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SYNTHESIS OF 1,4,8 - TRIHYDROXY-9 (10 H)-ANTHRACENONE

H. Sharghi[1] and I. M. Bruce[2]

[1] *Department of Chemistry, Shiraz University, Shiraz, Islamic Republic of Iran*
[2] *Department of Chemistry, The University of Manchester, England*

Abstract

The title compound has been synthesized starting from 2-methoxy-benzdiethylamide (1).

Introduction

Although anthralin is an effective antipsoriatic, it has been reported [1] that its 4-hydroxy congener, 1,4,8-trihydroxy-9-anthrone, is inactive. However, the source of this compound was not specified, and no synthesis of it has been described in the literature covered by Chemical Abstracts. An attempt to prepare it by selective reduction of 1,4,5-trihydroxy-9, 10-anthraquinone using tin and hydrochloric acid gave a complex mixture from which the required anthrone was not isolated [2].

In this paper, a total synthesis of 1,4,8-trihydroxy-9 (10 H)- anthracenone is described.

Results and Discussion

The directed metallation reaction of aromatic systems has been developed into a significant method for the regiospecific synthesis of polysubstituted aromatic compounds, especially those which are difficult to prepare by classical electrophilic reactions [3]. Among the variety of directing groups, the tertiary amide group on an aromatic ring system has proved to be particularly useful for *ortho* metallation [4].

The synthesis of 1,4,8-trihydroxy-9-anthrone outlined in Scheme 1 illustrates our general approach via *ortho* metallated benzdiethylamide intermediates. Lithiation of 2-methoxybenzdiethylamide (1) with sec-butyl-lithium in diethyl ether in the presence of tetramethylethylenediamine (TMEDA) followed by treatment with 2,5-dimethoxybenzaldehyde afforded 2-diethylamido-2',3,5'-trimethoxydiphenylmethanol (2) in 84% yield, m.p. 144-146°C [5].

The amide (2) was treated with 4-toluensulfonic acid in refluxing toluene to give the highly crystalline 2',5',7-trimethoxy-3-phenylphthalide (3) in 87% yield, m.p. 149-150°C (lit.,[7] 156-158.5°C) [6].

Reduction of the phthalide (3) with zinc dust in aqueous sodium hydroxide gave 2', 5', 6-trimethoxy-2-benzylbenzoic acid (4) in 96% yield as white crystals, m.p. 143-144°C [8-10]. Cyclisation was effected with trifluoroacetic anhydride and trifluoroacetic acid in dichloromethane for 1h at -10°C, and afforded 1,4,8-trimethoxy-9-anthracenol (5) in 92% yield as golden plates, m.p. 172-173°C [10, 11]. The anthracenol structure in solution, rather than the anthrone, was confirmed by ^{1}H NMR spectroscopy in $CDCl_3$ which showed a singlet at 8.16 due to 10-H and a singlet at δ 10.97 due to 9-OH; absorption due to the 10-methylene group of a 9-anthrone, expected to be in the δ 4-5 region, was absent. The ultraviolet spectrum in dichloromethane showed absorption in the λ 363-419 nm region typical of the anthracene chromophore. The infrared spectra of a solution in chloroform and of a solid film did not show a carbonyl absorption band. The compound therefore exists, at least almost exclusively, in the enolic form both in solution and in the solid state. The intramolecular hydrogen bond (δ OH 10.97, in $CDCl_3$) probably controls the position of equilibrium.

Attempts to completely demethylate the trimethoxy-anthracenol (5) with 3 mol of boron tribromide in dichloromethane were unsuccessful. Partial demethylation, as shown by mass spectrometry, could be effected using 2 mol of boron tribromide, but a complex mixture was

