SYNTHESIS OF 2-PROPYLANTHRALIN AND 2,7-DIPROPYLANTHRALIN VIA REDUCTIVE CLAISEN REARRANGEMENT OF ALLYLOXYANTHRAQUINONES

J. Khalafy[1] and J. M. Bruce[2]

[1]*Department of Chemistry, Urmia University, Urmia, Islamic Republic of Iran*
[2]*Department of Chemistry, University of Manchester, Manchester, U. K.*

Abstract

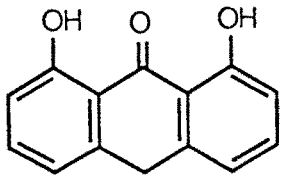
Reductive Claisen rearrangement of 1-allyloxy-8-methoxy-9, 10-anthraquinone followed by demethylation and reduction, and of 1,8-bisallyloxy-9,10-anthraquinone followed by reduction provides regiospecific syntheses of 2-propyl- and 2,7-dipropyl-anthralin.

Introduction

Psoriasis is a widely distributed disorder of the skin characterised by basal cell hyperproliferation and impaired differentiation which lead to the formation of squamous plaques [1, 2]. There is no cure, but it can be controlled by treatment with a variety of drugs, [3] of which topical anthralin (dithranol) is particularly important. [1-5].

Many analogues of anthralin [1, 8-dihydroxy-9-anthrone, (1)], particularly those substituted at the 10-position, have been synthesised in order to establish structure-activity relationships, [6, 7] but routes to 2-mono- and 2,7-di-substituted anthralins are limited. Thus treatment of anthralin with alkenes (or the corresponding alkanols) in the presence of sulfuric or phosphoric acid is reported [8] to yield mixtures of 2- and 4- mono- and 2,7-di-alkylanthralins, but rigorous characterisation is not described. However, the Marschalk reaction [9] of 1-hydroxy- and 1,8-dihydroxy-9, 10-anthraquinones provides for alkylation in the synthesis [10] of 2-carboxymethyl- and 2,7-biscarboxymethyl-anthralin.

Keywords: Anthralin; Dithranol; Psoriasis; Anthraquinones; Anthrones; Claisen rearrangement



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We now report on the synthesis of new 2-alkyl- and 2,7-dialkyl-anthralins for which the reductive claisen rearrangement [11] of allyloxyanthraquinones is used to effect regiospecific alkylation.

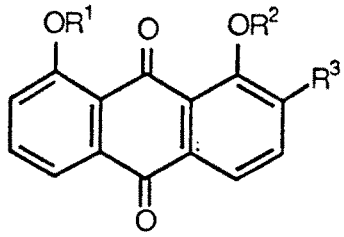
Results and Discussion

Treatment of 1-hydroxy-8-methoxy-9, 10-anthraquinone [12] with allyl bromide in the presence of potassium carbonate afforded the allyl ether (2) [13, 14] which on reductive Claisen rearrangement [11] with sodium dithionite in aqueous dimethylformamide followed by aerial oxidation gave the 2-allylanthraquinone (3) from which the 2-propyl analogue (4) was obtained by hydrogenation over palladium-charcoal. Demethylation with sodium ethanethiolate in dimethylformamide [15] gave the

dihydroxyanthraquinone (5), which was reduced [16] with tin and hydrochloric acid to afford 2-propylanthralin (6) as yellow needles.

Demethylation of 2-allyl-1-hydroxy-8-methoxy-9, 10-anthraquinone with hydrogen bromide in acetic acid afforded the bromopropyldihydroxyanthraquinone (7).

Similarly, bisallylation of 1,8-dihydroxy-9, 10-anthraquinone afforded the bisallyl ether (8) which on double Claisen rearrangement followed by hydrogenation of the alkene moieties and reduction of the 10-carbonyl group as above gave 2,7-dipropylanthralin (9) as orange needles.



(2) R^1 = Me; R^2 = Allyl; R^3 =H
(3) R^1 = Me; R^2 = H; R^3 = Allyl
(4) R^1 = Me; R^2 = H; R^3 = Pr
(5) R^1 = R^2 = H; R^3 = Pr
(7) R^1 = R^2 = H; R^3 = CH_2 CHBrMe
(8) R^1 = R^2 = Ally; R^3 = H

Unexpectedly, hydrogenation of 2,7-diallyl-1,8-dihydroxy-9,10-anthraquinone over Adams' platinum oxide catalyst afforded 10-hydroxy-2,7-dipropylanthralin (10).

