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DESIGN AND SYNTHESIS OF A NEW ETHER-BENZONITRILE-STEROID DERIVATIVE

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ABSTRACT
There are several reports for the preparation of steroid derivatives using some protocols which requires special conditions. In this way, the aim of this study was to synthesize a new ether-benzonitrile-steroid derivative from 17α-ethynyl-2-nitro-estradiolusing some series of reactions such as aldolization, addition, and etherification. The chemical structure was evaluated through both ^{1}H NMR and ^{13}C NMR or spectroscopic analysis. The results showed a good yielding from steroid derivatives. It is noteworthy, that the reagents used in this investigation are not expensive and do not require special conditions for handling.

KEYWORDS: Ether, benzonitrile-steroid, derivative, imino, addition.

INTRODUCTION
For several years, there has been great interest to synthesis of some steroid derivatives in organic chemistry field[i-iii]. In this way, some steroid-derivatives have prepared; for example, the synthesis of 7*α*-hydroxypregnenolone from pregneno-lone/CrO_3/$NaBH_4$[iv]. Other report showed the reaction of 3*β*-hydroxyandrosta-5,7-diene-17-one and eosin to form the compound 5*α*,8*α*-cyclicobioxygen-6-vinyl-3*β*-dehydroepiandrosterone[v]. In addition, a study displayed the preparation of compound 16α,7α-Epoxy-3β-hydroxypregna-5-en-20-one *via* epoxidation of 16-dehydropregnenolone acetate in basic medium[vi]. Also, some data indicate

the synthesis of (*E*)-16-(1-phenyl-1*H*-1,2,3-triazole-4-yl)methylene-5α-andro-stan-3β-ol-17-one from epiandrosterone and a carbaldehyde derivative[vii]. Additionally, the compound 3β-propionyl-oxypregnenolon-20-semicarbazone was prepared from pregnenolone and semicarbazidehydrochloride[viii]. Recently, an estrogens analog (pyridine-steroid derivative) was synthesized from estradiol and ammonium acetate[ix]. In addition, a study showed the reaction of 2-nitroestradiol with hydroxyethylaminonitro-estrone to form an estradiol derivative (chloroacetyl-steroid-oxazolone)[x].All these data show different protocols for the preparation of several steroid derivatives using some reagents which are dangerous and require special conditions. Analyzing these data, the aim of this research was to develop an ether-benzonitrile-steroidderivative from 17α-ethynyl-2-nitro-estradiolusing some chemical strategies.

EXPERIMENTAL

2.1 General methods

17α-Ethynyl-2-nitro-estradiolwas prepared using a previously method reported[xi]. In addition, all reagents used in this investigation were acquired from Sigma-Aldrich Co., Ltd. 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 Chemical synthesis

2-[2-(6-Hydroxy-hex-1-ynyl)-2H-pyridin-1-yl]-1-phenyl-ethanone (2)

***Method A*:** In a round bottom flask (10 ml), 1-(2-Oxo-2-phenyl-ethyl)-pyridinium iodide (200 mg. 0.61 mmol), 5-hexyn-1-ol (100 µl, 0.90 mmol), sodium acetate (40 mg, 0.48 mmol) in 5 ml of ethanol were stirred at reflux for 4 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 44% of product; m.p. 52-54 ^{o}C; IR (V_{max}, cm^{-1}) 3320, 2144 and 1722: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.58-1.60 (m, 4H), 1.94 (broad, 1H), 2.20 (m, 2H), 3.66 (m, 2H), 4.68-4.72 (m, 2H), 4.80-6.40 (m, 5H), 7.50-8.02 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 18.44, 25.52, 31.82, 47.22, 53.92, 62.10, 75.60, 78.24, 112.40, 121.02, 126.54, 127.94, 130.22, 132.92, 135.62, 143.90, 190.94 ppm. EI-MS m/z: 295.15. Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; O, 10.83. Found: C, 77.22; H, 7.14.

***Method B*:** In a round bottom flask (10 ml), 1-(2-Oxo-2-phenyl-ethyl)-pyridinium iodide (200 mg. 0.61 mmol), 5-hexyn-1-ol (100 µl, 0.90 mmol), potassium carbonate anhydrous (60 mg, 0.43 mmol) in 5 ml of ethanol were stirred at reflux for 4 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 61% of product. Both ^{1}H NMR and ^{13}C NMR spectra for compound **5** were in a similar manner to Method A.

7-[1-(2-Oxo-2-phenyl-ethyl)-1,2-dihydro-pyridin-2-yl]-hept-6-ynal (3)

In a round bottom flask (10 ml), compound **2** (200 mg. 0.67mmol) and 5 ml of dimethyl sulfoxide were stirred at reflux for 24 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. 86-88 ^{o}C; IR (V_{max}, cm^{-1}) 2144, 1740 and 1720: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.62-2.54 (m, 8H), 4.68-4.72 (m, 2H), 4.80-6.40 (m, 5H), 7.50-8.02 (m, 5H), 9.70 (*d*, 1H), ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 18.30, 22.10, 26.66, 44.62, 47.22, 53.92, 75.60, 79.40, 112.40, 121.02, 126.50, 127.94,

130.22, 132.92, 135.62, 143.90, 190.94, 202.44 ppm. EI-MS m/z: 307.15. Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56; O, 10.41. Found: C, 78.12; H, 6.85.