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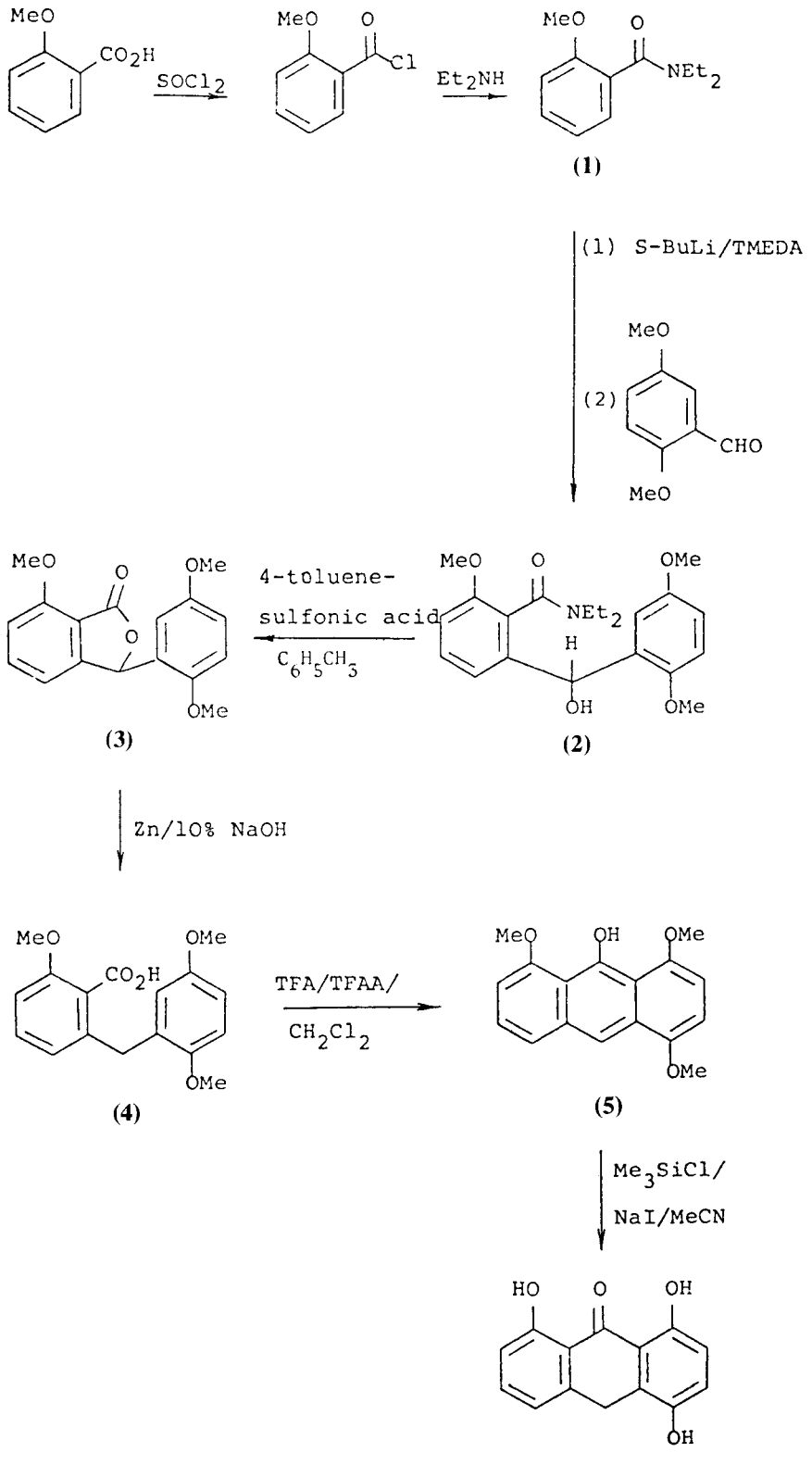
MeO
CO2H
SOCl2
MeO
O
Cl
Et2NH
MeO
O
NEt2
(1)
(1) S-BuLi/TMEDA
(2)
MeO
CHO
MeO
MeO
O
OMe
O
O
OMe
4-toluene-
sulfonic acid
C6H5CH3
MeO
O
OMe
NEt2
H
OH
OMe
(3)
(2)
Zn/10% NaOH
MeO
OMe
CO2H
OMe
TFA/TFAA/
CH2Cl2
MeO
OH
OMe
OMe
(4)
(5)
Me3SiCl/
NaI/MeCN
HO
O
OH
OH
(6)

Scheme 1

produced and no pure product was isolated. Attention was then turned to other methods of demethylation, and it was established that the anthracenol (5) was demethylated very readily when it was treated with trimethylsilyl chloride and sodium iodide in acetonitrile at room temperature under nitrogen, giving 1,4,8-trihydroxy-9-anthrone (6) in 90% yield as orange needles, m.p. 172-174°C decomp [12]. The anthrone structure is favoured by the two intramolecular hydrogen bonds, and was confirmed by ^{1}HNMR spectroscopy in $CDCl_3$ which showed a singlet at 4.33 due to the 10-methylene group, and one-proton singlets 11.76 and 12.36 due to the hydroxy groups *peri* to carbonyl.

