Heterocyclic Letters
Vol. 10| No.2|183-192|Feb–April | 2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

DESIGN AND SYNTHESIS OF TWO DIOXA-BICYCLO[5.3.1]PREGNEN-DIAZA DERIVATIVES FROM PREGNENOLONE.

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ABSTRACT
There are several reports to synthesis of steroid derivatives using some protocols; however, these methods use some reagents which could be dangerous and require special conditions. Analyzing these data, the aim of this study was to synthesize two new dioxabicyclo[5.3.1]pregnen-diazacine derivatives (**8** or **9**) from pregnenolone using some chemical strategies. The chemical structure was determinate through NMR spectroscopic analysis. The results showed a higher yield from **9** compared with **8**. In conclusion in this study, a facile method for preparation of either **8** or **9** is reported.

KEYWORDS: Dioxabicyclo,steroid, pregnenolone ,diazacine, derivatives.

INTRODUCTION
Since several years ago, some steroid derivatives have been synthesized for therapeutic purposes[i-iv]; in this way, various functional groups involved in the steroid nucleus have been modified; for example, a series of 5β-nor-19-pregnan-20-one analogs were prepared from androstenedione[v]. Other data indicate the synthesis of hydroxy-3,-phenyl-5-pregnan-20-one *via* reaction of 5-pregnane-3,20-dione cyclic with phenylmagnesium bromide[vi]. In addition, a study showed the preparation of 17-Hydroxy-5β-pregnan-20-one from allylic alcohol and nitroethane[vii]. Other reports indicate the synthesis of 15β-acetoxy-17α-hydroxy-5α-pregnan-3,20-dione through the reaction of 3β,5β,17α-trihydroxy-5a-pregnan-20-one with pyridinium chlorochromate[viii]. Furthermore, a study has shown the

synthesis of a pregnenolone-pregnenolone dimer from pregnenolone-hemisuccinate and ethylenediamine[ix]. In addition, a report showed the preparation of 16α,17α-Epoxy-3β-hydroxypregna-5-en-20-one *via* reactionof 6-dehydropregnenolone acetate and sodium hydroxide[x]. Also, a study showed the reaction of pregnenolone with cyanoacetylhydrazine to form a pregnenolone-hydrazone derivative[xi]. All these data show different protocols for the preparation of several pregnenolone derivatives; however, there are not data to the synthesis of dioxa-bicyclo[5.3.1]pregnen-diaza analogs. The aim of this research was to synthesize two new dioxa-bicyclo[5.3.1]pregnen-diaza derivatives using several chemical strategies; it is noteworthy that the steroid nucleus was bound to both diazecin ring and dioxabicyclo [5.3.1] system.

EXPERIMENTAL

General methods

All reagents used in this investigation were acquired from Sigma-Aldrich Co., Ltd. Flash chromatography was performed on E. Merck (60230-400 mesh silica gel). The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were determinate using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR300/5 FT NMR spectrometer at 300 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

2.2 Synthesis of a hydroxynaphthalene-*steroid* propenone *derivative*

(E)-1-((10R,13S,17R)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(2-hydroxynaphthalen-1-yl)prop-2-en-1-one (2)

In a round bottom flask (10 ml), pregnenolone (200 mg, 0.63 mmol), 2-Hydroxy-naphthalene-1-carbaldehyde (110 mg, 0.63 mmol), sodium hydroxide (30 mg, 0.75 ml) and 5 ml of ethanol were stirred at reflux for 12 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:water (4:1) system; yielding 58% of product; m.p. 138-140 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 1722 and 1602: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96-1.08 (m, 2H), 1.16 (s, 3H), 1.18-1.94 (m, 13H), 2.12-3.50 (m, 6H), 5.46 (d, 1H, *J* = 1.90 Hz), 6.40 (broad, 2H), 6.82 (d, 1H, J = 3.10 Hz), 7.28-7.88 (m, 4H), 7.92 (d, 1H, 1.10 Hz), 8.02-8.06 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.82, 19.62, 21.10, 26.02, 31.50, 31.90, 32.05, 35.20, 37.72, 38.12, 39.65, 42.22, 44.12, 50.19, 54.78, 57.06, 71.35, 117.50, 121.35, 122.40, 122.44, 124.22, 124.34, 126.02, 128.33, 130.62, 130.94, 133.53, 141.62, 146.64, 152.50, 211.52 ppm. EI-MS m/z: 470.28. Anal. Calcd. for $C_{32}H_{38}O_3$: C, 81.66; H, 8.14; O, 10.20. Found: C, 81.64; H, 8.11.