2-{2-[6-(2-Amino-ethylimino)-hex-1-ynyl]-2H-pyridin-1-yl}-1-phenyl-ethano-ne (4)

In a round bottom flask (10 ml), compound **3** (200 mg. 0.65 mmol), ethylenediamine (60 µl, 0.90 mmol), boric acid (50 mg, 0.80 mmol) in 5 ml of methanol were stirred at room temperature for 48 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 66% of product; m.p. 130-132 ^oC; IR (V_{max}, cm^{-1}) 3450, 3320, 2142 and 1722: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.70-2.40 (m, 6H), 3.10-3.50 (m, 4H), 4.30 (broad, 2H), 4.64-4.72 (m, 2H), 4.82-6.40 (m, 5H), 7.50-7.60 (m, 3H), 7.70 (m, 1H), 8.02 (m, 2H), ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 17.70, 23.92, 27.30, 40.50, 47.22, 51.64, 53.92, 75.60, 86.24, 112.40, 121.06, 126.50, 127.94, 130.22,132.92, 135.64, 143.94, 156.20, 190.90 ppm. EI-MS m/z: 335.19. Anal. Calcd. for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53; O, 4.77. Found: C, 75.16; H, 7.50.

(chloromethyl-λ^4-sulfanyl)-1,4,4a,5,6,7,8,8a-octahydroquinolin-2-yl)pyridine-1(2*H*)-yl)-1-phenylethan-1-one (5)

In a round bottom flask (10 ml), compound **4** (200 mg. 0.60mmol) and hydrochloride acid (0.5 ml) in dimethyl sulfoxide (5 ml) were stirred at reflux for 24 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol: water (3:1) system; yielding 44% of product; m.p.96-98 ^oC; IR (V_{max}, cm^{-1}) 3450 and 1722: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.36-2.74 (m, 11H), 3.05 (s, 6H), 3.12 (m, 1H), 4.68-4.76 (m, 2H), 5.10-6.52 (m, 5H), 7.12 (broad, 1H), 7.50-8.10 (m, 5H)ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 24.30, 25.12, 25.92, 28.79, 29.22, 34.21, 34.22, 40.54, 54.92, 59.50, 60.32, 112.30, 114.70, 118.80, 127.94,128.72, 130.22, 132.41, 132.92, 135.10, 140.84, 194.32 ppm. EI-MS m/z: 430.18. Anal. Calcd. for $C_{24}H_{31}ClN_2OS$: C, 66.88; H, 7.25; Cl, 8.23; N, 6.50; O, 3.71; S, 7.44. Found: C, 66.85; H, 7.22.

2-(2-{3-[(3,17-Dihydroxy-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-deca-hydro-6H-cyclopenta[a]phenanthren-17-yl-ethynyl)-dimethyl-l4-sulfanyl]-1,4,4a,5,6,7,8,8a-octa-hydro-quinolin-2-yl}-2H-pyri-din-1-yl)-1-phenyl-ethanone (6)

In a round bottom flask (10 ml), compound **5** (200 mg. 0.46mmol) and 17α-ethynyl-2-nitro-estradiol (160 mg, 0.47 mmol), Copper(II) chloride anhydrous (60 mg, 0.47 mmol) in 5 ml of methanol were stirred at room temperature for 24 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 67% of product; m.p. 136-138 ^oC; IR (V_{max}, cm^{-1}) 3450, 3322, 2142, 1722 and 1350: ^1H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.94 (s, 3H), 1.24-1.34 (m, 2H), 1.36-1.38 (m, 2H), 1.40 (m, 1H), 1.44 (m, 1H), 1.52 (m, 1H), 1.60-1.62 (m, 2H), 1.70 (m, 1H), 1.72 (m, 2H), 1.74 (m, 1H), 1.78 (m, 1H), 1.80-1.84 (m, 2H), 1.94 (m, 1H), 2.10-2.30 (m, 3H), 2.42 (m, 1H), 2.50-2.60 (m, 2H), 2.66 (s, 6H), 2.78-2.92 (m, 3H), 3.12 (m, 1H), 4.70-4.76 (m, 2H), 5.00-5.42 (m, 3H), 5.90 (broad, 3H), 6.10-6.52 (m, 2H), 6.64 (m, 1H), 7.50-7.60 (m, 3H), 7.82 (m, 1H), 8.10 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.32, 23.12, 24.30, 25.12, 25.94, 27.12, 27.56, 29.22, 29.56, 29.82, 30.54, 34.84, 39.22, 39.60, 42.44. 44.96, 47.20, 49.34, 54.92, 60.32, 61.40, 79.94, 85.72, 95.44, 112.32, 114.05, 114.70, 123.54, 124.52, 126.82, 127.94, 130.22, 132.32, 132.90, 132.92, 132.94, 135.12, 142.02, 145.12, 148.50, 194.32 ppm. EI-MS m/z: 735.37. Anal. Calcd. for $C_{44}H_{53}N_3O_5S$: C, 71.81; H, 7.26; N, 5.71; O, 10.87; S, 4.36. Found: C, 71.78; H, 7.24.

