Est. 1984

**ORIENTAL JOURNAL OF CHEMISTRY**
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2013, Vol. 29, No. (2):
Pg. 465-468

# Design and Synthesis of an Aromatic-steroid Derivative

**L. FIGUEROA-VALVERDE[1]*, F. DÍAZ-CEDILLO[2], E. GARCÍA-CERVERA[1], E. POOL GÓMEZ[1], M. ROSAS-NEXTICAPA[3], M. LÓPEZ-RAMOS[1] and I. MAY-GIL[1]**

[1]Laboratory of Pharmaco-Chemistry at the Faculty of Chemical Biological Sciences of the University Autonomous of Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P.24039 Campeche Cam., México.
[2]Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, México, D.F. C.P. 11340.
[3]Facultad de Nutrición, Universidad de Veracruz (Campus Xalapa). Médicos y Odontologos s/n Unidad del Bosque C.P. 91010, Xalapa Veracruz, México.
*Corresponding author E-mail: lauro_1999@yahoo.com

(Received: March 28, 2013; Accepted: April 30, 2013)

**ABSTRACT**

In this study, an aromatic derivative was synthetized; the first stage involve the reaction of 3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,-14,-15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-2,4-dicarbaldehyde (compound **1**) with ethylenediamine to form 2,4-Bis-[(2-amino-ethylimino)-methyl]-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol(**3**) using boric acid as catalyst. The second stage was achieved by the reaction of **3** with 4-hydroxybenzoic acid usingcarbodiimide derivative as catalyst to form the compound **5** (N-(2-{[3,17-Dihydroxy-4-({2-[1-(4-hydroxy-phenyl)vinylamino]-ethyl-imino}-methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]- phenanthren-2-yl-methylene]-amino}-ethyl)-4-hydroxy-benzamide. The structure of compounds obtainedwas confirmed by elemental analysis, spectroscopy and spectrometry data. In conclusion, this method offers some advantages such as good yields, simple procedure, low cost, and ease of workup.

**Key words**: Aromatic steroid derivatives, boric acid and catalyst.

## INTRODUCTION

There are several methods reported for synthesis of phenolic steroids; for example, the synthesis of an estradiol analog by the reaction of the estradiol-ethylenediamine derivative with succinic acid using 1,3-dyclohexylcarbodiimide as catalyst[1]. Other data showed the synthesis of nitrile derivatives of estrogensbyreaction of 7α-cyano-19-nortestosterone with copper(II)bromide in acetonitrile at room temperature, resulting in aromatization of the A-ring of steroid[2].In addition, other estradiol derivative(17α-(ruthenocenylmethyl) estra-1,3,5(10)-trien-3,17β-diol) was synthetizedby the reaction between 17β-spiro-oxiranyl estradiol and Lithium ruthenocenyl in THF[3]. Other aromatic-steroid derivative (17β-[azidopentyn-2-yl]-3,17β-estradiol)was development using estrone, KOEt, propargyl alcohol in THF[4].Additionally, several 17β-*O*-alkyl ethers (methyl, ethyl, propyl, butyl, hexyl, and octyl) of estradiol were obtained from 3-*O*-benzyl-17β-

estradiol with sodium hydryde/alkyl halide, followed by the removal of *O*-benzyl protecting group via catalytic transfer hydrogenation[5].

Other reports shown the synthesis of an estradiol derivative by the Reformatsky reaction of 3,17β-bis[(2-trimethylsilyl)ethoxymethyl]-1,3,5(10)-estratrien-6-one with bromoethyl ace-tate and zinc[6]. Also a series of 17α-substituted mercaptoalkyny lestradiols have been prepared by addition of lithium acetylides to TBDMS-protected estrone[7].In addition, other aromatic derivative (14β-dihydroxyestrone) has been synthesized from 6-methoxytetralone in 5 steps involving a new acid catalysed 1,3-shift of an allylic nitro group[8].All these experimental results show several procedures which are available for synthesis of aromatic derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study an aromatic derivative was synthetized using some strategies.

## EXPERIMENTAL

### General methods

The compound **1** (3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,-14,-15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-2,4-dicarbaldehyde) was prepared according to a previously reported method[9]. The other compounds evaluated in this study 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. $^{1}H$ 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.

