

## Syntheses of Some 10-Anthralin Ester Derivatives as Antipsoriatic Drugs

N. GHARJB NASERI†, A. ASHNAGAR\* and J.M. BRUCE ‡

School of Pharmacy, Ahwaz University of Medical Sciences, Ahwaz, Iran

E-mail: aashnagar2003@yahoo.com

In the present study, a number of 10-alkyloxy-, 10-allyloxy-, 10-phenyloxy- and 10-benzyloxycarbonyl derivatives of anthralin were synthesized with the aim of reducing the above mentioned side effects while retaining the drug efficacy for the treatment of psoriasis.

**Key Words:** Synthesis, 10-Anthralin ester derivatives, Antipsoriatic drugs.

### INTRODUCTION

1,8-Dihydroxy-9-(10H)-anthracenone is known in the chemical literature as 1,8-dihydroxy-9-anthrone (**I**) and most commonly as anthralin. In the pharmaceutical and medical literature, it is known as anthralin, dithranol or cignolin. There are many formulations for the clinical application of anthralin, all of which have been developed in attempts to reduce the two major side effects of the drug which have constantly limited its usefulness as a universally acceptable antipsoriatic, namely the erythema at the site of application and the staining of the skin to a purple colour<sup>1-3</sup>.

It is well established that a free radical mechanism is involved in the therapeutic activation of anthralin and its further oxidation to staining, therapeutically inactive dimers. The brown end-product of anthralin oxidation which is the major cause of staining is known as “anthralin brown”. The other major side effect associated with anthralin therapy is an erythematous reaction at the site of application. A lot of research has been carried out with the aim of constructing some derivatives of anthralin with lower staining and irritating properties but still retaining sufficient antipsoriatic activity. Since esterification of the two hydroxyl groups at positions 1 and 8 of the anthralin molecule did not improve the situation, therefore, attention was directed on the very reactive methylene group at position 10, which easily gives up a hydrogen atom to form inflammatory anthralin and oxygen radicals and staining dimers. When both hydrogen atoms at position 10 were replaced with other substituents, the new molecules had lost not only the irritating and staining properties, but also lost the antipsoriatic activity of the parent compound. Mustakallio *et al.*<sup>4</sup> have shown that when only one of the hydrogen atoms was replaced with an acyl group, the staining and even the irritating properties of the new molecule were reduced. Mustakallio<sup>3</sup> proposed that if the substituent at C-10 is less bulky than glucose, the other hydrogen atom of the 10-methylene group might retain enough reactivity to be therapeutically active and the staining ought to be diminished owing to the steric hindrance to dimerization by the substituent at

†Ahwaz Faculty of Petroleum Engineering, University of Petroleum Industry, Ahwaz, Iran

‡Department of Chemistry, University of Manchester, United Kingdom.

position 10. Regarding the results obtained by Mustakallio and his co-workers<sup>4</sup>, it is decided to prepare 10-alkyloxy-, 10-allyloxy, 10-phenyloxy- and 10-benzyloxycarbonyl derivatives of anthralin and investigating their therapeutic as well as the side effects mentioned above.

## EXPERIMENTAL

### (1) 10-Methoxycarbonyl-1,8-dihydroxy-9-anthrone

Anthralin (0.9 g, 3.98 mmol) was dissolved in freshly distilled benzene (45 mL) at reflux. Pyridine (5 mL, 61.9 mmol) was added to give a yellow-orange solution, followed by methyl chloroformate (0.38 mL, 460 mg, 4.87 mmol). The solution turned yellow-orange colour and a white solid (pyridinium hydrochloride) was precipitated. Reflux was continued for 2.5 h followed by filtration on suction and evaporation of the filtrate which resulted in a yellow-brown solid material (1.125 g). Analytical TLC on silical gel (CH<sub>2</sub>Cl<sub>2</sub>) showed six spots. Column chromatography (1.125 g of the crude product) on silica gel 60 (CH<sub>2</sub>Cl<sub>2</sub>) gave four fractions:

Fraction (I) was identified as pure anthralin (381 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-methoxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (290 mg, 1.02 mmol, 25.7%), m.p. 159–161°C (Found: C, 67; H, 4.2; C<sub>16</sub>H<sub>12</sub>O<sub>5</sub> requires C, 67.6; H, 4.2%).  $\bar{\nu}$ : 2953 s, 2724 m, 1721 m, 1629 m, 1600 m, 1273 m, 1220 m, 1188 m 1148 m, 1023 m, 750 m and 672 m cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 3.62 (s, CH<sub>3</sub>), 5.21 (s, H-10), 6.96 (d, J = 8 Hz, H-2 + H-4 + H-5 + H-7), 7.48 (t, J = 8 Hz, H-3 + H-6), 12.16 (s, 2 × OH); m/z (EI): 284 (M<sup>+</sup>, 45.6%), 226, 225, 197, 169 and 168 (25.5, 100, 39.4, 3.8 and 4.8%); m/z (CI): 302, [(M + NH<sub>4</sub>)<sup>+</sup>], 285, (M + H)<sup>+</sup>, 227 and 226 (8.3, 100, 41.9 and 7.2%).

Fraction (III) was obtained (38 mg) as a yellow-green semi-solid material. It had  $\delta$  (CDCl<sub>3</sub>, 60 MHz): 3.91 (s, CH<sub>3</sub>), 4.3 (broad, 2 × H-10), 6.60–6.90 (broad, H-2 + H-7), 7.1–7.5 (m, H-3 + H-4 + H-5 + H-6), 12.58 (s, 1 × OH). This fraction was identified as mono-substituted compound at 1-OH group.

Fraction (IV) was a complicated mixture.

### (2) 10-Ethoxycarbonyl-1,8-dihydroxy-9-anthrone

The foregoing procedure was repeated but ethyl chloroformate was used. The crude product obtained was a green solid material (1.149 g). Analytical TLC on silical gel (CH<sub>2</sub>Cl<sub>2</sub>) showed three spots. Column chromatography (1.149 g of crude product) on silica gel 60 (CH<sub>2</sub>Cl<sub>2</sub>) gave three fractions:

Fraction (I) was identified as pure anthralin (192 mg).

Fraction (II): Sublimation of fraction (II) at 110°C/0.1 mmHg gave 10-ethoxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (290 mg, 0.973 mmol, 24.5%), m.p. 120–122°C (Found: C, 68.7; H, 4.7; C<sub>16</sub>H<sub>14</sub>O<sub>5</sub> requires C, 68.5; H, 4.7%).  $\bar{\nu}$  (mull in nujol): 2953 s, 2924 m, 1767 m, 1716 m, 1630 m, 1602 m, 1557 m, 1487 m, 1330 m, 1273 m, 1220 m, 1182 m 1152 m, 1096 m, 750 m and 672 m cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 1.15 (t, J = 7 Hz, CH<sub>3</sub>), 4.08 (q, J = 7 Hz, CH<sub>2</sub>), 5.20 (s, H-10), 7.0 (dd, J<sub>1</sub> = 8 Hz, J<sub>2</sub> = 2.5 Hz, H-2 + H-4 + H-5 + H-7), 7.52 (t, J = 8 Hz, H-3 + H-6), 12.18 (s, 2 × OH); m/z (EI): 298, 254, 226, 225, 197, 180, 169 and 168 (M<sup>+</sup>, 25, 4.6, 90.2, 100, 65.3, 7.3, 8.9 and 13%); m/z (CI): [316, (M + NH<sub>4</sub>)<sup>+</sup>] [299, (M + H)<sup>+</sup>], 227 and 226 (6.3, 100, 86.3 and 10.6%).

Fraction (III) was obtained (230 mg) as a brown-solid material. It had  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 1.15 (t, J = 7 Hz, CH<sub>3</sub>), 4.08 (q, J = 7 Hz, CH<sub>2</sub>), 5.20 (s, H-10), 7.0 (dd, J<sub>-1</sub> = 8 Hz, J<sub>-2</sub> = 2.5 Hz, H-2 + H-4 + H-5 + H-7), 7.52 (t, J = 8 Hz, H-3 + H-6), 12.18 (s, 2 × OH); m/z (EI): 298, 254, 226, 225, 197, 180, 169 and 168 (M<sup>+</sup>, 21.2, 3.8, 57.9, 100, 52.8, 2.8, 5.6 and 7.5%); m/z (CI) [460, (triethoxycarbonyl substituted isomer + NH<sub>4</sub>)<sup>+</sup>, 1.3%], [443, (triethoxycarbonyl-substituted isomer + H)<sup>+</sup>, 0.3%], [388, (diethoxycarbonyl-substituted isomer + NH<sub>4</sub>)<sup>+</sup>, 1.5%], [371, (diethoxycarbonyl-substituted isomer + H)<sup>+</sup>, 2.6%], [316, (M + NH<sub>4</sub>)<sup>+</sup>, 0.5%], [299, (M + H)<sup>+</sup>, 100%], 227 and 226 (27.4 and 26.5%).

