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Reduction of bromoathralins; a novel method for the preparation of aromatic ring substituted bromoanthralins

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Abstract: During the course of preparing 10-bromanthralin, we prepared a host of aromatic substituted bromoanthralins with a bromine atom at the benzylic position as well. In the present work, removal of the bromine at the benzylic position of these multibrominated anthralins by using zinc dust in acetic acid is reported. Aromatic substituted bromoanthralins with free benzylic position were obtained with good yields.
Keywords: Anthralin, 1,8-dihydroxy-9-anthrone, 10-bromoanthralin, aromatic ring substituted bromoanthralins.

INTRODUCTION

Psoriasis is a common, inflammatory, and hyperproliferative skin disease, mainly characterized by abnormal keratinocyte proliferation and differentiation, accumulation of polymorphonuclear leukocytes in the skin, and T-cell activation.[1]The treatment for psoriasis is targeted at both the inflammatory and hyperproliferative aspect of the disease. For more than a century, anthralin (Dithranol, Cignolin, 1,8-dihydroxy-9(lOH)-anthracenone)) has been of biological and pharmaceutical importance as an efficient drug in the treatment of psoriasis and other skin diseases. The substance was for many years believed to be 1,8,9-anthracenetriol, but spectroscopic and X-ray crystallographic investigations have demonstrated that the molecular constitution is that of the tautomer 1,8-dihydroxy-9-anthrone (1,8-dihydroxy-9(10H)-anthracenone)(fig.1). Anthralin is a reactive compound that readily participates in acid–base and red–ox equilibria. Anthralin is among the most effective agents for the topical treatment of psoriasis. While many therapeutics are targeted towards a single feature of the disease, all psoriatic features are resolved following topical therapy with anthralin. However, this drug causes unpleasant side-effects such as inflammation and staining of the nonaffected skin surrounding a psoriatic lesion.[2]More details concerning psoriasis and chemistry of anthralin are given in other author's works.[3-6]

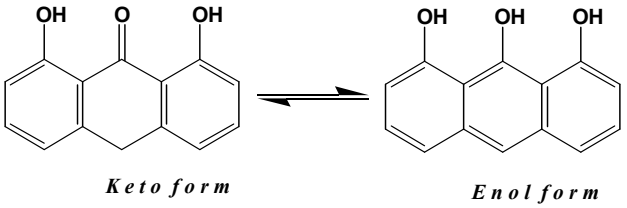

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Fig. 1 Keto-enol tautomerization of anthrlin

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. All the chemicals were purchased from BDH, Aldrich, Fluka and Merck suppliers. All solvents and liquid reagent were distilled prior to use.

Reduction of 10-bromo-1,8-dihydroxy-9-anthrone:10-bromo-1,8-dihydroxy-9-anthrone (362 mg, 1.19 mmol) was dissolved in acetic acid (60 mL) with stirring at room temperature. Zinc dust (0.8 g, 12.3 mmol) was added and the progress of the reaction was monitored by HNMR. After 1 hour the reduction was completed. Filtration followed by removal of the solvent on a rotary evaporator and finally pumping off any trace of acetic acid on a vacuum pump, resulted a yellow solid material (265 mg, 1.17 mmol, 98.5%). It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 4.27 (s, 2×C_{-10} –H), 6.86 (d, J=8 Hz, H-2 + H-4 + H-5+ H-7), 7.46 (t, J=8 Hz, H-3 + H-6), 12.24 (s, 2×OH); ^{13}CNMR δ ($CDCl_3$, 75 MHz) ppm 32.795 (C-10), 115.567, 116.736, 136.256, 141.945, 162.942 (C-1+C-8), 194 (C-9); M.S. (E.I.) m/z 227[$(M+1)^+$,41.8%], 226 (M^+, 100%), 225 (19.6%), 198 [$(M-CO)^+$,51.2%], 197[$(M-CHO)^+$,64.2%], 181 (21.8%), 168 (14.8%); C.I. (NH_3) m/z 228 (46.7%), 227 [$(M+1)^+$,100%], 226 (M^+, 69.9%), 198 (12.2%),197 (12.1%), 168 (3.7%).

