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Design and Synthesis of Naphthol Derivative

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In this study a naphthalene derivative was synthetized using several strategies; in first stage a steroid derivative (**3**) was development by the reaction between androsterone and ethylenediamine using boric acid as catalyst. In the second stage compound **3** was used in the three-component system (β-naphthol, benzaldehyde and compound **3**) for the synthesis of 17-(2-[[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]amino]ethylamino)-10,13-dimethyl-2,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]-phenanthren-3-ol (**6**). In addition, a second method was used to form **6**. In this technique 1-[(2-amino-ethylamino)-phenyl-methyl]-naphthalen-2-ol was made reacting with androsterone to form **6** using boric acid as catalyst. The structure of all compounds obtained was confirmed by spectroscopic and spectrometric methods.

Key Words: β-Naphthol, Benzaldehyde androsterone and ethylenediamine.

INTRODUCTION

The development of aromatic-condensed derivatives are important heterocyclic compounds which induced several biological activities such as antibacterial[1,2] and as material in the production of polyesters fibers and plastics[3]. There are several methods reported for synthesis of aromatic-condensed derivatives; for example, the synthesis of naphthyl ketone by the reaction of o-alkynylbenzaldehydes with alkynes using $AuCl_3$ as catalyst[4]. In addition, other studies shown the synthesis of 1,3-disubstituted naphthalenes from the Baylis-Hillman acetates with the aid of manganese(III) acetate[5]. Other reports indicate the tandem pummerer-Diels-Alder sequence for the preparation of α-thio substituted naphthalene derivatives[6]. Additionally, other studies[7] showed the synthesis of 1,8-diphenylnaphtalene and 1-iodo-8-phenylnaphtalene by the reaction of lithium diphenylcuprate and aryl halides. Other studies reported by Ganapathy and Viswanathan[8] shown the synthesis of polysubstituted naphthalene derivatives through gallium trichloride catalyzed by alkyne-aldehyde coupling. In addition, some carbamato-alkyl-naphthol derivatives[9] have been synthesized by condensation of β-naphthol, aromatic aldehyde and methyl carbamate in ionic liquid media. All these experimental results show several procedures are available for synthesis of naphthalene derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study a naphthalene derivative was synthetized using several strategies; in first stage a steroid derivative (**3**) was development by the reaction between androsterone and ethylenediamine using boric acid as catalyst. In the second stage the compound 17-(2-[[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino]-ethylamino)-10,13-dimethyl-2,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradeca-hydro-1*H*-cyclopenta[a]-phenanthren-3-ol (**6**) was synthetized using the three-component system (β-naphthol, benzaldehyde and compound **3**). Additionally, a second method was used to form **6**. In this technique 1-[(2-amino-ethylamino)-phenyl-methyl]-naphthalen-2-ol[10] was made reacting with androsterone to form **6** using boric acid as catalyst.

EXPERIMENTAL

The compound 1-[(2-amino-ethylamino)-phenyl-methyl]-naphthalene-2-ol was synthesized according to methods previously reported[10]. Androsterone and other compounds were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra (IR) were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5

FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/ 0 2400 elemental analyzer.