(10R,13S)-17-((E)-3-(2-formylnaphthalen-1-yl)acryloyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-te-tradecahydro-1H-cyclopenta[a]phenanthrene-3-carbaldehyde (3)

In a round bottom flask (10 ml), compound **2** (200 mg, 0.63 mmol), and 5 ml of dimethyl sulfoxide were stirred at reflux for 12 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (3:1:1) system; yielding 45% of product; m.p. 176-178 ^{o}C; IR (V_{max}, cm^{-1}) 1740, 1722 and 1600: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96 (m, 1H), 1.00 (s, 3H), 1.18-2.00 (m, 16H), 2.12-5.46 (m, 5H), 6.78 (d, 1H, J = 3.10 Hz), 7.44-7.88 (m, 3H), 7.96 (d, 1H, 1.10 Hz), 7.98-8.62 (m, 3H), 9.70 (s, 1H), 10.40 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.82, 19.44, 21.10, 22.03, 26.04, 31.26, 31.50, 31.96, 33.32, 35.20, 38.84, 39.65, 44.12, 48.82, 51.99, 54.76, 57.09, 124.70, 125.52, 127.39, 128.54, 128.74,

128.93, 129.48, 129.72, 131.06, 132.76, 135.92, 137.53, 142.12, 146.40, 191.52, 203.96, 211.52 ppm. EI-MS m/z: 494.28. Anal. Calcd. for $C_{34}H_{38}O_3$: C, 82.55; H, 7.74; O, 9.70. Found: C, 82.53; H, 7.72.

(10R,13S,17R)-17-((1E,3E,7Z)-5,6-dihydronaphtho[2,1-f][1,4]diazecin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3-carbaldehyde (4)

In a round bottom flask (10 ml), compound **3** (200 mg, 0.40 mmol), ethylenediamine (80 µl, 0.74 mmol), and boric acid (40 mg,0.65 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (3:1:1) system; yielding 72% of product; m.p. 156-158 ^{o}C; IR (V_{max}, cm^{-1}) 3322 and 1740: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96 (m, 1H), 1.00 (s, 3H), 1.22-2.32 (m, 20H), 4.10-4.28 (m, 4H), 5.42 (m, 1H, J = 1.90 Hz), 6.82-7.26 (m, 2H), 7.60-8.16 (m, 5H), 8.44 (m 1H), 8.52 (m, 1H), 9.70 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.90, 19.44, 21.16, 22.00, 23.06, 26.90, 31.22, 31.98, 33.32, 33.60, 38.04, 38.87, 44.10, 48.80, 51.24, 51.96, 52.72, 56.39, 63.30, 126.04, 126.08, 126.85, 127.34, 127.92, 128.14, 128.56, 130.28, 130.60, 131.10, 132.12, 136.84, 137.62, 138.82, 142.12, 160.76, 203.96 ppm. EI-MS m/z: 518.32. Anal. Calcd. for $C_{36}H_{42}N_2O$: C, 83.35; H, 8.16; N, 5.40; O, 3.08. Found: C, 83.32; H, 8.14

(4S)-5-((10R,13S,17R)-17-((1E,3E,7Z)-5,6-dihydronaphtho[2,1-f][1,4]diazecin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-4-hydroxypentan-2-one (5)

In a round bottom flask (10 ml), compound **4** (200 mg, 0.38 mmol), *L*-proline (70 mg, 60 mmol), and acetone (10 ml) in 5 ml of methanol were stirred at reflux for 12 h. Then, the solvent was evaporated under reduced pressure and following the crude oil product was purified by column chromatography using the ethyl acetate: hexane:methanol system (1:1:2) to give the compound **5**; yielding 45% of product; m.p. 138-140 ^{o}C; IR (V_{max}, cm^{-1}) 3400, 2122 and 1731: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96 (m, 1H), 1.00 (s, 3H), 1.12-1.42 (m, 4H), 1.46-1.48 (m, 2H), 1.50-1.98 (m, 12H), 2.12 (s, 3H), 2.14-2.32 (m, 4H), 2.58-3.96 (m, 3H), 4.10-4.28 (m, 4H), 5.22 (m, 1H, J = 1.70 Hz), 5.30 (broad, 1H), 6.82-7.26 (m, 2H), 7.60-8.16 (m, 5H), 8.44 (m 1H), 8.52 (m, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.90, 19.44, 21.16, 23.06, 26.90, 27.52, 30.32, 31.96, 33.54, 33.60, 34.50, 37.04, 37.98, 38.04, 38.26, 40.96, 44.10, 50.84, 51.26, 51.96, 52.72, 56.39, 63.30, 68.26, 121.22, 126.04, 126.10, 126.82, 127.30, 127.94, 128.16, 130.28, 130.60, 131.10, 132.14, 136.84, 137.62, 138.82, 142.80, 160.74, 205.50 ppm. EI-MS m/z: 590.38. Anal. Calcd. for $C_{40}H_{50}N_2O_2$: C, 81.31; H, 8.53; N, 4.74; O, 5.42. Found: C, 81.30; H, 8.50

