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Multi-bromination of 1,8-dihydroxy-9-anthrone, important intermediates in the synthesis of antipsoriatic drugs

Ashnagar, A[1]* and Bruce, J.M.[2]

***[1]Pasteur Institute of Iran, Nanobiotechnology department, Pasteur Avenue, SQ.NO. 69, Post Code No. 1316943551, Tehran, Iran.**

[2]University of Manchester, Dept. of Chemistry, UK.
***Corres.author: alamdarashnagar@yahoo.com, Tel. No. 00982166953311, Fax No. 00982166465132**

Abstract: 10-bromo-1,8-dihydroxy-9-anthrone (10-bromoanthralin) was synthesized with precise ratio of bromine to anthralin (1.10:1), respectively. With this ratio of the reagents, the reaction is repetitive at any scale. This compound is a highly significant intermediate for the synthesis of many anthralin derivetised antipsoriatic drugs. Bromination at both benzylic and aromatic ring positions of anthralin was achieved without using any conventional Lewis acid catalyst. Also, multibromination of aromatic rings of anthralin was achieved exclusively in acetic acid and acetic acid/chloroform solvent.
Keywords: Anthralin, 1,8-dihydroxy-9-anthrone, antipsoriatic drugs, 10-bromoanthralin.

INTRODUCTION

Anthralin **(I)** is an effective topical agent for the treatment of psoriasis. It was first synthesized in 1916. Anthralin was first used in Germany, and later in the Ingram regimen in Britain, but it has never been popular with American dermatologists. This is probably due to the side effects of staining and irritation of the skin. Attempts to reduce these side effects by using low concentration, short contact therapy, and concomitant steroid therapy, have been only partially successful.[1]

The structural formula of anthralin is given in the US Pharmacopoeia as 1,8,9-trianthracenetriol[2] or in chemical references as 1,8,9-trihydroxyanthracene.[3] The central hydroxyl group in its enolic form readily undergoes tautomerism to form a ketonic structure by migration of the hydrogen atom from the 9-hydroxyl group to the 10-carbon atom. This results in a carbonyl group in the 9 position and a methylene group in the 10 position (Fig. 1). Anthralin with two hydroxyl groups in the 1 and 8 positions is stabilized by hydrogen bonding in the ketonic form. For this reason anthralin exists totally in the ketonic form. This was confirmed by Hellier and Whitefield[4] using infrared (IR) absorption spectroscopy, by Avdovich and Neville[5] using nuclear magnetic resonance (NMR) spectroscopy, and by Ahmed[6] using x-ray analysis.

The accepted systematic chemical name for anthralin is 1,8-dihydroxy-9-anthrone as defined in the British Pharmacopoeia, where it is called dithranol.[7]

The anthralin molecule possesses the required dual solubility characteristics for efficient penetration through the epidermis. The upper part of the molecule is hydrophilic due to the presence of the oxygen atoms, while the lower part of the molecule, consisting of only carbon and hydrogen in the anthracene nucleus, is lipophilic (Fig. 1). Krebs and Schaltegger[8] have shown that the association of the hydroxyl and the carbonyl groups at one end with the 10-methylene group at the other end is essential for the antipsoriatic activity of anthralin.

The release of a hydrogen atom from the methylene group in the 10 position initiates the formation of biologically active free radicals (**XI**). Although these radicals may be responsible for skin irritancy and produce oxidation products that cause staining, they are presumably central to the clinical action of the drug; hence difficulty of separating activity from side effects (a mechanism is proposed in figure 2).

Prevention of free radical formation by substitution of both hydrogen atoms at C-10 by alkyl, propyl or propanal groups produced inactive compounds.[9] Omission of the methylenic group altogether, or replacement by oxygen again led to loss of antipsoriatic activity.[8]

Since Unna first examined anthralin and 1-hydorxy-9-anthrone for the treatment of psoriasis[10], much research has been performed into discovering derivatives that retain clinical efficacy with reduced side effects. In order to synthesis anthralin derivatives with retaining clinical efficacy and reduced side effects, one has to synthesis 10-bromoanthralin; a very interesting intermediary compound. In the present work a lot of attention was focused on the synthesis of this intermediary compound. This substituted10-bromo atom can be replaced by many other susbtituents like alkyl, acyl, and ester groups. During the course of this work, other interesting bromoanthralin compounds where obtained with bromine atoms substituted on the various positions of the aromatic rings without using any Lewis acid catalyst.

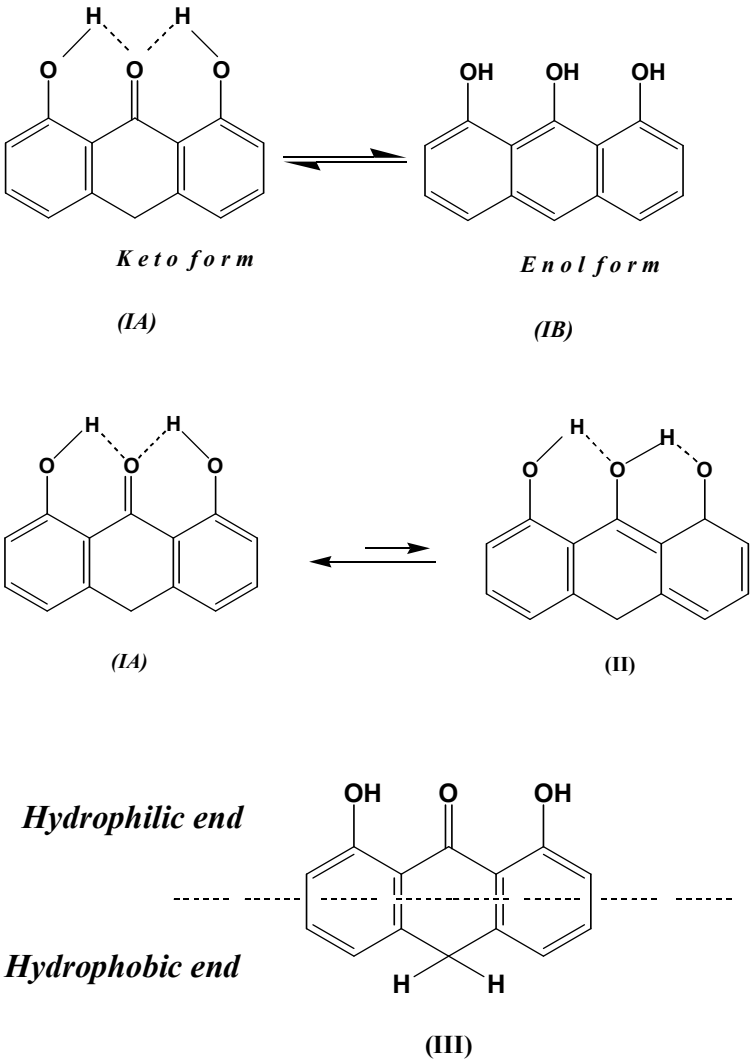
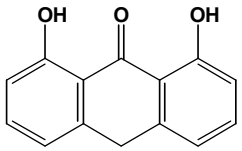


