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DESIGN AND SYNTHESIS OF TWO BICYCLO[3.3.1]NONANE-STEROID DERIVATIVES

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Abstract. Several studies for the synthesis of bicyclo[3.3.1]nonane analogues have been reported, however, there is little information on the preparation of bicyclo[3.3.1]nonane-steroid derivatives. In this way, the aim of this study was to synthesize two steroid-bicyclo[3.3.1]nonane analogues (**11** or **12**) from either estradiol or estrone using some reactions such as etherification, addition, nucleophilic substitution and cyclization. The chemical structure was evaluated through NMR spectroscopic analysis. The results showed higher yield for **11** compared with **12**. It is noteworthy, that the reagents used in this investigation are not expensive and do not require special conditions for handling.

Keywords: bicyclo, steroid, estrone derivative, synthesis, NMR.

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Introduction

For several years, some derivatives of bicyclo[3.3.1]nonane have been prepared using different protocols; for example, the synthesis of a bicyclo[3.3.1]nonane derivative (garsubellin-A) from a silyl-enol ether and malonyl dichloride was reported [1]. Other report showed the preparation of some bicyclo[3.3.1]nonan-9-one analogues *via* cyclization of alkenyl-substituted *β*-di-carbonyls using selenium as catalyst [2]. In addition, a study showed the reaction of *N*-(l,4-cycloheptadienyl)morpholine with crotonyl chloride to form the 7-methylbicyclo[4.3.1]dec-3-ene-9,10-dione [3]. Furthermore, another study showed the synthesis of clusianone (bicyclo[3.3.1]nonane-2,4,9-trione derivative) through lithiation of some enol ether derivatives [4]. The compound tetramethoxycarbonylbicyclo[3.3.1]nonane was, also, prepared from dimethyl malonate, paraformaldehyde and piperidine [5]. Other data indicated the synthesis of a byciclo[3.3.1]nonan-3-one derivative by the reaction of cyclohexanediacetic acid with acetic anhydride [6]. The 3,3-dimethyl-2-bicyclo[3.3.l]nonanone was prepared from 2-bi-cyclo[3.3.1]nonanone and *t*-butoxide [7]. In addition, some bicyclo[3.3.1]nonane derivatives have been prepared *via* cyclization of cyclohexanol in the presence of *p*-toluensulphonic acid [8]. Other previous studies presented the synthesis of a byciclo[3.3.1]-nona-9-one *via* cyclization of 5-chlorocarbonylcyclooctene using aluminium trichloride as catalyst [9]. Recently, a bicyclo[3.2.2]nonane-steroid derivative (phomopsterone-A) from isocyathisterol has been prepared *via* some Wagner-Meervein rearrangement/epoxidation reactions [10]. Also, a spiro[bicyclo[3.2.2]-nonane-2,1'-cyclohexane]-steroid derivative (spiroaspertrione-A) was developed from farnesyl pyrophosphate and 5,7-dihydroxy-4,6-dimethyl-3*H*-isobenzofuran-1-one [11]. All these data show different protocols for the preparation of several bicyclo[3.3.1]nonane derivatives, however, there are few data regarding the synthesis of bicyclo[3.2.2]nonane derivatives bound to steroid nucleus.

The aim of this research was to develop two bicyclo[3.2.1]nonano-steroid derivatives using a series of reaction such as etherification, aromatic nucleophilic substitution, [2+2] addition, acylation and an internal cyclization which do not require special conditions.

Experimental

Generalities

All reagents such as ninhydrin (**1**), 1-fluoro-2,4-dinitrobenzene (**2**) used in this investigation were acquired from Sigma-Aldrich Co., Ltd. The *melting point* values of the obtained compounds were determined on an Electrothermal apparatus (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 VXR300/5 FT NMR spectrometer at 300 MHz in $CDCl_3$ using TMS as internal standard. *Electron ionization mass spectrometry* (EI-MS) was obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. *Elemental analysis* data were acquired from a Perkin Elmer II CHNS/02400 elemental analyzer.

Synthesis of 8-fluoro-1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene (3)

A solution containing of **1** (100 mg, 0.56 mmol), **2** (100 μL, 0.79 mmol), potassium carbonate (60 mg, 0.43 mmol) in 5 mL of dimethyl sulphoxide were stirred under reflux (120°C) for 24 h, then, the solvent was removed under reduced pressure, the reaction progress was monitored by thin layer chromatography. Further, the product was purified by crystallization using the methanol:water:hexane (3:1:1) system; yielding 66% of product; m.p. 48-50°C; IR (ν_{max}, cm^{-1}) 1136 and 1112. ^{1}H NMR δ_H: 5.84-7.34 (m, 3H), 8.04-8.20 (m, 4H) ppm. ^{13}C NMR δ_C: 78.00, 98.40, 108.80, 114.81, 126.00, 135.26, 138.20, 142.92, 146.60, 149.64, 184.62, 186.54 ppm. EI-MS m/z: 270.03. Calc. for $C_{15}H_7FO_4$: C, 66.67; H, 2.61; F, 7.03. Found: C, 66.64; H, 2.60.

Synthesis of N-(2,4-dinitrophenyl)-N-(3-ethynylphenyl)amine (4)

A solution of **2** (100 μL, 0.79 mmol), 3-ethynylaniline (100 μL, 0.88 mmol), and acetonitrile (5 mL) were stirred under reflux for 24 h; then, the solvent was removed under reduced pressure. Afterwards, the product was purified by crystallization using the methanol:water (3:1) system; yielding 75% of product; m.p. 42-44°C; IR (ν_{max}, cm^{-1}) 3322, 2110 and 1622. ^{1}H NMR δ_H: 2.88 (s, 1H), 7.12-7.30 (m, 4H), 7.88-9.00 (m, 3H), 9.70 (broad, 1H) ppm. ^{13}C NMR δ_C: 78.20, 84.02, 106.52, 118.20, 120.72, 123.36, 124.24, 124.34, 125.50, 128.04, 131.57, 134.74, 136.22, 141.52 ppm. EI-MS m/z: 283.05. Calc. for $C_{14}H_9N_3O_4$: C, 59.37; H, 3.20; N, 14.84. Found: C, 59.34; H, 3.20; N, 14.82.