(2S)-1-((13S)-17-((1E,3E,7Z)-5,6-dihydronaphtho[2,1-f][1,4]diazecin-3-yl)-13-methyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)pentane-2,4-diol (7)

In a round bottom flask (10 ml), compound **5** (200 mg, 0.34 mmol), sodium borohydride (30 mg, 0.79 mm0l), zinc powder (20 mg, 0.30 mmol) and 5 ml of ethanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (3:1:1) system; yielding 65% of product; m.p. 144-146 ^{o}C; IR (V_{max}, cm^{-1}) 3400 and 3320: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96 (m, 1H), 1.00 (s, 3H), 1.12 (m, 1H), 1.20 (s, 3H), 1.22 (m, 1H), 1.34-1.38 (m, 2H), 1.40-1.44 (m, 2H), 1.46-1.50 (m, 2H), 1.51-2.32 (m, 16H), 3.00 (broad, 2H), 3.68-3.96 (m, 2H), 4.10-4.26 (m, 4H), 5.22 (d, 1H, *J* = 1.70 Hz), 6.80-7.26 (m, 2H), 7.60-8.16 (m 5H), 8.44 (m,1H), 8.52 (m, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.90, 19.44, 21.16, 23.08, 23.52, 26.90, 27.52, 31.98, 33.61, 34.50, 35.32, 37.06, 37.96, 38.03, 40.52, 44.13, 45.07, 51.26, 51.96, 52.70, 56.36, 63.30, 66.95, 67.76,

121.22, 126.04, 126.10, 126.85, 127.33, 127.90, 128.14, 130.26, 130.60, 131.12, 132.14, 136.86, 137.62, 138.80, 142.80, 160.76 ppm. EI-MS m/z: 592.40. Anal. Calcd. for $C_{40}H_{52}N_2O_2$: C, 81.04; H, 8.84; N, 4.73; O, 5.40. Found: C, 81.02; H, 8.82.

12-[3-(10-Fluoro-5-methyl-2,6-dioxa-bicyclo[5.3.1]undeca-1(11),7,9-trien-3-ylmethyl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthrene-17-yl]-9,10-dihy-dro-8,11-diaza-cy-clodeca[a]naphthalene (8)

In a round bottom flask (10 ml), compound **7** (200 mg, 0.34 mmol), 1-fluoro-2,4-dinitro-benzene (50 µl, 0.39 mmol), potassium carbonate (50 mg, 0.36 mmol) and 5 ml of dimethyl sulfoxide were stirred at reflux for 12 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (3:1:1) system; yielding 52% of product; m.p. 122-124 ^oC; IR (V_{max}, cm^{-1}) 3322 and 1148: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96 (m, 1H), 1.00 (s, 3H), 1.04-1.20 (m, 2H), 1.32 (s, 3H), 1.34-1.38 (m,2H), 1.48-1.50 (m, 2H), 1.51-1.69 (m, 7H), 1.70 (m, 2H), 1.82-2.28 (m, 9H), 3.50 (m, 1H), 4.10-4.28 (m, 4H), 4.30 (m, 1H), 5.22 (d, 1H, *J* = 1.70 Hz), 5.50-6.46 (m, 2H), 6.82 (m, 1H), 6.96 (m, 1H), 7.26 (m, 1H), 7.60-8.16 (m, 5H), 8.46 (m 1H), 8.52 (m, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.90, 19.44, 21.20, 21.57, 23.06, 26.90, 27.87, 31.96, 33.60, 33.82, 34.50, 37.40, 37.96, 38.04, 39.92, 40.12, 44.12, 51.24, 51.96, 52.72, 56.36, 63.30, 73.66, 76.27, 100.00, 110.22, 116.32, 121.22, 126.04, 126.10, 126.83, 127.34, 127.82, 128.14, 130.28, 130.62, 131.14, 132.12, 136.88, 137.62, 138.82, 142.80, 149.10, 150.16, 150.98, 160.74 ppm. EI-MS m/z: 684.40. Anal. Calcd. for $C_{46}H_{53}FN_2O_2$: C, 80.66; H, 7.80; F, 2.77; N, 4.09; O, 4.67. Found: C, 80.64; H, 7.78.