Fig. 1. Anthralin tatuomerism showing stabilization of ketonic form by hydrogen bonds



(XI)

$^{\cdot}$AnH

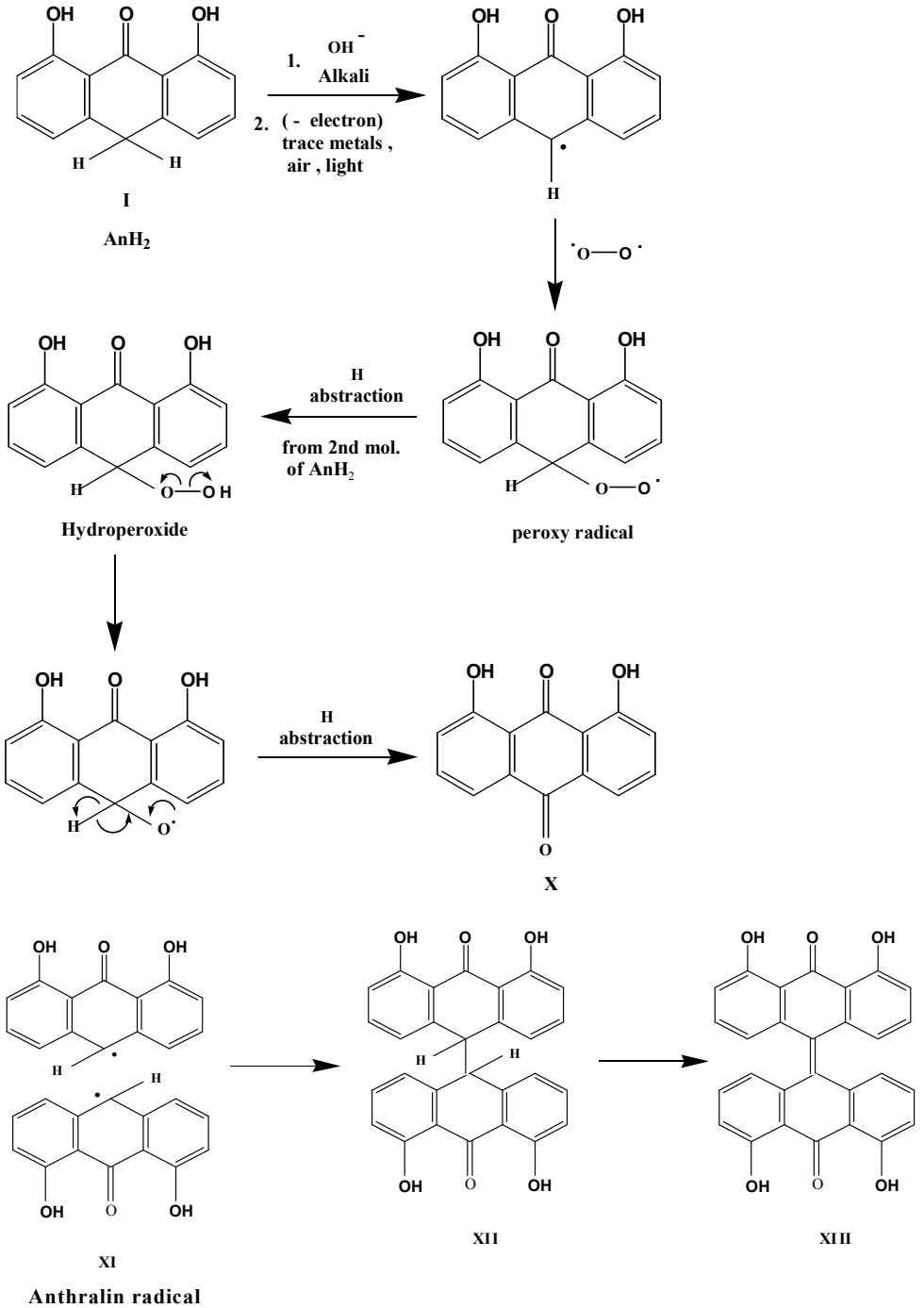


Fig.2. Mechnism of the formation of by products from anthralin therapy

EXPERIMENTAL

Nuclear magnetic resonance (n.m.r.) spectra were recorded with Brucker (300 MHz) spectrometers. Tetramethylsilane (TMS) was used as an internal standard and coupling constants (J) are expressed in Hz. Low resolution Electron Impact (EI) mass spectra were recorded on A.E.I. MS30 and Kratos MS25 instruments; mass measurements (M.M.) were made on the former, and Chemical Ionization (CI) spectra were recorded on the latter using ammonia as the reagent gas. All the chemicals were purchased from BDH, Aldrich, Fluka and Merck suppliers. All solvents and liquid reagent were distilled prior to use. Analytical and preparative TLC were carried out with Merck silica gel plates (5×10 cm×0.25 mm and 10×20 cm×0.25 mm), type $60F_{254}$.

