SPECTROSCOPIC STUDIES OF NEWLY SYNTHESIZED STEROIDAL DIHYDROPYRROLES

Ayaz Mahmood Dar [a]*, Shafia Mir [b], Masrat Jan [b] and Shamsuzzaman[a]

Keywords: Steroidal oxime, hydroxylamine, dihydropyrrole, vinyl chloride.

A convenient procedure for the synthesis of 3β-acetoxy-3′-chloro-5α-cholest-6-eno[7,6-*d*]-2′,3′-dihydro-1H-pyrrole (**4**), 3β,3′-dichloro-5α-cholest-6-eno[7,6-*d*]-2′,3′-dihydro-1H-pyrrole, (**5**) and 3′-chloro-5α-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, ^{1}H NMR, 13C NMR, MS and analytical data.

*Corresponding Authors
Tel: +91 9286990247
E-Mail: ayazchem09@gmail.com
[a] Department of Chemistry Aligarh Muslim University, Aligarh-202002, UP India
[b] Department of Chemistry OPJS University, Churu -331001, Rajasthan India

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 contractions[32] 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 work[37] 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 5α-cholestane-6-one oximes (**1-3**) into 3′-chloro-5α-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}. ^{1}H NMR and ^{13}C NMR spectra were run in $CDCl_3$ 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, 5α-cholest-6-eno [7, 6 - *d*] 2′, 3′-dihydro-1H-pyrroles (4-6)

To a mixture of 5α-cholestane-6-one oxime **1-3** (1 mol) and p-TsOH (0.5 mg) in CH_3CN (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**.

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

Yield (73 %); Anal. Calc. for $C_{31}H_{50}NO_2Cl$: C, 73.85, H, 10.01, N, 2.78. found: C, 73.73, H, 9.96, N, 2.70; IR (υ cm^{-1}): 3270 (N-H), 1735 (O*CO*CH_3), 1620 (C=C), 1080 (C-O), 1105 (C-N), 742 (C-Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5 (s, 1H, N*H*, exchangeable with D_2O), 4.6 (m, 1H, C_3α-*H*, $W_{½}$ = 15Hz), 3.9 (m, 1H, C_3′*H*Cl, $W_{½}$ =17 Hz), 3.3 (d, 2H, C′H_2), 2.01(s, 3H, OCOCH_3), 1.12 (s, 3H, C_{10}-CH_3), 0.71 (s, 3H, C_{13}-CH_3), 0.90 & 0.80 (other methyl protons); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171, 132, 128, 72.8, 52, 50, 42 40, 37, 29, 27, 26; ESI-MS: *m/z* 503/505 [$M^{+\cdot}$].

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

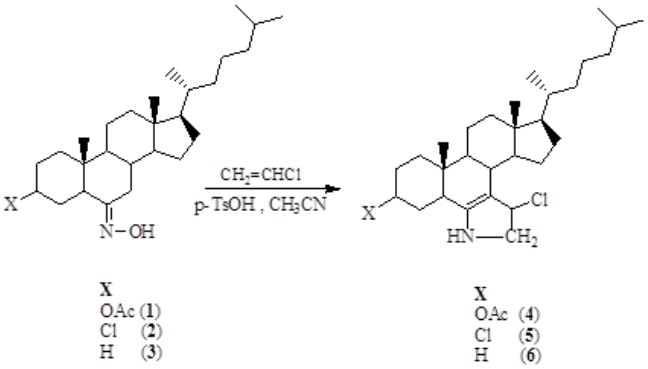
Yield (70 %); Anal. Calc. for $C_{29}H_{47}NCl_2$: C, 72.47, H, 9.86, N, 2.91. found: C, 72.39, H, 9.79, N, 2.88; IR (υ cm^{-1}): 3260 (N-H), 1622 (C=C), 1110 (C-N), 750, 744 (2×C-Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.7 (s, 1H, N*H*, exchangeable with D_2O), 4.3 (m, 1H, C_3α-*H*, *W*½ = 15 Hz), 3.7 (m, 1H, C_3′*H*Cl, $W_{½}$ =17 Hz), 3.5 (d, 2H, C′H_2), 1.12 (s, 3H, C_{10}-CH_3), 0.71 (s, 3H, C_{13}-CH_3), 0.90 & 0.80 (other methyl protons); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130, 127, 54, 51, 42 40, 37, 29, 27, 26; ESI MS: *m/z* 479/481 [$M^{+\cdot}$].