5-(10,13-Dimethyl-17-(9,10-dhydro-8,11-diaza-cyclodeca[a]naphtalen-12-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16, 17-tetradecahydro-1H-cyclopenta[a]phenanthrene-3-ylmethyl)-3-methyl-2,6-dioxa-bicyclo[5.3.1]undeca-1(10), 7(11),8-triene-9-carboxyl acid (9)

In a round bottom flask (10 ml), compound **7** (200 mg, 0.34 mmol), 3,5 dinitrobenzoic acid (75 mg, 0.35 mmol), potassium carbonate (50 mg, 0.36 mmol) and 5 ml of dimethyl sulfoxide were stirred at reflux for 12 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:water (4:1) system; yielding 64% of product; m.p. 112-114 ^oC; IR (V_{max}, cm^{-1}) 3320, 1702 and 1148: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.86 (s, 3H), 0.96 (m, 1H), 1.00 (s, 3H), 1.06-1.20 (m, 2H), 1.32 (s, 3H), 1.34-1.38 (m, 2H), 1.48-1.50 (m, 2H), 1.51-1.69 (m, 7H), 1.70 (m, 2H), 1.82-2.32 (m, 9H), 3.50-3.98 (m, 2H), 4.10-4.28 (m, 4H), 5.22 (d, 1H, *J* = 1.70 Hz), 5.68 (broad, 1H), 5.96-6.82 (m, 3H), 7.26 (m, 1H), 7.60-8.16 (m, 5H), 8.46 (m 1H), 8.52 (m, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.90, 19.44, 21.20, 21.54, 23.06, 26.90, 27.87, 31.96, 33.60, 33.82, 34.50, 37.42, 37.88, 30.04, 39.92, 40.12, 44.12, 51.26, 51.96, 52.72, 56.38, 63.30, 76.02, 76.24, 101.52, 111.85, 112.18, 121.22, 126.04, 126.10, 126.85, 127.32, 127.56, 127.92, 128.15, 130.28, 130.62, 131.12, 132.14, 136.88, 137.62, 138.82, 142.80, 156.92, 157.58, 160.74, 168.02 ppm. EI-MS m/z: 710.40. Anal. Calcd. for $C_{47}H_{54}N_2O_4$: C, 79.40; H, 7.66; N, 3.94; O, 9.00. Found: C, 79.38; H, 7.63.

RESULTS AND DISCUSSION

Several pregnenolone derivatives have been developed using different methods which involves some reagents that could be dangerous and require specific conditions[xii-xv]. In this study, two dioxa-bicyclo-pregnen-diaza-cyclodeca[a]naphthalene derivatives were prepared using some chemical strategies as follows:

Preparation of an enone-steroid derivative

It important to mention that several enone derivatives have been prepared using several reagents such as $PdCl_2(PPh_3)_2$[xvi], $MeSO_3H$[xvii], m-chloroperbenzoic acid[xviii], PPh_3AuNTf_2[xix], chromium hexacarbonyl[xx], NaOH/EtOH[xxi] and others. It is important to mention that in this investigation, an enone-steroid derivative (**2**) was prepared form pregnenolone (1) and 2-Hydroxy-naphthalene-1-carbaldehyde on basic conditions (Figure 1).

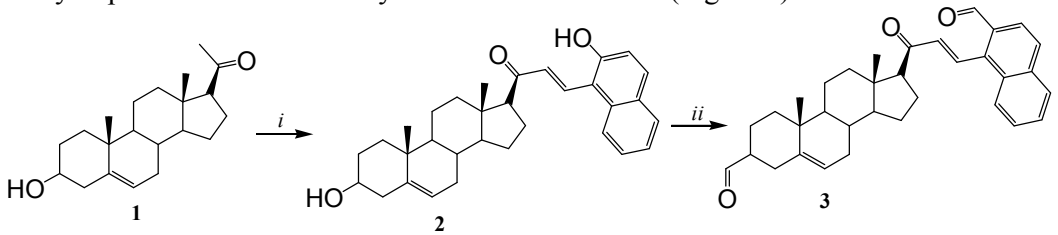

Figure 1. Synthesis of a formylnaphthalenyl-acryloyl steroid-carbaldehyde (**3**).*Reagents and conditions*: 2-Hydroxy-naphthalene-1-carbaldehyde, NaOH (*i*); dimethyl sulfoxide (*ii*).

