



Design and Synthesis of New Steroid-cyclobutanone Derivative

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ABSTRACT

In this study, a prednisone derivative was synthesized; the first stage involve the reaction of the compound 1 (11-Bis-(2-amino-ethylimino)-17-[1-(2-amino-ethylimino)-2-hydroxy-ethyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-ol) with chloroacetyl chloride in presence of triethylamine to form 2[(3-chloro-2-oxo-cyclobutyl)(1-(3,11-bis-(2-[(2-[(chlorocarbonyl)amino]-ethyl)(3-chloro-2-oxo-cyclobutyl)amino]-17-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl))-2-hydroxyethyl)-amino]ethylcarbamoyl chloride (3). The second stage was achieved by the reaction of 3 with thiourea in methanol to form the compound 5(2-[(2-Amino-ethyl)-[1-(3,11-bis-[(2-amino-ethyl)-(3-chloro-2-oxo-cyclobutyl)-amino]-17-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl))-2-hydroxy-ethyl]-amino]-4-chloro-cyclobutanone). The structure of compounds obtained was 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: Prednisone, Thiourea, Chloroacetyl chloride, Triethylamine.

INTRODUCTION

Since several years ago, diverse corticosteroid derivatives have been developed; for example, the synthesis of 3 α -acetoxy-16 α -

methylpregnane-11,20-dione by catalytic reduction of 3 α -acetoxy-16-methyl-16-pregnene-11,20-dione using palladium on charcoal in acetic acid¹. Other reports indicate the preparation of 17 α -Hydroxy-3,11,20-triketone-21-azido-4-pregnene by the reaction of

cortisone-21-mesylate with sodium azide in acetone². In addition, other studies indicate the synthesis of 6 α -6 β -Dichloro-16 α -methylallopregnan-3 β -ol-20-one acetate by the reaction of 16 α -methyl- Δ^5 -pregnen-3 β -ol-20-one acetate with carbon tetrachloride in pyridine³. Other studies showed the development of 21-Desoxy-cortisone (7 α -Hydroxy- Δ^4 -pregnene-3,11,20-trione) by the reaction of cortisone with *p*-toluenesulfonyl chloride in pyridine⁴. Additionally, other corticosteroid derivative (Prednisolone 21-[4'-(Bromo)butyrate]) was synthesized by the reaction of prednisone with 4-bromo-butryl chloride in presence of triethylamine⁵. Other data indicate the preparation of a prednisone derivative (2-oxo-3-cyano-substituted-androsteno[17,16-c]pyran-3 β -ol) by the reaction of prednisolone with ethyl cyanoacetate in the presence of sodium ethoxide⁶. In addition, a study show the esterification of prednisolone with L-carnitine by the reaction of prednisolone with L-carnitine using 4-dimethylamino-pyridine/*N,N'*-dicyclohexylcarbodiimide⁷. Also, other report showed the development of prednisolone 21-(4'chlorobenzoate) by the reaction of prednisolone with 4-(chloromethyl) benzoyl chloride and triethylamine⁸. All these experimental results show several procedures which are available for synthesis of corticosteroid derivatives; nevertheless, expensive reagents and special conditions are required. Therefore, in this study a prednisone derivative was synthesized using some strategies.

EXPERIMENTAL

The compound 1 (11-Bis-(2-amino-ethylimino)-17-[1-(2-amino-ethylimino)-2-hydroxy-ethyl]-10,13-dimethyl-6,7,8,9,10,11, 12, 13, 14, 15, 16, 17-dodecahydro-3*H*-cyclopenta[a]-phenanthren-17-ol)¹⁰ was prepared mainly previously method reported. 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. ¹H and ¹³C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in CDCl₃ 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/O 2400

elemental analyzer.

Synthesis of 2[(3-chloro-2-oxo-cyclobutyl)(1-{3,11-bis-(2-[(2-[(chlorocarbonyl)amino]-ethyl)(3-chloro-2-oxocyclobutyl)amino]-17-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12, 13,14,15,16,17-dodecahydro-3*H*-cyclopenta[a] phenantren-17-yl))-2-hydroxyethyl)-amino] ethylcarbamic chloride