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

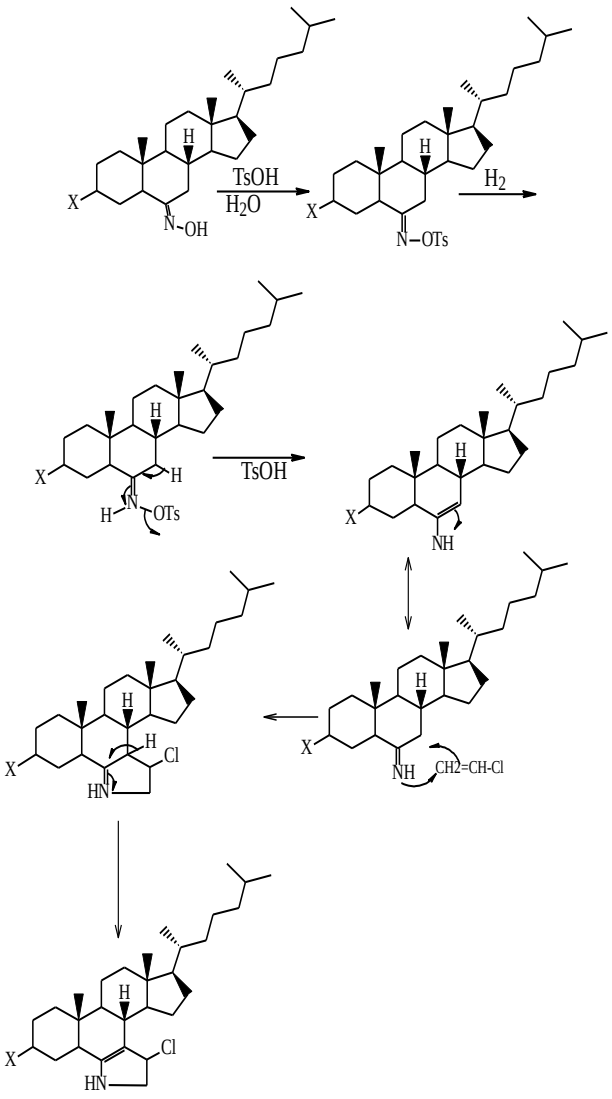
Yield (75 %); Anal. Calc. for $C_{29}H_{48}NCl$: C, 78.07, H, 10.84, N, 3.14. found: C, 77.96, H, 10.81, N, 3.11; IR (υ cm^{-1}): 3275 (N-H), 1628 (C=C), 745 (C-Cl), 1120 (C-N); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5 (s, 1H, N*H*, exchangeable with D_2O), 3.9 (m, 1H, C_3′*H*Cl, $W_{½}$ = 17 Hz), 3.4 (d, 2H, C′H_2), 1.12 (s, 3H, C_{10}-CH_3), 0.71 (s, 3H, C_{13}-CH_3), 0.90 & 0.80 (other methyl protons); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 132, 128, 52, 50, 42 40, 37, 29, 27, 26; ESI MS: *m/z* 445/447 [$M^{+\cdot}$].

Results and discussion

The substrates employed for initial studies are 3β-acetoxy-5α-cholestan-6-one oxime **1b** (*m/z* 459)**,** 3β-chloro-5α-cholestan-6-one oxime **2** (*m/z* 435) and 5α-cholestan-6-one oxime **3** (*m/z* 401) which were synthesized by the treatment of steroidal ketones[38] with $NH_2OH.HCl$ 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 ^{1}H NMR spectra. Assignments of the signals are based on the chemical shift and intensity pattern. The ^{1}H NMR spectra of the compounds exhibited a singlet (exchangeable with D_2O) for one proton (N*H*) at δ 7.5-7.7. It also predicts multiplet for one proton at δ 3.3-3.5 suggested the presence of C_3′H-Cl. ^{13}C 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 mechanism[40] 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.