The results showed several signals involved in the ^{1}H NMR spectrum for compound **2** at 0.86 and 1.16 ppm for methyl groups bound to steroid nucleus; at 6.40 ppm for both hydroxyl groups; at 6.82 and 7.92 ppm for alkene group; at 7.82-7.88 and 8.02-8.06 ppm for naphthalene group. The ^{13}C NMR spectra display chemical shifts at 12.82 and 19.62 ppm for methyl groups bound to steroid nucleus; at 117.50, 122.40-130.62, 133.53 and 152.50 ppm for naphthalene group; at 211.52 for ketone group. Additionally, the mass spectrum (m/z) from compound **2** was found to 211.52.

Synthesis of a formylnaphthalenyl-acryloyl steroid-carbaldehyde

Several studies have been reported to the preparation of aldehyde derivatives via oxidation of primary alcohols using some reagents such as chromium(VI) palladium, rhodium or ruthenium, and hydrogen peroxide reagents; however, some reagents may be toxic by the generation of sub-products involved in the reaction mixtures[xxii]. Analyzing these data and another report which showed for the synthesis of aldehyde analogs in the presence of dimethyl sulfoxide[xxiii]. In this study (Figure 1), the compound **2** reacted with dimethyl sulfoxide to form a formylnaphthalenyl-acryloyl steroid-carbaldehyde (**3**). The ^{1}H NMR spectrum for compound **3** displayed several signals at 6.78 and 7.96 ppm for alkene group; at 7.44-7.88 and 7.96-8.62 ppm for naphthalene group; at 9.70-10.40 ppm for aldehyde groups. In addition, the ^{13}C NMR spectra showed some bands at 124.70-127.39, 128.74-132.76 and 137.53 ppm for naphthalene group; at 135.92 and 146.40 ppm for alkene group; at 192.52-203.96 ppm for aldehyde groups; at 211.52 ppm for ketone group. Furthermore, the mass spectrum (m/z) from compound **3** was found to 494.28.

Synthesis of a diazecine-steroid derivative

There are some reports to the preparation of several diazecine analogs using different protocols; these methods involve various reagents such as CuI_2[xxiv], periodate[xxv], *p*-toluensulfonic acid[xxvi], 1,2-bis[2-(bromomagnesio)benzyloxy]ethane[xxvii], boric acid[xxviii] and others. In this study, **3** reacted with ethylenediamine in the presence of boric acid (Figure 2) to form a diazecine-steroid derivative (**4**). It is noteworthy, that boric is not a dangerous reagent and not require special conditions. The ^{1}H NMR spectrum for compound **4** showed some signals at 4.10-4.28 and 6.82-7.26 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 7.60-8.16 and 8.52 ppm for naphthalene group; at 8.44 ppm for imino group; at 9.70 ppm for aldehyde group. Other data showed several signals involved in the ^{13}C NMR spectrum for

compound **4** at at 51.24 and 52.72 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 126.04-126.08, 127.34-128.14, 130.28-132.12 and 136.84-138.82 ppm for naphthalene group; at 126.85 and 160.76 for imino groups; at 203.96 ppm for aldehyde group. Finally, the mass spectrum (m/z) from compound **4** was found to 592.40.

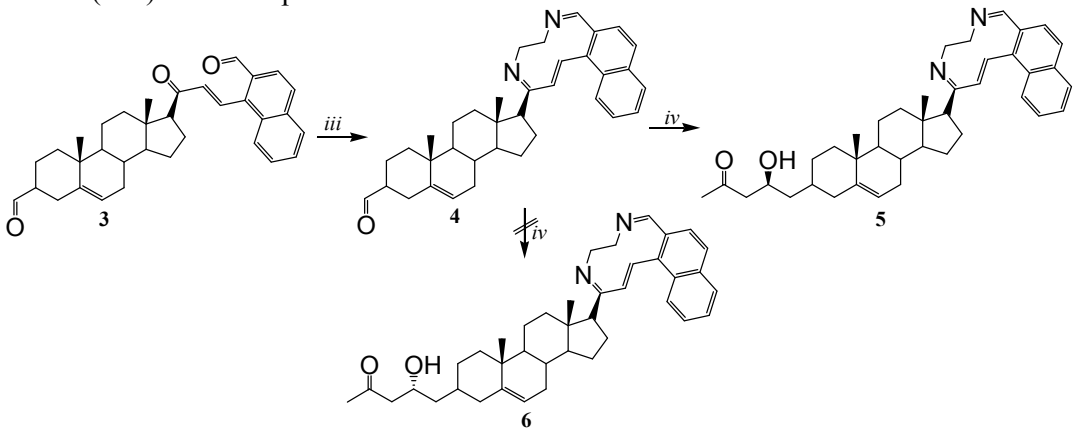

Figure 2. Synthesis of a hydroxy-keto-steroid derivative (**5**).*Reagents and conditions*: ethylenediamine, boric acid (*iii*); *L*-proline, acetone (*iv*).