### Synthesis of 2,4-Bis-[(2-amino-ethylimino)-methyl]-13-methyl-7,8,9,11,12,13,14,15,16, 17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (3)

A solution of compound **1** (100 mg, 0.30 mmol), ethylenediamine (40 mg, 0.66 mmol) and boric acid (40 mg, 65 mmol) in 10 mL of ethanol was stirring for 72 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 75 % of product, m.p. 116-118°C; IR ($V_{max}$, $cm^{-1}$):3412, 3380, 3322;$^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.71 (s, 3H), 0.81-1.24 (m, 3H), 1.30-2.97 (m, 12H), 3.27 (d,d, 4H, *J* = 6.54), 3.57 (s, 1H), 3.60 (d,d, 4H, *J* = 6.54), 7.02 (broad, 6H), 7.04 (d, 1H, *J* = 1.27), 7.99 (d,d, 2 H, *J* = 1.20) ppm.$^{13}$ C NMR (75.4 Hz, $CDCl_3$) $d_C$: 13.20(C-19), 23.87(C-9), 25.50 (C-11), 25.84(C-6), 27.90 (C-10), 31.10(C-8), 35.60(C-7), 38.73 (C-4), 40.68(C-23, C-29), 44.30(C-2), 46.10 (C-5), 49.78 (C-3),61.26 (C-28, C-22), 81.13 (C-1), 108.34(C-17), 118.02(C-15), 128.70 (C-13), 135.46 (C-14), 149.59 (C-12), 158.70(C-16), 162.34(C-26), 162.52(C-20) ppm. EI-MS *m/z:* 412.18 ($M^+$10). Anal. Calcd.for $C_{24}H_{36}N_4O_2$: C, 69.87; H, 8.80; N, 13.58; O, 7.76.Found: C, 69.84; H, 8.82.

### Synthesis of N-(2-{[3,17-Dihydroxy-4-({2-[1-(4-hydroxy-phenyl)vinylamino]-ethyl- imino}-methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phe- nanthren-2.ylmethylene]-amino}-ethyl)-4-hydroxy-benzamide (5)

A solution of compound 3(100 mg, 0.24 mmol), 4-hydroxybenzoic acid (60 mg, 0.49 mmol) and carbodiimide (69 mg, 0.36 mmol) in 10 mL of methanol was stirring for 72 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 % of product, m.p. 146°C; IR ($V_{max}$, $cm^{-1}$):3408, 3382, 1676; $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.70 (s, 3H), 0.81-1.30 (m, 4H), 1.38-188 (m,6H), 1.98-2.95 (m, 4H), 3.25 (s, 1H), 3.55 (d,d, 4H, *J* = 6.44), 3.59 (s, 1H), 4.12 (d,d, 4H, *J* = 6.44), 6.45 (d,d, 4H, *J* = 8.42), 6.52 (d,d, 4H, *J* = 8.42),7.02 (d, 5H, *J* = 8.42), 7.04 (d, 1H, *J* = 1.27), 7.70 (broad, 6H), 790-7.96 (d,d, 2H) ppm. $^{13}C$ NMR $d_C$: 13.20 (C-19), 23.87 (C-9), 25.50 (C-11), 25.84 (C-6), 27.90 (C-10), 31.10 (C-8), 35.60 (C-7), 38.73 (C-4), 41.18(C-23, C-31), 44.30 (C-2), 46.10 (C-5), 49.78 (C-3), 62.36 (C-2C-30), 81.13 (C-1),

109.60(C-17), 11509 (C-37, C-39), 118.02 (C-15), 128.40 (C-35, C-41), 128.80 (C-13), 129.10 (C-36, C-40, C-42, C-46), 135.46 (C-14), 149.59 (C-12), 158.70 (C-16), 160.40 (C-38, C-44), 162.50(C-28), 162.52 (C-20), 163.38 (C-25, C-33) ppm. EI-MS *m/z:* 652.32 ($M^+$10). Anal. Calcd. for $C_{38}H_{44}N_4O_6$: C, 69.92; H, 6.79; N, 8.58; O, 14.71. Found: C, 69.90; H, 6.76.

