J. Sci. I. R. Iran

Vol. 7 No. 2
Spring 1996

Research Note

SYNTHESIS OF 1,1'-DIHYDROXY-2,2'-(THIODIMETHYLENE) BIS-9(10H)-ANTHRONE

H. Sharghi* and A. Forghaniha

Department of Chemistry, Shiraz University, Shiraz, Islamic Republic of Iran

Abstract

An efficient synthesis of the 1,1'-dihydroxy-2,2'-(thiodimethylene)bis-9(10H)-anthrone (**5**) is described. Reaction of 1-methoxy-2-(bromomethyl)-9,10-anthraquinone (**1**) with excess sodium sulfide in ethanol, demethylation to the corresponding hydroxy and subsequent selective reduction produced the title compound in high yield.

Natural and synthetic anthrones and derivatives attract wide interest because of their biological and pharmacological properties. Among these, 1,8-dihydroxy-9(10H)-anthrone (dithranol, anthralin) has been in clinical use for the topical treatment of psoriasis, a proliferative skin disease, since 1916 [1-3]. Its main disadvantages are that it burns the skin surrounding the psoriatic lesion to which it is applied and stains the skin and other materials with which it comes into contact [3]. The other anthrone derivatives such as 1-hydroxy-9(10H)-anthrone have been known to show antipsoriasis activity and, like anthralin, produce inflammatory and psoriasis healing effects [4]. Efforts aimed at minimizing these side effects are currently being expended by many research groups [5-11]. This paper describes the synthesis of 1,1'-dihydroxy-2, 2'-(thiodimethylene)bis-9(10H)-anthrone (**5**) as a new derivative of 1-hydroxy-9(10H)-anthrone. Scheme 1 illustrates our general approach to compound **5**.

The reaction of compound **1** [14] with excess sodium sulfide in boiling ethanol produced a new compound 1,1'-dimethoxy-2, 2'-(thiodimethylene)bis-9,10-anthraquinone (**3**) in 92% yield as yellow crystals. Demethylation of compound **3** with a mixture of hydrobromic and acetic acid gave 1,1'-dihydroxy-2,2'-(thiodimethylene)bis-9, 10-anthraquinone (**4**) in 94% yield as yellow needles. Compound **4** can also be obtained from the reaction of 1-hydroxy-2-(bromethyl)-9,10-anthraquinone (**2**) [14] with excess sodium sulfide in boiling ethanol in 90% yield.

Reduction of compound **4** with tin and hydrochloric acid in glacial acetic acid gave 1,1'-dihydroxy-2,2'-(thiodimethylene)bis-9(10H)-anthrone (**5**) in 85% yield as yellow needles. The anthrone structure is favored by the intramolecular hydrogen bond, and was confirmed by ^1H NMR spectroscopy in $CDCl_3$ which showed a singlet at 4.33 due to the 10-methylene group, and one-proton singlet 13.31 due to the hydroxy groups peri to carbonyl.

