

SYNTHESIS OF 1,5- DIHYDROXY -9,10- ANTHRA- QUINONE

Shockravi, Abbas *

*Department of Chemistry, Teacher Training University,
Postcode 15614, Tehran, Iran.*

Bruce, J.M.

Department of Chemistry, Manchester University, M13 9PL England

(Received: May, 8th 1994 , Accepted: Feb. 20th 1995)

ABSTRACT : *The synthesis of 1,5- dihydroxy-9,10- anthraquinone (17); (1,5- DHA) was accomplished during, attempts towards the synthesis one of its derivatives called anthralin (1,8- dihydroxy- 9- anthrone) which is known as an antipsoriasis drug since 1916 [1]. This work is a new reigiospecilic preparation of 1,5- DHA based on Friedel- Crafts reaction starting from 1,4- dimethoxybenzene. This synthetic route, in addition to being successful, produced interesting by-products, in terms of biological activities. The advantage of this work over other attempts is the use of inexpensive materials and mild reaction conditions.*

KEY WORDS : *Anthraquinone, 1,5- DHA, Anthralin, Antipsoriasis, Friedel crafts cyclisation, Butanoic-acid.*

INTRODUCTION :

The synthesis of 1,5- dihydroxy-9,10- anthraquinone, (17) has been approached via different strategies. Diels-Alder strategy has been employed by different workers [2-5] for this purpose. The disadvantage of this approach is often the cost of the starting material. Anionic condensations are also another approach of interest [6].

RESULTS AND DISCUSSION :

Our synthetic strategy involves the classical Friedel-Crafts chemistry. The first step is the preparation of 4- (2,5- dimethoxyphenyl) 4- oxobutanoic acid (3) from 1,4- dimethoxybenzene (1) a known compound, synthesised by different workers [7].

The carbonyl group of the acid was reduced using triethylsilane (TES) in trifluoroacetic acid

* To whom correspondence should be addressed

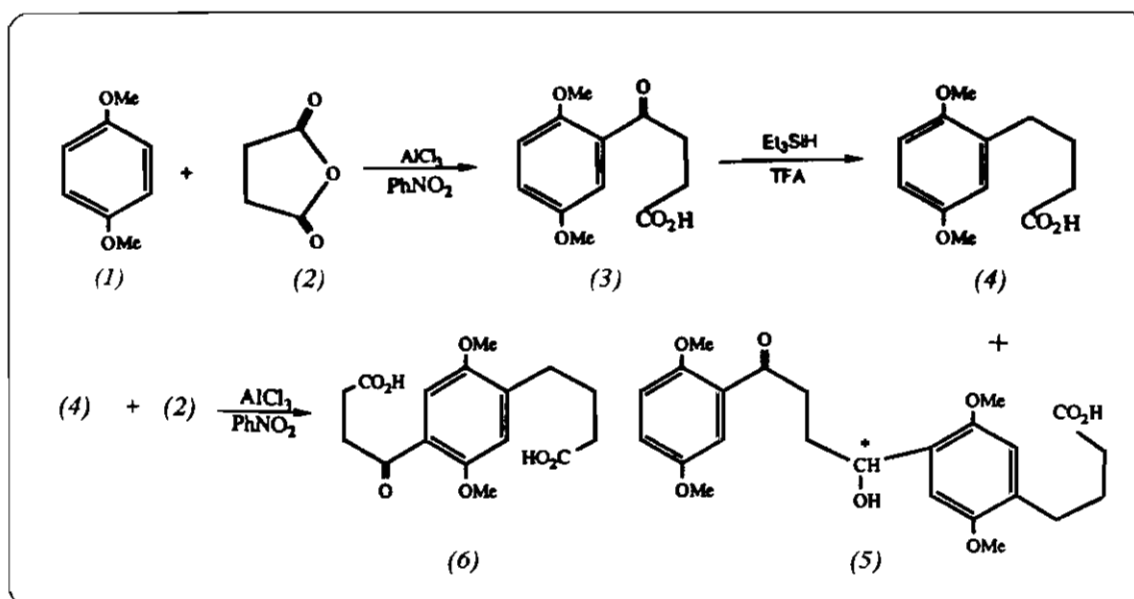
(TFA) [8-17]. The result was as 4- (2,5-dimethoxyphenyl) butanoic acid (4) in good yield. A colorless crystalline by-product (5) was obtained in about 10% yield which was identified and characterized.

The synthesis of 4- [4-(3- carboxypropyl)-2,5-dimethoxyphenyl] 4- oxobutanoic acid (6) from above acid (4) also involves a Friedel Crafts reaction. Because of electronic effects, the para-position in acid (4) is highly activated and the only isomer isolated was para- isomer in good yield. The reduction of ketonic carbonyl group in the keto-acid (6) under the same reduction conditions (TFA/TES) lead us to the preparation of 4- (3- carboxypropyl -2,5-dimethoxyphenyl) butanoic acid (7) in high yield.