This fraction was identified as a mixture of 10-ethoxycarbonyl-1,8-dihydroxy-9-anthrone, 1-O-, 10-C-diethoxycarbonyl-8-hydroxy-9-anthrone and 1-O-, 8-O-, 10-C-triethoxycarbonyl-9-anthrone.

### (3) 10-Isopropylloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with isopropyl chloroformate (0.48 mL, 4.8 mmol) was carried out. The crude product obtained was a dark green semi-solid material (1.612 g). Analytical TLC on silical gel (CH<sub>2</sub>Cl<sub>2</sub>) showed four spots. Column chromatography (1.612 g of crude product) on silica gel 60 (CH<sub>2</sub>Cl<sub>2</sub>) gave four fractions:

Fraction (I) was identified as pure anthralin (340 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-isopropylloxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (270 mg, 0.865 mmol, 21.7%), m.p. 124–125°C (Found: C, 69.2; H, 5.1; C<sub>18</sub>H<sub>16</sub>O<sub>5</sub> requires C, 69.2; H, 5.1%).  $\bar{\nu}$ : 2954 s, 1762 m, 1722 s, 1630 s, 1602 s, 1579 m, 1490 m, 1400 m, 1365 m, 1350 m, 1328 m, 1273 s, 1220 s, 1185 m, 1166 m, 1146 s, 1024 m, 758 s and 669 m cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 1.13 (d, J = 6 Hz, 2 × CH<sub>3</sub>), 4.90 (septet, J = 6 Hz, CH(CH<sub>3</sub>)<sub>2</sub>), 5.15 (s, H-10), 6.96 (dd, J<sub>-1</sub> = 8 Hz, J<sub>-2</sub> = 2.5 Hz, H-2 + H-4 + H-5 + H-7), 7.48 (t, J = 8 Hz, H-3 + H-6), 12.18 (s, 2 × OH); m/z (EI): 312, 268, 226, 225, 197, 180, 169, 168 and 43 (M<sup>+</sup>, 2.5, 1, 57.5, 56.2, 25.6, 2.8, 4, 5.1 and 100%); m/z (CI): [330, (M + NH<sub>4</sub>)<sup>+</sup>, 1.1%], [313, (M + H)<sup>+</sup>, 100%], 227 (87, 9%), 226 (38.2%).

Fraction (III): A yellow-orange sticky oil (96 mg) was obtained. On the basis of its <sup>1</sup>H NMR MS (EI and CI) and IR, it was identified as a 1 : 1 mixture of 10-isopropylloxycarbonyl-1,8-dihydroxy-9-anthrone and 1-O- and 10-C-di-isopropylloxycarbonyl-8-hydroxy-9-anthrone, respectively.

Fraction (IV): A yellow-green solid material (133 mg) was obtained. On the basis of its <sup>1</sup>H NMR, MS (EI and CI) and IR, it was identified as a 1 : 9 mixture of 10-isopropylloxycarbonyl-1,8-dihydroxy-9-anthrone and 1-O- and 10-C-di-isopropylloxycarbonyl-8-hydroxy-9-anthrone, respectively.

### (4) 10-*n*-Propylloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with 1-propyl chloroformate (0.64 mL, 4.8 mmol) was carried out. The crude product obtained was a dark green semi-solid material (1.594 g). Analytical TLC on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) showed four spots. Column chromatography (1.594 g of crude product) on silica gel 60 (CH<sub>2</sub>Cl<sub>2</sub>) gave four fractions:

Fraction (I) was identified as pure anthralin (321 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-propylloxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound

(320 mg, 1.026 mmol, 25.8%), m.p. 93–95°C (Found: C, 69.1; H, 5.1;  $C_{18}H_{16}O_5$  requires C, 69.2; H, 5.1%).  $\bar{\nu}$ : 2924 s, 2854 s, 1721 m, 1630 s, 1601 s, 1491 m, 1365 m, 1328 m, 1275 s, 1219 s, 1184 m, 1146 s, 1076 m, 1054 m and 792  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 0.75 (t,  $J = 7.5$  Hz,  $\text{CH}_3$ ), 1.51 (sextet,  $J = 7$  Hz,  $\text{CH}_2$ , 3.96 (t,  $J = 6.5$  Hz,  $\text{O}-\text{CH}_2$ ), 5.2 (s, H-10), 6.98 (dd,  $J_{-1} = 8$  Hz,  $J_{-2} = 4$  Hz, H-2 + H-4 + H-5 + H-7), 7.51 (t,  $J = 8$  Hz, H-3 + H-6), 12.17 (s,  $2 \times \text{OH}$ );  $m/z$  (EI): 312, 226, 225, 197 and 43 ( $M^+$ , 16.6, 100, 89.6, 36.9 and 86.1%);  $m/z$  (CI): [330, ( $M + \text{NH}_4$ ) $^+$ , 43.4%], [313, ( $M + \text{H}$ ) $^+$ , 51.6%], 227 (100%), 112 (72.8), 197 (5.6%).

Fraction (III) (30 mg) and fraction (IV) (126 mg) were complicated and no further work was done on them.

### (5) 10-*n*-Butyloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with 1-butyl chloroformate (0.61 mL, 4.8 mmol) was carried out. The crude product obtained was a dark green semi-solid material (1.572 g). Analytical TLC on silica gel ( $\text{CH}_2\text{Cl}_2$ ) showed three spots. Column chromatography (1.572 g of crude product) on silica gel 60 ( $\text{CH}_2\text{Cl}_2$ ) gave four fractions:

Fraction (I) was identified as pure anthralin (130 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-butyloxy-carbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (263 mg, 0.832 mmol, 21%), m.p. 96–98°C (Found: C, 70; H, 5.6;  $C_{19}H_{18}O_5$  requires C, 69.94; H, 5.5%).

$\bar{\nu}$ : 2924 s, 2854 s, 1723 m, 1630 s, 1577 m, 1488 m, 1363 m, 1329 m, 1273 s, 1219 s, 1174 m, 1150 s, 1073 m, 1026 m and 792  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 0.8 (t,  $J = 7$  Hz,  $\text{CH}_3$ ), 1.26 (sextet,  $J = 7$  Hz,  $\text{CH}_2\text{CH}_3$ ), 1.47 (quintet,  $J = 7$  Hz,  $\text{CH}_2-\text{CH}_2\text{CH}_3$ ), 4 (t,  $J = 6.5$  Hz,  $\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 5.2 (s, H-10), 6.98 (dd,  $J_{-1} = 8$  Hz,  $J_{-2} = 4$  Hz, H-2 + H-4 + H-5 + H-7), 7.51 (t,  $J = 8$  Hz, H-3 + H-6), 12.18 (s,  $2 \times \text{OH}$ );  $m/z$  (EI) 326, 226, 225, 197, 180, 169, 168 and 57 ( $M^+$ , 12.5, 100, 70.8, 34, 3.2, 4.8, 6.9 and 60.2%);  $m/z$  (CI): [344, ( $M + \text{NH}_4$ ) $^+$ , 17.8%], [327, ( $M + \text{H}$ ) $^+$ , 93%], 227 (100%).

Fraction (III) (211 mg) and Fraction (IV) (68 mg) were complicated and no further work was done on them.

### (6) 10-Isobutyloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with 1-isobutyl chloroformate (0.63 mL, 4.8 mmol) was carried out. The crude product obtained was a dark green semi-solid material (1.512 g). Analytical TLC on silica gel ( $\text{CH}_2\text{Cl}_2$ ) showed four spots. Column chromatography (1.512 g of crude product) on silica gel 60 ( $\text{CH}_2\text{Cl}_2$ ) gave four fractions:

Fraction (I) was identified as pure anthralin (190 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-isobutyloxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (380 mg, 1.166 mmol, 29.3%), m.p. 122–124°C (Found: C, 69.64; H, 5.51;  $C_{19}H_{18}O_5$  requires C, 69.94; H, 5.5%).  $\bar{\nu}$ : 2923 s, 2854 s, 1726 m, 1627 s, 1599 m, 1448 m, 1375 m, 1336 m, 1271 s, 1200 s, 1174 m, 1166 s, 1074 m, 1031 m and 769  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 0.7 (t,  $J = 7$  Hz,  $2 \times \text{CH}_3$ ), 1.76 (m,  $J = 7$  Hz,  $\text{CH}(\text{CH}_3)_2$ ), 3.76 (d,  $J = 7$  Hz,  $\text{CH}_2$ ), 5.21 (s, H-10), 7 (dd,  $J_{-1} = 8$  Hz,  $J_{-2} = 4.5$  Hz, H-2 + H-4 + H-5 + H-7), 7.50 (t,  $J = 8$  Hz, H-3 + H-6), 12.17 (s,

2 × OH); *m/z* (EI): 326, 226, 225, 197, 180, 169, 168 and 57 ( $M^+$ , 20.2, 95.5, 72.3, 48.2, 7, 7.3, 11 and 100%); *m/z* (CI): [344, ( $M + NH_4$ )<sup>+</sup>, 22.4%], [327, ( $M + H$ )<sup>+</sup>, 86%] 227 (100%).

Fraction (III): A green-dark sticky oil (150 mg) was obtained. On the basis of its <sup>1</sup>H NMR, MS (EI and CI) and IR, it was identified as a 1 : 1 mixture of 10-isobutyloxycarbonyl-1,8-dihydroxy-9-anthrone and 1-O- and 10-C-di-isobutyloxycarbonyl-8-hydroxy-9-anthrone, respectively.

Fraction (IV): A dark sticky oil (70 mg) was obtained. On the basis of its <sup>1</sup>H NMR, MS (EI and CI) and IR, it was identified as a 1 : 6 mixture of 10-isobutyloxycarbonyl-1,8-dihydroxy-9-anthrone and 1-O-, 10-C-di-isobutyloxycarbonyl-8-hydroxy-9-anthrone, respectively.

### (7) 10-Phenylloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with phenyl chloroformate (0.6 mL, 4.8 mmol) was carried out. The crude product obtained was a dark green semi-solid material (1.645 g). Analytical TLC on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) showed four spots. Column chromatography (1.645 g of crude product) on silica gel 60 (CH<sub>2</sub>Cl<sub>2</sub>) gave four fractions:

Fraction (I) was identified as pure anthralin (63 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-phenyloxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (600 mg, 1.1734 mmol, 43.6%), m.p. 155–157°C (Found: C, 72.6; H, 4.2; C<sub>21</sub>H<sub>14</sub>O<sub>5</sub> requires C, 72.8; H, 4.1%).

$\bar{\nu}$ : 2924 s, 2854 s, 1751 m, 1630 s, 1598 m, 1448 m, 1370 m, 1329 m, 1273 s, 1217 s, 1193 m, 1164 s, 1074 m, 1024 m and 762 m cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>, 300 MHz): 5.45 (s, H-10), 6.82 (d, *J* = 8 Hz, H-2 + H-7), 7.0 (d, *J* = 8 Hz, H-4 + H-5), 7.16 (dd, *J*<sub>1</sub> = 7.5 Hz, *J*<sub>2</sub> = 1 Hz, H-2' + H-6'), 7.19 (t, *J* = 7.5 Hz, H-4'), 7.31 (t, *J* = 8 Hz, H-3' + H-5'), 7.57 (t, *J* = 8 Hz, H-3 + H-6), 12.24 (s, 2 × OH); *m/z* (EI): 346, 252, 226, 225, 197, 169, 168 and 77 ( $M^+$ , 11.7, 19.7, 34.4, 100, 36.8, 4.3, 7.8 and 24%); *m/z* (CI): [364, ( $M + NH_4$ )<sup>+</sup>, 2.2%], [327, ( $M + H$ )<sup>+</sup>, 50.8%], 253 (8.7%), 252 (2%), 227 (100%), 226 (25.4%), 225 (10.5%), 197 (9.4%).

Fraction (III): A dark brown solid material (240 mg) was obtained. On the basis of its <sup>1</sup>H NMR, MS (EI and CI) and IR it was identified as a 1 : 1 mixture of 10-phenyloxycarbonyl-1,8-dihydroxy-9-anthrone and 1-O-, 10-C-di-phenyloxycarbonyl-8-hydroxy-9-anthrone, respectively.

Fraction (IV): Its <sup>1</sup>H NMR showed a very complicated mixture. No further work was done on it.