Synthesis of 8-[(3-ethynylphenyl)-amino]-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene-1',3'-dione (6)

Method A: A solution of compound **3** (200 mg, 0.82 mmol), 3-ethynylaniline (100 μL, 0.88 mmol) and acetonitrile (5 mL) were stirred under reflux for 24 h; then, the solvent was removed under reduced pressure. Following, the product was purified by crystallization using the methanol:water (3:1) system, yielding 48% of product; m.p. 58-60°C; IR (ν_{max}, cm^{-1}) 3320, 2110, and 1136. ^{1}H NMR δ_H: 2.88 (s, 1H), 5.90 (m, 1H), 6.90 (broad, 1H), 6.96-7.25 (m, 6H), 8.04-8.20 (m, 4H) ppm. ^{13}C NMR δ_C: 74.58, 78.21, 84.00, 96.30, 108.64, 113.74, 118.00, 123.18, 123.20, 125.50, 125.96, 126.00, 130.52, 132.48, 134.76, 136.00, 138.21, 146.30, 184.62, 186.54 ppm. EI-MS m/z: 367.08. Calc. for $C_{23}H_{13}NO_4$: C, 75.20; H, 3.57; N, 3.81. Found: C, 81.38; H, 3.56; N, 3.80.

Method B: A solution of compound **4** (160 mg, 0.56 mmol), compound **1** (100 mg, 0.56 mmol), potassium carbonate (60 mg, 0.43 mmol) and 5 mL of dimethyl sulphoxide were stirred at room temperature for 48 h; then, the solvent was removed under reduced pressure. The obtained product was purified by crystallization using the methanol:water:hexane (3:1:1) system, yielding 58% of product; similar ^{1}H NMR and ^{13}C NMR data were obtained and compared with the method A product.

Synthesis of 8-[(3-{7,16-dihydroxy-17-methylpentacyclo[10.7.0.0^{2,9}.0^{3,6}.0^{13,17}]nonadeca-2(9),4,7-trien-4-yl}phenyl)-amino]-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene-1',3'-dione (7)

A solution of compound **6** (200 mg, 0.59 mmol), 17*β*-estradiol (160 mg, 0.58 mmol), cupric chloride anhydrous (55 mg, 0.41 mmol) in 5 mL of methanol were stirred at room temperature for 48 h; then, the solvent was removed under reduced pressure. Following, the product was purified by crystallization using the methanol:water (3:1) system, yielding 45% of product; m.p. 78-80°C; IR (ν_{max}, cm^{-1}) 3400, 3320, and 1134. ^{1}H NMR δ_H: 0.80 (s, 3H), 1.32-2.18 (m, 15H), 3.18-5.10 (m, 4H), 5.92 (m, 1H), 6.34 (d, 1H, *J*= 0.80 Hz), 6.96 (m, 1H), 6.97 (m, 1H), 7.08-7.40 (m, 4H), 8.06 (m, 2H), 8.08 (broad, 3H), 8.20 (m, 2H) ppm. ^{13}C NMR δ_C: 15.80, 22.22, 23.84, 28.14, 30.44, 32.78, 36.30,

36.82, 39.54, 42.10, 44.32, 45.26, 50.73, 74.61, 82.46, 96.30, 99.76, 108.62, 108.98, 111.84, 113.80, 120.34, 121.54, 126.00, 128.97, 132.69, 133.66, 136.06, 137.10, 137.90, 138.20, 140.32, 142.04, 146.34, 148.90, 155.16, 184.62, 186.54 ppm. EI-MS m/z: 639.26. Calc. for $C_{41}H_{37}NO_6$: C, 76.98; H, 5.83; N, 2.19. Found: C, 76.96; H, 5.80; N, 2.18.

Synthesis of 8-({3-[(17S)-7-hydroxy-17-methyl-16-oxopentacyclo[10.7.0.0^{2,9}.0^{3,6}.0^{13,17}]nonadeca-2(9),4,7-trien-4-yl]phenyl}-amino)-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-triene-1',3'-dione (8)

A solution of compound **6** (200 mg, 0.58 mmol), estrone (160 mg, 0.59 mmol), cupric chloride anhydrous (55 mg, 0.41 mmol) in 5 mL of methanol were stirred at room temperature for 48 h; then, the solvent was removed under reduced pressure. The product was purified by crystallization using the methanol:water (3:1) system, yielding 48% of product; m.p. 110-112°C; IR (ν_{max}, cm^{-1}) 3400, 3322, 1706, and 1336. ^{1}H NMR δ_H: 0.90 (s, 3H), 1.40-2.00 (m, 10H), 2.12-5.10 (m, 8H), 5.92 (m, 1H), 6.36 (*d*, 1H, *J*= 0.80 Hz), 6.96-7.40 (m, 6H), 8.06-8.20 (m, 4H), 8.90 (broad, 2H) ppm. ^{13}C NMR δ_C: 13.82, 21.52, 22.22, 26.00, 28.72, 30.42, 35.70, 36.82, 39.50, 42.14, 47.32, 48.12, 51.90, 74.60, 96.30, 99.76, 108.66, 108.98, 111.84, 113.80, 120.30, 124.26, 126.00, 128.94, 132.70, 133.66, 136.06, 136.14, 137.10, 137.90, 138.20, 142.04, 146.34, 148.90, 155.20, 184.62, 186.54, 220.14 ppm. EI-MS m/z: 637.24. Calc. for $C_{41}H_{35}NO_6$: C, 77.22; H, 5.53; N, 2.20. Found: C, 77.20; H, 5.50; N, 2.18.