17-(2-Amino-ethylimino)-10,13-dimethyl-2,3,6,7,8,9, 10,11,12,13,14,15,16,17-tetradeca-hydro-1*H*-cyclopenta[a]-phenanthren-3-ol (3): A solution of androsterone (100 mg, 0.35 mmol), ethylenediamine (42 mg, 0.70 mmol) and boric acid (50 mg, 0.80 mmol) in 10 mL of methanol was stirring for 24 h to room temperature. The reaction mixture was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (4:1) yielding 75 % of product, m.p. 242-244 ºC; IR (KBr, ν_{max}, cm^{-1}): 3380, 3332, 3260; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.00 (S, 3H), 1.02, 1.06 (s, 3H), 1.10-1.66 (m, 5 H), 1.80-2.28 (m, 11H), 2.70 (m, 1H), 3.05 (t, 2H, J = 6.0 Hz), 3.52 (t, 2H, J = 6.0 Hz), 3.70 (broad, 3H), 4.13 (m, 1H), 5.23 (m, 1H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) ν_C: 16.08 (C-22), 18.80 (C-23), 20.52 (C-8), 21.80 (C-3), 27.53 (C-4), 29.44 (C-12),31.92 (C-17), 32.04 (C-7), 32.34 (C-16), 34.96 (C-1), 35.32 (C-11), 38.4 (C-10), 41.02 (C-20), 41.21 (C-6), 51.07 (C-9), 54.14 (C-19), 55.92 (C-2), 67.80 (C-13), 123.2 (C-14), 147.3 (C-15), 176.85 (C-5) ppm. EI-MS m/z: 330.10 (M^+, 07). Anal. calcd. (%) for $C_{21}H_{34}N_2O$: C, 76.31; H, 10.37; N, 8.48. Found (%): C, 76.28; H, 10.34; N, 8.40.

17-(2-[[(2-Hydroxy-naphtalen-1-yl)phenyl-methyl]-amino]ethylamino)-10,13-dimethyl-2,2,6,7,8,9,10,11,12, 13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-ol (6)

Method A: A solution of **3** (100 mg, 0.30 mmol), benzaldehyde (46 µL, 0.45 mmol) and β-naphthol (44 mg, 0.30 mmol) in 10 mL of ethanol was stirring for 48 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (4:1) yielding 42 % of product, m.p. 56-58 ºC; IR (KBr, ν_{max}, cm^{-1}): 3330, 3254, 1182; 1H NMR (300 MHz, $CDCl_3$) δ_H: 1.00 (s, 3H), 1.05 (s, 3H), 1.05 (s, 3H), 1.14 (m, 1H), 1.43-1.70 (m, 5H), 1.80-2.33 (m, 11H), 2.72 (m, 1H), 2.98-3.05 (m, 2H), 3.51 (t, 2H, J = 6.0 Hz), 3.72 (broad, 3H), 4.14 (m, 1H), 5.25 (m, 1H), 5.75 (s, 1H), 6.88 (m, 2H), 7-10-7.13 (m, 3H), 7.21 (m, 1H), 7.40-7.56 (m, 3H), 7.68-7.74 (M, 2H) ppm. ^{13}C NMR (75.4 Hz, $CDCl_3$) δ_C: 16.12 (C-33), 18.86 (C-34), 20.52 (C-8), 21.83 (C-3), 29.40 (C-4), 30.80 (C-16), 30.98 (C-12), 31.92 (C-17), 32.04 (C-7), 34.27 (C-11), 34.98 (C-1), 37.25 (C-10), 46.20 (C-6), 50.60 (C-20), 51.45(C-9), 53.38 (C-19). 55.53 (C-22), 55.92 (C-2), 67.80 (C-13), 114.39 (C-25), 120.40 (C-14), 121.17 (C-29), 123.22 (C-31), 126.70 (C-30), 127.39 (C-39), 127.96 (C-23), 128.01 (C-27), 128.14 (C-26), 129.25 (C-41, C-37), 129.28 (C-32), 130.22(C-40, C-38), 138.12 (C-28), 139.38 (C-35), 147,30 (C-15), 152.11 (C-24), 166.39 (C-5) ppm. EI-MS m/z: 562.05 (M^+, 07), 315, 305.39, 233.28, 90.10. Anal. calcd. (%) for $C_{38}H_{46}N_2O_2$: C, 81.10; H, 8.24; N, 4.98. Found (%): C, 81.08; H, 8.20; N, 4.92.

Method B: A solution of 7 (100 mg, 0.34 mmol) androsterone (98 mg, 0.34 mmol) and boric acid (42 mg, 0.68 mmol) in 10 mL of ethanol was stirring for 48 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 68 %. ^{1}H and ^{13}C NMR data obtained were similar to the product synthesized by method A.