The Friedel-Crafts mechanism plays the main role in the cyclisation of the diacid (7) leading to the diketone (13). Although the ultimate target molecule was the tricyclic diketone (13), because of the deactivating effect of the carbonyl group in the tetralone (12), the second cyclisation step was not expected to take place under mild conditions. Although there are several low yield reports for similar cyclisations under deactivating effects [18,19], we applied several conditions for the cyclization process; e.g. acetyl chloride in acetic media, polyphosphoric acid, phosphonium

anhydride and oxalyl chloride in the presence of a traces of dimethylformamide. Under last conditions, 5,8- dimethoxytetralone (11) was obtained as a by-product which was isolated by column chromatography. Formation of such a compound could be due to cleavage (8) of one butanoic acid chain in the diacid (7) and cyclisation of the remaining one. However all above conditions lead to tetralone (12) without any trace of diketone (13) or the starting material. This meant that intramolecular acylation of ketoacid (12) is highly retarded by the deactivating ketonic carbonyl group. These unpromising results convinced us to reduce the deactivating effect of the tetralone carbonyl group in (12) via protection. The best conditions for such purpose was using 1,2- ethanedithiol to convert the tetralone (12) to 1,3- dithiolane derivative (14). Cyclisation of this acid was readily achieved under Friedel-Crafts type conditions using a ratio of 1:10:10 acid (14): trifluoroacetic acid: trifluoroacetic anhydride in chloroform at room temperature. These conditions lead to preparation of ethylene dithioacetal (15) in good yield.

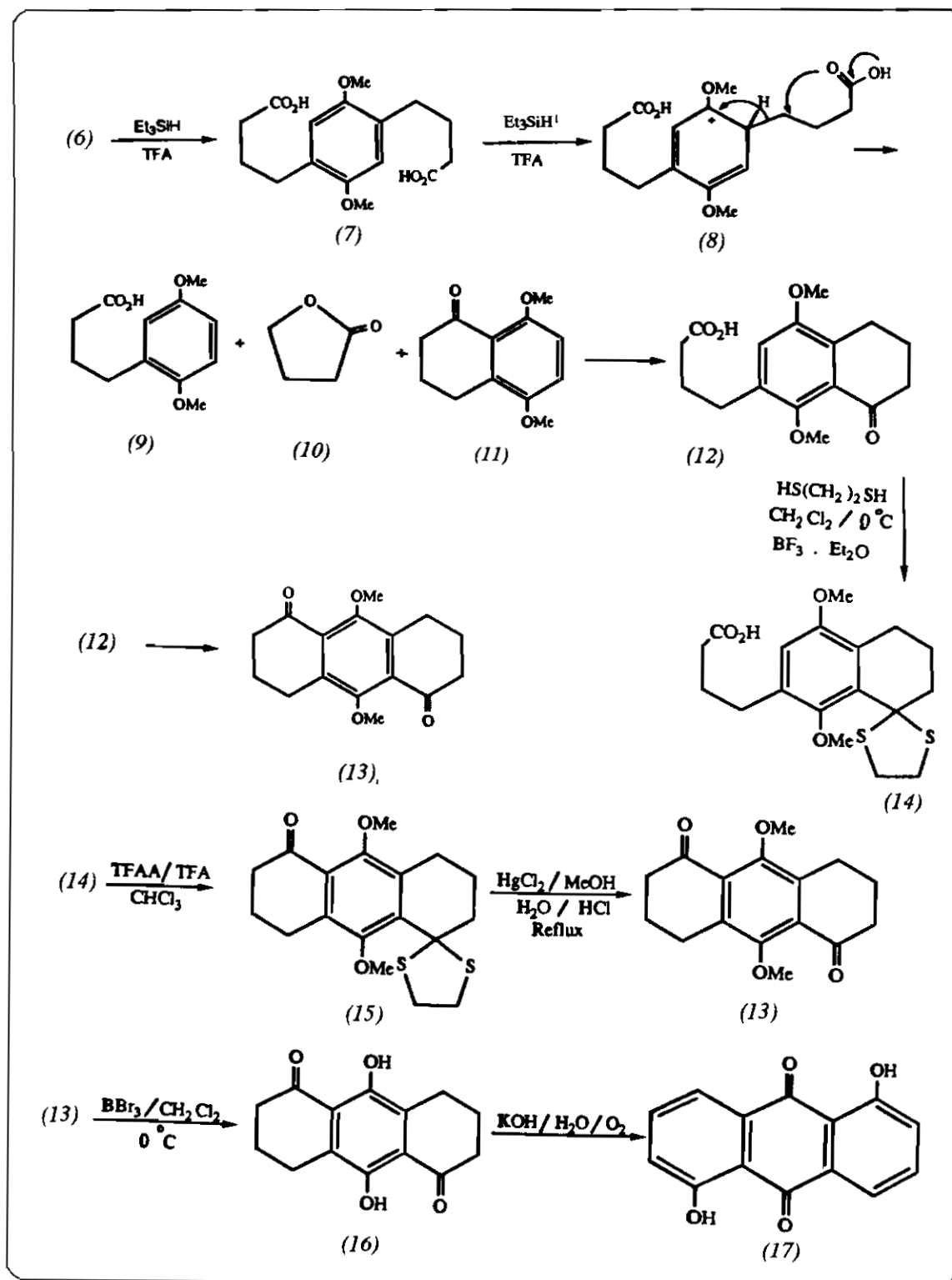
The best conditions for deprotection purpose was: mercury (II) chloride in aqueous methanolic hydrochloric acid under reflux, which resulted in the formation of 1,2,3,4,5,6,7, 8- octahydro-



9,10- dimethoxy-1,5- anthracendione (13) in 90% yield. Boron tribromide in dichloromethane was used at 0°C in which demethylation occurred smoothly leading to 1,2,3,4,5,6,7, 8- octahydro-

9,10- dihydroxy-1,5- anthracenedione (16).