## RESULTS AND DISCUSSION

There are many procedures fordevelopment of new aromatic-steroid derivatives. Nevertheless, despite its wide scope, have some drawbacks e.g., several agents used have a limited stability and their preparation require condition specials[10-13]. Analyzing these data, in this study we report a straightforward route for synthesis of 5 using some strategies. In this stage, 3was development by reaction ofcompound 1, and ethylenediamineto form a imino group involved in the compound 3 (Figure 1, see). It is important to mention that there are several procedures for the synthesis of imino groups which are described in the literature[14-17]; nevertheless, in this study boric acid was used as catalyst, because it is not an expensive reagent and special conditions for its use are not required[17]. On the other hand, the $^1$H NMR spectrum of 3 shows signals at 0.71 ppm for methyl group involved in steroid moiety; at 0.81-2.97 ppm for steroid nucleus; at 3.27 and 3.60 ppm for methylene groups involved in the arm bound to both imino and amino groups. Finally, other signals at 7.02ppm for both amino and hydroxyl groups; at 7.04 ppm for protons of aromatic ring; 7.09 ppm for methylene group bound to both imino and phenyl groups were found. The $^{13}$C NMR spectrum contains peaks at 13.20 ppm for methyl group; at 23.82-38.73, 44.30, 49.78 and

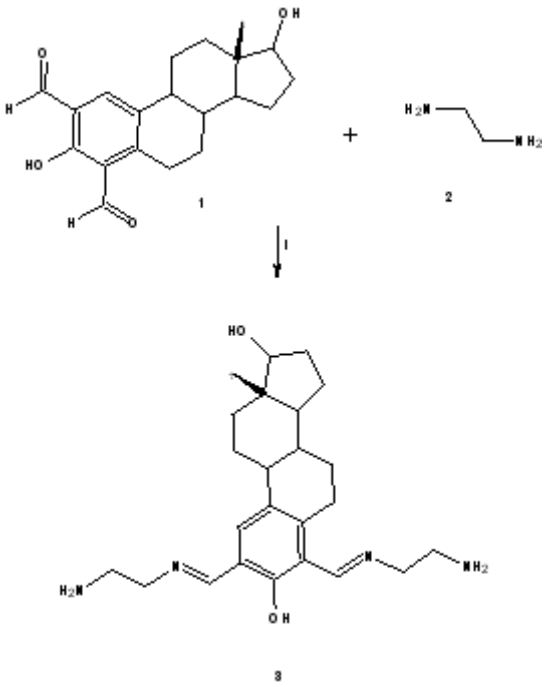

**Fig. 1: Synthesis of 2,4-Bis-[(2-amino-ethylimino)-methyl]-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (3). Reaction of 3,17-Dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]-phenanthre-ne-2,4-dicar-baldehyde(1) with ethylenediamine (2) to form 3. i = boric acid/methanol/rt**

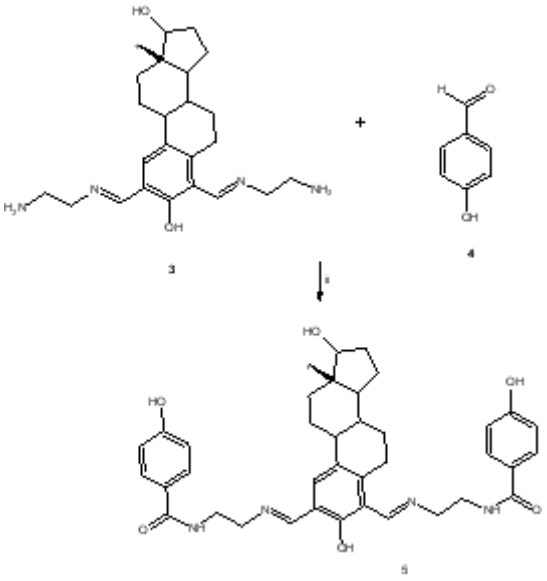

**Fig. 2: Synthesis of N-(2-{[3,17-Dihydroxy-4-({2-[1-(4-hydroxy-phenyl)vinylamino]-ethylimino}-methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]- phenanthren-2. ylmethylene]-amino}-ethyl)-4-hydroxy-benzamide (5). Reaction of 2,4-Bis-[(2-amino-ethylimino)-methyl]-13-methyl-7,8,9,11,12,13,14, 15,16,17-decahydro-6H-cy-clopenta[a] phenan-threne-3,17-diol (3) with 4-hydroxybenzoic acid (4) to form 5. i = carbodiimide/methanol/rt**

81.13-158.70 ppm for protons presents in the steroid nucleus; at 40.68 and 61.36 ppm for methylene groups involved in the arm bound to steroid nucleus. Finally, other signals at 162.34 and 162.52 ppm for methylene group bound to both imino and aromatic ring of steroid were found. Finally, the presence of 3 was further confirmed from mass spectrum which showed a molecular ion at m/z 412.18.