RESULTS AND DISCUSSION

In this study we report a straight forward route for the synthesis of a naphthol derivative (**6**) using several strategies. The first step was achieved by the synthesis of imine group (Schiff base) involved in the compound **3** (Fig. 1). It is important to mention that there are several procedures for the synthesis of imines which are described in the literature[10-12]. For example, the synthesis of imines by the reaction of benzaldehyde derivative with benzene-1,2-diamine using boric acid as catalyst[13]. Therefore, in this study the synthesis of the compound **3** was developed by the reaction of androsterone with ethylenediamine to yield **3** using boric acid as catalyst. The results indicate that ^{1}H NMR spectrum of **3** showed signals at 1.0 and 1.06 ppm corresponding to methyl groups. In addition, other signals at 1.02, 1.10-2.70 and 4.13-5.23 ppm for protons ofsteroid nucleus; at 3.05 and 3.52 ppm for methylenes involved in the arm bound to steroid nucleus were found. Finally, a signal at 3.72 ppm corresponding to both hydroxyl and amino groups were found. The ^{13}C NMR spectra displays chemical shifts at 20.52-38.40, 41.16-51.07 and 55.88-174.60 ppm for the carbons of methylenes groups presents in the heterocyclic rings. The chemical shifts of the methylenes involved in the arm bound to steroid nucleus were found out at 41.16 and 54.14 ppm. Finally, two signals at 16.08 and 18.80 ppm for the carbons of methyl groups. Additionally, the presence of steroid derivative (compound **3**) was further confirmed from mass spectrum which showed a molecular ion at m/z 330[10].

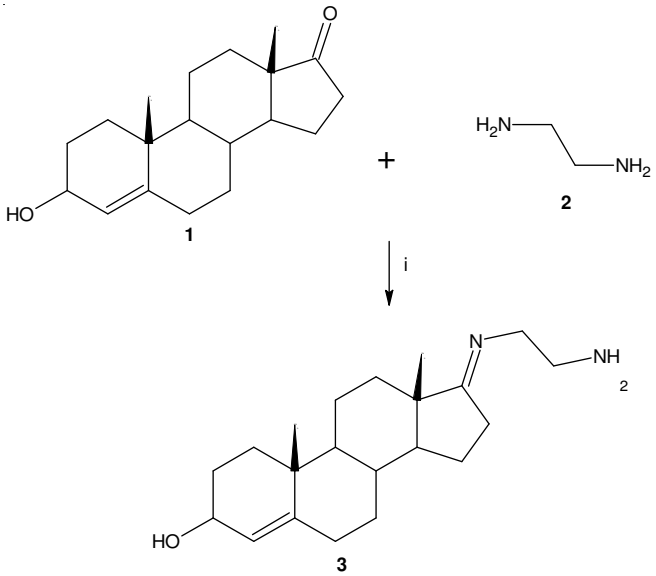

Fig. 1. Synthesis of 17-(2-amino-ethylimino)-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradeca-hydro-1*H*-cyclopenta[a]phenanthren-3-ol (**3**). Reaction between androsterone (**1**) and ethylenediamine (**2**) to form **3**. Reagents and conditions; (i) boric acid, MeOH, room temperature

The second step involves the synthesis of a new naphthol derivative (**6**). It is important to mention that many procedures for formation of naphthol derivatives are available in the literature. Nevertheless, despite their wide scope these procedures suffer from several drawbacks; some reagents are of limited stability and preparation can be dangerous[14-16].

In this study two different methods for synthesis of naphthol derivatives were employed, in the first one, the three-component system (β-naphthol, benzaldehyde and compound **3**) was used (Fig. 2). The ^{1}H NMR spectra of **6** showed signals at 20.52-46.20, 51.45, 55.92-67.80, 120.40, 147.30 and 166.39 ppm corresponding to protons presents in the steroid nucleus; and at 16.12 and 18.86 ppm for methyl groups. In addition, several signals at 114.39, 121.17-139.38 and 152.11 ppm for methylenes and phenyl groups; at 50.60 and 53.38 ppm form methylenes involved in the arm bound to both secondary amino and imino groups were found. Finally, other signal at 55.53 ppm for carbon bound to both phenyl and amino groups was found. In addition, the presence of the compound **6** was further confirmed from mass spectrum which showed a molecular ion at m/z 562.05.