10-bromo-1,8-dihydroxy-9-anthrone (10-Bromoan - thralin) (X): 1,8-Dihydroxy-9-anthrone (anthralin) (25 g, 110.6 mmol) was dissolved in freshly distilled carbon disulphide CS_2 (1000 mL) at reflux. Bromine (19.53 g, 122.06 mmol, 1.10 equivalents) was added dropwise over 20 minutes with stirring at reflux. The solution was left stirring at reflux for 8 hours then, cooled to room temperature and left standing overnight. Filtration gave a yellow needle crystalline material. The filtrate was concentrated to fifth (1/5) of its volume by removal of the solvent on rotary evaporator. The yellow precipitate was filtered off, dried and then recrystallized from CS_2 to give 10-bromo-1,8-dihydroxy-9-anthrone (10-Bromoanthralin) (total weight 25 g, 74%), m.p. 149-151 °C (Found: C, 55; H, 2.8; Br, 25.9; requires $C_{14}H_9BrO_3$; C, 55.1; H, 2.95; Br, 26.2%). It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 6.54 (s, C_{10} – H), 7.0 (dd, J_1=9, J_2=1.5 Hz, H-2 + H-7), 7.07 (d, J=9 Hz, H-4 + H-5), 7.37 (t, J=9 Hz, H-3 + H-6), 12.12 (s, 2×OH); ^{13}CNMR ppm ($CDCl_3$, 75 MHz) 43.734 (C-10), 114.109, 141.614, 163.120, 192.467 (C-9); MS (E.I.) m/z 307 (8.2%), 306 [$(M+2)^+$, 65.6%], 305 (16.4%), 304 [M^+, 68.1%], 277 [$(305\text{-}CO)^+$, 5.5%], 275[$(303\text{-}CO)^+$, 6.2%], 227 (5.5%), 226 (83.5%), 225 [$(M\text{-}Br)^+$, 100%], 197 (88.5%); C.I. (NH_3) m/z 307 [$(M+2+H)^+$,28.8%], 305 [$(M+H)^+$,29%], 227 (100%).

4-Bromo-1,8-dihydroxy-9-anthrone(VII) : Anthralin (2.26 g, 10 mmol) was dissolved in glacial acetic acid (180 mL), chloroform (45 mL), and ethanol (30 mL) at room temperature while magnetically stirring. Bromine (1.6 g, 10 mmol) was added to the solution. The progress of the reaction was monitored by ^{1}HNMR spectroscopy. After about 20 minutes from the addition of bromine, a voluminous precipitate was formed. After 1.5 hours, ^{1}HNMR showed a mixture of 4-bromo-1,8-dihydroxy-9-anthrone and an unknown compound. The mixture was left stirring at room temperature overnight. ^{1}HNMR showed a 4:1 mixture of the 4-bromo-isomer and an unknown compound, respectively. Suction filtration gave a yellow solid material (950 mg). Soxhlet extraction with n-hexane gave the following results:

(i)- A solid material formed in the distilling flask. ^{1}HNMR showed a 7:1 mixture of the 4-bromo-isomer and an unknown compound, respectively.

(ii)- Solid material left in the thimble. Its ^{1}HNMR showed a 7:1 mixture of the 4-bromo-isomer and an unknown compound, respectively.

Solid materials from both (i) and (ii) were combined and recrystallized from n-hexane, a yellow crystalline material (720 mg, 23.6%), m.p. 163-165 °C (lit.[11]169 °C) (Found: C, 54.6; H, 2.90; Br, 26.1; requires $C_{14}H_9BrO_3$; C, 55.08; H, 2.95; Br, 26.2%). It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 4.23 (s, 2× C_{10} – H), 6.87 (d, J=9, H-2), 6.94 (d, J=8 Hz, H-7), 6.98 (dd, , J_1=7.9, J_2=0.9 Hz, H-5), 7.54 (d, J=7.9 Hz, H-6), 7.7 (d, J=9 Hz, H-3), 12.12 (s, 1× OH), 12.52 (s, 1× OH); ^{13}CNMR ppm ($CDCl_3$, 75 MHz) 34.651 (C-10), 115.328, 115.842, 117.725, 117.899, 119.150, 136.873, 139.872, 140.038, 141.350, 162.739 (C-1+ C-8), 193.675 (C-9); MS (E.I.) m/z 306[$(M)^+$, 99.7%], 305 (22.3%), 304[$(M)^+$, 100%], 303 (7.3%), 226 (24.9%), 225 [$(M\text{-}Br)^+$, 97.6%], 197 (62.6%), 169 (5%), 168 (15.5%).

This fraction was identified as 4-bromo-1,8-dihydroxy-9-anthrone. Evaporation of the mother liquor from (i) gave a very bright yellow solid material which was shown by ^{1}HNMR to be pure 4,5-dibromo-1,8-dihydroxy-9-anthrone **(VIII).**

4,10-Dibromo-1,8-dihydroxy-9-anthrone(IV):

Anthralin (1.13 g, 5 mmol) was dissolved in CS_2 (80 mL) at reflux. Bromine (1.6 g, 10 mmol) was added dropwise over 10 minutes. The progress of the reaction was monitored by ^{1}HNMR. After 28 hours of refluxing, 8 more equivalents of bromine (6.4 g, 40 mmol) was added to the stirred solution. Refluxing was continued for totally 48 hours from the start, then, cooled to room temperature. The solvent was removed on a rotary evaporator. A solid material was recovered which was dried and recrystallized from CS_2 resulting a yellow crystalline material (1 g, 57%), m.p. 174-176 °C (Found: C, 43.7; H, 2.0; Br, 41.1; requires $C_{14}H_8Br_2O_3$; C, 43.75; H, 2.08; Br, 41.67%). It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 6.52 (s, C_{10} – H), 6.96 (d, J=9.1,H-2), 7.02(dd, J_1=8.3 Hz J_2=0.9 Hz, H-7), 7.1 (d, J=7.5 Hz, H-5), 7.54 (double doublets, J=8.3, J=7.5 Hz, H-6), 7.7 (d, J=9 Hz, H-3), 11.91 (s, OH), 12.33 (s, OH); ^{13}CNMR ppm ($CDCl_3$, 75 MHz) 44.547 (C-10), 113.736 (C-4), 113.775, 119.096, 120.87, 121.010, 121.191, 137.065, 137.601, 141.130, 141.407, 163.000 , 163.170, 192.072 (C-9); MS (E.I.)

m/z 386[$(M+4)^{+}$, 0.3%], 384[$(M+2)^{+}$, 0.5%], 382 [$(M)^{+}$, 0.3%], 307 [$(386\text{-}Br)^{+}$, 24.3%], 306 [$(384\text{-}^{81}Br+1)^{+}$, 86.2%], 305 [$(384\text{-}^{79}Br+1)^{+}$, 52.4%], 304 [$(382\text{-}Br+1)^{+}$, 85.5%], 303 [$(382\text{-}Br)^{+}$, 30.8%],277 [$(305\text{-}CO)^{+}$, 18.1%], 275[$(303\text{-}CO)^{+}$, 18.2%], 226 (51.9%), 225 (100%), 197 (87.8%), 168 (40.2%); C.I. (NH_3) m/z 387[$(386+1)^{+}$, 0.1%], 385[$(384+1)^{+}$, 0.3%], 383 [$(382)^{+}$, 0.1%], 308 (38.3%), 307 (100%), 306 (97.9%), 304 (30.8%), 228 (30.8), 227 (83.7), 226 (22.2%), 225 (23.9%). The ^{1}HNMR assignment was supported by NOE spectrum.