A solution of compound 1 (100 mg, 0.20 mmol), chloroacetyl chloride (64 μ l, 0.8 mmol) and triethylamine (112 μ l, 0.8 mmol) in 10 ml of methanol was stirring to reflux for 4 h. The reaction mixture was evaporated to dryness under reduced pressure. The obtained solid was washed with water, yielding 40 % of product, m.p. 196-198°C; IR } = 3402, 1662, 1712, 1198 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ _H: 0.91 (s, 3H), 0.96 (m, 1H), 1.25 (s, 3H), 1.31-1.65 (m, 5H), 1.67 (m, 1H), 1.68 (m, 1H), 1.79-1.93 (m, 4H), 1.97 (m 1H), 1.99 (m, 1H), 2.07 (m, 1H), 2.10-2.25 (m, 3 H), 2.28 (d, 1H), 2.32 (d, 1H), 2.33 (m, 1H), 2,37 (m, 1H), 2,38 (d, 1H), 2.41 (d, 1H), 2.43 (d, 1H), 2.87 (d, 1H), 3.23 (m, 1H), 3.34(t, 2H), 3.37 (t, 2H), 3.40 (m, 1H), 3.61 (t, 1H), 3.63 (m, 1H), 3.67 (t, 1H), 3.81, (m, 1H), 4.22-4.40 (m, 2H), 4.60 (m, 3H), 5.14-5.46 (m, 2H), 5.84 (broad, 5H) ppm. ¹³C NMR (75.4 Hz, CDCl₃) δ : 17.40 (C-24), 21.50 (C-33), 23.40 (C-8), 26.47 (C-17), 31.53 (C-16), 32.27 (C-53), 32.71 (C-40), 32.72 (C-48), 33.68 (C-7), 33.92 (C-3), 35.68 (C-9), 39.40 (C-10), 39.56 (C-36), 40.12 (C-20), 40.16 (C-29), 41.98 (C-5), 49.50 (C-4), 49.70 (C-35), 49.92 (C-28), 50.19 (C-19), 52.12 (C-13), 56. 62 (C-2), 56.70 (C-1), 60.22 (C-45), 62.10 (C-26), 62.96 (C-54, C-42, C-49), 69.50 (C-52), 70.16 (C-47), 71.12 (C-40), 86.66 (C-6), 113.22 (C-12), 135.98 (C-15), 144.80 (C-22, C-31, C-38), 148.86 (C-11), 200.98 (C-55), 201.10 (C-50), 206.10 (C-43) ppm. EI-MS *m/z*: 982.20 (M⁺10). Anal. Calcd. for C₄₂H₅₆Cl₆N₆O₈: C, 51.18; H, 5.73; Cl, 21.58; N, 8.53; O, 12.99. Found: C, 51.16; H, 5.70.

Synthesis of 2-[(2-Amino-ethyl)-[1-(3,11-bis-[(2-amino-ethyl)-(3-chloro-2-oxo-cyclo- butyl)-amino]-17-hydroxy-10,13-dimethyl-6,7,8,9,10,11, 12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta [a]phenantren-17-yl)-2-hydroxy-ethyl]-amino]-4-chloro-cyclobutane

A solution of compound 3 (100 mg, 0.10 mmol), thiourea (50 mg, 0.66 mmol) in 10 ml of methanol was stirring for 72 h to room temperature.

The reaction mixture was evaporated to dryness under reduced pressure. The obtained solid was washed with aqueous sodium thiosulfate to remove excess iodine and then washed with water, yielding 56% of product, m.p. 136°C; IR } = 3398, 3380, 1714, 1196 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ_{H} : 0.91 (s, 3H), 0.97 (m, 1H), 1.11 (s, 3H), 1.22 1.62 (m, 5H), 1.69 (m, 1H), 1.70 (m, 1H), 1.71-1.77 (m, 2H), 1.84 (broad, 8H), 1.86-1.96 (m, 2H), 1.97 (m, 1H), 1.98 (m, 1H), 2.07(m, 1H), 2.10-2.25 (m, 3H), 2.35 (m, 1H), 2.59 (t, 2H), 2.62 (t, 2H), 2.65-2.68 (t, 2H), 2.70 (t, 2H), 2.71 (t, 2H), 2.76 (t, 2H), 2.91 (m, 1H), 3.23 (m, 1H), 3.40 (m, 1H), 3.62 (t, 1H), 3.65 (m, 1H), 3.72 (t, 1H), 3.82 (m, 1H), 4.25-4.41 (m, 2H), 4.63 (m, 3H), 5.14-5.47 (m, 2H) ppm. ^{13}C NMR (75.4 Hz, CDCl_3) δ : 17.10 (C-22), 21.50 (C-29), 23.40 (C-8), 26.47 (C-17), 31.78 (C-16), 32.24 (C-45), 32.70 (C-35), 32.72 C-41), 33.68 (C-7), 33.90 (C-3), 35.68 (C-9), 39.40 (C-10), 42.12 (C-5), 42.96 (C-32), 47.12 (C-20), 47.16 (C-27), 49.50 (C-4), 50.28 (C-26), 50.52 (C-50.30), 52.95 (C-31), 56.65 (C-2), 56.71 (C-1), 60.22 (C-38), 62.17 (C-24), 62.96 (C-36), C-42, C-46), 69.52 (C-44), 70.16 (C-40), 71.02 (C-34), 86.46 (C-6), 113.16 (C-12), 121.68 (C-14), 136.30 (C-15), 148.80 (C-11), 201.36 (C-47), 201.76 (C-43), 202.02 (C-37) ppm. EI-MS m/z : 796.36 (M^+ 10). Anal. Calcd. for $\text{C}_{39}\text{H}_{59}\text{Cl}_3\text{N}_6\text{O}_5$: C, 58.68; H, 7.45; Cl, 13.32; N, 10.53; O, 10.02. Found: C, 56.64; H, 7.44.

