



SPECTROSCOPIC STUDIES OF NEWLY SYNTHESIZED STEROIDAL DIHYDROPYRROLES

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A convenient procedure for the synthesis of 3 β -acetoxy-3'-chloro-5 α -cholest-6-eno[7,6-*d*]-2',3'-dihydro-1H-pyrrole (**4**), 3 β ,3'-dichloro-5 α -cholest-6-eno[7,6-*d*]-2',3'-dihydro-1H-pyrrole, (**5**) and 3'-chloro-5 α -cholest-6-eno[7,6-*d*]-2',3'-dihydro-1H-pyrrole (**6**) has been made from steroidal oximes (**1-3**) under refluxing conditions. The structural assignment of the products was confirmed on the basis of IR, ¹H NMR, ¹³C NMR, MS and analytical data.

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Introduction

Pyrrole derivatives are ubiquitous among naturally occurring organic compounds.¹ They are vital building blocks for the construction of bio-active molecules such as porphyrins, alkaloids and co-enzymes.² The biological importance of pyrrole and its derivatives cannot be overemphasized because they have shown to possess extensive biological activities and pharmacological properties such as antimicrobial, analgesics, ionotropic, antitumor, anti-inflammatory, and antiallergic.³⁻¹⁰ These have also been employed as P38kinase,¹¹ prolyl -4-hydroxylase,¹² poly(ADP-ribose) polymerase inhibitors,¹³ estrogen receptor β -selective ligands,¹⁴ AT1-selective angiotensin II receptor antagonists,¹⁵ and minor groove recognition elements.¹⁶ Several macromolecular antibiotics having pyrrole structure were isolated from biological sources, and their activities were defined.^{18,19}

In the view of their importance, the synthesis of pyrroles itself remains an attractive area. And there is a continuing interest in developing versatile synthetic routes.²⁰ In the light of the previous introductory comments, it is not surprising that a vast amount of work has and is being devoted to the development of practical methods for the synthesis of pyrrole building blocks containing appropriate substitution patterns.²¹ However, a search of the literature for effective methods for the synthesis of pyrrole libraries to be employed in high-throughput screening remains a challenge for medicinal chemists.

Although construction of pyrrole ring has been done by several methods, for example, the Knorr,²² Paal-Knorr,^{23, 24} and Hantzsch syntheses.²⁵ [3 + 2]-cycloadditions,²⁶⁻²⁸ multi-component reactions,²⁹⁻³¹ and ring contractions³² or cyclizations,³³⁻³⁶ a novel and efficient synthetic method for the synthesis of pyrroles is currently being pursued.

Unfortunately, the usual reaction conditions are extremely harsh, requiring strong bases/high temperatures and unselective products. These factors limit the overall synthetic utility of above-mentioned methods.

Keeping all the above applications of pyrroles in consideration and in connection with our previous work³⁷ aimed at developing a convenient synthetic strategy, we sought to develop a milder reaction condition to broaden the scope of this important transformation. We wish to report herein, an efficient one-pot procedure for the conversion of 5 α -cholestane-6-one oximes (**1-3**) into 3'-chloro-5 α -cholest-6-eno[7,6-*d*]-2',3'-dihydro-1H-pyrroles (**4-6**) using p-TsOH and vinyl chloride in acetonitrile under reflux conditions.

Experimental

General Methods

The IR spectra were recorded in KBr on Pye Unicam SP3-100 spectrophotometer and its values are given in cm⁻¹. ¹H NMR and ¹³C NMR spectra were run in CDCl₃ on a JEOL Eclipse (400 MHz) instrument with tetramethylsilane (TMS) as internal standard and its values are given in ppm (δ). Mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer. Thin layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapours to check the homogeneity as well as the progress of the reaction. Sodium sulfate (anhydrous) was used as a drying agent. All chemicals used in this work were purchased from Merck India.

Synthesis of 3'-chloro, 5 α -cholest-6-eno [7, 6 - *d*] 2', 3'-dihydro-1H-pyrroles (**4-6**)

To a mixture of 5 α -cholestane-6-one oxime **1-3** (1 mol) and p-TsOH (0.5 mg) in CH₃CN (20 mL), was added vinyl chloride (1 mol) in the same solvent and reaction mixture was refluxed for 7 h. The progress and purity of the reaction were checked by TLC. After the completion of the reaction, excess solvent was removed to three-fourths of the original volume under reduced pressure. The reaction mixture was taken in diethyl ether (15 mL) and washed with water (40

mL) thrice successively and dried over anhydrous sodium sulfate. Removal of solvent and crystallization from methanol provided the desired product **4-6**.