4,5-Dibromo-1,8-dihydroxy-9-anthrone(VIII):
Anthralin (2.26 g, 10 mmol) was dissolved in glacial acetic acid (180 mL), chloroform (45 mL), and ethanol (30 mL) at room temperature while magnetically stirring. Bromine (3.2 g, 1 mL, 20 mmol, 2 equivalents) was added to the solution. The progress of the reaction was monitored by ^{1}HNMR spectroscopy. After about 1.5 hours, ^{1}HNMR showed a 2:1 mixture of the 4-bromoisomer **(VII)** and 4,5-dibromoisomer **(VIII)**, respectively. The mixture was left stirring overnight. Again, its ^{1}HNMR showed a 2:1 mixture of the 4-bromoisomer **(VII)** and 4,5-dibromoisomer **(VIII)**, respectively. At this point 1.5 more equivalents of bromine was added and stirring was continued at room temperature for further 10 hours. Its ^{1}HNMR showed a 3:2 mixture of the 4,5-dibromoisomer **(VIII)** and 4-bromoisomer **(VII)**, respectively. Once again, 4 more equivalents of bromine was added and stirring was continued at room temperature for further 8 hours. Its ^{1}HNMR showed almost pure 4,5-dibromoisomer **(VIII)**. Suction filtration gave a yellow solid material which on recrystallization from chloroform afforded a very bright yellow needle crystalline material (1.46 g, 3.802 mmol, 38%), m.p. 239-240 °C (lit.[11]239 °C) (Found: C, 43.40; H, 2.0; Br, 41.85; requires $C_{14}H_8Br_2O_3$; C, 43.75; H, 2.08; Br, 41.67%). It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 4.14 (s, 2× C_{10} – H), 6.94 (d, J=9, H-2+ H-7), 7.78 (d, J=9 Hz, H-3+ H-6), 12.39 (s, 2× OH); ^{13}CNMR ppm ($CDCl_3$, 75 MHz) 36.658 (C-10), 112.633, 116.552, 117.916, 139.532, 140.442, 162.711 (C-1+ C-8), 193.374 (C-9); MS (E.I.) m/z 386[$(M)^{+}$, 49.8%], 385 (15.8%), 384[$(M)^{+}$, 100%], 383 (9.4%), 382[$(M)^{+}$, 51%], 306 (17.3%), 305 (87.5%), 304 (19.6%), 303 (88.4%), 277 (43%), 275(43.7%), 226 (1.1%), 225 (4.5%), 223 (1.2%).
The mother liquor was concentrated. Its ^{1}HNMR ($CDCl_3$300 MHz) showed a 1:1:1 mixture of tri-: tetra-: penta-bromo-substituted anthralin. The MS (E.I.) showed that mixture as well.

4,5,10-Tribromo-1,8-dihydroxy-9-anthrone(IX):
Anthralin (1.13 g, 5 mmol) was dissolved in CS_2 (80 mL) at reflux. Bromine (32 g, 200 mmol) in CS_2 (20 mL) was added dropwise over 30 minutes. The progress of the reaction was monitored by ^{1}HNMR. After 9 hours of refluxing, the desired product was formed.
Removal of the solvent on a rotary evaporator gave a solid material which was dried and recrystallized from $CHCl_3$ / n-C_6H_{14} (1: v/v). A very bright yellow orange crystalline material (2.1 g, 82%), m.p. 185-187 °C was obtained (Found: C, 36.5; H, 1.4; Br, 51.65; requires $C_{14}H_7Br_3O_3$; C, 36.3; H, 1.5; Br, 51.8%). It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 6.71 (s, C_{10} – H), 6.97 (d, J=9 Hz, H-2+H-7), 7.75(d, J=9 Hz, H-3+H-6),12.15 (s, OH); ^{13}CNMR ppm ($CDCl_3$, 75 MHz) 45.328 (C-10), 113.899, 115.183, 120.903, 139.410, 141.566, 162.931, 191.641 (C-9); MS (E.I.) m/z 466 [$(M+6)^{+}$, 0.2%], 464 [$(M+4)^{+}$, 1.1%], 462 [$(M+2)^{+}$, 1.1%], 461 [$(M+1)^{+}$, 0.2%], 387 (5.8%), 386 [$(M+4\text{-}^{79}Br+1)^{+}$, 42.7%], 385 [$(M+6\text{-}^{81}Br)^{+}$, 61.5%], 384 [$(M+2\text{-}^{79}Br+1)^{+}$, 71.1%], 383 [$(M+4\text{-}^{81}Br)^{+}$, 82.7%], 382 (42.3%), 381 [$(M\text{-}^{79}Br)^{+}$, 50.1%], 357 (15.4%), 355 (32.5%), 353 (16%), 306 (13.4%), 305 (69.8%), 304 (69.3%), 277 (45%), 276 (19.7%), 275 (46.7%), 226 (5.3%), 225 (7.5%), 139 (100%); C.I. (NH_3) m/z 455 [$(M+4+H)^{+}$, 0.3%], 463 [$(M+2+H)^{+}$, 0.3%], 387 (47.1), 386 (43.5%), 385 (100%), 384 (66.3%), 383 (88.9%), 382 (30.6%), 381 (24.6%). The ^{1}HNMR assignment was supported by NOE spectrum.

2,4,5,10-Tetrabromo-1,8-dihydroxy-9-anthrone (V):

a. Anthralin (1.130 g, 5 mmol) was dissolved in freshly distilled CS_2 (80 mL) at reflux. Bromine (48.05 g, 300 mmol , 60 equivalents) was added dropwise over 10 minutes. The progress of the reaction was monitored by ^{1}HNMR.

