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ORIGINAL ARTICLE

Synthesis of [9, 10-dihydro-9-(4-methylaminobutyl)-9, 10-propanoanthracene] using Diels–Alder cycloaddition

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Abstract The synthesis of [9, 10-dihydro-9-(4-methylaminobutyl)-9, 10-propanoanthracene] (2) as a homolog of the antidepressant [9, 10-dihydro-9-(3-methylaminopropyl)-9, 10-ethanoanthracene] (1) is described in the present paper. The key intermediate [9, 10-dihydro (4-pentyl)-9, 10- propanoanthracene-12-one] (7) is successfully synthesized by using the reaction of α-bromoacrolein with 9-pent-4-enyl-anthracene (4) followed by ring expansion and samarium diiodide deoxygenation.

1. Introduction

There are some compounds derived from anthracene which have biological activity, such as Maprotiline (Ludiomil*) that has been synthesized and developed into a clinically useful drug for the treatment of schizophrenia and as an antidepressant by the Ciba-Geigy research group in Switzerland (Fig. 1). The key step was the Diels–Alder addition of ethylene under high pressure leading to the addition across the 9, 10 positions and the formation of the central 2, 2, 2-bicyclooctyl moiety (Wilhelm and Schmidt, 1969).

The synthesis of homologies homobenzoctamine and homomaprotiline was done by using [4 + 3] cycloaddition of tetrabromoacetone with vinyl and allyl anthracene (Hoffmann and Karama, 1992). The synthesis of bishomobenzoctamine by using [4 + 2] cycloaddition of allyl anthracene with α-bromoacroline and [3 + 4] cycloaddition of allyl anthracene with tetrabromoacetone was done (Karama et al., 2010a,b), but the biological activities of these compounds were not published yet.

In the present work we outline a simple method and suitable route to the corresponding Bishomomaprotiline (2) by using the Diels–Alder reaction.

2. Results and discussion

Here we have used seven-steps for the synthesis of Bishomomaprotiline, the key intermediate step is [9,10-dihydro(4-pentyl)-9,10-propano anthracene-12-one] (7) which is synthesized in three steps starting from 9-pent-4-enyl-anthracene (4) which is obtained by the reaction of anthrone (3) with 5-Bromo-1-

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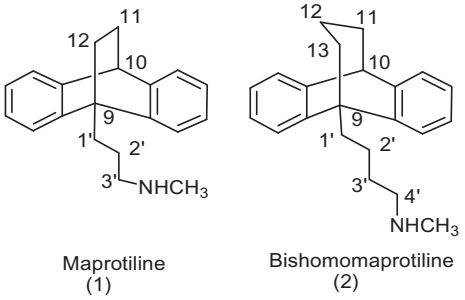


Figure 1 Maprotiline and Bishomomaprotiline.

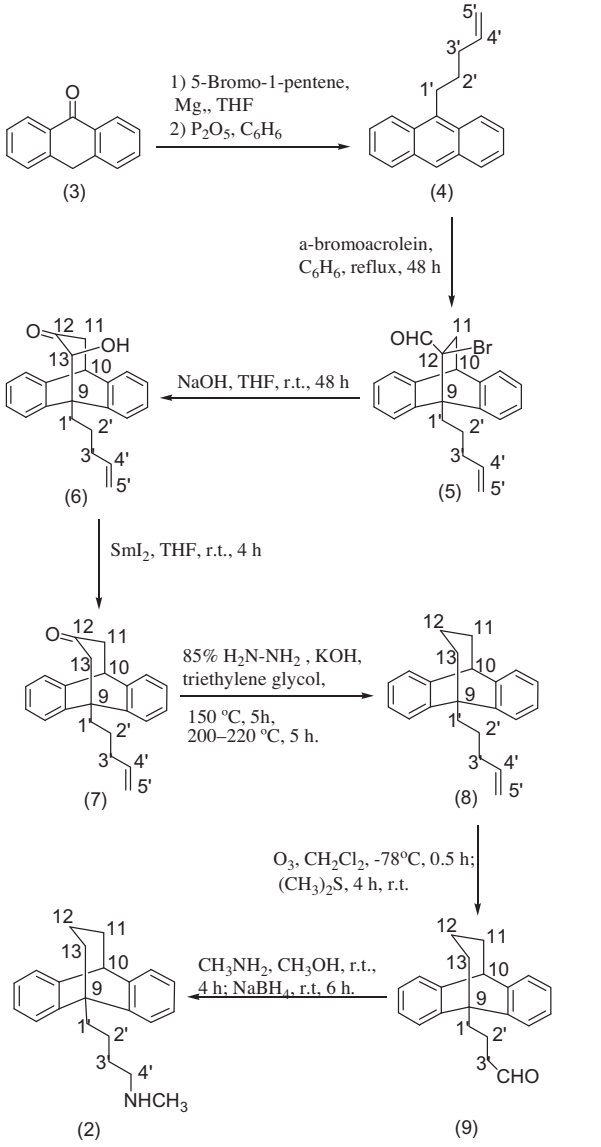
pentene and magnesium. It is followed by dehydration by using P_4O_{10} (Fieser and Heymann, 1942; Willner and Halpern, 1979; Coudane, 1981). The IR spectrum of compound (4) exhibits an absorption band in the range of 3049–2853 cm^{-1} for C–H stretching aroma and shows a peak in the range of 1636–1445 cm^{-1} for C═C stretching, and the absorption band is observed at 733 cm^{-1} for C–H bonding. The ^1H NMR spectrum of this compound exhibits a characteristic quintet at δ 1.92 ppm for two protons, H2′ and exhibits a quartet at δ 2.33 ppm for two protons, H3′.The mass spectrum of this compound reveals the molecular ion peak at m/z 246 which resembles the formula weight 246.140851.

