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Synthesis of novel [6,7-B] indole of cholestane series

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ABSRTACT

An efficient synthesis of steroidal indole in one operation by rection of steroidal ketones with phenylhydrazine in acetic acid, using BF_3-etherate as catalyst. Compounds obtained are purified by column chromatography and their structure supported by IR, 1HNMR, 13CNMR and MS spectral studies.

Key words: Steroids, Steroidal ketones, Steroidal indoles, Indoles.

INTRODUCTION

The synthesis of indoles is very active field due to their wide spread occurrence in nature and their wide ranging biological activities[8]. These compounds are found to posses antitumer[9], anti – HIV metabolites[10] and antibacterial [11-13]activity.Invitably they may be used on manufacture of pharmaceutical intermediate in industry. As a result a number of indoles have been synthesized using different methods. But only a few studies have been reported regarding the steroidal indoles. In continuation with the synthesis of modified steroids and the fact that very limited number of steroidal indoles are reported[14],prompted us to prepare some steroidal compounds with fused indole ring from easily accessible ketones in the cholestane series. The present study includes, the attempts to obtain [6,7-b] steroidal derivatives. The compounds obtained have been characterized on the basis of their elemental analysis and spectral studies (table – 1) 5α-cholestan-6-one[15] (i) its 3βchloro[16](ii)and 3α-acetoxy-5α-cholestan-6-one13(iii) analogues were treated with phenylhydrazine in glacial acetic acid under reflux condition for four hours which afforded 5n -cholestano[6,7-b] indole (iv), 3β-chloro-5β-cholestano[6,7-b] indole (v) and 5β-choles -3 – eno[6,7-b] indole (vi) respectively.

RESULTS AND DISCUSSION

The easily accessible steroidal ketones (I,II,and III) were synthesized by the reported method[11-13] A condensation reaction involving ketones and phenylhydrazine in acetic acid under reflux afforded steroidal indoles (iv, v, and vi) is an oil which failed to crystallized. The structure of compound (iv, v and vi) was established by IR, ^{1}HNMR, ^{13}CNMR and MS with microanalytical data (Table 1).

IR spectrum exhibited the characteristic absorption bands at 1600 (aromatic), 1582(C=C), 3047 (C-H, starch aromatic) and 3497 cm^{-1} (NH) these frequencies supports the presence of indole moiety attached at the 6.7 position of the cholestane skeleton B ring. The ^{1}HNM spectrum displayed signals in the downfield region at δ7.1 to 7.6 integrating for four protons which could be assigned to aromatic protons. A broad signals appeared as a singlet at δ6.7 (exchangeable with deuterium,) which was ascribed to – N<u>H</u> proton. A multiple band at δ2.81 and δ2.22 assigned to C_5-α<u>H</u>, however angular (C_{10}-CH_3), (C_{13}-CH_3) and side chain methyl (C_{21}-CH_3), (C_{25}-CH_3)$_2$) groups were observed at δ1.1,0.93,0.86 and 0.65 respectively.

The spectral studies and microanalytical data are good agreement with the structure (iv) hence it has been attested as 5α-cholestano [6,7-b] indole (iv) indoel. Product (v) was also characterized on the basis of similar account. Moreever, the tentative mechanism, proposed on the basis of spectral studies as well as previous result (v) further establishes its formation. Under similar conditions steroidal ketone (iii) afforded the product 5α-cholestano-3-eno [6,7-b] indole (vi) with $OCOCH_3$ group intact at C-3 was not obtained as seen in the product (v) with chloro group at C-3, the unexpected product (vi) was confirmed by the absence of three proton singlet for $OCOC\underline{H}_3$ around δ2.1 and a one proton multiplet around δ4.7-4.9 due to $C_3\alpha$-H in its PMR spectrum. However its ^{1}HNMR spectrum displayed a broad singlet at δ5.6-5.9 was assigned to vinylic protons. These resonating signal provided the evidence for the formation of product (v) therefore the product (v) has been identified as 5α- cholestano -3 – eno [6,7-b] indole (v).