Keywords: Derivative; 1-Hydroxy-9(10H- anthrone); Synthesis

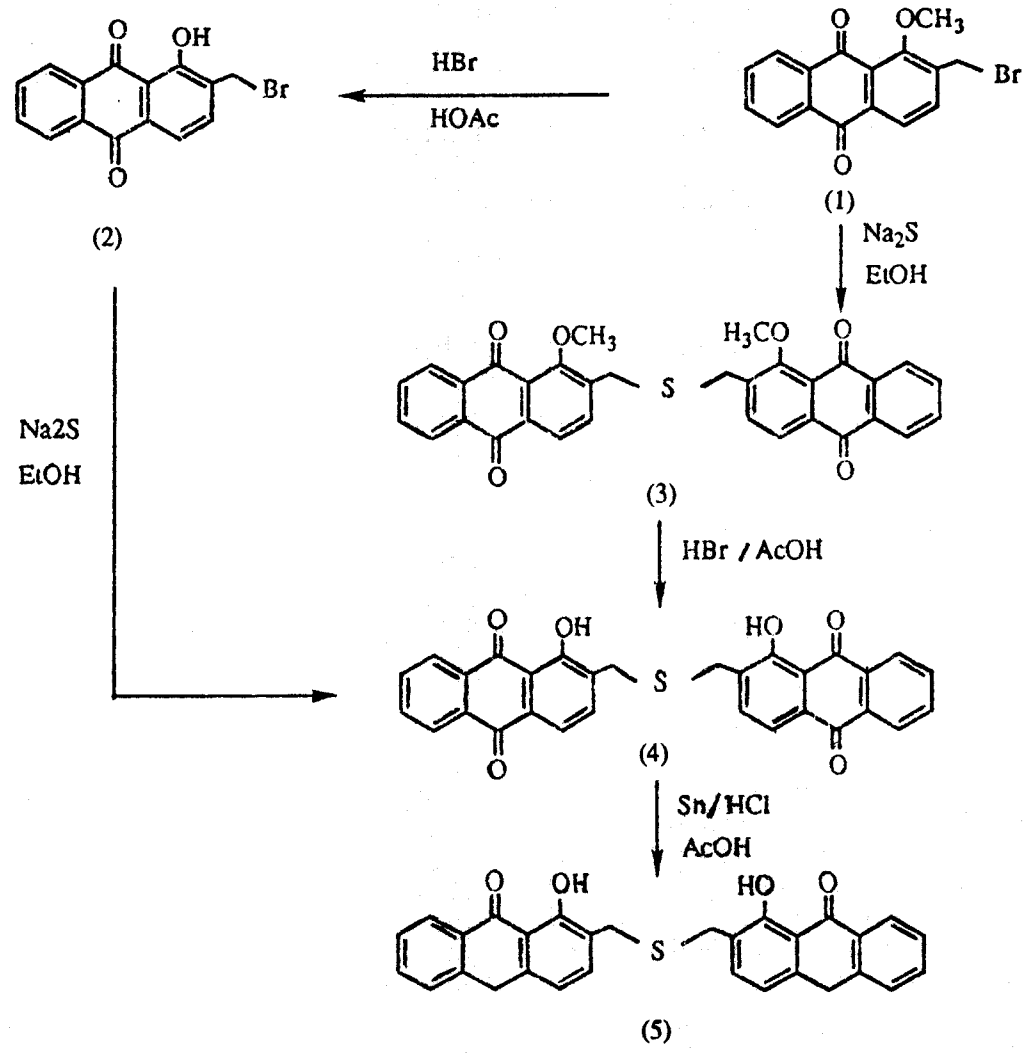
Experimental Section

General Remarks

Solvent, reagents, and chemical materials were obtained from Merck (Darmstadt Germany) and Fluka (Switzerland). Melting points were determined in open capillary tubes in a Buchi-510 circulating oil melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer-157G and 781 spectrophotometers. Nuclear Magnetic Resonance Spectra were recorded on a Hitachi R-248 60 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were determined with a GCMS-QP 1000 EX spectrometer at 70 eV.

1,1'-Dimethoxy-2,2'-(thiodimethylene)bis-9,10-anthraquinone (3)

1-Methoxy-2-(bromomethyl)-9, 10- anthraquinone (**1**) (0.33 g, 1 mmol) was added to a solution of sodium sulfide



Scheme 1

(0.85 g, 11 mmol) in ethanol (120 ml) and refluxed for 20 minutes. The ethanol was evaporated and by addition of chloroform (100 ml) and water (100 ml) the product was extracted to organic layer. Washing with water (2×75 ml) and drying ($CaCl_2$) gave compound **3** in 92% yield (0.245 g) as yellow needles, m. p.: 218-219°C; ^{1}H-NMR ($CDCl_3$): δ 2.38 (s, 4H, CH_2SCH_2), 3.86 (s, 6H, 2×OCH_3), 7.35-8.40 (m, 12H, ArH); IR (KBr): ν_{max} 3075 (w), 2940(w), 2860(w), 1675(s), 1595(m), 1580(m), 1575(m), 1450(w), 1400(w), 1380(w), 1330(s), 1280(s), 1200(w), 1055(m), 980(w), 355(w), 800(w), 710 (s)cm^{-1}; UV (chloroform): λ_{max} 205 (ε=47100), 234 (ε=66750), 256 (ε=84300), 335 nm (ε = 15100). (Found: C, 71.72; H, 4.30. $C_{32}H_{22}O_6S$ requires C, 71.9; H, 4.10%): MS: m/z=534 (M^+).

1,1'-Dihydroxy-2,2'-(thiodimethylene)bis-9,10-anthraquinone (4)

Method A:

Compound **3** (0.534 g, 1 mmol) in a mixture of hydrobromic acid (46%, 10 ml) and trifluoroacetic acid (20 ml) was refluxed for 15 minutes. After addition of water (30 ml), the product was extracted with chloroform (2 × 50 ml) washed with water (2 × 50 ml), and dried ($CaCl_2$) to give compound **4** in 94% yield (0.475 g).