1,5 Dihydroxy-9,10- anthraquinone (17) was obtained in good yield via aerial oxidation of diketone- dihydroxy (16) under-basic conditions.



EXPERIMENTAL :**4- (2,5- Dimethoxyphenyl)-4- oxobutanoic acid (3)**

A solution of 1,4- dimethoxybenzene (2.76g, 0.02mol) in dry nitrobenzene (60mL) was prepared in a dry 250mL three-necked round bottom flask equipped with a pressure equalising separatory funnel, condenser and drying tube. Succinic anhydride (2.5g, 0.025mole) was added as a powder, and the mixture was stirred magnetically at room temperature. A solution of aluminium chloride (6.67g, 0.05mol) in dry nitrobenzene (15mL) was then added over 45 minutes at room temperature. Stirring was continued for six hours. The reaction mixture was added with stirring to a mixture of 20% hydrochloric acid (300mL) and ice (about 200g). The mixture was extracted with ether (1×100mL, then 3×10mL). The combined extracts were then washed with water (3×30mL) and extracted with saturated sodium hydrogen carbonate (1×100mL +5×20mL). The bicarbonate extract was washed with ether (3×20mL), acidified with concentrated hydrochloric acid and cooled to give small grey needles which were filtered off and washed with cold water, and dried. m.p. 92-99°C, as crude. Crystallisation from water yielded colourless long prismatic needles (4.4g, 93%), m.p. 100-102°C (lit 7, m.p. 101-102°C). (Found: C, 60.2; H, 5.8. Calc. for C₁₂H₁₄O₅; C, 60.5, H, 5.9%).

ν_{\max} (film) 3200-2600s and broad; 1715s, 1673s, 1611s, 1496s, 1466m, 1280s, 1223s cm⁻¹.

δ (300MHz, CDCl₃) 2.73 (t, J=6.5, 2H), 3.33(t, J=6.5, 2H), 3.78(s, OMe), 3.89(s, OMe), 6.9(t, J=9.5, 1H), 7.29(dd, J₁=9.5, J₂= 3, 1H), 7.32(d, J=3, 1H).

m/z (EI) 239, 238 (2.2, 19.2, M⁺), 224 (M-Me)⁺, 193 [0.7, (M-COOH)⁺], 165, 166 (100.0, 9.5, (MeO)₂(C₆H₃CO)⁺), 151 (10.1, MeO(OH) C₆H₃CO⁺).

m/z (CI/NH₃) 257, 256 [0.7, 5.2 (M + NH₄)⁺], 243, 242 [42, 26.8 [(M-Me) + NH₄]⁺], 239, 238 [100, 9.5 (M+H)⁺].

4-(2,5-Dimethoxyphenyl) butanoic acid (4)

A solution of 4- (2,5- dimethoxyphenyl)-4-oxobutanoic acid (2.38g, 0.01mol) in trifluoro-

acetic acid (20mL) was prepared in a dry two-necked round bottom flask equipped with a condenser, pressure equalising separating funnel and drying tube. Triethylsilane (2.9g, 4mL, 0.025mol) was added to the vigorously magnetically stirred solution, and stirring was continued for six hours. A relatively colourless, cloudy solution was obtained when the reaction was complete. The solvent was evaporated (rotavap, water-pump) and traces of trifluoroacetic acid, triethylsilane and triethylsilanol were then removed at oil-pump pressure. The product was crystallised from petroleum (b.p. 100/120°C) giving colourless long needles (2.04g, 92%), m.p. 66-67°C (lit. 7, m.p. 68-69°C). (Found C, 64.4; H, 7.3; Calc. for C₁₂H₁₆O₄; C, 64.28; H, 7.14%). ν_{\max} (film 3200 -2600s, broad, 1707s, 1591s, 1224s cm⁻¹).

δ (300MHz, CDCl₃) (quintet, J= 7.5, 2H), 2.34(t, J= 7.5, 2H), 2.61 (t, J= 7.5, 2H), 3.74 (2×5 in expansion, 2×s, OMe) 6.7 (quintet, 3H).

m/z(EI) 226, 225, 224, (2, 13.5, 100.0. M⁺), 207 {[8.2, [(C₆H₅(CH₂)₃CO)⁺]], 155, 164 {4.7, 26.2 [(MeO)₂C₆H₃(CH₂)₂]⁺}, 152, 151 {5.2, 34.1 [(MeO)₂C₆H₃CH₂]⁺].

m/z (CI/NH₃) 244, 243, [2.1, 13.5, 100.0 (M+NH₄)⁺], 226, 225 [47.6, 6.8, (M+H)⁺], 224 (63.5, M⁺), 209, 208, 207, ν_{\max} (6.5, 4.4, 31.9).