Synthesis of a hydroxy-keto-steroid derivative

There are some reports to preparation of several hydroxy-keto derivatives using some protocols; however, some methods use reagents may be expensive and require special conditions[xxix-xxxi]. In addition, a study showed the preparation of hydroxy-keto derivatives via reaction of ketone and aldehyde groups in the presence of *L*-proline[xxxii]. Analyzing these data, in this study, a hydroxy-keto-steroid derivative (**5**) was prepared from compound **4**, acetoneand *L*-proline (Figure 2 and 3). The ^{1}H NMR spectrum for compound **5** showed several bands at 2.12 ppm for methyl bound to ketone group; at 1.46-1.48, 2.58-3.96 ppm for methylene groups of arm bound to hydroxyl, ketone groups and steroid nucleus; at 4.10-4.28 and 6.82-7.26 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 5.30 ppm for both hydroxyl groups; at 8.44 ppm for imino group. ^{13}C NMR spectrum for compound **5**showed several signnals at 30.32, 40.96, 50.84 and 68.26 ppm for methylene groups of arm bound to hydroxyl, ketone groups and steroid nucleus; at 51.26, 52.72 and 136.84 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 126.04-126.10, 127.30-132.14 and 132.82 ppm for naphthalene group; at 126.82 and 160.74 ppm for imino groups; at 205.50 ppm for ketone group. Finally, the mass spectrum (m/z) from compound **5** was found to 590.38. It is noteworthy that compound **6** was not observed.