Synthesis of (17S)-16-[(2-chloroacetyl)oxy]-4-(3-{1',3'-dioxo-2,4-dioxaspiro[bicyclo[3.3.1] nonane-3,2'-indene]-1(9),5,7-trien-8-ylamino} phenyl)-17-methylpentacyclo [10.7.0.0^{2,9}.0^{3,6}.0^{13,17}]nonadeca-2(9),4,7-trien-7-yl 2-chloro-acetate (9)

A solution of compound **7** (200 mg, 0.32 mmol), chloroacetyl chloride (70 µL, 0.87 mmol), triethylamine (70 µL, 0.50 mmol) in 5 mL of dimethyl sulphoxide were stirred at room temperature for 24 h; then, the solvent was removed under reduced pressure. The product was purified by crystallization using the methanol:water:hexane (3:1:1) system; yielding 48% of product; m.p. 132-134°C; IR (ν_{max}, cm^{-1}) 3320, 1722, and 1332. ^{1}H NMR δ_H: 0.80 (s, 3H), 1.30-400 (m, 17H), 4.10-4.26 (m, 4H), 4.80-5.84 (m, 2H), 5.92 (m, 1H), 6.28 (broad, 1H), 6.34 (d, 1H, *J*= 0.80 Hz), 6.96-7.40 (m, 6H), 8.06-8.20 (m, 4H) ppm. ^{13}C NMR δ_C: 14.40, 22.22, 24.27, 28.00, 30.00, 30.44, 36.20, 36.80, 37.56, 40.80, 41.00, 42.12, 44.02, 45.28, 50.90, 74.60, 84.62, 96.30, 108.62, 109.74, 111.82, 113.82, 115.62, 121.06, 125.66, 126.00, 128.96, 130.90, 132.70, 136.02, 137.12, 138.04, 138.20, 142.04, 146.34, 146.84, 148.40, 150.66, 163.79, 168.00, 184.62, 186.54 ppm. EI-MS m/z: 791.20. Calc. for $C_{45}H_{39}Cl_2NO_8$: C, 68.18; H, 4.96; Cl, 8.94; N, 1.77. Found: C, 68.15; H, 4.94; N, 1.76.

Synthesis of (17S)-4-(3-{1',3'-dioxo-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-trien-8-ylamino}phenyl)-17-methyl-16-oxopentacyclo[10.7.0.0^{2,9}.0^{3,6}.0^{13,17}]nonadeca-2(9),4,7-trien-7-yl 2-chloroacetate (10)

A solution of compound **8** (200 mg, 0.32 mmol), chloroacetyl chloride (50 µL, 0.62 mmol), triethylamine (70 µL, 0.50 mmol) in 5 mL of dimethyl sulphoxide was stirred at room temperature for 24 h; then, the solvent was removed under reduced pressure. The obtained product was purified by crystallization using the methanol:water:hexane (3:1:1) system; yielding 48% of product; m.p. 158-160°C; IR (ν_{max}, cm^{-1}) 3320, 1722, 1706 and 1330. ^{1}H NMR δ_H: 0.90 (s, 3H), 1.40-2.46 (m, 15H), 3.70-4.00 (m, 2H), 4.24-4.26 (m, 2H), 5.82 (m, 1H), 5.92 (m, 1H), 6.30 (broad, 1H), 6.33 (d, 1H, *J*= 5.32 Hz), 6.96-7.40 (m, 6H), 8.06-8.20 (m, 4H) ppm. ^{13}C NMR δ_C: 13.82, 21.52, 22.22, 26.00, 28.72, 30.42, 35.70, 36.78, 37.52, 41.00, 42.12, 47.34, 48.12, 51.90, 74.62, 96.28, 108.64, 109.74, 111.84, 113.80, 115.66, 121.10, 126.00, 128.34, 128.94, 130.96, 132.69, 136.02, 137.12, 138.04, 138.20, 142.06, 142.64, 146.30, 148.42, 150.64, 163.74, 184.62, 186.54, 220.20 ppm. EI-MS m/z: 713.21. Calc. for $C_{43}H_{36}ClNO_7$: C, 72.31; H, 5.08; Cl, 4.96; N, 1.96. Found: C, 72.30; H, 5.04; N, 1.94.

Synthesis of (5S)-21-(3-{1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-trien-8-ylamino}-phenyl)-5-methyl-16-oxo-17-oxahexacyclo[11.9.0.0^{2,10}.0^{5,9}.0^{14,18}.0^{19,22}] docosa-1(13),20-dien-6-yl-2-chloroacetate (11)

A solution of compound **9** (200 mg, 0.26 mmol), sodium hydroxide (25 mg, 0.62 mmol) in dimethyl sulphoxide (5 mL) was stirred under reflux for 48 h; then, the solvent was removed under reduced pressure. The obtained product was purified by crystallization using the methanol:water:hexane (3:1:1) system; yielding 66% of product; m.p. 120-122°C; IR (V_{max}, cm^{-1}) 3322, 1722, and 1332. ^{1}H NMR δ_H: 0.80 (s, 3H), 1.32-2.02 (m, 12H), 2.20-2.24 (m, 3H), 2.26 (m, 1H), 2.50 (m, 1H), 2.94-3.10 (m, 2H), 3.76 (m, 1H), 4.10 (m, 2H), 4.57-4.82 (m, 2H), 5.92 (m, 1H), 6.28 (d, 1H, *J*= 5.32 Hz), 6.30 (broad, 1H), 6.98-7.36 (m, 6H), 8.06-8.20 (m, 4H) ppm.