Conclusion

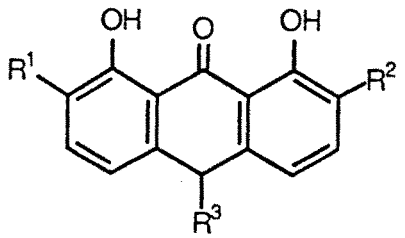
Each of the foregoing reactions proceeds in high yield. Collectively, they provide regiospecific syntheses of 2-propyl- and 2,7-dipropyl-anthralin, and in principle can be extended to the synthesis of homologues of these compounds from appropriate allyloxyanthraquinones.

Experimental Section

Infrared spectra were obtained using a Perkin-Elmer 1710 FT instrument. NMR spectra, referenced to internal tetramethylsilane, were recorded using Perkin-Elmer R32 (220 MHz) and Varian SC300 instruments. Mass spectra were determined with a Kratos MS30 spectrometer.

1-Allyloxy-8-methoxy-9,10-anthraquinone (2)

A mixture of 1-hydroxy-8-methoxy-9, 10-anthraquinone [12], (1.14 g, 0.0045 mol), allyl bromide (2.7 g, 0.022 mol) and anhydrous potassium carbonate (3 g) in dry acetone (85 ml) was vigorously stirred and refluxed under nitrogen for 20 h, cooled, filtered, and the solvent was evaporated. The residue was extracted with chloroform (30 ml), and the extract was filtered and the solvent was removed from the filtrate. Recrystallisation of the residue from 10: 1 light petroleum (b. p. 40 - 60°C) - chloroform gave the allyl ether (1.165 g, 88%) as yellow needles, m. p. 171 - 172°C (lit. [13, 14] m. p. 174 - 175°C; 177° C). It had ν_{max} (film) 1666m, 1586m, 1439m, 1319vs, 1233vs cm^{-1}; δ ($CDCl_3$, 220 MHz) 4.01 (OMe), 4.75 (dt, J_1 5.4, J_2 1.7, OCH_2), 5.33 (dt, J_1 11, J_2 1.4, 1H of H_2C =), 5.56 (dt, J_1 17.5, J_2 1.6, 1H of H_2C=), 6.0 - 6.3 (m, -CH=), 7.26 (d, J 5, H-2 or H-7), 7.31 (d, J 5, H-7 or H-2), 7.60 (t, J 8.3, H-3 or H-6), 7.64 (t, J 8.3, H-6 or H-3), 7.84 (dd, J_1 7.8, J_2 1.4, H-4 + H-5); **m/z** 294 (M^+ 25%), 279 (32), 265 (65), 253 (40), 209 (36), 180 (30), 152 (32), 139 (100).



(6) R^1 = R^3 = H; R^2 = Pr
(9) R^1 = R^2 = Pr; R^3 = H
(10) R^1 = R^2 = Pr; R^3 = OH

2-Allyl-1-hydroxy-8-methoxy-9, 10-anthraquinone (3)

A solution of the foregoing allyl ether (1 g) and sodium dithionite (1.3 g) in a mixture of dimethylformamide (30 ml) and water (30 ml) under nitrogen was heated at 60°C overnight, and then cooled to room temperature and bubbled with air for 1 h. The mixture was extracted with dichloromethane (100 ml) and the extract was washed with water and dried (Na_2SO_4). Removal of the solvent and crystallisation of the residue from ethanol gave the anthraquinone (930 mg, 93%) as orange needles, m.p. 171-172°C (lit. [13, 14] m.p. 172°C; 175°C). It had ν_{max} (film) 1632s, 1375s, 1284vs, 1243vs, 996s cm^{-1}; δ ($CDCl_3$, 220 MHz) 3.49 (d, J 5.5, $-CH_2-$), 4.05 (s, OMe), 5.13 (bd, J 13, H_2C=), 5.9 - 6.2 (m, -CH=), 7.35 (d, J 8.5, H-3 or H-7), 7.49 (d, J 8.3, H-7 or H-3), 7.72 (d, J 7.8, H-4), 7.72 (t, J 8.3, H-6), 7.95 (d, J 7.9, H-5), 13.29 (s, OH); **m/z** 294 (M^+ 61%), 280 (20), 279 (100), 205 (20), 189 (22), 176 (31), 165 (50), 152 (46), 139 (57), 77 (55), 76 (45).