Experimental Section

General Remarks. Melting points (m.p.) were determined on a Kofler microscope and hot stage apparatus and are uncorrected. Infrared spectra (i.r.) were recorded on a Perkin-Elmer FT-IR 1710 spectrometer, with absorption positions quoted in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (p.m.r.) were recorded on a Perkin-Elmer R12B (60 MHz), Bruker wp 80 (80 MHz), Varian SC 300 (300 MHz) and Bruker Ac 300 spectrometers, and the chemical shifts (values in δ) were related to internal tetramethyl silane (TMS) as standard.

Mass spectra (m.s.) were recorded on an A.E.I. MS 30 instrument connected to a DS 55 data system for low resolution electron impact (EI) work, and on a Krates MS 25 spectrometer coupled to the same data system for EI and for chemical ionisation (CI) work using ammonia as reagent gas unless specified otherwise. The relative abundances (% of base peak) of fragments are quoted in parentheses after the corresponding value of m/z.

2-Diethylamido-2',3,5'-trimethoxydiphenylmethanol

A solution of sec-butyl-lithium (15.5 ml, 1.35M in cyclohexane; 0.021 mole) was injected into a stirred solution of 2-methoxybenzdiethylamide (4.12 g; 0.02 mole) and tetramethylethylenediamine (TMEDA) (2.32 g; 0.02 mole) in dry (CaH_2) diethyl ether (100 ml) at -78°C (dry ice-acetone) under nitrogen during 30 mins. After the brown solution had been stirred for 1 h, a solution of 2,5-dimethoxybenzaldehyde (3.3 g; 0.02 mole) in dry diethyl ether (10 ml) was injected to give a yellow solution, and the dry ice-acetone bath was removed. After being stirred for a further 24 h, the white suspension was treated with water (20 ml) and then acidified with 10% hydrochloric acid (15 ml), and the crystalline precipitate was filtered off and washed with water (50 ml) and then with diethyl ether (30 ml). The product was recrystallized from methanol to give 2-diethylamido-2', 3, 5'-trimethoxydiphenyl-methanol (6.25 g, 84%) as white rectangular prisms, m.p. 144-146°C (Found: C, 67.8; H, 7.5; N, 3.8. $C_{21}H_{27}O_5N$ requires C, 67.6; H, 7.2; N, 3.8%). It had δ (300 MHz, $CDCl_3$) 1.08 (t, **J** 7, amide Me), 3.20 (q, **J** 7, CH_2), 3.52 (s, OMe), 3.59 (q, **J** 7, CH_2), 3.76 (s, 2 x OMe), 5.90 (s, CH.OH), 6.46 (d, **J** 8, 3 or 5-H), 6.73 (d, **J** 8.5 3'-H), 6.77 (d, **J** 8.5, 5 or 3-H), 6.79 (dd, J_1 8, $J_2$3, 4'-H), 7.14 (t, **J** 8, 4-H), 7.30 (d, **J** 3, 6'-H); ν_{max} (solid film) 3608 w, 2978 m, 2835 s, 1695 m, 1499 s, 1471 m, 1435 s, 1267 m, 1240 s, 1177 m, 1156 s, 1110 s, 1029 m, cm^{-1}; m/z (E.I.) 373 [M^+., 33], 356 [(M^+. - OH)$^+$, 1], 300 [(M^+. -NEt_2)$^+$, 75], 299 [(M^+. -$HNEt_2$)$^+$., 55], 285 [(300 - Me)$^+$., 30], 269 [(300 - OMe)$^+$., 100], 241 [(269 - CO)$^+$., 28], 206 [($MeO.C_6H_3CONEt_2$)$^+$, 39], 165 [$(MeO)_2$ - C_6H_3CO]$^+$, 23, 135 [($MeO.C_6H_4CO$)$^+$, 24], 107 [($MeO.C_6H_4$)$^+$, 6%].