^{13}C NMR δ_C: 14.40, 24.26, 25.68, 26.04, 28.66, 30.00, 33.60, 35.64, 36.22, 40.00, 40.82, 40.90, 42.20, 43.38, 44.00, 50.90, 74.62, 84.62, 86.22, 96.24, 108.60, 108.76, 111.82, 113.82, 120.12, 126.00, 128.96, 129.76, 132.67, 132.80, 135.06, 136.02, 13710, 137.12, 138.20, 142.02, 146.34, 151.14, 168.00, 175.70, 184.62, 186.54, ppm. EI-MS m/z: 757.24. Calc. for $C_{45}H_{40}ClNO_8$: C, 71.28; H, 5.32; Cl, 4.68; N, 1.85. Found: C, 71.25; H, 5.32; N, 1.84.

Synthesis of (5S)-21-(3-{1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-trien-8-ylamino}-phenyl)-5-methyl-17-oxahexacyclo[11.9.0.0^{2,10}.0^{5,9}.0^{14,18}.0^{19,22}]docosa-1(13),20-diene-6,16-dione (12)

A solution of compound **10** (200 mg, 0.29 mmol), sodium hydroxide (25 mg, 0.62 mmol) in dimethyl sulphoxide (5 mL) was stirred under reflux for 48 h; then, the solvent was removed under reduced pressure. Following, the product was purified by crystallization using the methanol:water:hexane (3:1:1) system; yielding 45% of product; m.p. 208-210°C; IR (V_{max}, cm^{-1}) 3320, 1720, 1706 and 1330. ^{1}H NMR δ_H: 0.90 (s, 3H), 1.40-2.22 (m, 13H), 2.24 (m, 1H), 2.28-2.50 (m, 3H), 2.94-3.10 (m, 2H), 3.76-4.56 (m, 2H), 5.92 (m, 1H), 6.28 (d, 1H, *J*= 0.80 Hz), 6.30 (broad, 1H), 6.96-7.36 (m, 6H), 8.06-8.20 (m, 4H) ppm. ^{13}C NMR δ_C: 13.82, 21.52, 25.70, 26.76, 28.67, 33.02, 33.60, 35.64, 35.70, 40.92, 42.16, 42.86, 43.36, 47.32, 51.92, 74.62, 86.22, 96.24, 108.60, 108.79, 111.82, 113.82, 120.12, 126.00, 128.94, 129.79, 132.66, 132.83, 135.04, 136.02, 137.06, 137.12, 138.20, 142.02, 146.32, 151.16, 175.70, 184.62, 186.54, 220.20 ppm. EI-MS m/z: 679.25. Calc. for $C_{43}H_{37}NO_7$: C, 75.98; H, 5.49; N, 2.06. Found: C, 75.94; H, 5.46; N, 2.04.

Results and discussion

Synthesis and characterization

Several bicyclo-derivatives have been developed using different methods which involve some reagents that could be dangerous and require specific conditions [1-11]. In this study, two steroid-bicyclo[3.3.1]nonane derivatives were prepared using alternative chemical strategies: etherification and nucleophilic substitution.

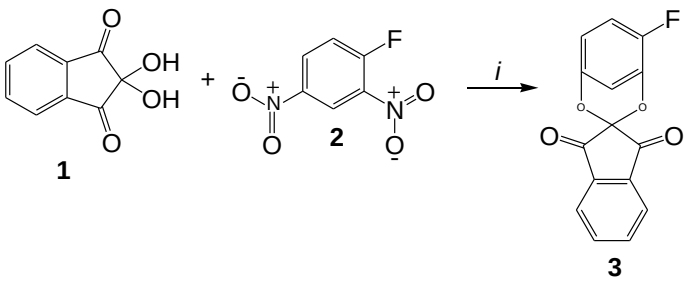
Etherification

It is important to mention that ether derivatives have been prepared through the displacement of nitro groups using several reagents such as hexamethylphosphoramide [12], [^{18}F]fluoride [13], nitro-cyclohexanone [14], sodium phenoxide [15], dimethyl sulphoxide (DMSO) [16,17], and others. In this investigation, an ether derivative **3** was prepared from ninhydrin and 1-fluoro-2,4-dinitrobenzene using mild reaction conditions (Scheme 1 and 2).

The NMR results showed several signals present in the ^{1}H spectrum for compound **3** at 5.84-7.32 ppm for phenyl group bound to both ether groups; at 8.04-8.20 ppm for the indan fragment. The ^{13}C spectrum displayed chemical shifts at 78.00, 126.00-138.20 ppm for the indan fragment; at 98.40-114.81 and 142.92-149.64 ppm for phenyl bound to both ether groups; at 184.62-186.54 ppm for ketone groups. Additionally, the mass spectrum signal (m/z) from compound **3** was found at 270.02.