(i) After 8 hours of refluxing, almost pure 4,5,10-tribromo-1,8-dihydroxy-9-anthrone was obtained.

(ii) After 80 hours of refluxing, a mixture of 1:8 of tetra- : tri-substituted isomers was formed. At this time, more bromine (80 g, 100 equivalents) was added dropwise.

(iii) After 100 hours of refluxing from the start, a 1:1 mixture of tetra- :trisubstituted isomers was obtained.

(iv) After 118 hours of refluxing from the start, a mixture of 2:0.5:1 of tetra-:penta:trisubstituted isomers was obtained. At this time, more bromine (24.0g, 150 mmol, 30 equivalents) was added dropwise.

(v) After 125 hours of refluxing from the start, a 2:1 mixture of tetra-:pentasubstituted isomers was obtained. Longer refluxing resulted in the same mixture.

b. Anthralin (0.565 g, 2.5 mmol) was dissolved in freshly distilled CS_2 (50 mL) at reflux. Bromine (80 g, 500 mmol, 200 equivalents) was added dropwise over 10 minutes. The progress of the reaction was monitored by ^{1}HNMR. After 5 hours of refluxing, ^{1}HNMR showed the formation of a 2:1 mixture of tetra-:pentasubstituted isomers. Removal of the solvent on rotary evaporator gave a yellow solid material (1.383 g). Separation of the mixture was attempted by various conventional, preparative thin layer and column chromatography methods, but to no avail. It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 6.58 (s, C_{10} – H, penta-isomer), 6.62 (s, C_{10} – H, tetra-isomer), 6.98 (d, J=7.1 Hz, H-7 of tetra-isomer), 7.76(d, J=7.1 Hz, H-6 of tetra-isomer), 8.03 (s, H-3 of tetra-isomer), 8.06 (s, H-3+H-6 of penta-isomer), 11.95 (s, 1× OH of tetra-isomer), 12.64 (s, 2× OH of penta-isomer), 12.82 (s, 1× OH of tetra-isomer; MS (E.I.) m/z 545 (0.4%), 541 (1%), 543 (1.5%), 542 (1.7%), 541 (2.1%), 540 (0.9%), 539 (1.5%), 466 (5%), 465 (6.1%), 464 (15.9%), 463 (14.7%), 462 (15.5%), 461 (14.3%), 43 (100%); C.I. (NH_3) m/z 543 (1%), 542 (0.4%), 541 (0.7%), 539 (0.4%), 468 (1.6%), 467 (9.7%), 466(7.2%), 465 (28.8%), 464 (13.7%), 463 (34%), 462 (9.9%), 461 (12.7%), 387(55.7%), 386 (30.1%), 385 (76.8%), 384 (37.4%), 383 (60.9%), 307(83.6%), 305 (86.1%), 227 (80.1%), 32 (100%).

2,4,5,7,10-Pentabromo-1,8-dihydroxy-9-anthrone (VI):

Anthralin (1.130 g, 5 mmol) was dissolved in freshly distilled CS_2 (80 mL) at reflux. Bromine (80 g, 500 mmol , 100 equivalents) in CS_2 (30 mL) was added dropwise over 20 minutes. The progress of the reaction was monitored by ^{1}HNMR.

(i) After 6 hours of refluxing, almost pure 4,5,10-tribromo-1,8-dihydroxy-9-anthrone was obtained.

(ii) After 70 hours of refluxing, a 2:1 mixture of tetra-: tri-substituted isomers was formed. At this time, more bromine (80 g, 100 equivalents) in CS_2 (30 mL) was added dropwise.

(iii) After 100 hours of refluxing from the start, a 11:3 mixture of tetra- :pentasubstituted isomers was obtained.

(iv) After 112 hours of refluxing from the start, a mixture of 8:3.5 tetra-:penta:trisubstituted isomers was obtained. At this time, more bromine (80g, 500 mmol, 100 equivalents) in CS_2 (30 mL) was added dropwise.

(v) After 138 hours of refluxing from the start, a 1:2 mixture of tetra-:pentasubstituted isomers was obtained.

(vi) After 150 hours of refluxing from the start, almost pure pentasubstituted isomer was obtained which on recrystallization from CS_2 gave a yellow-orange needle crystalline material (2.07 g, 67%) m.p. 213-215 °C. It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 6.49 (s, C_{10} – H), 8.10 (s, H-3+H-6), 12.63 (s, 2× OH); ^{13}CNMR ppm ($CDCl_3$, 75 MHz) 54.091 (C-10), 114.142, 114.185, 114.333, 115.107, 137.814, 144.152, 159.532, 191.482 (C-9); MS (E.I.) m/z 546 [$(M-Br)^+$, 3.5%], 545 [$(M-Br)^+$, 20.9%], 544 (14.2%), 543 [$(M-Br)^+$, 69.7%], 542 (15.6%), 541 [$(M-Br)^+$, 72.7%], 540 (12.7%), 539 [$(M-Br)^+$, 79.2%], 538 (5.2%), 537 [$(M-Br)^+$, 19.1%], 497 (10.3%), 495 (10.3%), 463 (3.2%), 461 (6.7%), 459 4.5%), 297 (20.7%); C.I. (NH_3) m/z 623 (0.4%), 622(0.2%), 621 (0.6%), 619 (0.5%), 547 (22.9%), 546 (50.4%), 545 (76.8%), 544 (78.1%), 543 (100%), 542 (87.6%).541 (95.3%), 540 (80.8%), 539 (94.7%), 538 (44.5%), 537 (67.8%).