2, 5', 7-Trimethoxy-3-phenylphthalide

A solution of 2-dimethylamido-2', 3, 5'-trimethoxydiphenylmethanol (5 g, 0.013 mole) and 4-toluenesulfonic acid (5 g, 0.026 mole) in toluene (200 ml) was refluxed for 24 h. The cooled mixture was washed with three portions of aqueous 5% sodium hydrogen carbonate solution, and then dried (Na_2SO_4). The solvent was evaporated (water pump) and the crystalline residue was recrystallized from methanol to give 2', 5', 7-trimethoxy-3-phenylphthalide (3.5 g, 87%) as white needles, m.p. 149-150°C (lit.,[7] 156-158°C). It had δ (300 MHz, $CDCl_3$) 3.64 (s, OMe), 3.85 (s, OMe), 4.33 (s, OMe), 6.64 (d, **J**3, 6'-H), 6.73 (s, 3-H), 6.81 (dd, J_1 9, $J_2$3, 4'-H), 6.89 (d, **J**9, 3' - H), 6.89 (d, **J** 7.5, 6-H), 6.97 (d, **J** 7.5, 4-H), 7.52 (t, **J** 8, 5-H); ν_{max} (solid film) 1778 s, 1611 m, 1501 s, 1488 s, 1295 s, 1219 s, 1034 m cm^{-1}; m/z (E.I.) 300 (M^+., 87), 285 [(M^+. -Me)$^+$, 22], 269 [(M^+. -OMe)$^+$, 44], 255 [(285-CH_2O)$^+$, 17], 241 [(269-CO)$^+$, 32], 211 [(241-CH_2O)$^+$, 18], 165 [$(MeO)_2C_6H_3CO$]$^+$, 41, 163 [($C_9H_7O_3$)$^+$, 18], 135 [$MeO.C_6H_4CO$)$^+$, 54], 107 [MeO. C_6H_4CO)$^+$, 13], 92(22.6), 77(40%).

2', 5', 6-Trimethoxy-2-benzylbenzoic acid

2',5,7-Trimethoxy-3-phenylphthalide (3 g, 0.01 mole) was suspended in aqueous 10% sodium hydroxide (300 ml), and heated to reflux with vigorous stirring. Zinc powder (30 g, excess) was added and the mixture was heated under reflux with stirring for 24 h. The mixture was cooled and filtered. The filtrate was acidified with 2M hydrochloric acid to give white crystals which were filtered off and dried to give 2', 5', 6-trimethoxy-2-benzyl-benzoic acid (2.9 g, 96%) as white crystals m.p. 142-144°C (Found: C, 67.5; H, 6.05. $C_{17}H_{18}O_5$ requires C, 67.6; H, 6.0%). It had δ (300 MHz, $CDCl_3$) 3.68 (s, OMe), 3.70 (s, OMe) 3.88 (s, OMe), 4.09 (s, CH_2), 6.68 (dd, J_1 8, $J_2$3, 4' - H), 6.72 (d, **J** 3, 2' -H), 6.75 (d, **J** 8, 3-H), 6.78 (d, **J** 8, 5'

-H) 6.81 (d, **J** 8, 5-H), 7.26 (t, **J** 8, 4-H); ν_{max} (solid film) 3003 w, 1699 m, 1584 m, 1501 s, 1469 s, 1226 s, 1071 s, 1047 s cm^{-1}; m/z (E.I.) 302 M^+., 100, 300 [$(M^+.-H_2)^+$., 41], 285 [$(M^+.-OH)^+$, 7], 269 [(300-OMe)$^+$, 39], 256 [(285-CHO)$^+$., 4], 255 [(285-CH_2O)$^+$, 9], 254 [(285-OMe)$^+$., 11] 253 [(285-MeOH)$^+$, 34], 241 [(269-CH_2O)$^+$, 19], 211 [(241-CH_2O)$^+$, 15], 165 $(MeO)_2C_6H_3CO]^+$, 18 163 [$(C_9H_7O_3)^+$, 22], 135 [$(MeO.C_6H_4CO)^+$, 21%].