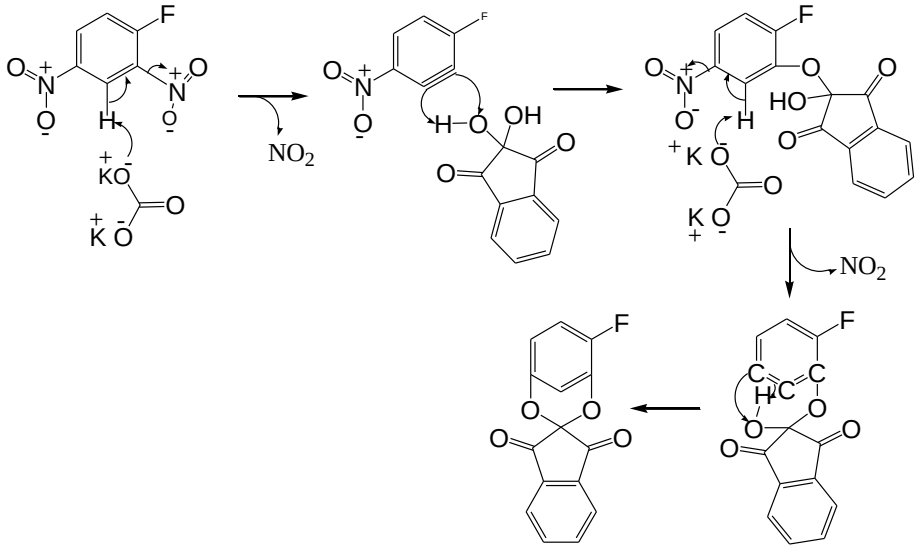
Nucleophilic substitution

There are several reports which show different aromatic nucleophilic substitution reactions; however, some of these reactions require special conditions thus greatly limiting the possibility of their application [18-22]. It is important to mention that a study indicates that there is no nucleophilic substitution of a 4-nitrofluorobenzene in liquid ammonia and only 4-nitroaniline is formed [23]. Based on that, the compound *N*-(3-ethynylphenyl)-2,4-dinitroaniline (**4**) was prepared in this study from 1-fluoro-2,4-dinitrobenzene and 3-ethynylaniline in the presence of acetonitrile in mild conditions (Scheme 3); here it is noteworthy that the formation of compound **5** (*N,N'*-bis-(3-ethynyl-phenyl)-4,6-dinitro-benzene-1,3-diamine) was not observed.

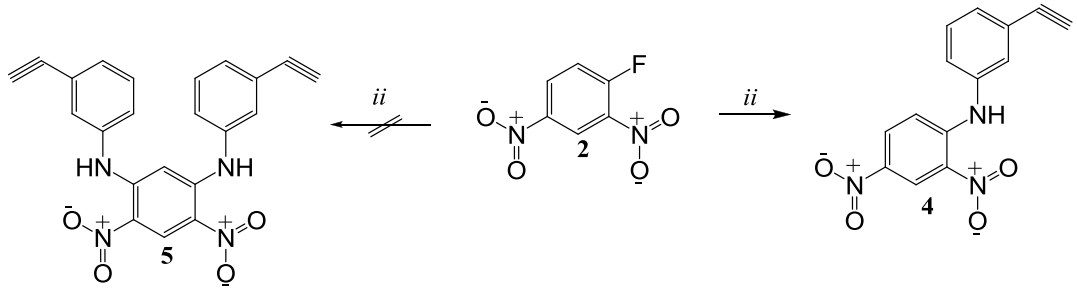


Reagents and conditions: i. K_2CO_3, DMSO, reflux, 24 h, 66%.

Scheme 1. Synthesis of 8-fluoro-1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]--1(9),5,7-triene (3).



Scheme 2. Reaction mechanism involved in the synthesis of compound 3.



Reagents and conditions: ii. 3-ethynylaniline, acetonitrile, reflux, 24 h, 75%.
Scheme 3. Synthesis of *N*-(3-ethynylphenyl)-2,4-dinitroaniline (4).

The signals observed in the ^{1}H NMR spectrum for compound **4** displayed at 2.88 ppm for alkyne group, at 7.14-9.00 ppm for phenyl groups, and at 9.70 ppm for amino groups. In addition, the ^{13}C NMR spectrum showed bands at 78.20-84.02 ppm for alkyne group and at 106.52-141.52 ppm for phenyl groups. Additionally, the compound **4** was found at 283.05 in the mass spectrum.

Synthesis of N-(3-ethynylphenyl)-1',3'-dihydro-2,4-dio-xaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-trien-8-amine (6)

Compound **6** was prepared using two methods: method A - *via* reaction of **3** with 3-ethynylaniline in the presence of acetonitrile in mild conditions (Scheme 4); method B - from compound **4** and ninhydrin. It is noteworthy, that there was a higher yield with method B in comparison to method A; this difference was attributed to the reaction conditions in each method. Several signals in the ^{1}H NMR spectrum for compound **6** were shown at 2.88 for alkyne group; 5.90 and 6.96-7.26 ppm for phenyl groups; at 6.90 ppm for amino group; at 8.04-8.20 ppm for indan fragment. Moreover, signals were registered in the ^{13}C NMR spectrum for compound **6** at 74.58, 126.00-130.52 and 136.00-138.21 ppm for the indan fragment; at 78.21-84.00 ppm for the alkyne group. Finally, the mass spectrum signal (m/z) from compound **6** was found at 376.05.

[2+2] addition reaction

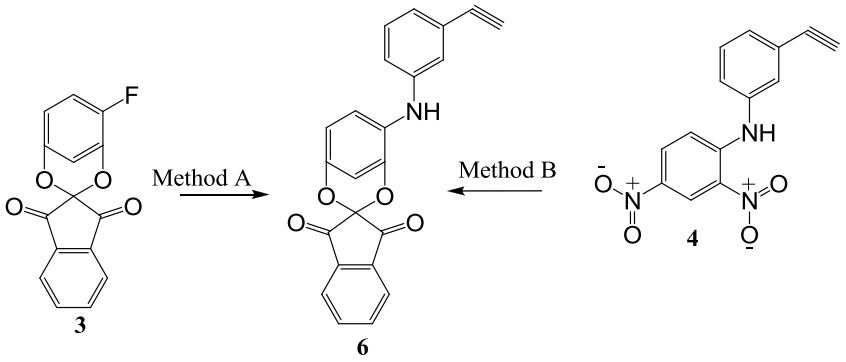
Several cyclobutene have been prepared using reagents such as organolithium derivative [24], rhodium [25], palladium [26], nickel [27], cobalt complexes [28], copper(I) [29]. In this study, a cyclobutene derivative (compound **7**) was prepared *via* [2+2] addition of an alkyne derivative (compound **6**) to estradiol or estrone using copper(II) as catalyst (Scheme 5). Signals in the ^{1}H NMR spectrum for compound **7** were found at 0.80 for methyl linked to steroid nucleus; at 6.34 ppm for cyclobutene fragment; at 8.08 ppm for both hydroxyl and amino groups.