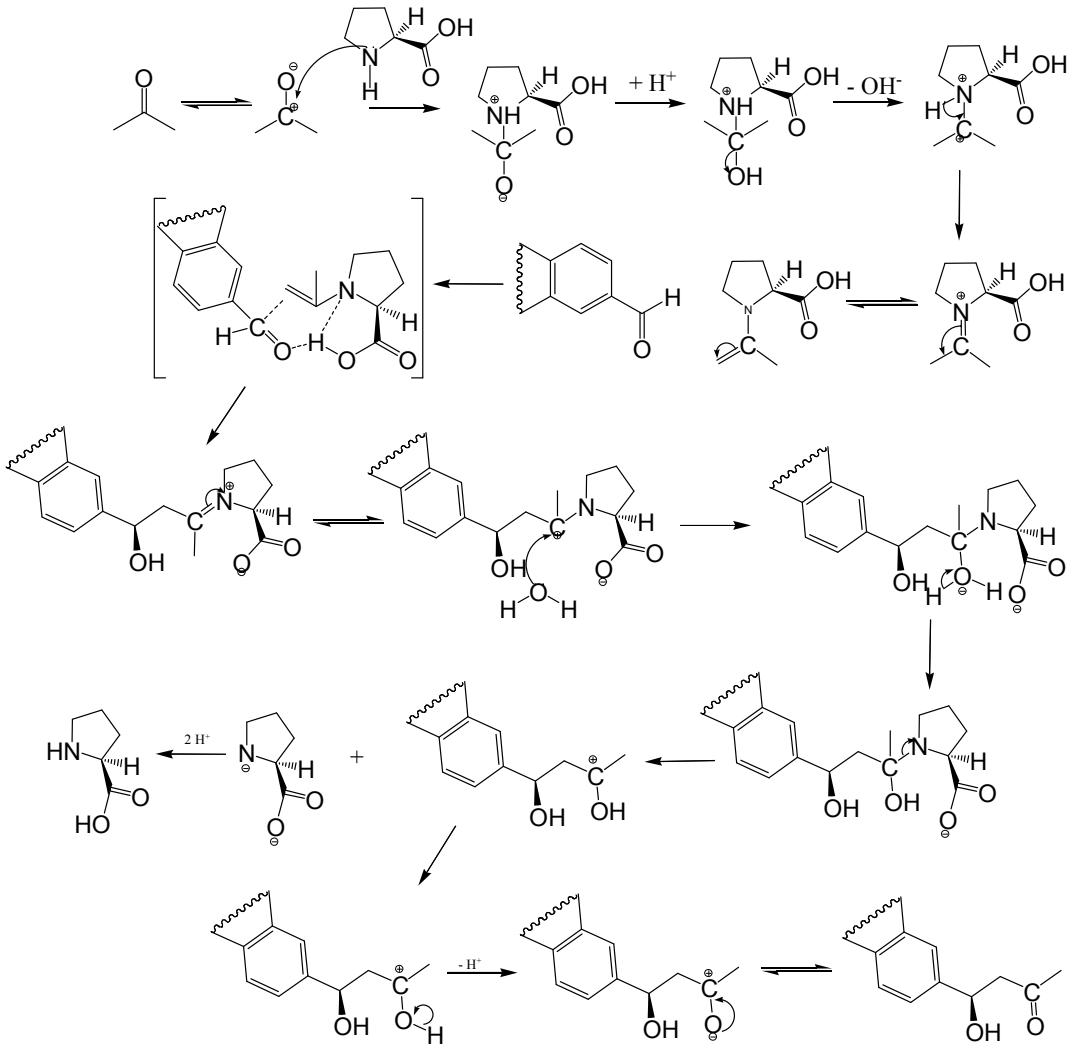

Figure 3. Reaction Mechanism involved in the synthesis of compound 5.

Reduction reaction

Several reagents have used to ketone reduction such as zinc[xxxiii], Samarium(II) iodide[xxxiv], rodhium(III)[xxxv], titanocene borohydride[xxxvi], sodium borohydride[xxxvii] and others. In this research, the ketone involved in the chemical structure of **5** was reduced with sodium borohydride/zinc (Figure 4) to form a diazecine-steroid-diol derivative (**7**). The ^{1}H NMR spectrum for compound **7** showed several bands at 1.20 ppm for methyl group bound to hydroxyl group; at 1.46-1.50 and 3.68-3.96 ppm for methylene groups of arm bound to hydroxyl, ketone groups and steroid nucleus; at 3.00 ppm for hydroxyl group; at 4.10-4.26 and 6.80-7.26 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 7.60-8.16 and 8.52 ppm for naphthalene group ; at 8.44 ppm for imino group. ^{13}C NMR spectrum for compound **7** showed several signals at 23.52 ppm for methyl group bound to hydroxyl group; at 40.52, 45.07 and 66.95-67.76 ppm for methylene groups of arm bound to hydroxyl, ketone groups and steroid nucleus; at 51.26, 52.70 and 136.86-138.80 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 126.04-126.10 and 127.33-132.14 ppm for naphthalene group; at 126.85 and 160.76 ppm for imino groups. In addition, the mass spectrum (m/z) from compound **7** was found to 590.38.

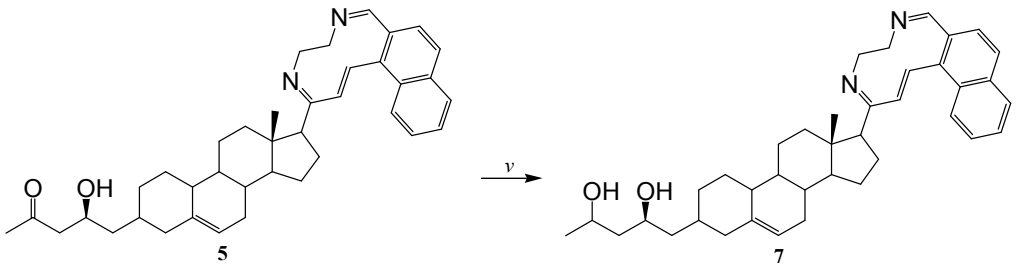

Figure 4. Synthesisof dihydronaphtho[2,1-f][1,4]diazecin-steroid-pentane-2,4-diol (**7**).*Reagents and conditions*: sodium borohydride, zinc (*v*).

Synthesis of two Dioxa-bicyclo[5.3.1]pregnen-diaza derivatives

Since several years ago, have been prepared several bicylo-derivatives using several reagents such as piperidinone[xxxviii], lithium hexamethyldisilazane[xxxix], sodium hydride[xL], azodicarboxylate[xLi], di-tertbutyldicarbonate[xLii] and others. In this study, the first stage was achieved via reaction of **7** with 1-fluoro-2,4-dinitro-benzene using dimethyl sulfoxide as catalyst (Figure 5) to form a to form the compound Fluoro-dioxa-bicyclo[5.3.1]pregnen-diaza derivative (**8**).