4- {2,5- Dimethoxy [4- (2,5- dimethoxyphenyl)- 4- oxo- 1- butanolyl] phenyl} butanoic acid (5)

This compound was obtained as a by-product during the reduction of the keto acid (3) from which the crude reduction product was soluble in methanol and this by-product did not dissolve. It was filtered and washed with methanol. It formed colourless flat needles, in about 10% yield, m.p. 132-135°C.

ν_{\max} (film) 3200-2600s, broad, 2937s, 2833s, 1706s, 1501s, 1215s cm⁻¹.

δ (300MHz, CDCl₃) 2.0-2.9 (complex 2×CH₂, at δ 2.15 and δ 2.65 changed to simpler coupling pattern by irradiation at δ 4.71); 3.75-3.81 (4×s, 4×OMe), 4.71(dd, J₁= 11, J₂= 3.4, 1H; changed to doublet, J₁= 11, by irradiation at 2.15, and

collapsed to a doublet ($J_2 = 3.4$) by irradiation at $\delta(2.65)$, 6.61 (s, 1H), 6.68 (dd, $J_1 = 8.5$, $J_2 = 2.8$, 1H), 6.71 (s, 1H), 6.91 (d, $J = 2.8$, 1H; collapsed to a singlet by irradiation at $\delta 6.66$).

m/z (EI) 448, 447, 446 (4.6, 24.3, 100.0, M^+), 438, 432 [1.0, 3.8, (M-Me)⁺], 374, 373, (7.9, 32.5), 429 [15.6, (M-OH)⁺], 165 [3.8 (MeO)₂C₆H₃CO]⁺, 151 [47.6, [MeO(OH)C₆H₃CO]⁺].

m/z (CI) 466, 465, 464 [5, 22.8, 87.2 (M+NH₄)⁺], 448, 447 [4.9, 21.7 (M+H)⁺].

(Found m/z : M^+ , 446.1929, C₂₄H₃₀O₈ requires, 446.1941).

4- [4- (3- Carboxypropyl)-2,5- dimethoxyphenyl] 4- oxobutanoic acid (6)

A solution of 4- (2,5- dimethoxyphenyl) butanoic acid (4), (8.96g, 0.04mol) in dry nitrobenzene (50mL) was prepared in a 250mL three-necked round bottom flask equipped with a condenser, drying tube and pressure equalising separatory funnel and thermometer. Aluminium chloride (6.7g, 0.05mol) dissolved in nitrobenzene (40mL) was added to the vigorously magnetically stirred solution over 20 minutes. Powdered succinic anhydride (5.0g, 0.05mol) was added and then a second portion of aluminium chloride (17.4g, 0.13mol) dissolved in dry nitrobenzene (90mL) was added to the reaction mixture dropwise at room temperature. The reaction was exothermic. The mixture was then stirred for four hours at room temperature. The reaction mixture was poured slowly with stirring into a mixture of aqueous 20% hydrochloric acid (350mL) and ice (about 250g). The reaction mixture was extracted with ether (1×150mL and 3×15mL). The combined ether extracts were then washed with water (3×20mL), and extracted with saturated sodium hydrogen carbonate (1×80mL and 5×20mL). The bicarbonate extract was washed with ether (3×15mL) and finally acidified with concentrated hydrochloric acid at ice-bath temperature. The red-brown solid product was crystallised from water to give colourless long flat needles which were washed with cold chloroform (11.2g, 87%) m.p. 172-175°C (Found: C, 58.9; H, 6.2. C₁₆H₂₀O₇ requires

C, 59.26; H, 6.17%).

ν_{max} (film) 3400-2600m and broad, 2939m, 2080w, 1736s, 1667m, 1610m, 1499s, 1214m, cm^{-1} .

δ (300MHz, CD₃OD) 1.82 (quintet, $J = 7.2$, CH₂), 2.25 (t, $J = 7.2$, CH₂), 2.59(m, 2×CH₂), 3.3 (CH₂, partly obscured by CD₃OH), 3.7 (s, OMe), 3.8(s, OMe), 6.7(s, 1H, 5-H), 7.2(s, 1H, 3-H). m/z (EI) 325, 324, (4.0, 22.1, M^+), 306 [1.0, (M-H₂O)⁺], 307 [0.4, (M-OH)⁺], 252, 251 {8.5, 60.4 [(MeO)₂(C₄H₇O)C₆H₂CO]⁺}. m/z (CI/NH₃) 326, 325 (4.6, 25.5 (M+H)⁺), 309 [2.1, (M-Me)⁺], 307 [1.2, (M-OH)⁺], 306 [0.3, (M-H₂O)⁺], 279 [3.7, (M-CO₂H)⁺], 252, 251 {2.0, 6.4 [(MeO)₂(C₄H₇O) C₆H₂CO]⁺}. m/z (CI/NH₃) 326, 325 (4.6, 25.5 (M+H)⁺), 309 [2.1, (M-Me)⁺], 307 [1.2, (M-OH)⁺], 306 [0.3, (M-H₂O)⁺], 279 [3.7, (M-CO₂H)⁺], 252, 251 {2.0, 6.4 [(MeO)₂(C₄H₇O) C₆H₂CO]⁺}. m/z (CI/NH₃) 330, 329, 328 [3, 17.7, 100.0 (M+NH₄)⁺], 312, 311 [2.6, 13.6, (M+H)⁺], 310 (54.6, M^+), 294, 293 [5.8, 20.4 (M-OH)⁺], 292 [4.9, (M-H₂O)⁺].