2-(2-(3-(((2-((((10*S*)-1-hydroxy-10a-methyl-2,3,3a,3b,4,5,8,9,11,12,13,14,15,16,17-deca-hydro-6*H*-cyclo-penta[a]phenanthrene-4-yl)methyl)amino)ethyl)amino)dimethyl-λ^4-sulfanyl)1,4,4a,5,6,7,8,8a-octahy-droquinolin-2-yl)pyri-din-1(2*H*)-yl)1-phenylethan-1-one (7)

In a round bottom flask (10 ml), compound **6** (200 mg. 0.46mmol) and potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide were stirred at reflux for 28 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 55% of product; m.p. 68-70 ^{o}C; IR (V_{max}, cm^{-1}) 3452, 3320, 1722 and 1250: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.94 (s, 3H), 1.22-1.34 (m, 2H), 1.36-1.38 (m, 2H), 1.40 (m, 1H), 1.42 (m, 1H), 1.52 (m, 1H), 1.60-1.62 (m, 2H), 1.70 (m, 1H), 1.72 (m, 2H), 1.74 (m, 1H), 1.78 (m, 1H), 1.82-1.86 (m, 2H), 1.94 (m, 1H), 2.10-2.30 (m, 3H), 2.42 (m, 1H), 2.44-2.50 (m, 2H), 2.60 (m, 1H), 2.66 (s, 6H), 2.76-2.80 (m, 2H), 3.12 (m, 1H), 4.06 (broad, 2H), 4.70-4.76 (m, 2H), 5.00-6.08 (m, 4H), 6.30-6.32 (m, 2H), 6.52 (m, 1H), 7.50-8.10 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 12.32, 23.12, 24.32, 25.12, 25.92, 27.12, 27.62, 29.22, 29.52, 29.82, 30.57, 34.85, 39.24, 39.59, 42.45, 45.40, 47.22, 49.34, 54.92, 60.30, 61.40, 79.95, 85.72, 95.50, 108.85, 108.90, 112.32, 114.70, 124.52, 126.83, 127.95, 130.22, 130.34, 132.91, 132.93, 134.92, 135.10, 142.02, 147.40,147.64, 194.32. EI-MS m/z: 688.36. Anal. Calcd. for $C_{44}H_{52}N_2O_3S$: C, 76.71; H, 7.61; N, 4.07; O, 6.97; S, 4.65. Found: C, 76.68; H, 7.59.

4-(((10aS)-1-((dimethyle(2-(1-(2-oxo-2-phenylethyl)-1,2-dihy-dropyridin-2-yl)-1,4,4^a,5,6,7,8,8^a-octahy-droquinolin-3-yl)-λ^4-sulfaneyl)ethynyl)-10a-me-thyl-2,3,3^a,3b,4,5,8b,9,10,10^a-decahydro-1*H*-cyclopenta[7,8]phenanthro[2,3-*b*]oxiren-1-yl)oxy)bezonitrile (8)

In a round bottom flask (10 ml), compound **7** (200 mg. 0.29 mmol), 4-nitro-benzonitrile (35 mg, 0.30 mmol) and potassium carbonate anhydrous (50 mg, 0.36 mmol) in 5 ml of dimethyl sulfoxide were stirred at reflux 24 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol: water (3:1) system; yielding 45% of product; m.p.144-146 ^{o}C; IR (V_{max}, cm^{-1}) 2240, 2142, 1722 and 1250: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.00 (s, 3H), 1.22-1.30 (m, 3H), 1.36-1.43 (m, 3H), 1.44-1.58 (m, 3H), 1.60-1.73 (m, 4H), 1.75 (m, 1H), 1.78 (m, 1H), 1.86 (m, 1H), 1.94 (m, 1H), 1.98-2.24 (m, 4H), 2.42 (m, 1H), 2.46 (m, 2H), 2.60 (m, 1H), 2.66 (s, 6H), 2.78-2.80 (m, 2H), 3.12 (m, 1H), 4.64 (broad, 1H), 4.70-4.76 (m, 2H), 5.08-6.08 (m, 4H), 6.30-6.32 (m, 2H), 6.52 (m, 1H), 6.98 (m, 2H), 7.50-7.60 (m, 3H), 7.84 (m, 2H), 8.10 (m, 2H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.84, 22.20, 24.31, 25.12, 25.95, 27.44, 27.56, 29.22, 29.56, 29.82, 30.56, 32.20, 36.46, 37.10, 42.44, 45.40, 47.80, 50.00, 54.92, 60.30, 61.40, 85.22, 88.44, 92.30, 105.24, 108.88, 108.92, 112.32, 114.73, 114.87, 118.52, 124.52, 126.84, 127.95, 130.22, 130.33, 132.92, 132.94, 133.82, 135.10, 135.86, 142.02, 147.36, 147.64, 159.40, 194.32 ppm. EI-MS m/z: 789.39. Anal. Calcd. for $C_{51}H_{55}N_3O_3S$: C, 77.53; H, 7.02; N, 5.32; O, 6.08; S, 4.06. Found: C, 77.50; H, 7.00.