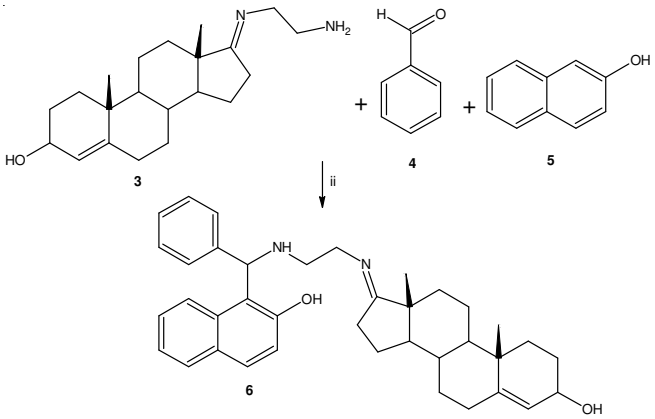

Fig. 2. Synthesis of 17-(2-[[(2-hydroxy-naphtalen-1-yl)-phenyl-methyl]-amino]ethylamino)-10,13-dimethyl-2,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-ol (**6**). Reaction between 17-(2-amino-ethylimino)-10,13-dimethyl-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]-phenanthren-3-ol (**3**) with benzaldheyde (**4**) and β-naphthol to form **6**. Conditions; (ii) EtOH, room temperature

On the other hand, the second method involved the reaction between 1-[(2-amino-ethylamino)-phenyl-methyl]-naphthalen-2-ol (**7**) and androsterone to form **6** using as catalyst boric acid (Fig. 3). It is important to mention that yielding was higher in comparison with method A. This phenomenon is possibly because; (1) the formation of imino group involved in the compound **6** is faster and more selective, (2) there is less steric hindrance between the reagents.

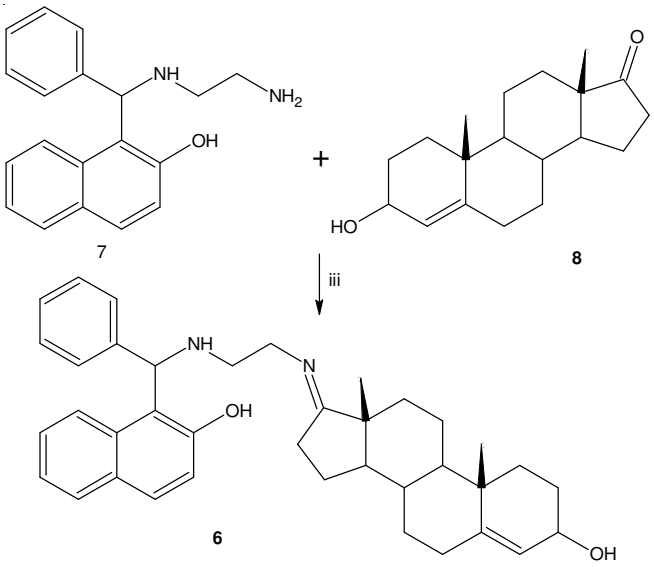

Fig. 3. Synthesis of 17-(2-[[(2-hydroxy-naphtalen-1-yl)phenyl-methyl]-amino]ethylamino)-10,13-dimethyl-2,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-ol (**6**). Reaction between 1-[(2-amino-ethylamino)phenyl-methyl]-naphthalen-2-ol (**7**) and androsterone to form **6** using as catalyst boric acid (iii)

Conclusion

In this study, we reported an efficient and simple method for synthesis of naphthol derivative (**6**). It is important to mention that this method is highly versatile and the yield is good.

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