Acknowledgements

Authors thank the Chairman, Department of Chemistry, A.M.U., Aligarh, for providing necessary research facilities. Facilities provided by SAP (DRS-I) for their generous research support are also gratefully acknowledged. Authors SM and MJ also thank Head department of Chemistry OPJS University for research support.

References

[1]Boger, D. L., Boyce, C. W., Labroli, M. A., Sehon, C. A., Jin, Q., *J. Am. Chem. Soc*., **1999**, *121*, 54-62 https://doi.org/10.1021/ja982078+

[2]Franck, B., Nonn, A., *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1795-1811. https://doi.org/10.1002/anie.199517951

[3]Demirayak, S., Karaburun, A. C., Kiraz, N., *Eur. J. Med. Chem.*, **1999**, *34*, 275-278. https://doi.org/10.1016/S0223-5234(99)80062-2

[4]Joshi, S. D., Vagdevi, H. M., Vaidya, V. P., Gadaginamath, G. S., *Eur. J. Med. Chem*., **2008**, *43*, 1989-1996. https://doi.org/10.1016/j.ejmech.2007.11.016

[5]Jonas, R., Klockow, M., Lues, I., Pruecher, H., Schliep, H. J., Wurziger, H., *Eur. J. Med. Chem*., **1993**, *28*, 129-140. https://doi.org/10.1016/0223-5234(93)90005-Y

[6]von der Saal, W., Hoelck, J. P., Kampe, W., Mertens, A., Mueller-Beckmann, B., *J. Med. Chem*., **1989**, *32*, 1481-1491. https://doi.org/10.1021/jm00127a015

[7]Denny, W. A., Rewcastle, G. W., Baguley, B. C., *J. Med. Chem.*, **1990**, *33*, 814-819. https://doi.org/10.1021/jm00164a054

[8]Toja, E., Selva, D., Schiatti, P., *J. Med.Chem*., **1984**, *27*, 610-616. https://doi.org/10.1021/jm00371a010

[9]Demopoulos, V. J., Rekka, E., *Eur. J. Pharm. Sci.*, **1995**, *84*, 79-82. https://doi.org/10.1002/jps.2600840119

[10]Mustafa, S., Hilal, B., Ertan, A., *Bull. Korean Chem. Soc*., **2012**, *33*, 90-94. https://doi.org/10.5012/bkcs.2012.33.1.90

[11]de Laszlo, S. E., Visco, D., Agarwal, L., Chang, L., *J. Bioorg. Med. Chem. Lett*., **1998**, *8*, 2689-2694. https://doi.org/10.1016/S0960-894X(98)00495-8

[12]Dowell, R. I., Hales, N. H., Tucker, H., *Eur. J. Med. Chem*., **1993**, *28*, 513-516. https://doi.org/10.1016/0223-5234(93)90019-B

[13]Ferraris, D., Ficco, R. P., Dain, D., Mark G., *Bioorg. Med. Chem*., **2003**, *11*, 3695-3708. https://doi.org/10.1016/S0968-0896(03)00333-X

[14]Chesworth, R., Wessel, M. D., Heyden, L., Mangano, F. M., *Bioorg. Med.Chem. Lett*., **2005**, *24*, 5562-5566. https://doi.org/10.1016/j.bmcl.2005.08.010

[15]Bovy, P. R., Reitz, D. B., Collins, J. T., Chamberlain, T. S., *J. Med. Chem.*, **1993**, *36*, 101-110. https://doi.org/10.1021/jm00053a013

[16]Renneberg, D., Dervan, P. B., *J. Am. Chem. Soc*., **2003**, *125*, 5707-5716. https://doi.org/10.1021/ja0300158

[18]Jones, R. A., Bean, G. P., *The Chemistry of Pyrroles*, Academic Press, London, **1977**, 51-57

[19]Jones, R. A., *Pyrroles, Part II: The Chemistry of Heterocyclic Compounds*, Wiley, New York. **1992**. https://doi.org/10.1002/9780470187340

[20]Ballini, R., Barboni, L., Bosica, G., Petrini, M., *Synlett*, **2000**, *4*, 391-393.