Results and Discussion

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

Preparation of an alkyn-alcohol derivative

Several methods for preparation of some alkyn-alcohol derivatives use different reagents such as disulfide-oxazolidine[xii], Ti(O-i-Pr)4-BINOL complex[xiii], chiral diamine-coordinated tin(II) triflate[xiv], $P(PhCH_2NCH_2CH_2)_3N$[xv] and others; however some of these reagents are difficult to handle and require special conditions. Analyzing these data, in this study, a pyridinium iodide salt (**1**) reacted with 5-hexyn-1-ol in the presence of either sodium acetate (Method A) or potassium carbonate(Method B) to form the compound **2**(Figure 1).

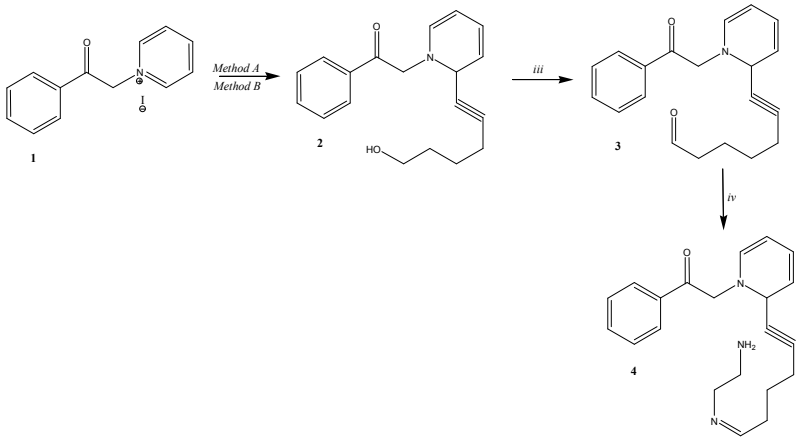

Figure 1. Synthesis of an imino derivative (**4**). *Conditionsand reagents*; *Method A* = sodium acetate, 5-hexyn-1-ol, reflux, 4 h; *Method B* = potassium carbonate, 5-hexyn-1-ol, reflux, 4 h; *iii* = dimethyl sulfoxide, reflux, 24 h; *iv* = ethylenediamine, boric acid, room temperature, 24 h.

The ^{1}H NMR spectrum of **2**showed several signals at 1.58-1.60, 2.20-3.66 ppm for methylene groups bound to both hydroxyl and alkyne groups; at 1.94 ppm for hydroxyl group; at 4.68-4.72 ppm for methylene group bound to both ketone group and pyridine ring; at 4.80-6.40 ppm for pyridine; at 750-8.02 ppm for phenyl group. ^{13}C NMR spectra showed chemical shifts at 18.44-31.82, 62.10 ppm for methylene groups bound to both hydroxyl and alkyne groups; at 47.22, 112.40-126.54 and 143.90 ppm for pyridine; at 75.60-78.24 ppm for alkyne group; at 53.92 ppm for methylene bound to both ketone group and pyridine ring; at 127.94-135.62 ppm for phenyl group; at 190.94 ppm for ketone group. Finally, the mass spectrum from **2**showed a molecular ion (m/z) 295.15.The results showed a higher yield with the method B compared with Method A. These data indicated that potassium carbonateappeared as most efficient base to synthesis of **2**.

Preparation of an aldehyde derivative

There are several protocols for preparation of aldehyde derivatives *via* primary alcohols oxidation to form the corresponding aldehydes. These methods use some stoichiometric amounts of metallic oxidants such as chromium(VI) palladium, rhodium or ruthenium, and hydrogen peroxide[xvi] It is noteworthy that these reagents may induce risks of toxicity by generation of several substances involved on some reaction mixtures. Analyzing these data, in this investigation a method previously reported[xvii] for the oxidation of hydroxyl groups was used. In this way, the compound **2** reacted with dimethyl sulfoxide to form **3** (Figure 4).The ^{1}H NMR spectrum from **3**showed several signals at 1.60-2.54 for methylene groups bound to both alkyne and aldehyde groups; at 4.68-4.72 for methylene group bound to pyridine ring and ketone group; at 4.80-6.40 ppm for pyridine; at 7.50-8.02 ppm for phenyl group; at 9.70 ppm for aldehyde group. ^{13}C NMR spectra showed chemical shifts at 18.30-44.62 ppm for methylene groups bound to both aldehyde and alkyne groups; at 47.22, 112.40-126.50 and

143.90 ppm for pyridine; at 53.92 for methylene bound to both pyridine ring and ketone group; at 75.60-79.40 ppm for alkyne group; at 127.94-135.62 ppm for phenyl group; at 190.94 ppm for ketone group; at 202.44 ppm for aldehyde group. Additionally, the mass spectrum from **3**showed a molecular ion (m/z) 307.15.