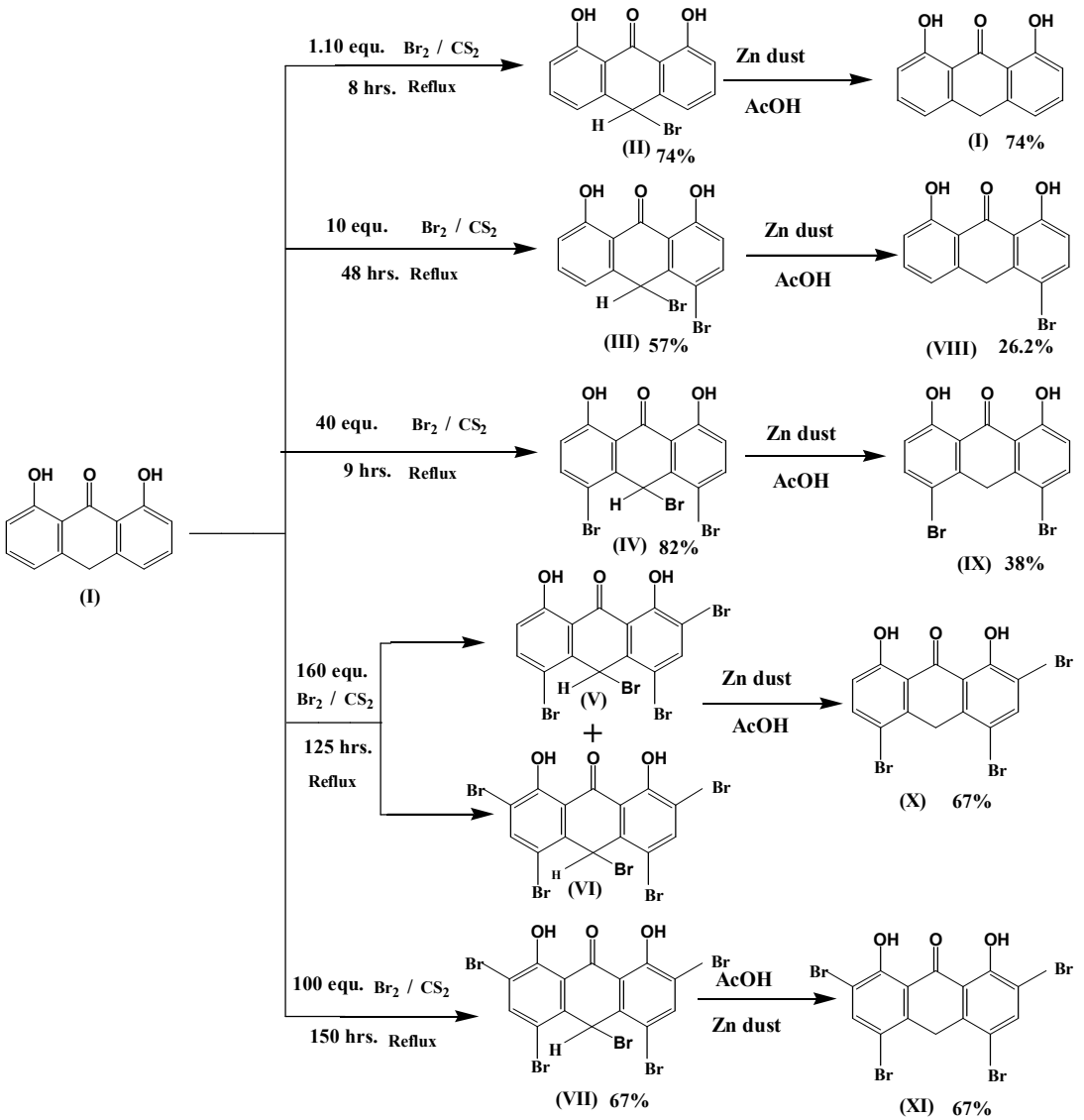
Reduction of 4,10-dibromo-1,8-dihydroxy-9-anthrone:4,10-dibromo-1,8-dihydroxy-9-anthrone (38.4 mg, 0.1 mmol) was dissolved in acetic acid (10 mL) with stirring at room temperature. Zinc dust (0.1 g, 1.54 mmol) was added and left the mixture stirring at room temperature for 1 hour. Filtration followed by removal of the solvent on a rotary evaporator and finally pumping off any trace of acetic acid on a vacuum pump, resulted a yellow solid material. Recrystallization from n-hexane gave a yellow crystalline compound (25 mg, 0.082 mmol, 82%), m.p. 163-165 °C. It had δ ($CDCl_3$, 80 MHz) 4.22 (s, 2×C_{-10} –H), 6.87 (d, J=9 Hz, H-2), 6.94 (d, J=8 Hz, H-7), 6.98 (d, J=8 Hz, H-5), 7.54 (t, J=8 Hz, H-6), 7.69 (d, J=9 Hz, H-3), 12.12 (s, 1×OH), 12.52 (s, 1×OH).