m/z (CI/NH₃) 326, 325 (4.6, 25.5 (M+H)⁺), 309 [2.1, (M-Me)⁺], 307 [1.2, (M-OH)⁺], 306 [0.3, (M-H₂O)⁺], 279 [3.7, (M-CO₂H)⁺], 252, 251 {2.0, 6.4 [(MeO)₂(C₄H₇O) C₆H₂CO]⁺}. m/z (CI/NH₃) 330, 329, 328 [3, 17.7, 100.0 (M+NH₄)⁺], 312, 311 [2.6, 13.6, (M+H)⁺], 310 (54.6, M^+), 294, 293 [5.8, 20.4 (M-OH)⁺], 292 [4.9, (M-H₂O)⁺].

2,5- Dimethoxyphenyl-1,4- benzenedi-butanoic acid (7)

A solution of keto-diacid (6) (0.65g, 2mmol) in trifluoroacetic acid (10mL) was prepared in a dry 100mL two-necked round bottom flask equipped with a pressure equalising separating funnel. Triethylsilane (0.8mL, 0.583g, 5mmol) was added to the vigorously magnetically stirred solution over 15 minutes at room temperature, and stirring was then continued for four hours.

The solvent was evaporated (rotavap, water-pump) and the product was obtained as colourless crystalline beads (0.55g, 88.7%) which were washed with cold chloroform, m.p. 181-182°C (Found: C, 62.1; H, 7.2, C₁₆H₂₂O₆ requires C, 61.93; H, 7.02%).

ν_{max} (film) 3500-2600m and broad, 2935m, 2858m, 2833m, 1735s, 1211s cm^{-1} .

δ (300MHz, CDCl₃) 1.84 (quintet, $J = 7.5$, 2×CH₂), 2.28(t, $J = 7.5$, 2×CH₂), 2.55 (t, $J = 7.5$, 2×CH₂), 3.08(s, 2×OMe), 6.6(s, 2H).

m/z (EI) 311, 310 (12.4, 87.8, M^+) 237, 238 {6.6, 29.6 [M-(CH₂)₂CO₂H]⁺}. m/z (CI/NH₃) 330, 329, 328 [3, 17.7, 100.0 (M+NH₄)⁺], 312, 311 [2.6, 13.6, (M+H)⁺], 310 (54.6, M^+), 294, 293 [5.8, 20.4 (M-OH)⁺], 292 [4.9, (M-H₂O)⁺].

m/z (CI/NH₃) 330, 329, 328 [3, 17.7, 100.0 (M+NH₄)⁺], 312, 311 [2.6, 13.6, (M+H)⁺], 310 (54.6, M^+), 294, 293 [5.8, 20.4 (M-OH)⁺], 292 [4.9, (M-H₂O)⁺].

4-(5,8-Dimethoxy-1-tetralone-7-yl) butanoic acid (12)

A solution of the diacid(7)(7.00g, 0.0226mol)

in dry dichloromethane (100mL) was prepared in a dry 250mL two-necked round bottom flask equipped with a drying tube. Fresh oxalyl chloride (7.17g, 4.81mL, 0.057mol) was added dropwise. N,N-Dimethylformamide (8 drops) was then added to the solution; vigorous bubbling occurred. The mixture was stirred magnetically for 30 minutes. Tin(IV) chloride (8.47g, 3.81mL, 0.034mol) was added dropwise, and the colour of the reaction mixture turned to deep red within one minute. Stirring was continued for 45 minutes. 15% Hydrochloric acid (100mL) was then added to the reaction mixture, slowly and with vigorous stirring.

A pale yellow two-phase solution was formed. It was extracted with ether (1×100mL + 3×10mL). The combined ether extracts were then washed with water until the aqueous wash was neutral (pH paper 1-14 was used as the indicator) and then extracted with aqueous saturated sodium hydrogen carbonate (1×50mL + 5×15mL). The bicarbonate extract was washed with ether (3×10mL), giving a light yellow solution which was then acidified with concentrated hydrochloric acid. A yellowish solid was obtained on cooling. The product was filtered and dried (6.2g, 93%), m.p. 87-95°C. Crystallisation of this product from toluene yield colourless long needles (5.9g, 90%), m.p. 103-104°C. (Found: C, 65.6; H, 6.8, C₁₆H₂₀O₅ requires C, 65.75; H, 6.8%).

ν_{\max} (film) 3900-2400s and broad, 2940s, 1777m, 1738m, 1738s, 1722s, 1629m, 1228s cm⁻¹.