Method B:

1-Hydroxy-2-(bromomethyl)-9, 10-anthraquinone (**2**) (0.317 g, 1 mmol) and sodium sulfide (0.42 g, 5.4 mmol) in absolute ethanol (60 ml) were refluxed for 25 minutes. The solvent was evaporated and the residue was dissolved in chloroform (100 ml), washed with water (2 × 100 ml),

and dried ($CaCl_2$) to give compound **4** in 90% yield (0.228 g). Recrystallization from n-hexane gave shiny yellow needles, m.p.: 179-180°C; ^{1}H-NMR ($CDCL_3$): δ 2.27 (s, 4H, CH_2SCH_2), 7.25-8.40 (m, 12H, ArH), 12.87 (s, 2H, 2 ×OH); IR(KBr): ν_{max} 2960(w), 2925(w), 1675(s), 1640(s), 1595(s), 1430(s), 1360(s), 1295(s), 1265(s), 1200(m), 1150(w), 1010(m), 895(w), 8509(w), 775(m), 710(s) cm^{-1}; UV (chloroform): λ_{max} 209 (ε = 42075), 250 (ε=68750), 330 (ε=9625), 415 nm (ε=15400). (Found: C, 71.27; H, 3.42. $C_{30}H_{18}O_6S$ requires C, 71.15; H, 3.56%): MS: m/z = 506(M^+).

1,1'-Dihydroxy-2,2'-(thiodimethylene)bis-9(10H)-anthrone (5)

To a boiling solution of compound **4** (0.2 g, 0.4 mmol) and powdered tin (0.3 g) in glacial acetic acid (12 ml), concentrated hydrochloric acid (1 ml) was added dropwise over 15 minutes. After last addition of hydrochloric acid, the contents were boiled for 10 minutes. Water was added to the mixture and the product was extracted with chloroform (2 × 50 ml), washed with water (2 × 50 ml), and dried ($CaCl_2$). Evaporating the solvent gave compound **5** in 85% yield (0.16 g) as fine yellow needles, m.p.: 62-63°C; ^{1}H-NMR ($CDCl_3$): δ 2.27 (s, 4H, CH_2SCH_2), 4.26 (s, 4H, 2 × CH_2) 6.50-8.50 (m, 12H, ArH), 13.31 (s, 2H, 2 × OH); IR (KBr): ν_{max} 3070(w), 2925(w), 1625(s), 1600(s), 1580(s), 1460(s), 1435(s), 1400(m), 1355(s), 1280(s), 1195(s), 1155(m), 1110(w), 1055 (m), 1010(m), 815(m), 750(s), 725(s), 670(m) cm^{-1}; UV (chloroform): λ_{max} 219 (ε = 21000), 235 (ε = 23800), 260 (ε = 29370), 286 (ε=30380), 368 nm (ε= 8310). (Found: C, 75.12; H, 4.54. $C_{30}H_{22}O_4S$ requires C, 75.31; H, 4.60%): MS: m/z = 478 (M^+).

Acknowledgements

We are thankful to the Shiraz University Research Council for its financial support (grant No. 71-SC-711-383).

References

1. Ashton, R.E., Andre, P., Lowe, N.J. and Whitefield, M. *J. Am. Acad. Dermatol.*, **9**, 173, (1983) and references therein.
2. Roenigk, H.H. and Maibach, H.I. *Psoriasis*. Dekker, New York, (1985).
3. CIRD Anthralin Symposium. *Brit. J. Dermatol.*, **105**, Suppl. 20, (1981).
4. Krebs, A. and Schaltegger, H. *Dermatological*, **131**, (1), 1-27, (1965); CA: 63, 152382e.
5. Berset, J.D. and Krebs, A. *Pharm. Acta. Helv.*, **65**, 290, (1990).
6. Sharghi, H., Tamaddon, F. and Rezaie, R. *Iran. J. Chem. and Chem. Eng.*, **12**, 1, (1993).
7. Shamsipur, M., Ghasemi, J., Tamaddon, F. and Sharghi, H. *Talanta*, **40**., (5), 697, (1993).
8. Dadfarnia, S., Shamsipur, M., Tamaddon, F. and Sharghi, H. *J. Membrane Sci.*, **78**, 115, (1993).
9. Sharghi, H. and Bruce, J. M. *J. Sci. I.R. Iran*, **4**, (2), 122, (1993).
10. d'Ishia, M. and Prota, G. *Synthesis*, 430, (1986).
11. Khalafy, J. and Bruce, J.M. *Iran. J. Chem. and Chem. Eng.*, **13**, 35, (1990).
12. Roberts, J.L., Rutledge, P.S. and Trebilcok, M.J. *Aust. J. Chem.*, **30**, 1553, (1977).
13. Bhavsar, M.D., Tilak, B.D. and Venkataraman, K. *J. Sci. Ind. Research*, **16B**, 392, (1957).
14. Sharghi, H. and Forghaniha, A. *Iran. J. Chem. and Chem. Eng.* **14**, (1), 16, (1995).