Other signals from the ^{13}C NMR spectrum were found at 15.80 ppm for methyl group; at 74.61, 126.00, 136.08 and 138.20 ppm for the indan fragment; at 133.66 and 148.90 ppm for cyclobutene ring; at 184.62 and 186.54 ppm for ketone groups. In addition, the mass spectrum signal (m/z) from compound **7** was found at 639.26.

Signals in the ^{1}H NMR spectrum for compound **8** were found at 0.90 ppm for methyl linked to steroid nucleus; at 8.06-8.20 ppm for the indan fragment; at 6.36 ppm for the cyclobutene fragment; at 8.90 ppm for both amino and hydroxyl groups. Other signals, from the ^{13}C NMR spectrum were found at 13.82 ppm for the methyl group; at 74.60, 126.00, 136.06 and 138.20 ppm for the indan fragment; at 133.66 and 148.90 ppm for the cyclobutene fragment; at 184.62-220.14 ppm for ketone groups. In addition, the mass spectrum (m/z) from compound **8** was found at 637.24.

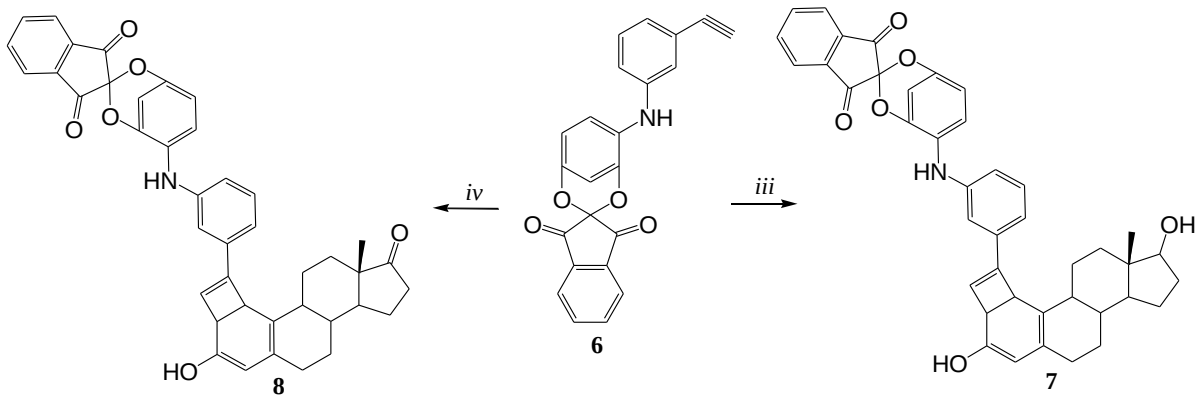
Acylation of compounds 9 or 10

Some reports have shown the acylation of alcohol groups using several reagents such as cobalt(II) chloride [30], bismuth(III) trifluoromethanesulphonate [31], di-stannoxane [32], scandium trifluoro-methane sulphonate [33], tantalum(V) chloride [34] and others. However, some of the reagents require special conditions. Analysing these data, in this investigation the compounds **7** or **8** were acylated with chloroacetyl chloride in the presence of triethylamine to form the compounds **9** or **10** (Scheme 6). It is noteworthy, that the ^{1}H NMR spectrum for compound **9** showed signals at 0.80 ppm for the methyl group linked to the steroid nucleus, at 8.06-8.20 ppm for the indan fragment, at 6.34 ppm for the cyclobutene fragment, at 6.28 ppm for the amino group linked to phenyl and at 4.10-4.26 ppm for methylene bound to both ester group and chloride atom.



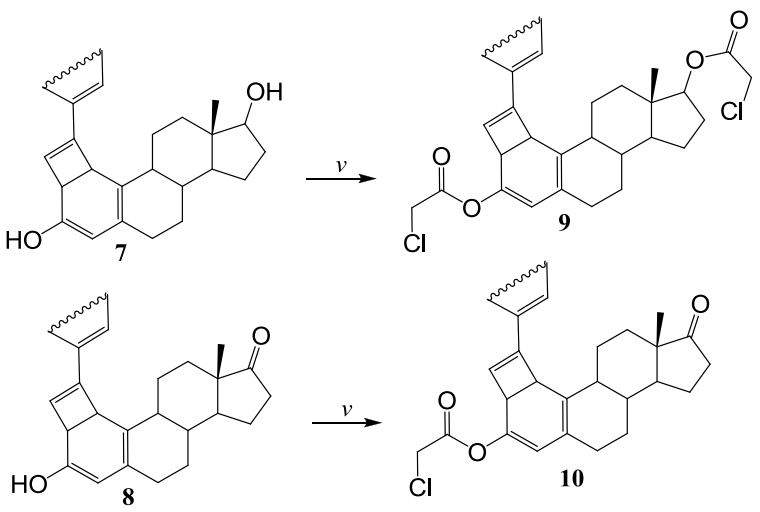
Reagents and conditions: Method A. 3-ethynylaniline, acetonitrile, reflux, 24 h, 48%;
Method B. ninhydrin, K_2CO_3, DMSO, rt, 48 h, 58%.

Scheme 4. Synthesis of *N*-(3-ethynylphenyl)-1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]-nonane-3,2'-indene]-1(9),5,7-trien-8-amine (6).



Reagents and conditions: iii. 17*β*-estradiol, cupric chloride, MeOH, rt, 48 h, 45%;
iv. estrone, cupric chloride, MeOH, rt, 48 h, 48%.

Scheme 5. Synthesis of two bicyclo[3.3.1]nonane-steroid derivatives (7 or 8).



Reagents and conditions: v. chloroacetyl chloride, Et_3N, DMSO, rt, 24, 48%;
Scheme 6. Synthesis of two bicyclo[3.3.1]nonane-steroid chloroacetate derivatives (9 or 10).