δ (300MHz, CDCl₃) 1.95 (quintet, J= 7.5, 2H), 2.1 (quintet, J= 7, 2H), 2.4(t, J= 7.5, 2H), 2.6(t, J= 7, 2H), 2.7 (t, J= 7.5, 2H), 2.85(t, J= 7, 2H), 3.72(s, 3H, OMe), 3.82 (s, 3H, OMe), 6.88(s, 1H).

m/z(EI) 294, 293, 292 (6.2, 36.3, 100.0, M⁺), 275 [12.8, (M-OH)⁺], 274 [5.6, (M-H₂O)⁺], 247[2.6, (M-CO₂H)⁺], 233 [11.0, (M-CH₂CO₂H)⁺], 219{21.3, [M-(CH₂)₂CO₂H]⁺}, 205 {14.2, [M-C(CH₂)₃CO₂H]⁺}.
m/z (CI/NH₃), 311, 310 [0.6, 3.2(M+NH₄)⁺], 294, 293 [17.7, 100.0 (M+H)⁺], 275 [2.0, (M-OH)⁺], 274 [0.5, (M-H₂O)⁺], 219 [2.1,

{M-(CH₂)₂CO₂H]⁺}.

4- (5,8- Dimethoxy-1- tetralone-7-yl) butanoic acid Ethylene dithioacetal (14)

Caution:

Because of the toxicity and unpleasant smell of ethanedithiol, the reaction must be carried out in the *Hazard Laboratory* in a highly efficient fume cupboard. A solution of 4-(5,8-dimethoxy-1- tetralone-7-yl) butanoic acid (12) (0.5g, 1.7mmol) in dry dichloromethane (5mL) was prepared in a dry 25mL flask equipped with a drying tube. The temperature of the solution was lowered to 0°C using an ice-bath, and then 1,2-ethanedithiol (0.264g, 0.24mL, 2.8mmol) was added with stirring magnetically. Then boron trifluoride etherate (0.1mL, 0.8mmol) was added giving a deep red solution which was stirred for 45 minutes at 0°C. The mixture was then removed from the ice-bath and stirring was continued for another two hours at room temperature. The reaction mixture was diluted with dichloromethane to give a total volume of 10mL, and then washed with water (3×3mL); the dichloromethane phase became yellow-orange. This organic layer was extracted with saturated sodium hydrogen carbonate (3×3mL), and the combined bicarbonate extracts were washed with dichloromethane (3×3mL) and then acidified with concentrated hydrochloric acid. A green oily material was obtained, which did not solidify overnight. It was extracted with ether (3×5mL), the extract was washed with water until the washings were neutral, dried with sodium sulphate and then evaporated. A fluffy solid (0.45g, 72%) material was obtained which usually became sticky after being exposed to air. No suitable solvent was found for crystallisation of this material and was not obtained in a pure state.

ν_{\max} (film) 3600-2500s and broad, 2935s, 1706s, 1599w, 1461s, 1400s, 1238s cm⁻¹.

δ (300MHz, CDCl₃) 1.93(m, J=6.75, 2H), 2.0 (m, J= 7.5, 2H), 2.32 (t, J=6.75, 2H), 2.45 (t, J=7.5, 2H), 2.64 (t, J=6.75, 2H), 2.74 (t, J=7.5, 2H), 3.5 (m, complex symmetrical AA'BB' pattern,

2×CH₂), 3.55 (s, 3H, OMe), 3.58 (s, 3H, OMe), 6.6(s, 1H).

m/z (EI), 370 [2.7 (M+2)⁺], 368 (30.2, M⁺), 366 [51.2 (M-2)⁺], 351 [0.5 (M-OH)⁺], 309 [37.3(M-59)⁺], 309 [37.3 (M-2-57)⁺].

m/z (CI/NH₃) 384 [2.4 (M+NH₄)⁺], 369 [100.0 (M+H)⁺].

(Found m/z: M⁺, 368.1127. C₁₈H₂₄O₄S₂ requires 368.116.).

9,10-Dimethoxy-1,2,3,4,5,6,7,8-octahydroanthracene-1,5-dione-1,1-ethylenedithioacetal (15)

A solution of acid-thioacetal (14) (0.15g, 0.41mmol) in dry chloroform (5mL) was prepared in a dry 25mL round bottom flask. A mixture of trifluoroacetic anhydride (0.57mL, 4.1mmol) and trifluoroacetic acid (0.32mL, 4.1mmol) was added with magnetic stirring; the solution became deep red after about 2 minutes. Stirring was continued for 10 minutes. Water (10mL) was added dropwise, and the mixture was then diluted to 50mL with water and extracted with ether (3×15mL). The combined ether extracts were washed with water (10×20mL), then with saturated sodium hydrogen carbonate (3×10mL), then with 5% sodium hydroxide (3×5mL), and finally with water until the solution was neutral. The colourless ether layer was dried with sodium sulphate and evaporated (rotavap, water-pump and then oil-pump). The crude product was a greenish solid which was crystallised from petroleum (b.p. 100/120°C) to give colourless short needles (0.1g, 72%), m.p. 163-165°C. (Found: C, 61.3; H, 6.4. C₁₈H₂₂O₃S₂ requires: C, 61.71; H, 6.28%).

ν_{\max} (film) 2936m, 1684s, 1569m, 1455m, 1399s, 1279s cm⁻¹.