The Diels–Alder reaction between compound (4) and α-bromoacroline afforded the cycloadduct (5) Phutdhawong et al., 2002; Atherton and Jones, 2003; Dhaneshwar Singh, 2010a,b, and this compound was characterized by spectral analysis. IR spectra shows a strong peak at 1717 cm^{-1} for (C═O).The ^1H NMR exhibits a characteristic triplet at δ 4.28 ppm for one proton, H10 and shows a characteristic singlet at δ 9.57 ppm for (CHO). The ^{13}C NMR shows one peak in δ 191.14 ppm for carbon (C═O).The mass spectrum of this compound reveals the molecular ion peak at *m*/*z* 380 which resembles the formula weight 380.077590.

Treatment of compound (5) with 1 M aq. NaOH resulted in transformation into the ring expanded α-hydroxy ketone (6) which is confirmed by the IR spectra. A broad peak in IR in the range 3513, 3457 cm^{-1} is seen for O–H stretching and a strong peak at 1701 cm^{-1} is seen for C═O. The ^{13}C NMR exhibits one peak at δ 208.31 ppm for carbon (C═O). The mass spectrum of this compound confirmed the molecular ion peak at *m*/*z* 318 which resembles the formula weight 318.161976.

Deoxygenation of compound (6) by samarium diiodide led to the desired key intermediate ketone (7) Karama et al., 2010a; Asano et al., 2007, the synthesis of parent ketone (7) is confirmed by using spectral analysis. The IR spectra appear as a strong peak at 1694 cm^{-1} for (C═O) and the disappearance of a broad peak in the range of 3513, 3457 cm^{-1} for O–H stretching. The mass spectrum is confirmed for this compound for which there appeared a molecular ion peak at *m*/*z* 302 which resembles the formula weight 302.167066.

Wolff-Kishner reduction of the ketone 7, gives the tetracyclic hydrocarbon 8 Kishner, 1911, which is confirmed by spectral analysis. In the IR spectrum the disappearance a strong peak at 1694 cm^{-1} is seen for C═O.^{13}C NMR disappearance of a singlet peak at δ 209.19 ppm for C═O is



Scheme 1 Synthesis of Bishomomaprotiline (2) from anthrone.

indicative of transference of carbonyl to methylene. The mass spectrum for this compound confirmed the molecular ion peak at *m*/*z* 288 which resembles the formula weight 288.187801.

Ozonolysis of tetracyclic hydrocarbon 8 gives the crystalline aldehyde 9.The IR spectrum shows a strong peak at 1726 cm^{-1} for aldehyde (C═O). The ^1H NMR shows a characteristic singlet at δ 10.88 ppm for (CHO). The ^{13}C NMR shows a peak at δ 202.08 ppm for carbon (CHO).The mass spectrum of this compound confirmed the molecular ion peak at *m*/*z* 290 which resembles the formula weight 290.167066.

Reductive amination of the aldehyde (9) using a combination of a commercially available solution of methylamine in methanol, titanium (IV) isopropoxide and sodium borohydride (Kumpaty et al., 2003), afforded the Bishomomaprotiline (2).The synthesis of the target compound is confirmed by spectral analysis. The IR spectrum shows one peak at 3410 cm^{-1} for (N–H secondary amine) with