3 β -Acetoxy-3'-chloro-5 α -cholest-6-eno[7,6-d]-2',3'-dihydro-1H-pyrrole (**4**)

Yield (73 %); Anal. Calc. for C₃₁H₅₀NO₂Cl: C, 73.85, H, 10.01, N, 2.78. found: C, 73.73, H, 9.96, N, 2.70; IR (ν cm⁻¹): 3270 (N-H), 1735 (OCOCH₃), 1620 (C=C), 1080 (C-O), 1105 (C-N), 742 (C-Cl); ¹H NMR (CDCl₃, 400 MHz): δ 7.5 (s, 1H, NH, exchangeable with D₂O), 4.6 (m, 1H, C₃ α -H, $W_{1/2}$ = 15Hz), 3.9 (m, 1H, C₃'HCl, $W_{1/2}$ = 17 Hz), 3.3 (d, 2H, C'H₂), 2.01 (s, 3H, OCOCH₃), 1.12 (s, 3H, C₁₀-CH₃), 0.71 (s, 3H, C₁₃-CH₃), 0.90 & 0.80 (other methyl protons); ¹³C NMR (CDCl₃, 100 MHz): δ 171, 132, 128, 72.8, 52, 50, 42, 40, 37, 29, 27, 26; ESI-MS: m/z 503/505 [M⁺].

3 β ,3'-Dichloro-5 α -cholest-6-eno[7,6-d]-2',3'-dihydro-1H-pyrrole (**5**)

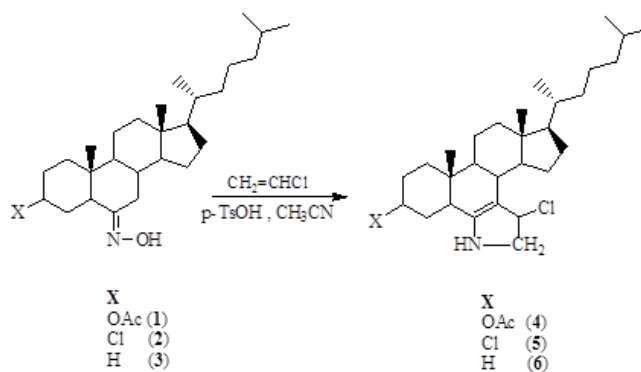
Yield (70 %); Anal. Calc. for C₂₉H₄₇NCl₂: C, 72.47, H, 9.86, N, 2.91. found: C, 72.39, H, 9.79, N, 2.88; IR (ν cm⁻¹): 3260 (N-H), 1622 (C=C), 1110 (C-N), 750, 744 (2 \times C-Cl); ¹H NMR (CDCl₃, 400 MHz): δ 7.7 (s, 1H, NH, exchangeable with D₂O), 4.3 (m, 1H, C₃ α -H, $W_{1/2}$ = 15 Hz), 3.7 (m, 1H, C₃'HCl, $W_{1/2}$ = 17 Hz), 3.5 (d, 2H, C'H₂), 1.12 (s, 3H, C₁₀-CH₃), 0.71 (s, 3H, C₁₃-CH₃), 0.90 & 0.80 (other methyl protons); ¹³C NMR (CDCl₃, 100 MHz): δ 130, 127, 54, 51, 42, 40, 37, 29, 27, 26; ESI MS: m/z 479/481 [M⁺].

3'-Chloro-5 α -cholest-6-eno[7,6-d]-2',3'-dihydro-1H-pyrrole (**6**)