1- Hydroxy - 8 - methoxy - 2 - propyl - 9,10 - anthraquinone (4)

Hydrogenation of the foregoing allylanthraquinone (200 mg) in ethyl acetate (40 ml) over 10% palladium-charcoal (30 mg), filtration through Celite, removal of the solvent, and crystallisation of the residue from ethanol gave the **anthraquinone** (184 mg, 92%) as orange-yellow needles, m.p. 167 - 168°C (Found: C, 73.5; H, 5.6%; M^+, 296.1029. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.5.%; **M**, 296.1049). It had ν_{max} (film) 1631s, 1583s, 1429s, 1305s, 1283vs, 1246vs, 1181s, 1023s, 985s cm^{-1}; δ (CDCL$_3$, 220 MHz) 0.95 (t, **J** 7.3, Me-3'), 1.52- 1.74 (m, CH_2-2'), 2.19 (t, **J** 7.7, CH_2-1'), 4.04 (s, OMe), 7.43 (d, **J** 8.9, H-7), 7.47 (d, **J** 8, H-3), 7.68 (d, **J** 7.8 H-4), 7.72 (t, **J** 7.6 H-6), 7.95 (dd, J_1 7.8, J_2 1.2, H-5), 13.26 (s, OH); **m/z** 296 (M^+ 65%), 282 (28), 281 (100), 268 (31), 267 (90), 152 (17), 139 (20), 76 (15).

1,8-Dihydroxy-2-propyl-9, 10-anthraquinone (5)

A solution of the foregoing methyl ether (100 mg) and sodium ethanethiolate (170 mg) in dimethylformamide (20 ml) under nitrogen was refluxed for 1 h, cooled, diluted with water (20 ml), and then acidified with 5% sulphuric acid (2 ml). Extraction with dichloromethane (50 ml), thorough washing of the extract with water, drying (Na_2SO_4), evaporation, and crystallisation of the residue from ethanol gave the **anthraquinone** (85 mg, 87%) as orange-yellow needles, m.p. 143 - 144°C (Found: C, 72.5; H, 4.9. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%). It had ν_{max} (film) 1623s, 1472s, 1429vs, 1287vs, 1224vs, 1212vs, 852s cm^{-1}; δ (CDCl$_3$, 220 MHz) 0.98 (t, **J** 7.5, Me), 1.5 - 1.7 (m, CH_2-2'), 2.71 (t, **J** 7.5, CH_2-1'), 7.28 (dd, J_1 8.3, J_2 1.2, H-7), 7.54 (d, **J** 7.5, H-3), 7.66 (t, **J** 7.8, H-6), 7.73 (d, **J** 7.5, H-4), 7.83 (dd, J_1 7.2, J_2 1.2, H-5), 12.07 (s, OH-1 or OH-8), 12.40 (s, OH-8 or OH-1); **m/z** 282 (M^+ 91%), 267 (41), 254 (32), 253 (100), 225 (13).

1,8-Dihydroxy-2-propyl-9-anthrone (2-propylanthralin) (6)

A mixture of the foregoing anthraquinone (40 mg) and granulated tin (100 mg) in refluxing glacial acetic acid (2 ml) was treated dropwise during 30 min. with concentrated hydrochloric acid (2 ml), and then refluxed for 30 min. more, and filtered to remove tin residues. The filtrate was extracted with dichloromethane (30 ml), and the extract was washed with water and dried (Na_2SO_4). Removal of the solvent and crystallisation of the residue from ethanol gave the **anthrone** (31 mg, 82%) as pale yellow needles, m.p. 134°C (Found: C, 76.4: H, 6.0%; M^+ 268.1102. $C_{17}H_{16}O_3$ requires C, 76.1; H, 6.0%; **M** 268.1099). It had ν_{max} (film) 1618s, 1600s, 1479s, 1440s, 1426vs, 1271vs, 1214s cm^{-1}; δ (CDCl$_3$, 300 MHz), 1.02 (t, **J** 7.4, Me), 1.71 (sextet, **J** 7.4, CH_2-2') 2.69 (t, **J** 7.4, CH_2-1'), 4.36 (s, CH_2-10), 6.90 (d, **J** 7.8, H-4), 6.94 (d, **J** 8.3, H-5 + H-7), 7.43 (d, **J** 7.8, H-3), 7.54 (t, **J** 7.8, H-6), 12.42 (s, OH-1 or OH-8), 12.65 (s, OH-8 or OH-1); **m/z** 268 (M^+ 53%), 253 (15), 240 (23), 239 (100), 226 (15), 225 (30), 211 (24), 165 (24), 86 (19), 84 (32), 73 (18), 71 (15), 69 (22), 55 (28).