In addition, several signals were found in the ^{13}C NMR spectrum, at 14.40 ppm for the methyl group; at 74.60, 126.00, 136.02 and 138.20 ppm for the indan fragment; at 130.90 and 150.66 ppm for the cyclobutene fragment; at 163.79-168.00 for both ester groups; at 184.62 and 186.54 ppm for both ketone groups. The mass spectrum signal (m/z) from compound **9** was found at 791.20.

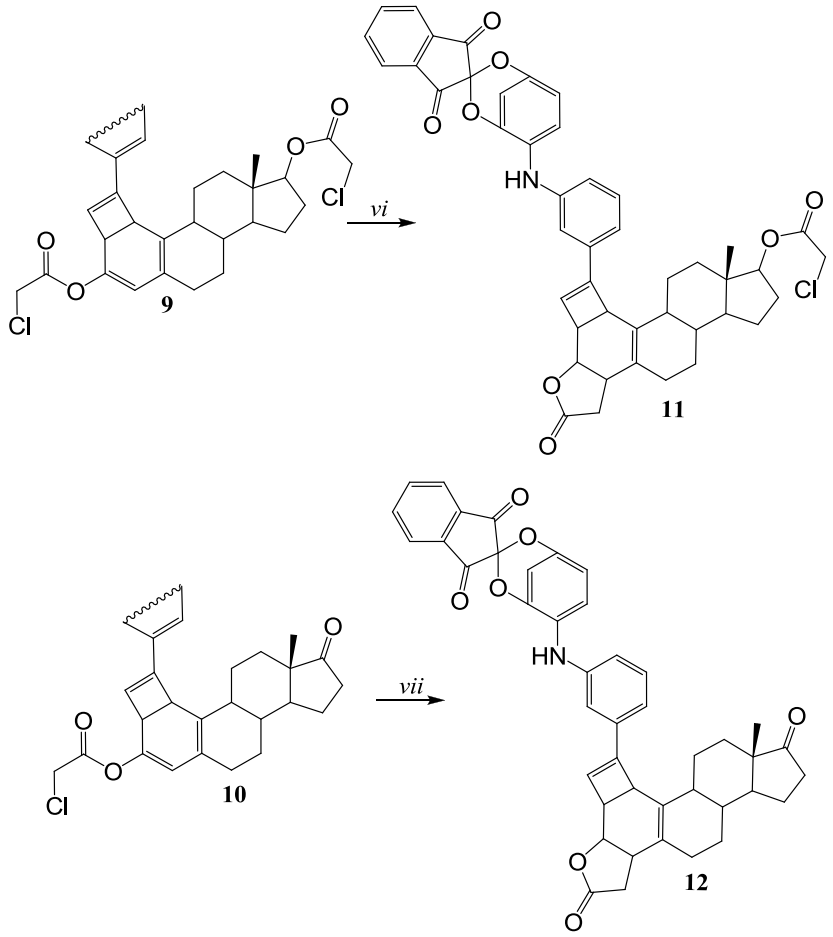
The ^{1}H NMR spectrum for compound **10** showed several signals at 0.90 ppm for the methyl group linked to steroid nucleus; at 8.06-8.20 ppm for the indan fragment; at 6.33 ppm for the cyclobutene ring; at 6.30 for amino group linked to the phenyl group. The ^{13}C NMR spectrum for the compound **10** showed signals at 13.82 ppm for the methyl group; at 74.62, 126.00, 136.02 and 138.20 ppm for the indan fragment; at 130.96 and 150.64 ppm for the cyclobutene ring; at 184.62-220.20 ppm for ketone groups. In addition, the mass spectrum (m/z) from compound **10** was found at 713.21.

Internal cyclization reaction

There are studies which show the cyclization of halide derivatives with internal double bound using reagents such as $Pd(PPh_3)_4$ [35], $Pd(OAc)_2$ [36], $Bi(OTf)_3$ [37], $CoCl_2$ [38], copper(I) [39] and others. Based on these data, in this study, a dihydro-furan-2-one ring was involved in the chemical structure of **11** or **12** formed *via* internal reaction of chloride with double bond in basic medium (Schemes 7 and 8).

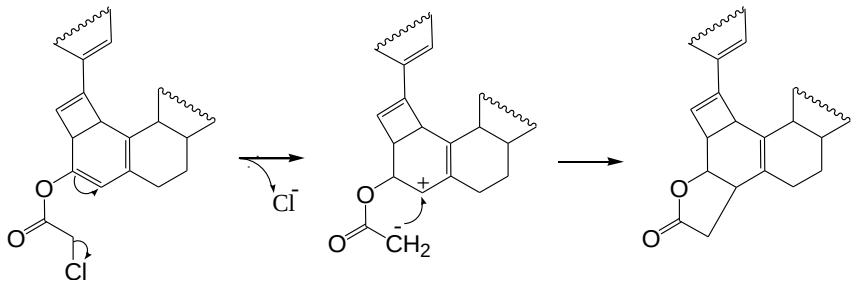
It is noteworthy that the ^{1}H NMR spectrum for compound **11** (Figure 1) showed several signals at 0.80 ppm for methyl linked to steroid nucleus; at 2.26 and 2.94-3.10 for the dihydro-furan-2-one ring; at 8.06-8.20 ppm for the indane fragment; 6.28 ppm for the cyclobutene ring; at 6.30 for the amino group; at 4.10 ppm for methylene bound to ester group; at 6.28 ppm for cyclobutene ring. Moreover, other signals of the ^{13}C NMR spectrum for compound **11** were found at 14.40 for the methyl group; at 76.62, 126.00, 136.02 and 138.20 ppm for the indan fragment; at 40.82 ppm for methylene bound to ester group; at 33.60 and 86.22 ppm for the dihydro-furan-2-one ring; at 132.80 and 151.14 ppm for the cyclobutene ring; at 168.00 ppm for the ester group; at 175.70-186.54 ppm for ketone groups. Additionally, the mass spectrum signal (m/z) from compound **11** was found at 757.24.