δ (300MHz, CDCl₃) 1.95(m, 4H, 2×CH₂), 2.34 (t, J= 6, 2H), 2.62 (t, J= 6.5, 2H), 2.78 (t, J= 6.5, 2H), 2.93(t, J= 6, 2H), 3.52 (m, symmetrical complex splitting pattern due to AA'BB' system in ethylenedithioacetal), 3.75 (s, 3H, OMe), 3.9 (s, 3H, OMe).

m/z (EI) 352 [15.6 (M+2)⁺], 351 [43.9,

(M+1)⁺], 350 (93.9, M⁺), 292 {19.7, [(M+1)-59]⁺}, 291 [100.0, (M-59)⁺], 257[56.8, (M-C₂H₅S)⁺].

m/z (CI/NH₃) 352, 351 [22.5, 100.0 (M+H)⁺], 291 [19.5, (M-59)⁺], 257 [4.4, (M-C₂H₅S)⁺].

Found m/z: M⁺, 350.1012. C₁₈H₂₂O₃S₂, requires, 350.1010.

Found m/z: (M-59)⁺, 291.0523. C₁₆H₁₉O₃S requires 291.0513.

Found m/z: (M-C₂H₅S)⁺, 257.1171. C₁₆H₁₇O₃ requires, 257.1176.).

1,2,3,4,5,6,7,8-Octahydro-9,10-dimethoxy-1,5-anthracenedione (13)

A solution of the foregoing dithioacetal (15) (0.1g, 0.29mmol) in a mixture of methanol (10mL), water (2mL), and concentrated hydrochloric acid (5 drops) was prepared in a 50mL round bottom flask equipped with a condenser, and was stirred magnetically. Mercury(II) chloride (0.194g, 0.714mmol) was added, and the mixture was heated for two and a half hours at reflux temperature in a water-bath with magnetic stirring. The mixture was cooled and diluted with ether to a total volume of 50mL, and then washed with water (1×10mL), then with aqueous 5% sodium hydroxide (2×10mL), and then with water until the wash was neutral. The colourless ether layer was dried with sodium sulphate and evaporated (rotavap, water-pump, then oil-pump) giving a yellowish solid. Crystallisation from methanol yielded yellowish needles (0.071g, 90%). m.p. 180-185°C. (Found: C, 69.3; H, 6.7. C₁₆H₁₈O₄ requires: C, 70.07; H, 6.56%)

ν_{\max} (film) 2945m, 1692s, 1457m, 1395s, 1246s, 1028m cm⁻¹.

δ (300MHz, CDCl₃) 2.07 (quintet, J= 6, 4H), 2.64 (t, J= 6, 4H), 2.96 (t, J= 6, 4H), 3.56 (s, 6H, 2×OMe).

m/z(EI) 276 [5.7, (M+2)⁺], 275 [37.3, (M+1)⁺], 274 (100.0, M⁺), 260, 259 [4.6, 24.1 (C₁₄H₆O₃CO)⁺].

m/z (CI/NH₃) 277, 276, 275 [4.4, 25.4, 100.0 (M+H)⁺].

(Found m/z: M⁺, 274.1199. C₁₆H₁₈O₄ requires

274.1205).

1,2,3,4,5,6,7,8-Octahydro-9,10-dihydroxy-1,5-anthracenedione (16)

A solution of dimethoxy-diketone (13) (10mg, 0.0364mmol) was prepared in dichloromethane (4mL), in a 25mL round bottom flask at 0°C (ice-bath) and stirred magnetically. Boron tribromide (0.007mL, 0.0728mmol; since measuring such a small volume was difficult, 0.7mL of a solution of this reagent with a concentration of 0.0262g/mL in dichloromethane was used) was added. The flask was closed with a stopper and stirred for 13 minutes. The reaction mixture became deep red. 15% hydrochloric acid (5mL) was added, and the mixture then diluted to 30mL, and extracted with ether (3×10mL). The combined extracts were washed with water (3×10mL), dried with sodium sulphate, and then evaporated (rotavap, water-pump and then oil-pump) giving the crude product (0.0075g, 85%) as a solid which had very good spectroscopic data, as given below.

Column chromatography (20:1 dichloromethane-methanol), on silica gel (C60 - 40/60) gave the relatively pure product as yellowish flat beads (0.007g, 78%), m.p. 188-195°C. This compound was also isolated by preparative T.L.C.

(Note: similar results were obtained when similar conditions were used but with both longer and shorter times of reaction).

ν_{\max} (film) 2950m, 1640s, 1413k, 1362m, 1337m, 1245s cm^{-1} .

δ (300MHz, CDCl_3) 2.12 (quintet, J= 6, 4H, 2×CH₂, collapsed to triplet by irradiation at either 2.75 or 2.94), 2.75 (t, J= 6, 4H, 2×CH₂ collapsed to singlet by irradiation at 2.12), 2.94 (t, 4H, 2×CH₂, collapsed to singlet by irradiation at 2.12), 11.88 (s, 2H, 2×OH).

m/z (EI) 248 [2.3 (M+2)⁺], 247 (18.8 (M+1)⁺], 246 [100.0 (M⁺)], 218 [5.5, (OH)₂C₆(CH₂)₃-CO(CH₂)₂CH₂⁺], 204 [3.5, (OH)₂C₆(CH₂)₃-COCH₂CH₂⁺], 190 [20.4, (OH)₂C₆(CH₂)₃COCH₂⁺]. m/z (CI/NH₃) 264 [0.6 (M+NH₄)⁺], 248 [39.8 (M+1+H)⁺], 247 [100.0 (M+H)⁺], 246 [40.9 (M)⁺], 218 (2.2), 204 (0.6), 190 (2.9).