Synthesis of an imino derivative

There are many procedures for the preparation of imino derivatives; However, several methods use some reagents that are expensive and difficult to handle[xviii-xx]. Analyzing these data, in this investigation an imino derivative (compound **4**) was synthetized *via* reaction of **6** withethylene diaminein the presence of boric acid (Figure 1). It is noteworthy that boric it is not an expensive reagent and no special conditions for its use[xxi]. The ^{1}H NMR spectrum from **4**showed several signals at 1.70-2.40 ppm for methylene groups bound to both alkyne and imino groups; at methylene groups bound to both imino and amino groups; at 4.30 ppm for amino group; at 4.68-4.72 ppm for methylene bound to both pyridine and ketone group; at 4.80-6.40 ppm for pyridine; at 7.50-7.60 and 8.02ppm for phenyl group; at 7.70 for imino group. ^{13}C NMR spectra showed chemical shifts at 17.70-27.30 ppm formethylene groups bound to both alkyne and imino groups; at 40.50 and 51.64 ppm for methylene groups bound to both imino and amino groups; at 47.22, 112.40-126.50 and 143.94 ppm for pyridine; at 53.92 ppm for methylene bound to both pyridine and ketone group; at 75.60-86.24 ppm for alkyne group; at 127.94-135.64 ppm for phenyl group; at 156.20 ppm for imino group; at 190.90 ppm for ketone group. In addition, the mass spectrum from **4**showed a molecular ion (m/z) 335.19.

Preparation of a quinoline derivative

Some studies have shown the synthesis of some quinoline analogs using different reagents such as lithium aluminum hydride[xxii], tetrakis(triphenylphosphine)palladium(0)[xxiii], phosphoryl chloride[xxiv], phosphortungstic acid[xxv] and others. In this investigation, **4** reacted with dimethyl sulfoxide in acid medium to form the compound **5**(Figure 2). The mechanism involves the addition of sulfonium ion to a carbanion actived to form a quinoline system. The second stage was achieved via chlorination of sulfonium ion to form a chloromethyl-λ^4-sulfanyl)-quinolin derivative (Figure 3).

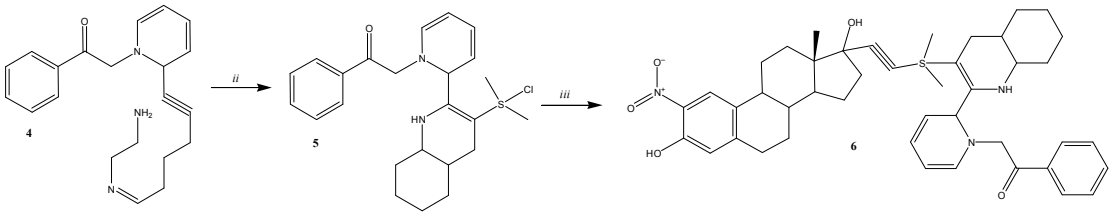

Figure 2. Synthesis of a Synthesis ofa a 2-nitroestradiol-sulfanyl-quinolin-phenyl-ethanone complex (**6**). *Reagents and conditions*: *ii* = dimethyl sulfoxide, hydrochloric acid, reflux, 24 h; *iii* = 17*α*-ethynylestradiol, Copper(II) chloride, room temperature, 24 h.

The ^{1}H NMR spectrum of **5**showed several signals at 1.34-2.70 and 3.12 ppm for octahydro-quinoline fragment; at 3.05 ppm for methyl groups; at 4.68-4.76 ppm for methylene group bound to both pyridine and ketone group; at 5.10-6.52 ppm for pyridine; at 7.12 ppm for amino group; at 7.50-8.10 ppm for phenyl group. ^{13}C NMR spectra showed chemical shifts at 24.30-29.22, 40.54,60.32, 118.80 and 128.72 ppm for octahydro-quinoline fragment; at 34 .21 for methyl groups; at 54.92 for methylene bound to both pyridine and ketone group; at 59.50, 112.30-114.70, 132.41 and 140.84 ppm for pyridine; at 127.94, 130.22 and 132.92-

135.10 ppm for phenyl group; at 194.32 ppm for ketone group. Finally, the mass spectrum from **5**showed a molecular ion (m/z) 430.18.