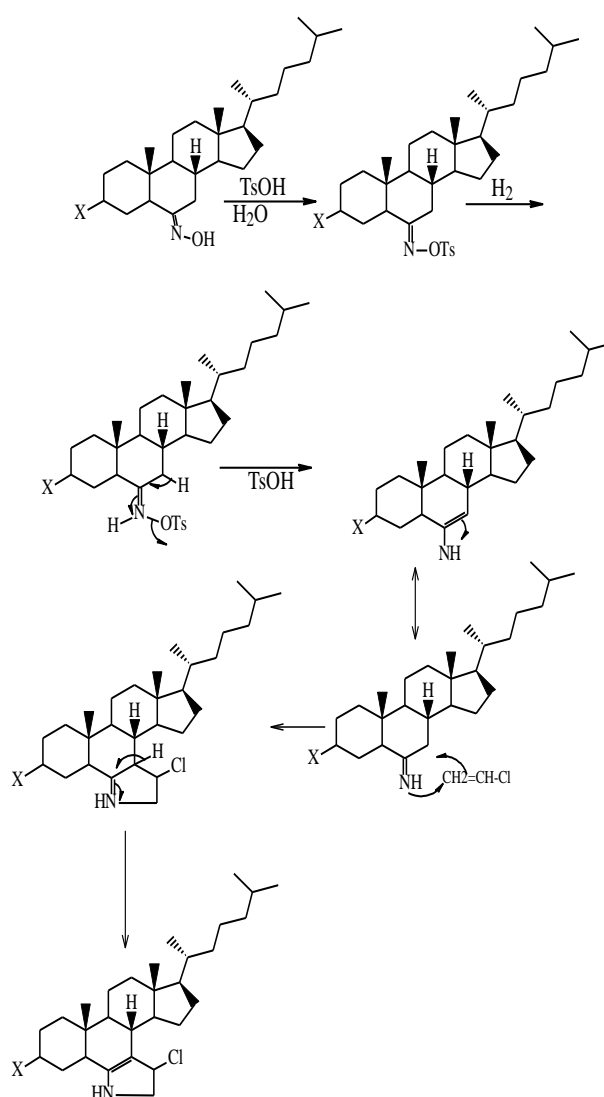
Yield (75 %); Anal. Calc. for C₂₉H₄₈NCl: C, 78.07, H, 10.84, N, 3.14. found: C, 77.96, H, 10.81, N, 3.11; IR (ν cm⁻¹): 3275 (N-H), 1628 (C=C), 745 (C-Cl), 1120 (C-N); ¹H NMR (CDCl₃, 400 MHz): δ 7.5 (s, 1H, NH, exchangeable with D₂O), 3.9 (m, 1H, C₃'HCl, $W_{1/2}$ = 17 Hz), 3.4 (d, 2H, C'H₂), 1.12 (s, 3H, C₁₀-CH₃), 0.71 (s, 3H, C₁₃-CH₃), 0.90 & 0.80 (other methyl protons); ¹³C NMR (CDCl₃, 100 MHz): δ 132, 128, 52, 50, 42, 40, 37, 29, 27, 26; ESI MS: m/z 445/447 [M⁺].

Results and discussion

The substrates employed for initial studies are 3 β -acetoxy-5 α -cholestan-6-one oxime **1b** (m/z 459), 3 β -chloro-5 α -cholestan-6-one oxime **2** (m/z 435) and 5 α -cholestan-6-one oxime **3** (m/z 401) which were synthesized by the treatment of steroidal ketones³⁸ with NH₂OH.HCl and sodium acetate trihydrate in ethanol under reflux conditions.³⁹ The oximes **1-3**, when allowed to react with vinyl chloride in an acidic medium under reflux conditions, afforded steroidal dihydropyrroles **4-6** (Scheme 1). The products have been characterized on the basis of their elemental and spectral studies.



Scheme 1. Schematic representation of the formation of steroidal pyrrole derivatives



Scheme 2. Mechanistic outline for cyclization of steroidal oxime into steroidal dihydropyrroles

All the compounds **4-6** exhibited IR absorption bands at 3260-3275 cm⁻¹ (N-H), 1105-1120 cm⁻¹ (C-N) and 1620-1628 (C=C) which suggested the formation of dihydropyrrole ring in the products. Further, stretching vibration at 742-750 (C-Cl) is attributed to the chlorine attached to the dihydropyrrole ring. The formation of steroidal pyrroles was further confirmed on the basis of ¹H NMR spectra. Assignments of the signals are based on the chemical shift and intensity pattern. The ¹H NMR spectra of the compounds exhibited a singlet (exchangeable with D₂O) for one proton (NH) at δ 7.5-7.7. It also predicts multiplet for one proton at δ 3.3-3.5 suggested the presence of C₃H-Cl. ¹³C NMR signals are in good agreement with the proposed structure of synthesized compounds.

All the compounds show δ 51-56 (C-Cl) which are attributed to the presence of chlorine. The signal in the range of 120-147 (C=C) and 46.5-46.8 (C-N) confirm the presence of pyrrole ring. The plausible mechanism⁴⁰ of this conversion is shown in Scheme 2. This conversion involves the initial reaction of steroidal oxime with *p*-toluenesulphonic acid to form the *o*-tosyl derivative. Protonation on nitrogen and subsequent removal of *p*-TsOH gives enamine intermediate. This upon reaction with vinyl chloride affords desired product **4-6**.

Conclusion

In conclusion, we have demonstrated an efficient and facile synthesis of steroidal dihydropyrrole derivatives in a one-pot operation from steroidal ketoximes. Moreover, this methodology offers significant advantages with regard to simplicity of operation, the yield of products, easy workup and mild reaction conditions. It provides a better alternative for the synthesis of dihydropyrroles. In short, the present procedure would shed new light on the convenient approach for the preparation of dihydropyrroles.

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