2-(2-Bromopropyl)-1, 8-dihydroxy-9, 10-anthraquinone (7)

A solution of the allylanthraquinone (3) (90 mg) in glacial acetic acid (25 ml) was saturated with hydrogen bromide, and then refluxed for 1 h. Removal of the solvent and crystallisation of the residue from 1 : 1 hexane-chloroform afforded the **bromo-compound** (63 mg, 57%) as yellow needles, m.p. 175 - 177°C (Found: M^+ 361.9971; 360.0009. $C_{17}H_{13}BrO_4$ requires **M** 361.9978; 359.9998). It had ν_{max} (film) 3090b, 2967b, 1665s, 1617vs, 1468s, 1423vs, 1295s, 1256s, 1204s, 1156s, 1019s cm^{-1}; δ (CDCl$_3$, 220 MHz) 1.78 (d, **J** 6.8, Me-3'), 3.18 (dd, J_1 14.5, J_2 8.3, H-1'), 3.33 (dd, J_1 14.5, J_2 5.5, H-1'), 4.55 (m, collapsed to dd, J_1 8.3, J_2 5.5, on irradiation at δ 1.78, H-2'), 7.29 (dd, J_1 8.5, J_2 1.3, H-7), 7.64 (d, **J** 7.5, H-3 or H-4), 7.68 (t, **J** 8.0, H-6), 7.82 (d, **J** 7.5, H-4 or H-3), 7.84 (dd, J_1 7.5, J_2 1.3, H-5), 11.99 (s, OH-1 or OH-8), 12.43 (s, OH-8 or OH-1); **m/z** 362 (M^+ 25%), 360 (M^+ 26), 282 (16), 281 (55), 280 (68), 267 (25), 254 (23), 253 (100), 84 (13).

1,8-Bis (allyloxy)-9,10-anthraquinone (8)

A mixture of 1,8-dihydroxy-9, 10-anthraquinone (1.0 g), allyl bromide (13.6 g, 10 ml), and anhydrous potassium carbonate (2.7 g) in dry acetone (100 ml) was stirred and refluxed under nitrogen for 48 h, concentrated to 20% of its volume, and diluted with aqueous 5% sodium hydroxide (30 ml). Extraction with chloroform (100 ml), washing of the extract successively with aqueous 5% sodium hydroxide and water, drying (Na_2SO_4), evaporation, and crystallisation of the residue from methanol gave the orange-yellow **anthraquinone** (1.09 g, 82%), m.p. 159 - 160°C (Found: C, 74.8; H, 5.0. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%). It had ν_{max} (film) 1666 m, 1316vs, 1235vs, 965s, 929s, cm^{-1}; δ (CDCl$_3$, 220 MHz), 4.72 (dt, J_1 5, J_2 1.75, 2 x OCH_2), 5.31 and 5.58 (dq, J_1 10.9, J_2 1.4, and dq J_1 17.5, J_2 1.6, 2 x H_2C=), 5.9 - 6.2 (m, 2 x H-2'), 7.26 (dd, J_1 8.3, J_2 1.1, H-2 + H-7 or H-4 + H-5), 7.57 (t, **J** 7.9, H-3 + H-6), 7.82 (dd, J_1 7.7, J_2 1.1, H-4 + H-5 or H-2 + H-7); **m/z** 320

(M^+, 0.3%), 280 (20), 279 (96), 251 (8), 223 (8), 139 (36), 138 (12), 41 (100).

2,7-Diallyl-1,8-dihydroxy-9, 10-anthraquinone

A solution of the foregoing diether (100 mg) in 1 : 1 dimethylformamide-water (12 ml) containing sodium diethionite (250 mg) was heated at 70°C for 20 h under nitrogen, cooled, and bubbled with air for 1 h. Water (10 ml) was added, and the product was isolated by extraction with dichloromethane, Crystallisation from ethanol gave the **anthraquinone** (89 mg, 89%), as orange needles, m.p. 155°C (Found: C, 74.6; H, 4.9. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%). It had ν_{max} (film) 3609b, 3074b, 1616s, 1426vs, 1291s, 1265vs cm^{-1}; δ ($CDCl_3$, 220 MHz) 3.48 (d, **J** 6.7, 2x $-CH_2-$), 5.16 (dm, J_1 13.5, 2 x = CH_2), 5.88 - 6.12 (m, 2x -CH=), 7.54 (d, **J** 7.5, H-3 + H-6 or H-4 + H-5), 7.76 (d, **J** 7.5, H-4 + H-5 or H-3 + H-6), 12.4 (s, 2 x OH); **m/z** 320 (M^+ 100%), 319 (10), 306 (13), 305 (58), 303 (10), 291 (12), 287 (12), 277 (17), 77 (10).