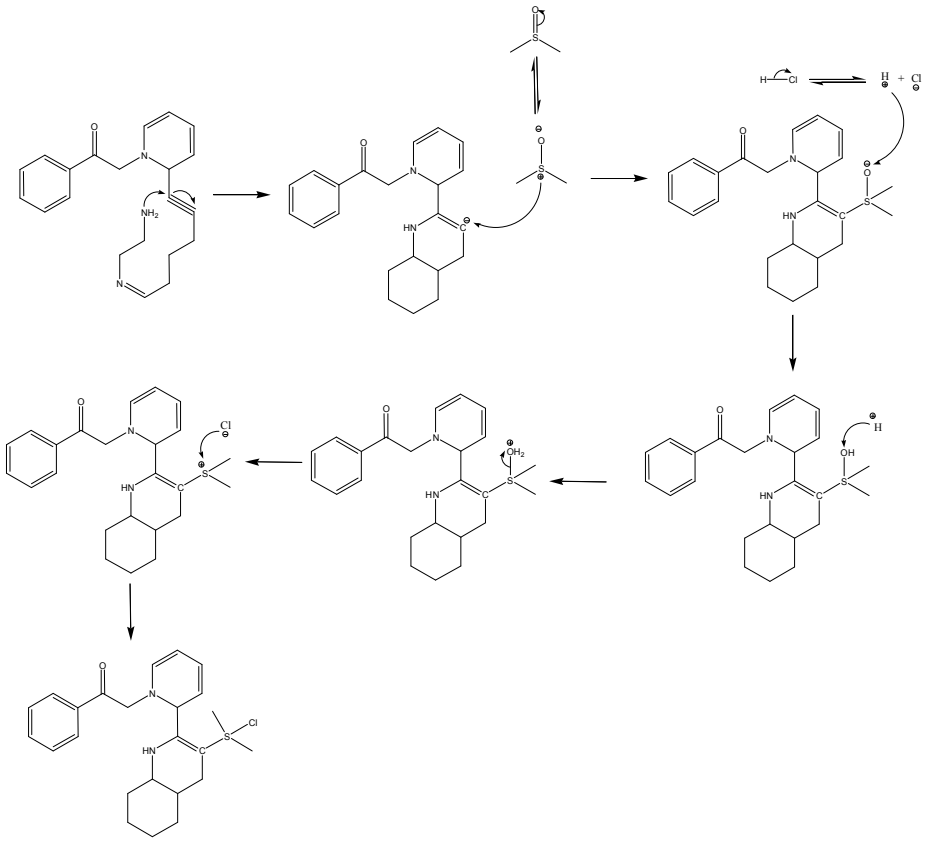

Figure 3. Reaction mechanism involved in in the synthesis of compound **5** derivative.

Reaction of alkyne with a halide derivative

There are several reports on the reaction of alkyne groups with halide derivatives using some protocols which require special conditions[xxvi-xxix]. Analyzing these data, in this study, the compound **6** was synthesized from **5**and 17α-ethynylestradiol using Copper(II) chloride as catalyst (Figure 2). The ^{1}H NMR spectrum of **6**(Figure 11) showed several signals at 0.94 ppm for methyl group bound to steroid nucleus; at 2.66 ppm for methyl groups bound to sulfur; at 1.24-1.34, 1.40, 1.52, 1.70, 1.74, 1.80-1.84, 2.10-2.30, 2.50-2.60, 2.78-2.92, 6.66 and 7.82 ppm for steroid nucleus; at 1.36-1.38. 1.44, 1.60-1.62, 1.72, 1.78, 1.94, 2.42 and 3.12 ppm for quinolin fragment; at 4.70-4.76 ppm for methylene group bound to both pyridine and ketone group; at 5.00-5.42 and 6.10-6.52 ppm for pyridine; at 5.90 ppm for both hydroxyl and amino groups; at 7.50-7.60 and 8.12 ppm for phenyl group. ^{13}C NMR spectra showed chemical shifts at 12.32 ppm for methyl group bound to steroid nucleus; at 23.12, 27.12-27.56, 29.82, 34.84, 39.60, 44.96-49.34, 79.94, 114.05, 123.54, 132.32 and 145.12-148.50 ppm for steroid nucleus; at 24.30-25.94, 29.22-30.54, 42.44, 60.32 and 124.52-126.82 ppm for quinoline fragment; at 29.56 ppm for both methyl groups bound to sulfur; at 54.92 ppm for methylene bound to both pyridine and ketone group; at 61.40, 112.32, 114.70, 132.92 and 142.02 ppm for pyridine; at 85.72 and 95.44 ppm for alkyne group; at 127.94-130.22, 132.90 and 135.12 ppm for phenyl group; at 194.32 ppm for ketone group. In addition, the mass spectrum from **6**showed a molecular ion (m/z) 735.37.

Preparation of an ether-steroid-sulfanylquinolin complex

This stage was achieved by the etherification of **6** via an internal reaction between both nitro and hydroxyl groups in the presence of dimethyl sulfoxide to form the compound **7**(Figure 4). The ^{1}H NMR spectrum of **7**showed several signals at 0.94 ppm for methyl group bound to steroid nucleus; at 1.22-1.34, 1.40, 1.52, 1.70, 1.74, 1.82-1.86, 2.10-2.30, 2.44-2.50, 2.76-2.80 and 6.30-6.32 ppm for steroid nucleus; at 1.36-1.38, 1.42, 1.60-1.62, 1.72, 1.78, 1.94, 2.42, 2.60 and 3.12 ppm for quinolin fragment; at 4.06 ppm for both amino and hydroxyl groups; at 2.66 ppm for methyl groups bound to sulfur; at 4.70-4.76 ppm for methylene group bound to both pyridine and ketone group; at 5.00-6.08 and 6.52 ppm for pyridine; at 7.50-8.10 ppm for phenyl group. ^{13}C NMR spectra showed chemical shifts at 12.32 ppm for methyl group bound to steroid nucleus; at 29.52 ppm for methyl groups bound to sulfur; at 23.12, 27.12-27.62, 29.82, 34.85-39.50, 45.40-49.34, 79.95, 108.90, 130.34, 134.92 and 147.40-147.64 ppm for steroid nucleus; at 24.32, 25.92, 29.22, 30.57, 42.45, 60.30 and 124.52-126.83 ppm for quinoline fragment; at 54.92 ppm for methylene group bound to both pyridine and ketone group; at 61.40, 112.32-114.70, 132.93 and 142.02 ppm for pyridine; at 85.72-95.50 ppm for alkyne group; at 127.95-130.22, 132.91 and 135.10 ppm for phenyl group; at194.32 ppm for ketone group. Additionally, the mass spectrum from **7**showed a molecular ion (m/z) 688.36.