1,5-Dihydroxy-9,10-anthraquinone (17)

This compound was obtained in about 53% yield as a by-product following demethylation of the dimethoxy-diketone (13) which was isolated by preparative thin layer chromatography in 20:1 dichloromethane-methanol on silica gel (C60-40/60) and was also synthesised via aerial oxidation of the dihydroxy-diketone (16) under basic conditions.

In this latter aromatisation process, a solution of 1,2,3,4,5,6,7,8-octahydro-9,10-dihydroxy-1,5-anthracenedione (16) (0.05g, 0.2mmol) in aqueous 10% potassium hydroxide (18mL) was prepared in a 50mL two-necked round bottom flask equipped with a condenser and a gas inlet tube. The red solution was heated at reflux while air was bubbled in, for two hours. After cooling, the deep red solution was acidified with concentrated hydrochloric acid and then diluted to 50mL with water. Extraction with ether (3×10mL) gave a pale yellow ethereal solution which was washed with water, dried with sodium sulphate, and evaporated (rotavap, water-pump and then oil-pump). The residue was crystallised from glacial acetic acid to give small pale yellow needles (37mg, 77%) m.p. 278-283°C (lit, 20, m.p. 280°C), identified as 1,5-dihydroxy-9,10-anthraquinone by comparison (T.L.C., N.M.R) with an authentic sample.

ν_{\max} (film) 1633s, 1600s, 1575m, 1449s, 1299s, 1238m cm^{-1} .

δ (200MHz, CDCl_3) 7.32 (d, J= 8.25, 2H), 7.69 (t, J= 8.25, 2H), 7.88 (d, J= 8.25, 2H), 12.64 (s, 2H, 2×OH).

m/z (EI) 241 (9.4), 240 [100.0, (M⁺)], 121 {15.0, [(OH)₂C₆H₄CO]⁺}. m/z (CI/NH₃) 259 (5.8), 258 [41.2, (M+NH₄)⁺], 242 [15.3 (M+1)H⁺], 241 [100.0, (M+H)⁺].

CONCLUSIONS :

The results obtained during the course of the present work establish the feasibility of constructing the 1,5-dihydroxy-9,10-anthraquinone nucleus via intramolecular acylation of alkylated para hydroquinones which provide the tricyclic ring system.

Although intramolecular acylation of the tetralone (12) requires prior protection of deactivating ketonic carbonyl group, the hydroquinone (16) subsequently obtained via deprotection and demethylation shows interesting properties in its own right. The new aspects of these properties will be discussed in a future report.

REFERENCES :

- [1] Galewsky, *Dematol. Wodis.*, **62**, 113 (1916).
- [2] Langrand, S., Guingant, A., Chassaguard, C., and D'Angelo, J., *J. Org. Chem.*, **53**, 1557 (1988).
- [3] Boisvent, L., and Brassard, P., *J. Org. Chem.*, **53**, 4052 (1988).
- [4] Guay, V., and Brassard, P., *Tetrahedron.*, **40**, 5039 (1984).
- [5] kraus, G.A., and Chen, L., *J. Org. Chem.*, **56**, 5098 (1991).
- [6] Dodsworth, D.J., Calcagno, M.P., and Ehrmann, E.V., *J. Chem. Soc., Perkin, Trans. I.*, 2120 (1981).
- [7] Moore, J.A., and Rahm, M., *J. Org. Chem.*, **26**, 1109 (1961).
- [8] Huang- Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
- [9] Horning, E.C., and Reisner, D.B., *J. Am. Chem. Soc.*, **71**, 1036 (1949).
- [10] Nystron, R.F., Raines, C., Berger, A., *J. Am. Chem. Soc.*, **80**, 2896 (1958).
- [11] Yamato, T., Tsuge, A., Koya, K., Kobayashi, K., Sakamoto, H., and Tashiro, M., *Org. Preparations Procedures int.*, **19**, 39 (1987).
- [12] Mitchell, R.H., and Hing Lai, Y., *Tetrahedron Lett.*, **21**, 2637 (1980).
- [13] Gribble, G.W., Kelly, W.J., and Emery, S.E., *Synthetic Commun.*, 763 (1978).
- [14] West, C.T., Donnelly, S.J., Kooistra, D.A., and Doyle, M.P., *J. Org. Chem.*, **38**, 2675 (1973).
- [15] Cory, F.A., and Tremger, H.S., *J. Org. Chem.*, **36**, 758 (1971).
- [16] Fry, J.L., Orfanopoulos, M., Adlington, M.G., Dittman, W.R., and Silverman, S., *J. Org. Chem.*, **43**, 374 (1978).
- [17] Olah, G.A., Arvanaghi, M., and Ohnnesian, L., *Synthetic Commun.*, 770 (1986).
- [18] Datta, S.K., *J. Chem. Soc., Perkin Trans. I.*, 62 (1972).
- [19] Ahmad, M.S., and Baddeley, G., *J. Chem. Soc.*, 5250 (1961).