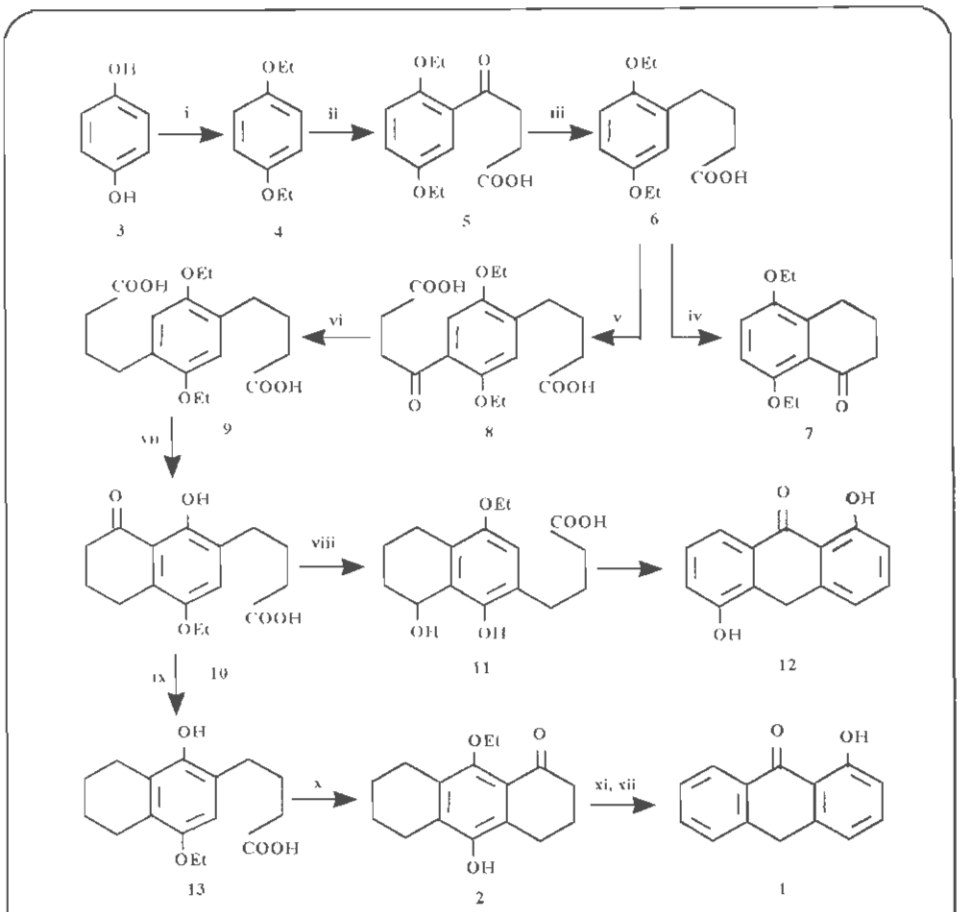
A solution of 4-(1-hydroxy-4-ethoxy tetralin-2-yl) butanoic acid (**13**) (0.306 g, 1 mmol) in an excess of polyphosphoric acid (about 20 mL) was prepared in a 50 mL round bottom flask and stirred with a glass rod at 90-95 °C (water bath). Stirring was continued for 15 minutes, giving a light brown-red glass solution. The mixture was poured into a mixture of water and ice (50 mL and 50 g respectively) and then extracted with ether (4×20 mL). The combined ether extracts were washed with saturated sodium hydrogen carbonate (5×20 mL) and then washed with ether (3×10 mL), acidified with concentrated hydrochloric acid and cooled to give a yellow oily material which did not solidify over night. It was extracted with ether (3×20 mL), the extract was washed with water until the washings were neutral, the ether layer was dried with sodium sulphate and evaporated. The residue was a semisolid (0.28 g, %50). The semisolid product was crystallized from a mixture of water-methanol or *n*-heptane (10:1). The yellow needle crystals was obtained. It had $\bar{\nu}_{max}$ (KBr) 3280 (m, broad), 3000-2800 (s), 1660 (s), 1300-1000 (s) cm^{-1}. δ(80 MHz, $CDCl_3$), 1.35(t, 3H), 1.6-2.3(m, 8H), 2.4-3(m, 6H), 3.8(q, 2H), 4.6(s, 1H).

RESULTS AND DISCUSSION

Anthraquinones (AQs) are the precursors which after one step reduction will be converted to biological active compounds [4]. Many researchers have been able to synthesis varieties of AQs [5-10]. The strategy used for synthesis of **1** is shown in scheme 1.

This work demostrates that using the conventional methods and cheap starting materials we can reach the important products.

Furthermore, during the first cyclization on diacid **9**, deethylation process was taken place on one of the ethoxy group simultaniously. In spite of geometrical and electronic similarities, corresponding deethyla-



(i) K_2CO_3/C_2H_5Br, (ii) $PhNO_2/Cl_2CHCHCl_2$/ Succinic Anhydride/$AlCl_3$, (iii) N_2H_4/KOH/DEG, (iv) PPA/90 °C/90 min., (v) $PhNO_2/Cl_2CHCHCl_2$/Succinic Anhydride/$AlCl_3$, (vi) N_2H_4/KOH, (vii) PPA/90 °C/12 min., (viii) $NaBH_4/H_2O$, (ix) KOH/N_2H_4 , (x) PPA/90 °C/12 min., (xi, xii) HBr 48%; KOH/O_2/H_2O.

Scheme 1

tion **6** and **7** was not occured. Finding the reasone(s) of this difference need further investigations.

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