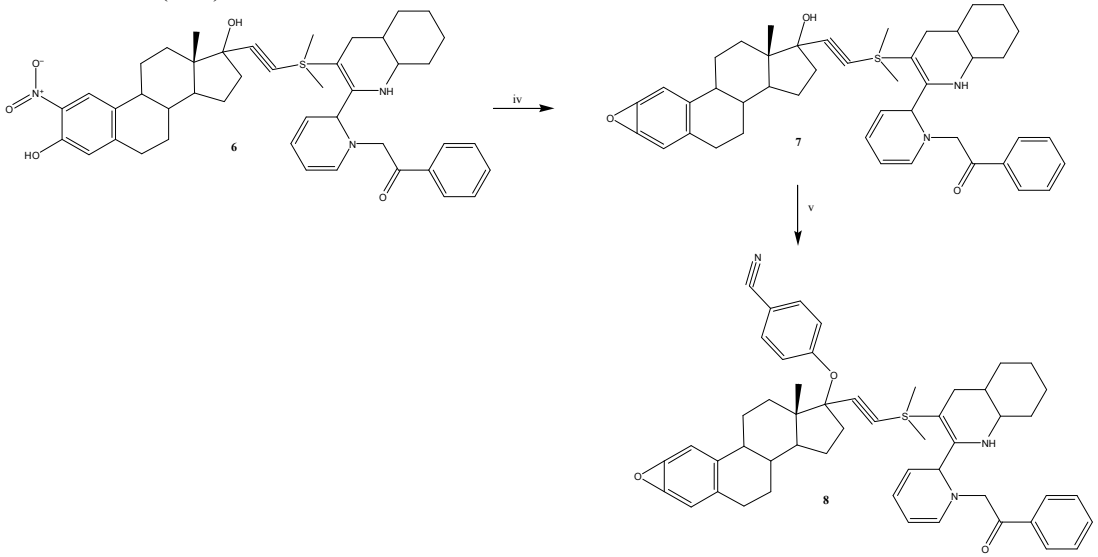

Figure 4. Synthesis of an ether-benzonitrile-steroid derivative (**8**). *Conditionsand reagents*; *iv* = dimethyl sulfoxide, potassium carbonate, reflux, 24 h; *v*= 4-nitro-benzonitrile, dimethyl sulfoxide, potassium carbonate, reflux 24 h.

Synthesis of an ether-benzonitrile-steroid derivative

In this study the compound **8**was prepared via reaction of **7**with 4-nitro-benzonitrile in the presence of dimethyl sulfoxide in middle conditions (Figure 4). The ^{1}H NMR spectrum of **8** showed several signals at 1.00 ppm for methyl group bound to steroid nucleus; at 2.66 ppm for methyl groups bound to sulfur; at 1.22-1.30, 1.44-1.58, 1.75, 1.86, 1.98-2.24, 2.46, 2.78-2.80 and 6.30-6.32 ppm for steroid nucleus; at 1.36-1.43, 1.60-1.73, 1.78, 1.94, 2.42, 2.60 and 3.12 ppm for quinolin fragment; at 4.62 ppm for amino group; at 4.70-4.76 ppm for methylene group; bound to both pyridine and ketone group; at 5.00-6.08 and 6.52 ppm for pyridine ring; at 6.88 and 7.84 ppm for phenyl bound to ether group; at 7.50-7.60 and 8.10 ppm for phenyl bound to ketone group. ^{13}C NMR spectra showed chemical shifts at 11.84 ppm for methyl group bound to steroid nucleus; at 29.56 ppm for methyl groups bound to sulfur; at 22.20, 27.44-27.56, 29.82, 32.20-37.10, 45.40-50.50, 85.22, 108.88-108.92, 130.33,

185.86 and 147.36-147.64 for steroid nucleus; at 24.31-25.95, 29.22, 30.56, 42.44, 60.30 and 124.52-126.84 ppm for quinolin fragment; at 54.92 ppm for methylene group bound to both pyridine and ketone group; at 61.40, 112.32-114.73, 132.94 and 142.02 ppm for pyridine; at 88.44-92.30 ppm for alkyne group; at 105.24, 114.87, 133.82 and 159.40 ppm for phenyl bound to ether; at 118.52 for nitrile group; at 127.95-130.22, 132.92-135.10 ppm for phenyl bound to ketone group. Additionally, the mass spectrum from **8** showed a molecular ion (m/z) 789.39.