[21]Kim, J. T., Gevorgyan, V., *Org. Lett.*, **2002**, *4*, 4697-4704. https://doi.org/10.1021/ol027129t

[22]Knorr, L., *Ber. Dtsch. Chem. Ges*., **1884**, *17*, 1635-1642. https://doi.org/10.1002/cber.18840170220

[23]Paal, C., *Ber. Dtsch. Chem. Ges*., **1885**, *18*, 367-371. https://doi.org/10.1002/cber.18850180175

[24]Braun, R. U., Mueller, T., *Synthesis*, **2004**, 2391-2406

[25]Hantzsch, A., *Ber. Dtsch. Chem. Ges*., **1890**, *23*, 1474-1476. https://doi.org/10.1002/cber.189002301243

[26]Van Leusen, A. M., Siderius, H., Hoogenboom, B. E., Van Leusen, D., *Tetrahedron Lett*., **1972**, 5337-5340. https://doi.org/10.1016/S0040-4039(01)85244-8

[27]Gribble, G. W., Saulnier, M. G., Pelkey, E. T., Kishbaugh, T. L. S., Liu, Y., Jiang, J., *Org. Chem*., **2005**, *9*, 1493-1519.

[28]Bean, G. P.; Jones, R. A., *The Synthesis of 1 H-Pyrroles*. Wiley, J. New York, **1990.**

[29]Cyr, D. J., Martin, N., Arndtsen, B. A., *Org. Lett*., **2007**, *9*, 449-452. https://doi.org/10.1021/ol062773j

[30]Balme, G., *Angew. Chem., Int. Ed*., **2004**, *43*, 6238-6241. https://doi.org/10.1002/anie.200461073

[31]Shimizu, M., Takahashi, A., Kawai, S., *Org. Lett.*, **2006**, *8*, 3585-3587. https://doi.org/10.1021/ol0615634

[32]Joshi, U., Pipelier, M., Naud, S., Dubreuil, D., *Curr. Org. Chem*., **2005**, *9*, 261-288. https://doi.org/10.2174/1385272053369132

33Tejedor, D., Gonzalez-Cruz, D., Garcia-Tellado, F., Marrero-Tellado, J. J., Rodriguez, M. L., *J. Am. Chem. Soc.*, **2004**, 126, 8390-8391. https://doi.org/10.1021/ja047396p

[34]Bellina, F., Rossi, R., *Tetrahedron*, **2006**, *62*, 7213-7256. https://doi.org/10.1016/j.tet.2006.05.024

[35]Padwa, A., Gruber, R., Pashayan, D., *J. Org. Chem.*, **1968**, *33*, 454-455. https://doi.org/10.1021/jo01265a108

[36]Binder, J. T., Kirsch, S. F., *Org. Lett.*, **2006**, *8*, 2151-2153. https://doi.org/10.1021/ol060664z

[37]Dar, A.M., Mir, S., Ishrat, U., Shamsuzzaman, *Eur. Chem. Bull.*, **2017**, *6(1)*, 13-20. https://doi.org/10.17628/ecb.2017.6.13

[38](a)Anagnostopoulos, C. E., Fieser, L. F., *J. Am. Chem. Soc.*, **1954**, *76*, 532-536. https://doi.org/10.1021/ja01631a059. (b) Backer, R. H., Squire, E. N., *J. Am. Chem. Soc*., **1948**, *170*, 1487-1490. https://doi.org/10.1021/ja01184a056

[39](a)Shopee, C. W., Lack, R. E., Roy, S. K., *J. Chem. Soc*., **1963**, 3767-3774. (b) Ford, E. G.; Chakravorty, P.; Wallis, E. S., *J. Am. Chem. Soc.*, **1938**, *60*, 413-415. https://doi.org/10.1021/ja01269a051

[40]Auera, L., Hewjtsox, R., *J. Org. Chem*., **1962**, *27*, 3982-3985. https://doi.org/10.1021/jo01058a054

Received: 14.06.2017.
Accepted: 15.07.2017.