### (8) Benzylloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with benzyl chloroformate (0.69 mL, 4.8 mmol), was carried out. The crude product obtained was a brown solid material (1.296 g). Analytical TLC on silica gel (CH<sub>2</sub>Cl<sub>2</sub>) showed three spots. Column chromatography (1.296 g of crude product) on silica gel 60 (CH<sub>2</sub>Cl<sub>2</sub>) gave three fractions:

Fraction (I) was identified as pure anthralin (537 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-benzylloxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (420 mg, 1.17 mmol, 29.3%), m.p. 112–114°C (Found: C, 73.2; H, 4.4; C<sub>22</sub>H<sub>16</sub>O<sub>5</sub> requires C, 73.3; H, 4.4%).

$\bar{\nu}$ : 2924 s, 2854 s, 1725 m, 1626 s, 1597 m, 1486 m, 1458 m, 1376 m, 1272 m, 1210 m, 1153 m, 1074 s, 963 w, 925 w and 738 m  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 5.05 (s,  $\text{CH}_2$ ), 5.25 (s, H-10), 6.99 (d,  $J = 8$  Hz, H-4 + H-5), 7.28 (dd,  $J_{-1} = 6.5$  Hz,  $J_{-2} = 2.5$  Hz, H-3' + H-4' + H-5'), 7.48 (t,  $J = 8$  Hz, H-3 + H-6), 12.19 (s,  $2 \times \text{OH}$ );  $m/z$  (EI): 360, 226, 225, 197, 169, 168 and 91 ( $\text{M}^+$ , 1.6, 27.3, 73.4, 17.8, 1.9, 2.8 and 100%);  $m/z$  (CI): [361, ( $\text{M} + \text{H}$ ) $^+$ , 38.7%], 227 (100%) and 197 (4.9%).

Fraction (III): A green sticky oil (111 mg) was obtained. On the basis of its  $^1\text{H}$  NMR, MS (EI and CI) and IR, it was identified as a 1 : 4 mixture of 10-benzoyloxycarbonyl-1,8-dihydroxy-9-anthrone and 1-O-, 10-C- di-benzoyloxycarbonyl-8-hydroxy-9-anthrone, respectively.

### (9) Allyloxycarbonyl-1,8-dihydroxy-9-anthrone

The same procedure as (1), but with allyl chloroformate (0.51 mL, 4.8 mmol) was carried out. The crude product obtained was a dark brown solid material (1.227 g). Analytical TLC on silica gel ( $\text{CH}_2\text{Cl}_2$ ) showed three spots. Column chromatography (1.227 g of crude product) on silica gel 60 ( $\text{CH}_2\text{Cl}_2$ ) gave three fractions:

Fraction (I) was identified as pure anthralin (390 mg).

Fraction (II): Recrystallization of fraction (II) from *n*-hexane gave 10-allyloxycarbonyl-1,8-dihydroxy-9-anthrone as a yellow-needle crystalline compound (320 mg, 1.032 mmol, 26%), m.p. 108–110°C (Found: C, 70.1; H, 4.6;  $\text{C}_{18}\text{H}_{14}\text{O}_5$  requires C, 69.7; H, 4.5%).  $\bar{\nu}$ : 2923 s, 2854 s, 1726 m, 1629 s, 1601 m, 1454 m, 1376 m, 1273 s, 1219 s, 1193 m, 1150 s, 970 s, 910 s and 739 m  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ , 300 MHz): 4.50 (dt,  $J_{-1} = 5.5$  Hz,  $J_{-2} = 1.4$  Hz,  $\text{OCH}_2$ ), 5.05 (dq,  $J_{-1} = 18.3$  Hz,  $J_{-2} = 1.4$  Hz,  $\text{H}_A$  of  $=\text{CH}_2$ ), 5.13 (dq,  $J_{-1} = 10.5$  Hz,  $J_{-2} = 1.4$  Hz,  $\text{H}_B$  of  $=\text{CH}_2$ ), 5.23 (s, H-10), 5.75 (m,  $\text{CH}=\text{CH}$ ), 6.98 (d,  $J = 8$  Hz, H-2 + H-7 or H-4 + H-5), 7.0 (d,  $J = 8$  Hz, H-4 + H-5 or H-2 + H-7), 7.52 (t,  $J = 8$  Hz, H-3 + H-6), 12.19 (s,  $2 \times \text{OH}$ );  $m/z$  (EI): 310, 226, 225, 197, 180, 169, 168 and 57 ( $\text{M}^+$ , 13.3, 89.7, 100, 63.5, 7.4, 8.7, 9.9 and 12.6%);  $m/z$  (CI): [328, ( $\text{M} + \text{NH}_4$ ), 1.8%], 311 [( $\text{M} + \text{H}$ ) $^+$ , 31.3%], 227 (100%) and 197 (2.5%).