RESULTS AND DISCUSSION

There are many procedures for development of corticosteroids derivatives. Nevertheless, despite its wide scope, have some drawbacks e.g., several agents used have a limited stability and their preparation require condition specials^{11,13}. Analyzing these data, in this study we report a straightforward route for synthesis of a prednisone derivative (5) using some strategies. The first stage step was achieved by the reaction of 1 with chloroacetyl chloride to form a chloroamide derivative involved in compound 3. It is important to mention that there are many procedures for the formation of chloroamides are known in the literature, for example the reaction of amine with Trichloroisocyanuric Acid¹⁴ or amide secondary with N-chlorobenzotriazole to form a chloroamide derivative¹⁵. In addition, since several years ago, have been prepared some chloroamides using chloroacetyl chloride¹⁶⁻¹⁸. Analyzing these data, in

this study chloroacetyl chloride was used to form a chloroamide involved in the compound 3. The ^1H NMR spectrum of compound 3 shows signals at 0.91 and 1.25 ppm for methyl groups; at 0.96, 1.31-1.65, 1.79-1.93, 2.10-2.25, 3.23, 4.22-4.40 5.14-5.46 ppm for steroid nucleus; at 1.67-2.07, 2.33, 3.40, 3.81 and 4.60 ppm for protons of cyclobutane rings; at 2.37, 243 and 3.34 ppm for arm bound to C-ring of steroid nucleus; at 2.28, 2.238 and 3.33 ppm for arm bound to B-ring of steroid nucleus; at 2.32, 2.41 and 3.37 ppm for arm bound to A-ring of steroid nucleus. Finally, other signals at 2.87 ppm for methylene group bound to both amino and cyclopentane groups; at 5.84 ppm for both chloroamide and hydroxyl groups; at 3.63 and 3.67 ppm for methylene group bound to hydroxyl group were found. The ^{13}C NMR spectrum contains peaks at 17.40 and 21.50 ppm for methyl groups; at 23.40-31.53, 33.68-39.40, 41.98-49.50, and 52.10-56.70, 86.66-135.98 and 148.86 ppm for steroid nucleus; at 32.27-32.72 and 62.50-71.12 ppm for carbons involved in cyclobutane rings; at 39.56, 49.70 ppm for methylene involved in the arm bound to A-ring of steroid nucleus; at 40.12 and 50.19 ppm for carbons involved in the arm bound to C-ring of steroid nucleus; at 40.16 and 49.92 ppm for methylene groups involved in the arm bound to D-ring of steroid nucleus; at 60.22 ppm for methylene group bound to hydroxyl group; at 60.10 ppm for carbon bound to both amino and cyclopentene groups. Finally, other signals at 144.80 ppm for chloroamide groups; at 200.98-206.10 ppm for cyclobutanone groups were found. In addition the presence of compound 3 was further confirmed from mass spectrum which showed a molecular ion at m/z 982.20.

The second stage was achieved by the removal of chloroacetyl group involved in the compound 3. It is important to mention that, there are some methods that show the removal of chloroacetyl groups of some compounds¹⁹; for example, the reaction of chloroacetylamine with thiourea to form an amine derivative²⁰⁻²¹. In this study, for the removal of chloroacetyl group was used thiourea to form a primary amine involved in the compound 5. This reaction is carried out an intramolecular amidinolysis to release the corresponding amine. The ^1H NMR spectrum of compound 5 shows signals at 0.91 and 1.11 ppm for methyl groups; at 0.97, 1.21-1.62, 1.71-1.77, 1.86-1.96, 2.10-2.25, 3.23, 3.65, 4.25-4.41 and