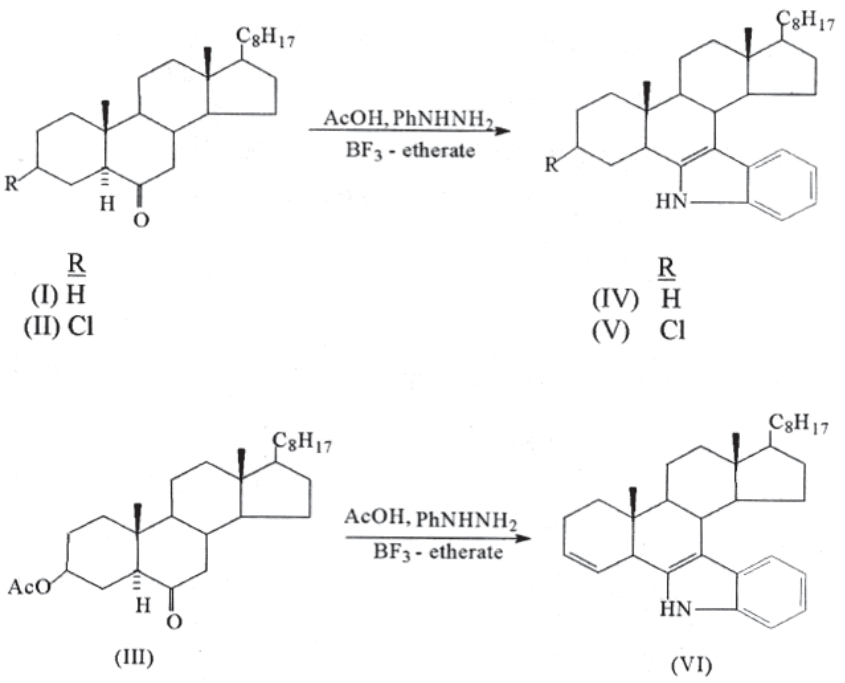
The compound (iii) also follows the mechanism as other product (iv & v) except during the formation, the ecetoxy group get eliminated at C-3 of (vi).

EXPERIMENTAL

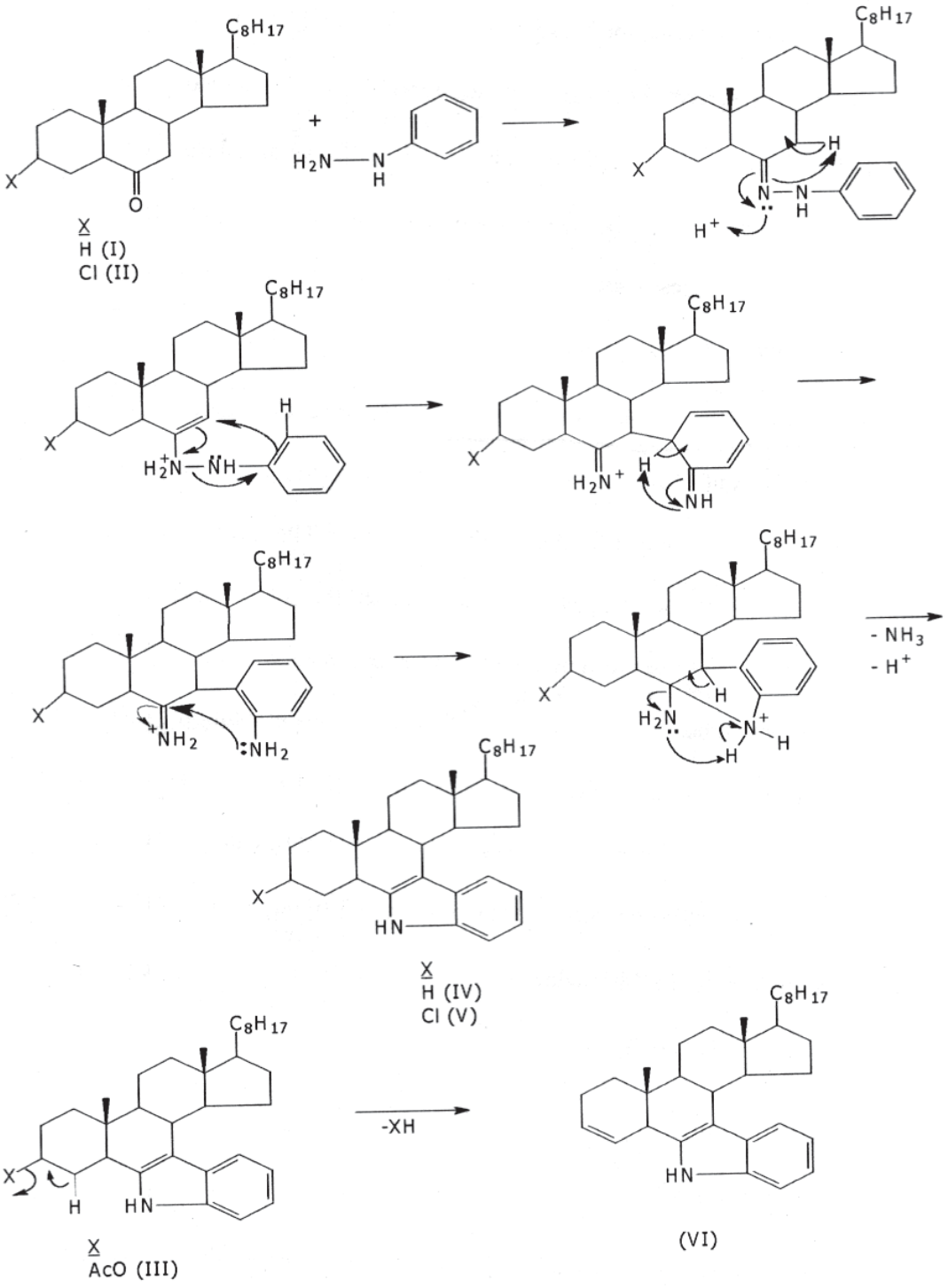
All the melting points are uncorrected infrared spectra (I.R.) were measured in KBr with perkin – Elmer 237 and Unichem SP 300 spectrophotometers. The I.R. value are given in cm^{-1} ((s-strong, m-medium, w-weak, br-broad) ^{1}H(300MHz) & ^{13}C(75MHz)NMR spectra were recorded on a $CDCl_3$ solvent chemical shifts are reported with reference to the δ7.27 signal of $CHCl^{13}$(^{1}HNMR) AND δ77.23Signal of $CDCl^3$(^{13}CNMR) as an internal standard. These values are given in ppm (s-singlet, d-doublet, t-triplet, b-broad, mc-multiplet centred). Thin layer chromatography plates were coated with silica gel G and developed in an iodine chamber light petroleum refers to fraction b.p. 60-80o.