On the other hand, the ^{1}H NMR spectrum for compound **12** (Figure 2) displayed signals at 0.90 for methyl linked to steroid nucleus; at 2.26 and 2.94-3.10 ppm for the dihydro-furan-2-one ring; 8.06-8.20 ppm for indan; at 6.28 ppm for the cyclobutene ring; at 6.30 ppm for the amino group. It should be mentioned that several signals, in the ^{13}C NMR spectrum, were found at 13.82 for the methyl group; at 33.60 and 42.16 ppm for the dihydro-furan-2-one ring; at 74.62, 126.00, 136.02 and 138.20 ppm for the indan fragment; at 132.83 and 151.16 ppm for the cyclobutene ring; at 175.70-220.20 ppm for ketone groups. In addition, the mass spectrum (m/z) from compound **12** was found at 679.25



Reagents and conditions: vi. NaOH, DMSO, reflux, 48 h, 66%; *vii*. NaOH, DMSO, reflux, 48 h, 45%.

Scheme 7. Synthesis of two bicyclo[3.3.1]docosa-steroids derivatives (11 or 12).



Scheme 8. Reaction mechanism involved in the synthesis of bicyclo[3.3.1]docosa-steroid derivatives.

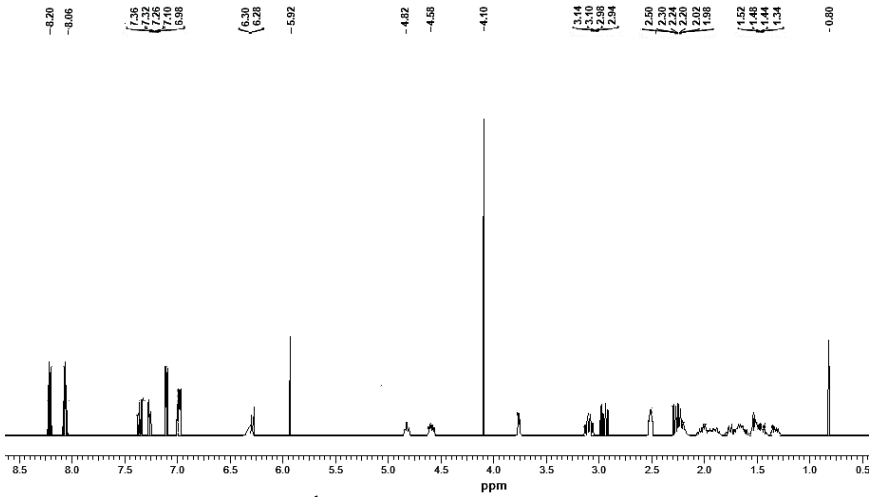


Figure 1. The ^{1}H NMR spectrum of compound 11.

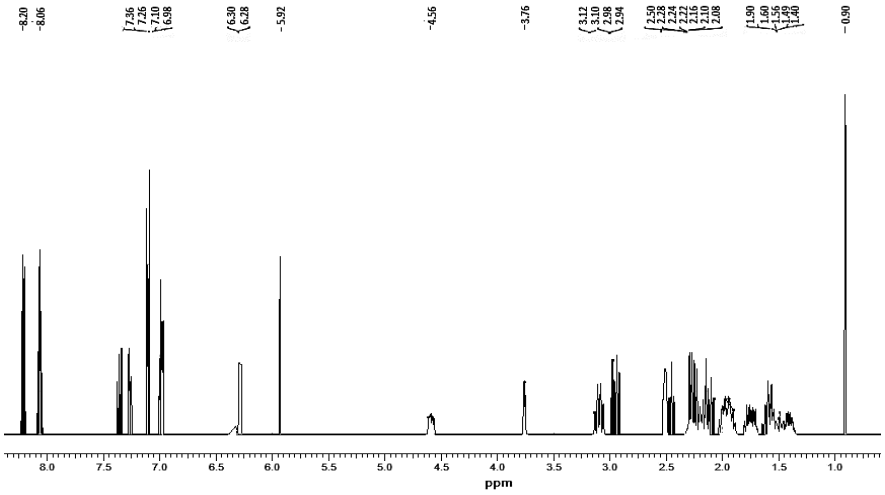


Figure 2. The ^{1}H NMR spectrum of compound 12.

Conclusions

In this study, the synthesis of two bicyclo[3.2.1]nonane-steroid derivatives was achieved from either estradiol or estrone using a series of reactions which involve etherification, nucleophilic aromatic substitution, [2+2] addition, acylation and an internal cyclization. It is noteworthy that the used reagents are easy to handle and do not require specific conditions. The presence of functional groups involved in their chemical structure was confirmed using both ^{1}H and ^{13}C NMR.

The yield of compound **11** ((5S)-21-(3-{1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1] nonane-3,2'-indene]-1(9),5,7-trien-8-ylamino}-phenyl)-5-methyl-16-oxo-17-oxahexacyclo[11.9.0.0^{2,10}.0^{5,9}. 0^{14,18}.0^{19,22}]docosa-1(13),20-dien-6-yl-2-chloroacetate) was higher compared to **12** ((5S)-21-(3-{1',3'-dihydro-2,4-dioxaspiro[bicyclo[3.3.1]nonane-3,2'-indene]-1(9),5,7-trien-8-ylamino}-phenyl)-5-methyl-17-oxahexacyclo[11.9.0. 0^{2,10}.0^{5,9}.0^{14,18}.0^{19,22}]docosa-13),20-diene-6,16-dione); this difference could be due to higher reactivity of compound **9** compared with **10** to form **11** or **12**.

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