1,8-Dihydroxy-2,7-dipropyl-9,10-anthraquinone

The foregoing diallyl-compound (100 mg) in ethyl acetate (25 ml) was hydrogenated over 10% palladium-charcoal (15 mg), until uptake of hydrogen ceased. The solution was then filtered, evaporated, and the residue crystallised from ethanol to give the **anthraquinone** (81 mg, 80%) as orange-yellow needles, m.p. 158°C (Found: C, 74.3, H, 6.1%; M^+ 324.1352. $C_{20}H_{20}O_4$ requires C, 74.1; H, 6.2%; **M**, 324.1361). It had ν_{max} (film) 2958m, 2929w, 2869w, 1668m, 1619s, 1427vs, 1266vs, 1235s, 1216s, 1051s cm^{-1}; δ ($CDCl_3$, 220 MHz) 0.97 (t, **J** 7.5, 2 x Me), 1.86 (sextet, **J** 7.5, CH_2-2' + CH_2-2"), 2.72 (t, **J** 7.5 CH_2-1' + CH_2-1"), 7.53 (d, **J** 7.7, H-3 + H-6 or H-4 + H-5), 7.76 (d, **J** 7.7, H-4 + H-5 or H-3 + H-6), 12.44 (s, 2 x OH); **m/z** 324 (100%), 310 (11), 309 (37), 296 (27), 295 (100), 267 (13), 266 (11).

1,8-Dihydroxy-2,7-dipropyl-9-anthrone (2,7-dipropylanthralin) (9)

A mixture of the foregoing anthraquinone (40 mg) and granulated tin (100 mg) in glacial acetic acid (6 ml) was refluxed whilst concentrated hydrochloric acid (3 ml) was added dropwise over 30 min. The mixture was filtered, diluted with water (15 ml) and extracted with dichloromethane (30 ml), and the extract was washed with water and dried (Na_2SO_4). Evaporation and crystallisation of the residue from ethanol gave the **anthrone** (35 mg, 90%) as pale yellow needles, m.p. 146°C (Found: C, 77.7; H, 7.1, $C_{20}H_{22}O_3$ requires C, 77.4; H, 7.2%). It had ν_{max} (film) 2958m, 2916m, 2861m, 1618s, 1608s, 1427vs, 1369s, 1248s cm^{-1}; δ ($CDCl_3$, 220 MHz) 0.97 (t, **J** 7.4, 2 x Me), 1.66 (sextet, **J** 7.4, CH_2-2' + CH_2-2"), 2.64 (t, **J** 7.4, CH_2-1' + CH_2-1"), 4.28 (s, CH_2-10), 6.83 (d, **J** 7.8, H-4 + H-5), 7.37 (d, **J** 7.7, H-3 + H-6), 12.62 (s, 2 x OH); **m/z** 310 (M^+, 82%), 282 (23), 281 (100), 268 (20), 267 (85), 239 (52), 238 (20), 126 (16), 84 (18).

1,8,10-Trihydroxy-2,7-dipropyl-9-anthrone (10-hydroxy-2,7-dipropylanthralin) (10)

Hydrogenation of 2,7-diallyl-1,8-dihydroxy-9, 10-anthraquinone (20 mg) in ethyl acetate (10 ml) over platinum oxide (4 mg) and under normal temperature and pressure for 15 min, filtration through Celite, removal of the solvent, and crystallisation of the residue from hexane gave the **anthrone** (18 mg, 89%) as pale yellow needles, m.p. 146 - 148°C (Found: C, 73.6; H, 6.6%; M.+ 326.1492. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.8%; **M**, 326.1518). It had ν_{max} (film) 3249b, 2961m, 2926m, 1623s, 1608s, 1420vs, 1265vs cm^{-1}; δ (CDCl, 220 MHz) 0.97 (t, **J** 7.5, 2 x Me), 1.66 (sextet, **J** 7.5, CH_2-2' + CH_2-2"), 2.15 (d, **J** 8.9, removed by D_2O, OH-10), 2.65 (t, **J** 7.5, CH_2-1' + CH_2-1"), 5.62 (d, **J** 8.9, collapsed to singlet by D_2O, H-10), 7.22 (d, **J** 7.8, H-4 + H-5 or H-3 + H-6), 7.45 (d, **J** 7.8, H-3 + H-6 or H-4 + H-5), 12.49 (s, OH-1 + OH-8); **m/z** 326 (M^+, 20%), 325 (20), 324 (91), 311 (17), 310 (78), 309 (44), 296 (27), 295 (100), 284 (10), 283 (58), 282 (19), 281 (80), 268 (16), 267 (69), 239 (36), 238 (23), 165 (16).

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