Reduction of 4,5,10-tribromo-1,8-dihydroxy-9-anthrone: 4,5,10-tribromo-1,8-dihydroxy-9-anthrone (108 mg, 0.23 mmol) was dissolved in acetic acid (15 mL) with stirring at room temperature. Zinc dust (0.2 g, 3.08 mmol) was added and left the mixture stirring at room temperature for 1 hour. Filtration followed by removal of the solvent on a rotary evaporator and finally pumping off any trace of acetic acid on a vacuum pump, resulted a yellow solid material (90 mg). Recrystallization from chloroform gave a yellow crystalline compound (60 mg, 0.155 mmol, 67%), m.p. 239-240 °C. It had δ ($CDCl_3$, 80 MHz) 4.12 (s, 2×C_{-10} –H), 6.90 (d, J=9 Hz, H-2+H-7), 7.78 (d, J=9 Hz, H-3+H-6), 12.37 (s, 2×OH).

Reduction of 2,4,5,7,10-pentabromo-1,8-dihydroxy-9-anthrone:2,4,5,7,10-pentabromo-1,8-dihydroxy-9-anthrone (62.1 mg, 0.1 mmol) was dissolved in acetic acid (15 mL) with stirring at room temperature. Zinc dust (0.2 g, 3.08 mmol) was added and left the mixture stirring at room temperature for 1 hour. Filtration followed by removal of the solvent on a rotary evaporator and finally pumping off any trace of acetic acid on a vacuum pump, resulted a yellow solid material (54 mg). Recrystallization from chloroform gave a yellow crystalline compound (30 mg, 0.155 mmol, 55.4%), m.p.> 290 °C. It had ^{1}HNMR δ ($CDCl_3$, 300 MHz) 4.09 (s, 2×C_{-10} –H), 8.10 (s, H-3+H-6), 12.90 (s, 2×OH); ^{13}CNMR δ ($CDCl_3$, 75 MHz) ppm 36.596 (C-10), 110.604, 112.772, 116.574, 139.672, 143.069, 155.287 (C-1+C-8), 192.606 (C-9); M.S. (E.I.) m/z 538 (M^+, tiny), 448 (5.9%), 447 (32.7%), 446 (100%), 352 (1.5%), 223 (8.8%), 68 (27.3%).

DISCUSSION

It is well documented in literature that antipsoriatic drug, anthralin, has been used clinically over decades in various forms for the treatment of this skin disease. However, its drawbacks i.e. irritancy and staining the non-psoriatic lision parts of the patient's body, linens, clothing, bath tiles and tabs were and still are highly disturbing and concerned both from economic point of view and patient's complacency . Therefore, huge sums of research have been carrying out to overcome these drawbacks while keeping the medical efficacy of the drug. For the preparation of many derivatives of anthralin, one needs to prepare 10-bromoanthralin as an excellent intermediary compound. During the preparation of this intermediary, authors have found[6] that without using any Lewis acid catalyst, bromination on the aromatic rings of anthralin took place as well and a host of bromoanthralins were obtained. We were persuaded to remove the bromine atom from the benzylic site of these derivatives and obtain pure aromatic substituted bromoanthralins. A very simple and well documented traditional reagent i.e. zinc dust in acetic acid was employed. After laboratory work up of the products, various spectroscopic results confirmed the assigned chemical structures. These bromoanthralins can be used for other purposes.



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