RESULTS AND DISCUSSION

As mentioned earlier, one of the main purposes of this work was to synthesis 10-bromoanthralin as an intermediary for synthesizing 10-alkyl-, acyl-, and ester derivatives of anthralin in order to reduce the side effects of anthralin while keeping their medical efficacies. This apparently simple and straightforward reaction is well documented in literature. However, the repetition of the procedures described in the literature over and over, all resulted in the formation of a mixture which the 10-bromoanthralin was the prominent fraction. It caused a lot of frustration; as usual the various reagents involved in this simple reaction were purchased from different suppliers (Aldrich, BDH, Fluka and Merck), and tried but to no avail. Then, the proportion of bromine to anthralin was changed by trial and error (4.38:1), respectively, and the progress of the reaction was monitored at intervals of 1, 2, 4, 6, 8, 10, 24, 48, 164,200, and 220 hours by 300MHz HNMR. The results indicated a mixture of the desired 10-bromoanthralin and other unwanted bromoanthralins with bromine atom/s substituted on the aromatic ring (table 1). The other proportions of bromine to anthralin (1.15:1; 1.5:1, respectively) were tried and the progress of the reaction was monitored at intervals of 1, 2, 4, 6 and 8 by 300MHz HNMR. Again the results indicated a mixture of the desired 10-

bromoanthralin and other unwanted bromoanthralin products with the bromine substituted on the aromatic ring (tables 2 and 3). Finally, the precise molar ratio of bromine to anthralin was obtained (1.10:1), respectively. The reaction with this molar proportion was used over and over again and at various scales; the results were promising and showed that the reaction is repetitive yielding the desired 10-bromoanthralin and without giving any by products. Preparation of 2,4,5,10-tetrabromo-1,8-dihydroxy-9-anthrone **(V)** was achieved as a 2:1 mixture with 2,4,5,7,10-pentabromo-1,8-dihydroxy-9-anthrone **(VI)** by using 200 equivalents of bromine to anthralin in carbon disulphide after refluxing for 5 hours. Separation of these two isomers was not successful. Preparation of almost pure 2,4,5,7,10-pentabromo-1,8-dihydroxy-9-anthrone **(VI)** was achieved by adding 200 equivalents of bromine to anthralin in carbon disulphide and refluxing for 150 hours. The isomers **(V)** and **(VI)** were not obtained under the conditions included in tables 1-3.

Therefore, we claim that by using this precise molar ratio of bromine to anthralin (1.10:1), respectively, this reaction can be carried out at any scale and is repetitive without needing for further separation of the desired product from any other by products which is a very difficult and time consuming process.

Regarding the formation of aromatic substitution products in this reaction, we were encouraged to pursue the formation of these compounds more carefully. By changing the molar ratio of bromine to anthralin, prolonging the reaction time in carbon disulphide solvent and monitoring the progress of the reaction by HNMR, we were able to synthesize 9-bromoanthralin, 4,10-dibromoanthralin, 4,510-tribromoanthralin, 2,4,5,10-tetrabromoanthralin and 2,4,5,7,10-pentabromoanthralin without using any conventional Lewis acid catalyst. The results are summarized in figure 3.

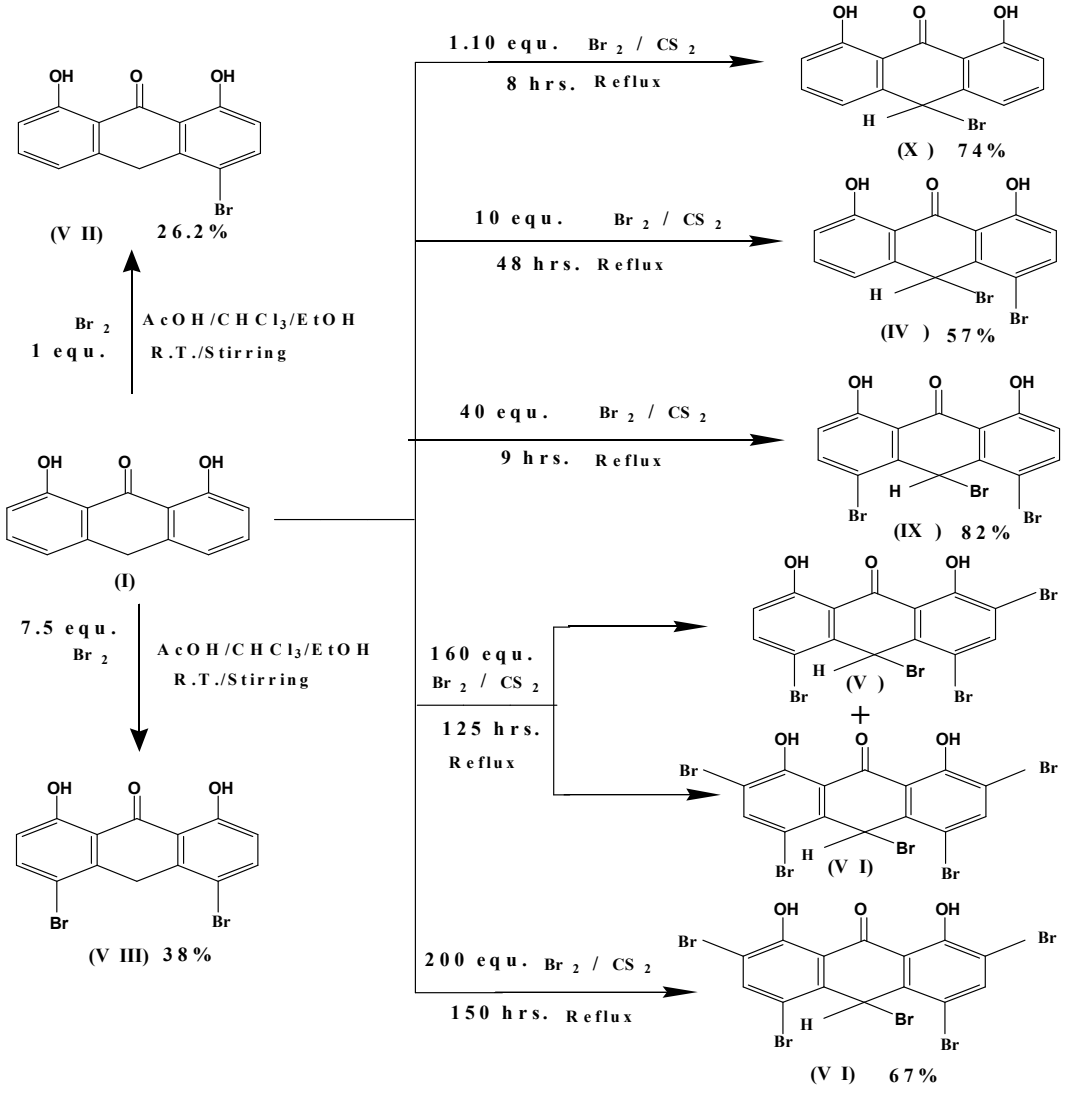


Figure 3. Bromination of anthralin under various conditions.