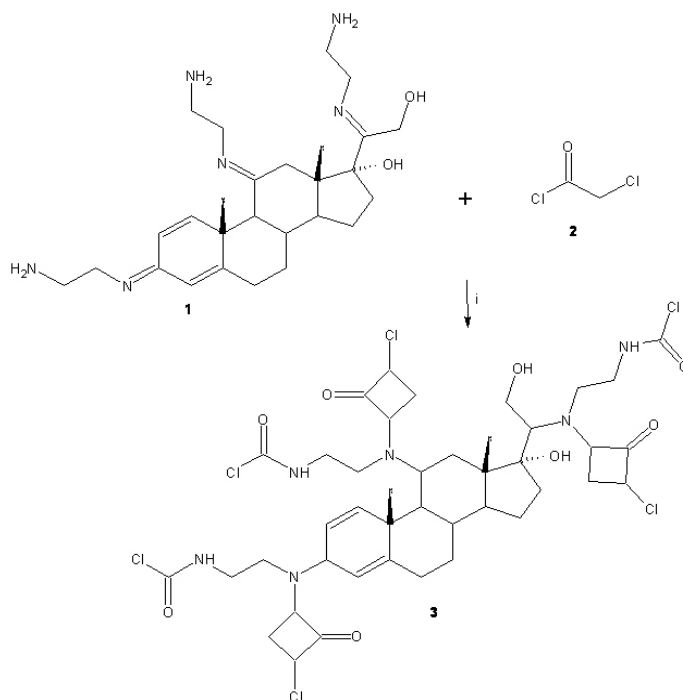


Fig. 1: Synthesis of 2[(3-chloro-2-oxo-cyclobutyl)(1-{3,11-bis-(2-[(2-[(chlorocarbonyl)-amino]-ethyl](3-chloro-2-oxo-cyclobutyl)amino]-17-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-hydroxyethyl)-amino]ethyl carbamic chloride (3). Reaction of the compound 1 (11-Bis-(2-amino-ethyl-imino)-17-[1-(2-amino-ethylimino)-2-hydroxy-ethyl]-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-ol) with chloroacetyl chloride to form 3. i = triethylamine

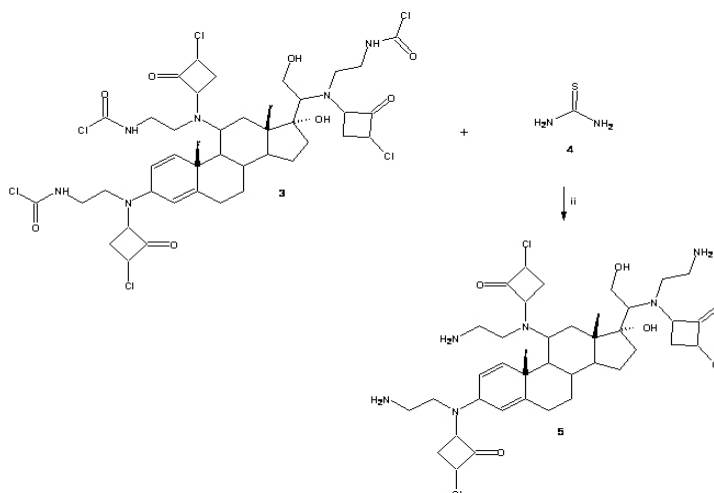


Fig. 2: Synthesis of 2-[(2-Amino-ethyl)-[1-(3,11-bis-[(2-amino-ethyl)-(3-chloro-2-oxo-cyclobutyl)-amino]-17-hydroxy-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-17-yl)-2-hydroxy-ethyl]-amino]-4-chloro-cyclobutane-1-one (5). Reaction of 3 with thiourea (4) to form 5. ii = methanol/rt

5.14-5.47 ppm for steroid nucleus; at 1.69, 1.70, 1.97, 1.98-2.07, 2.35, 3.40, 3.82 and 4.63 ppm for protons involved in cyclobutane rings; at 2.62 and 2.76 ppm for methylene groups involved in the arm bound to A-ring of steroid nucleus; at 2.59 and 2.71 ppm for protons involved in the arm bound to C-ring of steroid nucleus; at 2.65-2.70 ppm for methylene groups involved in the arm bound to D-ring of steroid nucleus. Finally, other signals at 1.84 ppm for both hydroxyl and amino groups; at 2.91 ppm for methylene group bound to both amino and cyclopentene groups; at 3.62 and 3.72 ppm for methylene group bound to hydroxyl group were found. The ^{13}C NMR spectrum contains peaks at 17.10 and 21.50 ppm for methyl groups; at 23.40-31.78, 33.68-42.12, 49.50, 56.65-56.71 and 86.46-148.80 ppm for steroid nucleus; at 32.24-32.72 and 62.96-71.02 ppm for carbons involved in cyclobutane groups; at 42.96 and 52.95 ppm for methylenes of arm bound to A-ring of steroid

nucleus; at 47.12 and 50.52 ppm for arm bound to C-ring of steroid nucleus; at 47.16 and 50.28 ppm for methylenes of arm bound to D-ring of steroid nucleus. Finally, other signals at 60.22 ppm for methylene bound to hydroxyl group; at 62.17 ppm for carbon bound to both amino and cyclopentene groups; at 201.36-202.02 ppm for cyclobutanone groups were found. In addition, the presence of compound **5** was further confirmed from mass spectrum which showed a molecular ion at m/z 796.36

CONCLUSIONS

In this study, we reported an efficient and simple method for synthesis of a steroid-cyclobutanone derivative. It is important to mention that this method is highly versatile and the yield is good.

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