The second step was achieved by the reaction of 3 with 4-hydroxybenzoic acid (4) to form an amide group involved in compound 5 (Figure 2, see). It is important to mention that although many procedures for the formation of amides are known in the literature, the most widely used employs carboxylic acid chlorides as the electrophiles which react with the amino group in the presence of an acid scavenger[18]. Despite its wide scope, this protocol suffers from several drawbacks: most notable are the limited stability of many acid chlorides and the need for hazardous reagents for their preparation (e.g., thionyl chloride)[19]. Therefore, in this study N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (EDC)[20] was used to form compound 5. The $^{1}$H NMR spectrum of compound 5 shows signals at 0.70 ppm for methyl group of steroid nucleus; at 0.81-2.95 and 3.59 ppm for steroid nucleus; at 3.55 and 4.12 ppm for methylene groups involved in the arm bound to both imino and amino groups; at 6.45-7.04 ppm for phenyl groups. Finally, the spectrum contains other signals at 7.70 ppm for both hydroxyl and amide groups; 7.90-7.96 for phenyl groups. The $^{13}$C NMR spectra displays chemical shifts at 13.20 ppm for methyl group; at 23.87-38.73, 44.30-49.78, 81.13-109.60, 118.02, 122.80, and 135.46-158.70 ppm for steroid nucleus; at 115.09, 128.40, 129.10 and 160.40 ppm for phenyl groups. Finally, other signals at 41.18 and 62.36 ppm for carbons involved in the spacer arm between both imino and amide groups; at 162.50-162.52 ppm for carbon bound to both imino and aromatic ring; at 163.38 ppm for amide group were found. In addition, the presence of the dehydroisoandrosterone derivativewas further confirmed from mass spectrum which showed a molecular ion at *m/z* 652.32

## REFERENCES


1. Figueroa-Valverde L., Díaz-Cedillo F., López-Ramos M., García-Cervera E. andPool-Gómez E., *African J.Pharm.Pharmacol.*,**14**: 1703-1712 (2011).
2. Ali H. andVan Lier J.,*Bioorg.Med. Chem. Lett.*,**12**: 2847-2849 (2002).
3. Top S., El Hafa H., Vessières A., Huché M., VaissermannJ. andJaouen G.,*Chem. Eur. J.*, **8**: 5241-5249 (2002).
4. Kasiotis K., Mendorou C., Haroutounian S. and Alexis M.,*Steroids.*, **71**, 249-255 (2006).
5. Prokai L.,Oon S.,Prokai K.,Abboud K.and Simpkins J.,*J. Med. Chem.,* **44**: 110-114 (2001).
6. Adamczyk M.,Johnson D. andReddy R., *Bioconjugate Chem.*, **9**: 403-408 (1998).
7. Wüst F.,SpiesH. andJohannsen B., *Tetrahedron Lett.*,**38**, 2931-2932 (1997).
8. Barlaam B., Boivin J., Elkaim L., Elton S. and Zard S.,*Tetrahedron.*,**51**: 1675-1684 (1995).
9. Figueroa L.,Díaz F., García E., Pool E., Rosas., Mendoza R., López M., May I. and Sarao A.,*Biomed.Res.*, **24**: (2013).In press.
10. Barlaam B., Boivin J., El Kaim L. andZard S.,*Tetrahedron Lett.*,**32**: 623-626 (1991).
11. Volpe T., Revial G., Pfau M. andD'Angelo J.,*Tetrahedron Lett.*,**28**, 2367-2370 (1987).
12. Chatterjee A. andHazra B.,*Tetrahedron.*, **36**: 2513-2519 (1980).
13. Tedesco R., Fiaschi R. andNapolitano E.,*J. Org. Chem.,* **60**: 5316-5318 (1995).
14. Shirayev A., Moiseev I. andKarpeev S.,*Arkivok.,***4**: 199-207 (2005).
15. Uppiah D., Bhowon M. andJhaumeer S.,*E-J.Chem.*, **6**: S195-S200 (2009).
16. M. Hania. *E-J. Chem.*, **6**: 629-632 (2009).
17. Khalid Omar Al-Footy and Reda M. Abdulrahman, *Orient J. Chem.*, **26**(1): (2010).
17. Figueroa-Valverde L., Díaz-Cedillo F., López-Ramos M., García-Cervera E. and Pool Gómez E., *Asian J. Chem.*, **24**: 2173-2176 (2012).
18. Medvedeva A., Andreev M., Safronova L. and Sarapulova G.,*Arkivok.*, **9**: 143-149 (2001).
19. Levin D.,*Org. Process.Res. Dev.*, **1**: 182 (1997).
20. DeSilva D.,*Am. J. Respir. Cell.Mol. Biol.*, **29**: 757-770 (2003).