The bromination of anthralin was carried out in polar solvent (acetic acid/chloroform/ethanol) at room temperature as well. This reaction condition was not suitable for the preparation of 10-bromoanthralin isomer, and pushed the reaction towards the aromatic ring substitution reaction. By using 7.5 equivalents of bromine and prolonging the reaction time, almost pure 4,5-dibromoanthralin was obtained. The results are summarized in figure 4.

The reaction was also carried out in only acetic acid at room temperature. Again, this reaction condition was not suitable for the preparation of 10-bromoanthralin, and therefore, aromatic ring substitution reaction took place. Under each of the conditions used, always a mixture of aromatic ring substituted products was obtained. No attempts were made to separate these isomers. The results are summarized in figure 5. Therefore, by choosing the precise ratio of bromine to anthralin, proper solvent and proper reaction time, one can obtain either of the substituted bromoanthralin, either at the benzylic site exclusively or at the aromatic ring positions or at both positions of benzylic and aromatic. A mechanism for the bromination of anthralin in carbon disulphide and acetic acid is proposed in figure 6. Of course, introduction of extra bromine atoms at the aromatic sites of anthralin can change the hydrophilicity-lipophilicity equilibrium of anthralin derivative drugs and may change the medical efficacy and side effects of these antipsoriatic drugs. Further investigation and research work are needed in this regard.

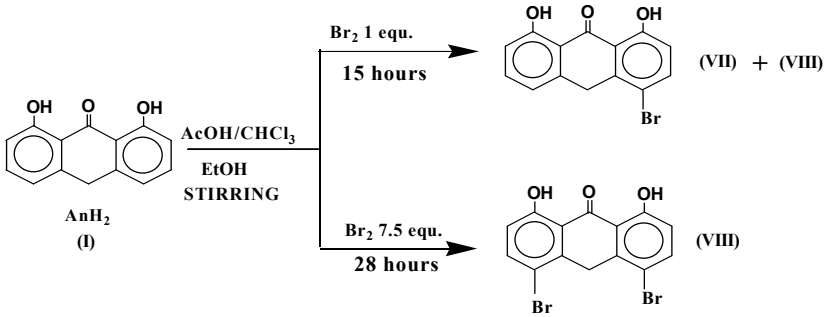


Figure 4. Bromination of anthralin in AcOH/$CHCl_3$ at different conditions.

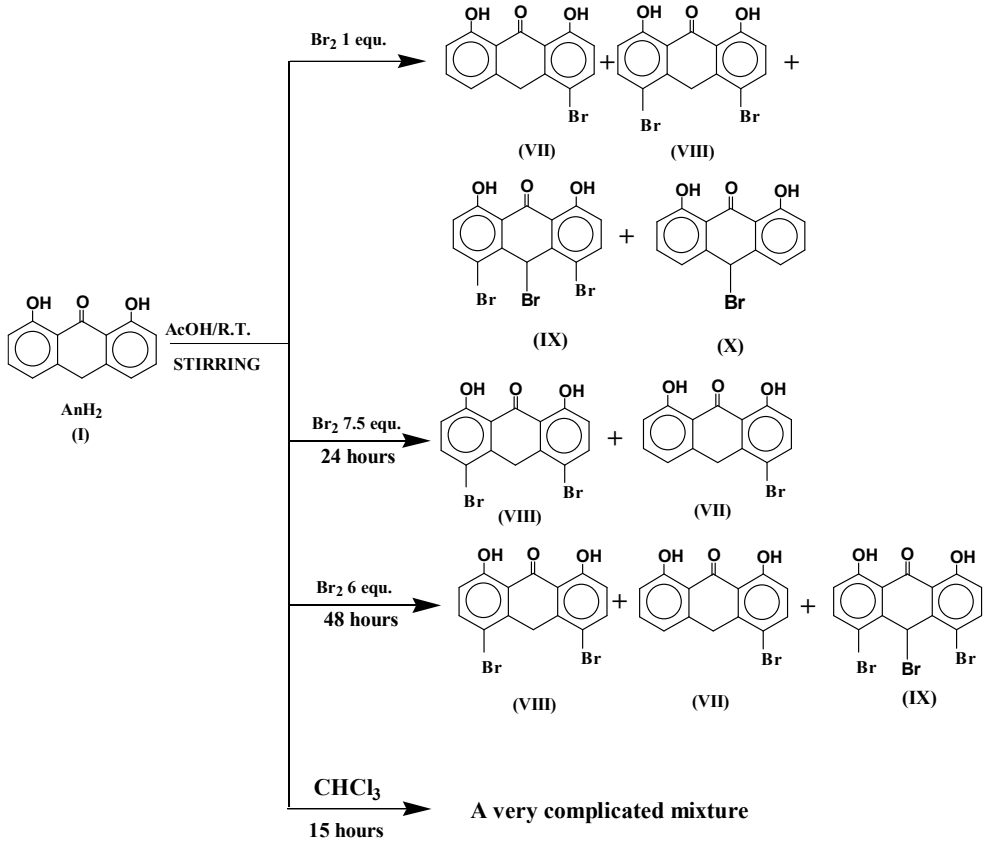


Figure 5. Bromination of anthralin in AcOH under various conditions.

Table 1. Isomer ratio of bromination of anthralin (AnH_2)

Reaction Interval Time (Hrs.)	AnH_2	4-$BrAnH_2$	10-$BrAnH_2$	4,5-Br_2AnH_2	4,10-Br_2AnH_2	4,5,10-Br_3AnH_2	2,4,5,10-Br_4AnH_2
1	1	1	-	2	-	-	-
2	-	1	0.33	0.33	2	0.16	-
4	-	1	0.25	0.25	2.8	0.4	-
6	-	1	Trace	0.125	2.75	0.5	-
8	-	1	Trace	Trace	2.5	0.57	-
10	-	1	Trace	Trace	4	1	-
24	-	1	Trace	Trace	13	3	-
48	-	-	Trace	-	12	3	-
80	-	-	-	-	10	3	-
164	-	-	-	-	5.4	3	-
220	-	-	-	-	1	2	-
250	-	-		-	-	4	1