CONCLUSIONS

In this study a facile method for the preparation of a new ether-benzonitrile-steroid derivative (compound **8**) from17α-ethynyl-2-nitro-estradiolusing some chemical strategies is reported.It is noteworthy that in these methods no expensive or dangerous reagents were used and no special conditions were required.

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REFERENCES

i. P. Hunt, S. Clements-Jewery, Neuropharmacol. 20, 357 (1981).
ii. B. Brassart, D. Gomez, A. De-Cian, R. Paterski, A. Montagnac, K. Qui, F. Riou, Mol. Pharmacol. 72, 631 (2007).
iii. G. Teutsch, M. Klich, F. Bouchoux, E. Cerede, D. Philibert, Steroids. 59, 22 (1994).
iv. F. Yoshimoto, H. Arman, W. Griffith, F. Yan, D. Wherritt, Steroids. 128, 50 (2017).
v. H. Li, H. Wang, J. Wang, Y. Lin, Y. Ma, M. Bu, Steroids.153, 108472 (2020).
vi. A. Chávez, A. Noriega, M. Apan, L. Miranda, E. Bratoeff, E, Steroids. 131, 37 (2018).
vii. J. Zhao, J. Guo, M. Huang, Y. You, Z. Wu, H. Liu, L. Huang, Steroids. 150, 108 (2019)
viii. J. Cui, L. Pang, M. Wei, C. Gan, D. Liu, H. Yuan, Y.Huang, Steroids.140, 151 (2018).
ix. E. Garcimarrero, L. Figueroa, A. Camach, M. Rosas, M. Mateu, F. Díaz, M. López, R. Cauich, A. Marin, R. Estrella, Biointerface Res.Appl. Chem. 9, 4598 (2019).
x. M. Rosas, L. Figueroa, F. Díaz, V. Mateu, E. Garcimarero, P. Hernandez, L. Benitez, T. Lopez, M. López, L. Hau, E. Pool, J. Cabrera, Y. Ortiz, Biointerface Res. Appl. Chem. 9, 4107 (2019).
xi. L. Figueroa-Valverde, F. Diaz-Cedillo, M. Rosas-Nexticapa, V. Mateu-Armand, M. Lopez-Ramos, R. Estrella, J. Biochem.Tech. 10, 19 (2019).
xii. A. Braga, H. Appelt, C. Silveira, L. Wessjohann, P. Schneider, Tetrahedron. 58, 10413 (2002),
xiii. J. Marshall, M. Bourbeau, Organic Lett. 5, 3197 (2003).
xiv. S. Kobayashi, M. Furuya, A. Ohtsubo, T. Mukaiyama, Tetrahedron:Asym. 2, 635 (1991).
xv. K. Wadhwa, V. Chintareddy, J. Verkade, J. Org. Chem. 74, 6681 (2009).
xvi. A. Dijksman, A. Marino, I. Mairata, I. Arends, R. Sheldon, J.Am.Chem. Soc. 123, 6826 (2001).
xvii. L. Figueroa, F. Diaz, L. Hau, E. García, M. Rosas, E. Pool, R. Camacho, M. García, M. Lopéz, Lett. Org. Chem. 13, 22 (2015).
xviii. A. Shirayev, I. Moiseev, S. Karpeev, Arkivoc.4, 199 (2005).

xix. R. Ottana, R. Maccari, M. Barreca, G. Bruno, A. Rotondo, A. Rossi, M. Vigorita, Bioorg. Med. Chem. 13, 4243 (2005).
xx. M. Hania, J. Chem. 6, 629 (2009).
xxi. L. Figueroa-Valverde, F. Diaz-Cedillo, E. García-Cervera, E. Pool-Gómez, M. López-Ramos, Bulgarian Chem.Comm. 45, 71 (2013).
xxii. R. Ghodsi, E. Azizi, A. Zarghi, Iranian J.Pharm.Res. 15, 169 (2016).
xxiii. C. Venkatesh, G. Sundaram, H. Ila, H. Junjappa, J.Org.Chem. 71, 1280 (2006).
xxiv. C. Alvarez, R. Fernández, M. Quiroga, A. Carbonell, F. Cárdenas, E. Giralt,J.Med.Chem. 40, 668 (1997).
xxv. M. Alami, F. Ferri, G. Linstrumelle, Tetrahedron Lett. 34, 6403 (1993).
xxvi. R. Rossi, A. Carpita, F. Bellina, Org.Prep. Proc.Inter. 27, 127 (1995).
xxvii. K. Okuro, M. Furuune, M. Miura, M. Nomura, Tetrahedron Lett. 33, 5263 (1992).
xxxviii.J. Nguefack, V. Bolitt, D. Sinou, Tetrahedron Lett. 37, 5527 (1996).
xxix. B. Tang, F. Wang, J. Li, H. Xie, M. Zhang, J. Org. Chem. 72, 6294 (2007).

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