Fraction (III): A sticky oil (100 mg) which solidified on standing was obtained. Its  $^1\text{H}$  NMR showed it is similar to fraction (II). No further work was done on it.

## RESULTS AND DISCUSSION

Anthralin does not come into the category of compounds, which always give good-yielding reactions; since the compound is so prone to oxidation, it is usual to isolate several products, including the dehydrodimer and the anthraquinone, when attempting synthesis from it. It is well known that anthralin is very prone to autooxidation, especially in alkaline medium, where the radical (II) is formed. This species can then dimerize to give (III) or undergo oxidation reactions in the presence of air to afford 1,8-dihydroxy-9,10-anthraquinone (IV) (Danthrone). On the other hand C-10 disubstituted anthralin derivatives do not undergo oxidation under these conditions. Therefore, the implication is that oxidation through to the final "anthralin brown-like compounds" is only possible in the presence of at least one free methylenic proton at the C-10. It also implies that oxidation is initiated at the 10-position.

The alkyloxycarbonyl series was chosen to study the effect of the growing carbon chain of the ester substituent on the lipophilicity and penetrating ability of

the drugs through the skin body of the psoriatic patients and also increasing the steric hindrance to the formation of the dimers.

The 10-monosubstituted products were formed as yellow crystalline needles with the yield from 21 up to 44%. A summary of the results is given in Table-1. Substitution at OH of C-1 and disubstitution at C-10 occurred with much lower yield but no further works were done on these di- and tri-substituted derivatives.

TABLE-1  
SUMMARY OF THE RESULTS

No.	R- group	Crude product weight (g)	Amount of anthralin recovered		10-Alkyloxycarbonyl-1,8-dihydroxy-9-anthrone			
			(mg)	Yield (%)	Wt. (mg)	m.w.	mmol	Yield (%)
1.	-CH <sub>3</sub>	1.125	381	42.40	312	284	1.099	27.6
2.	-C <sub>2</sub> H <sub>5</sub>	1.496	192	21.35	290	298	0.973	24.5
3.	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	1.612	340	37.78	270	312	0.865	21.7
4.	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	1.594	321	35.67	320	312	1.026	25.8
5.	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	1.572	130	14.44	263	326	0.832	21.0
6.	<i>i</i> -C <sub>4</sub> H <sub>9</sub>	1.512	190	21.11	380	326	1.166	29.3
7.	-C <sub>6</sub> H <sub>5</sub>	1.645	63	7.00	600	346	1.734	43.6
8.	-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	1.296	537	59.67	420	360	1.167	29.3
9.	-CH <sub>2</sub> =CHCH <sub>2</sub>	1.227	390	43.33	320	310	1.032	26.0

Preliminary results obtained on topical treatment of the newly synthesized anthralin derivatives on psoriatic patients at skin hospital in Manchester, U.K., were promising and have shown that these drugs are more effective with less severe side effects than the previously prescribed ones.

With increasing length of the carbon chain of the 10-alkoxycarbonyl substituent (from 1C to 4C), the staining and irritative activities of the molecule, due to bulkiness of the substituent and greater steric hindrance to the generation of staining dimers and inflammatory free radicals, decreased. More comprehensive and thorough clinical works and investigations are needed to clarify the application of these newly synthesized 10-alkoxycarbonylanthralin derivatives.

## REFERENCES

1. R.E. Ashton, P. Andre, N.J. Lowe and M. Whitefield, *J. Am. Acad. Derm.*, **9**, 173 (1983).
2. L. Juhlin, *Br. J. Derm.*, **105**, 20, 87 (1981)
3. K.K. Mustakallio, *Br. J. Derm.*, **105**, 20, 23 (1981).
4. K.K. Mustakallio, A.K. Pippi and E.K. Honkanen, *E.P.O.*, 017 420 A1 (1980).