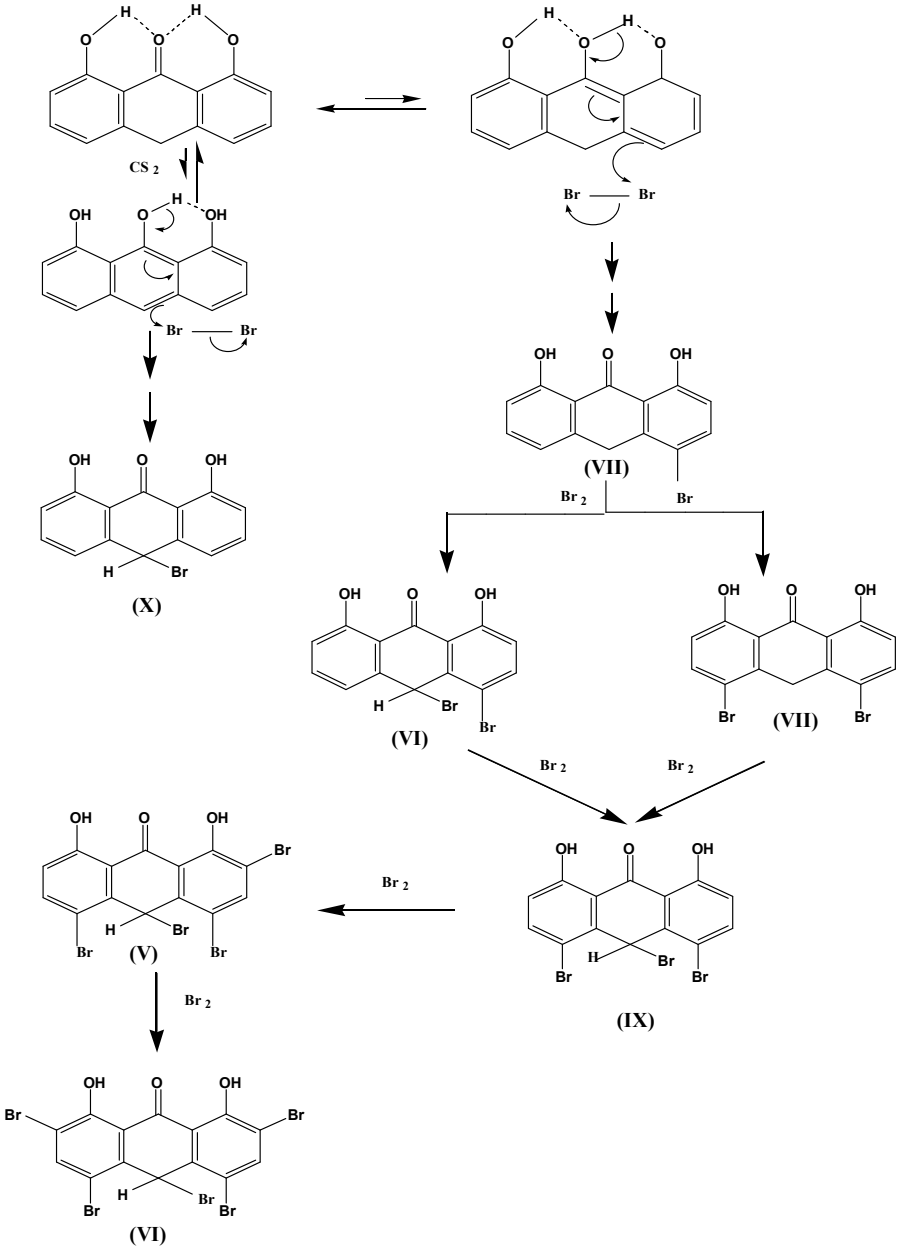


Fig. 6. A proposed mechanism for the bromination of anthralin

Table 2. Isomer ratio of bromination of anthralin (AnH_2) in AcOH/$CHCl_3$/EtOH

Reaction Interval Time (Hrs.)	AnH_2	4-$BrAnH_2$	10-$BrAnH_2$	4,5-Br_2AnH_2	4,10-Br_2AnH_2
1	1	-	0.4	0.16	0.11
2	1	-	1.27	0.27	0.13
4	1	-	2.14	0.36	0.45
6	1	-	3.65	0.5	0.65
8	1	-	6.30	0.57	1.14

Table 3. Isomer ratio of bromination of anthralin (AnH_2) in AcOH

Reaction Interval Time (Hrs.)	AnH_2	4-$BrAnH_2$	10-$BrAnH_2$	4,5-Br_2AnH_2	4,10-Br_2AnH_2
1	1	-	2.27	0.9	0.44
2	1	-	3.57	1.1	0.87
4	1	-	6.5	1.25	2
6	1	-	8.7	1.7	3.1
8	1	-	20	4	10

REFERENCES

1. Ashton RE, Lowe NJ, and Whitefield M; "Anthralin: Historical and current perspectives", American Academy of Dermatology, vol. 9, No. 2, 173-192, 1983.

2. United States Pharmacopeia information, ed^{n}. , 22, Rockville, MD, 1980, United States Pharmacopeia, p.48.

3. Dictionary of organic compounds, New York, 1965, Oxford University Press, vol. 5, p. 3130, 1965.

4. Hellier FF, Whitefield M: The treatment of psoriasis with triacetoxyanthracene. Br J Dermatol **79**: 491-496, 1967.

5. Avdovich HW, Neville GA: 1,8-Dihydroxy-9-anthrone. The revised structure for anthralin, a U.S.P. reference standard. Can J Spect **25**:110-113, 1980.

6. Ahmed FR, "The correct structural formula for anthralin", Acta Cryst B36:3183-3186, 1980.

7. British Pharmacopoeia, London, 1980, Her Majesty's Stationery Office, p.166.

8. Krebs A, Schaltegger H,"Untersuchungen zur Strukture spezifitat der Psoriasishhilmittel Chrysarobin und Dithranol", Hautarzt **20,** 204-209, 1969.

9. Mustakallio KK, " Irritation and staining by Dithranol and related compounds", II. Structure-activity relationships among 10-meso-substituted acyl analogues, Acta Derm Venereol (Stockh) **60**, 169-171, 1979.

10. Unna PG,"Cignolin als Heilmittel der Psorisis", Dermatol Wchnschr **6**, 116-137, 151-163, 175-183, 1916.

11. Brickl R, and Eberhardt H., E.P. 0 033 075 A1, 1981.

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