1,4,8-Trimethoxy-9-anthracenol

Trifluoroacetic anhydride (3.6 ml, 0.0123 mole) was injected dropwise into a stirred solution of 2', 5', 6-trimethoxy-2-benzylbenzoic acid (3 g, 0.01 mole) and trifluoroacetic acid (12 ml, excess) in dry dichloromethane (48 ml) at -10°C (sodium chloride - crushed ice bath), and the mixture was stirred for 1h. It was then poured into ice-water (50 g) and the product was extracted with dichloromethane (2 x 50 ml). The organic layer was washed with 5% sodium hydrogen carbonate solution (50 ml) and dried (Na_2SO_4). The solvent was evaporated (water pump) to give yellow crystals which were recrystallized from 1:1 ethanol-methanol to give 1,4,8-trimethoxy-9-anthracenol (2.6 g, 92%) as golden plates, m.p. 172-173°C. (Found: C, 71.7; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.6%). It had (300 MHz, $CDCl_3$) 3.95 (s, OMe), 3.98 (s, OMe), 4.01 (s, OMe), 6.55 (s, 2-H + 3-H), 6.68 (d, **J** 8, 7-H), 7.28 (t, **J** 8, 6-H), 7.50 (d, **J** 8, 5-H), 8.16 (s, 10-H), 10.97 (s, 9-OH); ν_{max} (solid film) 3299 s, 2944 m, 1629 s, 1594 s, 1559 s, 1091 s, 981 s cm^{-1}; **m/z** (E.I.) 284 [M^+., 100], 269 [$(M^+.-Me)^+$, 93], 254 [$(M^+.-CH_2O)^+$. or (269-Me)$^+$., 59], 236 [(254-H_2O)$^+$., 54], 226 [(254-CO)$^+$., 30], 225 [(254-CHO)$^+$, or (226-H)$^+$, 50], 224 [254-CH_2O)$^+$., 38], 211 [(226-Me)$^+$, 33], 197 [(225-CO)$^+$., 21], 195 [(226-OMe)$^+$, 13], 180(35), 168(33), 165(25), 155(36), 152(61), 142(68), 139(60), 127(43), 126(34%); λ_{max} (DMF) 267, 364, 382, 420 nm (ε_{max} 20140, 10000, 18230, 5240).

1,4,8-Trihydroxy-9 (10 H)-Anthracenone

Trimethylsilyl chloride (652 mg, 6 mole) was added slowly to a solution of 1,4,8-trimethoxy-9-anthracenol (268 mg, 2 mole) and sodium iodide (0.9 g, 6 mole) in dry acetonitrile (20 ml) and stirred under nitrogen. The brown suspension was stirred at room temperature for 3 days and then quenched with water (25 ml); diethyl ether (30 ml) was added. The ether layer was washed with 10% sodium thiosulphate solution (25 ml) (to remove iodine) and then with brine (25 ml), and dried (Na_2SO_4). The solvent was evaporated to give yellow orange crystals. Recrystallization from ethanol gave 1,4,8-trihydroxy-9 (10 H)-anthracenone (2.1 g, 90%) as orange needles, m.p. 172-174° decomp. (Found: C, 69.2; H, 4.35. $C_{14}H_{10}O_4$ requires C, 69,4; H, 4.1%). It had δ (300 MHz, d_6 - acetone) 4.33 (s, 2 x 10-H), 6.88 (d, **J** 9, 2-H), 6.98 (dd, J_1 8, J_2 1, 7-H), 7.19 (dd, J_1 8, J_2 1, 5-H), 7,23 (d, **J** 9, 3-H) 7.70 (t, **J** 8, 6-H), 8.61 (s, 4-**OH**), 11.76 (s, 1 or 8-**OH**), 12,36 (s 8 or 1-**OH**); ν_{max} (solid film) 3331 w, 1620 s, 1580 s, 1456 m, 1282 s, 1052 s cm^{-1}; **m/z** (E.I.) 242 (M^+., 25), 240 [$(M^+.-H_2)^+$., 100], 225 [(240-OH)$^+$, 2], 212 [(240-CO)$^+$., 8], 197 [(225-CO)$^+$, 2], 184 [(212-CO)$^+$., 11], 168 [(197-CO)$^+$, 1], 158(9), 138(7%); λ_{max} (DMF) 232, 265, 303, 315, 342, 374, 575 nm (ε_{max} 2270, 4110, 2440, 2480, 1910, 1710, 3080).

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