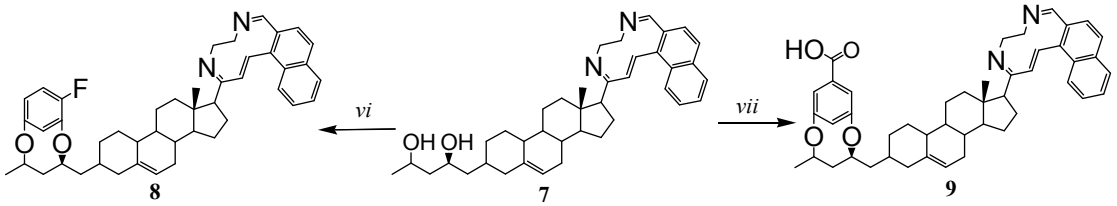

Figure 5. Synthesis of two Dioxa-bicyclo[5.3.1]pregnen-diaza derivatives (**8** and **9**).*Reagents and conditions*: 1-Fluoro-2,4-dinitro-benzene, DMSO, Na_2CO_3 (vi); 3,5-dinitrobenzoic acid, DMSO, Na_2CO_3 (vii).

The ^{1}H NMR spectrum (Figure 6) for compound **8** showed several bands at 1.32 ppm for methyl group bound to ether group; at 1,48-1.50, 1.70, 3.50 and 4.30 ppm for methylene groups of arm bound to ether groups and steroid nucleus; at 4.10-4.28, 6.82 and 7.26 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 5.50-6.46 and 6.96 for phenyl group bound to both ether groups; at 7.06-8.16 and 8.52 ppm for naphthalene group; at 8.46 ppm for imino group. ^{13}C NMR spectrum for compound **8** showed several signals at 21.57 ppm for methyl group bound to ether group; at 39.92-40.12 and 73.66-76.20 ppm for methylene groups of arm bound to ether groups and steroid nucleus; at 51.24, 52.72, 136.88-138.82 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 100.00-116.32 and 149.10-150.98 ppm for phenyl group bound to both ether groups; at 126.04-126.10 and 127.34-132.12 ppm for naphthalene group; at 126.83 and 160.74 ppm for imino groups. Additionally, the mass spectrum (m/z) from compound **8** was found to 684.40.

Finally, **9** reacted with 3,5-Dinitro-benzoic acid in the presence of dimethyl sulfoxide at middle conditions to form a Dioxa-bicyclo[5.3.1]pregnen-diaza carboxyl acid (**9**).The ^{1}H NMR spectrum (Figure 7) for compound **9** showed several bands at 1.32 ppm for methyl group bound to ether group; at 1.70 and 3.50-3.78 ppm for methylene groups of arm bound to ether groups and steroid nucleus; at 5.68 for carboxyl group; at 4.10-4.28 and 7.26 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 5.96-6.82 ppm for phenyl group bound to both ether groups; at 7.60-8.16 ppm for naphthalene group; at 8.52 ppm for imino group.

^{13}C NMR spectrum for compound **9** showed several bands at 21.54 ppm for methyl group bound to ether group; at 39.92-40.12 and 76.02-76.24 ppm for methylene groups of arm bound to ether groups and steroid nucleus; at 51.26, 52.70, 126.04-126.10 and 136.88-138.82 ppm for 2,3,6,7-Tetrahydro-[1,4]diazecine ring; at 101.52-112.18, 127.56 and 156.92-157.58 ppm for phenyl group bound to both ether groups; at 127.32 and 127.92-132.12 ppm for naphthalene group; at 126.85 and 160.74 ppm for imino groups; at 168.02 ppm for carboxyl group. Finally, the mass spectrum (m/z) from compound **9** was found to 710.40.

CONCLUSIONS

In this investigation is reported a facile synthesis of two Dioxa-bicyclo[5.3.1]pregnen-diaza derivatives(compounds **8** and **9**) using various chemical strategies; it is important to mention that the reagents used in this method are easy to handle and do not require specific conditions. Furthermore, it is noteworthy that the steroid nucleus of both compounds **8** and **9** was bound to both diazecin ring and dioxabicyclo [5.3.1] system. Here, it is worth mentioning that analyzing the chemical structure of these compounds, it could be interesting to evaluate their biological activity in some biological model.

ACKNOWLEDGEMENTS

None

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Received on April 23, 2020.