General Procedure For Fischer Indolisation

A mixture of ketones, (I,II and III) (300mg:0.67mmol) and glacial acetic acid (10ml) was heated at reflux three hour. During these periods the color changed from colorless to yellow. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed under the reduced pressure and the



Scheme 1:



Scheme 2:

Table 1: Physical, spectral and analytical data for the products IV to VI

Compound	State	Formula	Found (required) C	H	N	$\nu_{max/cm-1}$	^{1}HNMR(δ)ppm	^{13}CNMNR(δ)ppm
IV	oil	$C_{35}H_{51}N$	86.21 (86.11)	10.72 (10.27)	3.13 (3.11)	1600 (aromatic), 1582 (C=C) 3407 (C-H stretch aromatic) and 3497 (-NH)	7.1-7.6mc(4H, aromatic protons), 3.8 br(-NH) 2.8cm (C_5-αH) 2.2mc(C_8-H) 1.1, 1.0, 0.93, 0.91, 0.86 and 0.62 (Me)	145.6 (C=C)141.0, 136.3, 128.4,118.2, 110.5, 107.5 (aromatic)
V	oil	$C_{34}H_{50}NCl$	81.50 (81.41)	10.45 (10.26)	5.72 (5.43)	1658 (aromatic), 1589 (C=C) 2919-3060 (C-H stretch aromatic) 3272 and 735 (C-Cl)	9.8-7.5cm(4H, aromatic protons), 4.73 br(-NH) 3.8cm (C_3-αH) W½=16Hz axial), 2.28mc (C_5α-H) 2.0(C_8-H) 1.2, 1.0, 0.97 and 0.85 (Me)	143.8 (C=C)161.4, 133.5, 129.5,120.2, and 141.9 (aromatic)
VI	oil	$C_{34}H_{49}N$	83.74 (83.90)	11.63 (11.89)	3.27 (3.29)	1655 and 1624-1594 C=C-C=C-) 2492-3060 (C-H stretch aromatic) 3320-3400 (-NH)	7.1-7.5m(4H, aromatic protons), 7.7-7.9 br(-NH)5.6-5.9 br (N<u>H</u>) 5.6-5.9 br (vinylic protons) 2.2 br(C_5-α<u>H</u>) 1.25, 1.21, 1.18 and 0.9 (Me)	145.3 and 123.7 (C=C) 1542, 142.5 131.1, 128.5, 111.3 110.8, 107.0 and 100.5 (aromatic)

Mass Spectral data of IV-VI [m/z]

	Compound	M^+ calculated	M+observed
IV	$C_{35}H_{51}N$	485.3374	485.3385
V	$C_{34}H_{50}N$	507.5869	507.5884
VI	$C_{34}H_{49}N$	471.3556	471.3582

residue thus obtained was extracted with ether. The ethereal layer washed with several times with water and sodium bicarbonate solution $NaHCO_3$(5%) and dried over anhydrous sodium sulphate. ($NaSO_4$) Removal of the solvents gave an oil which failed to crystallize (iv) the oil was subjected to column chromatography and elutes with petroleum-ether (9:1) afforded 5α-cholestano-3-eno [6,7-b] indole (iv) (170mg: 0.36mmol), 3β-chloro-5α-cholestano[6,7-b] indole (v). (100mg: 0.19mmol), and 5α-cholestano[6,7-b] indole (vi). (110mg: 0.33mmol),

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REFERENCES

1. Gribble, G.W.*J.Chem. Soc. Perkin Trans* I 1045 (2000).
2. Yuichi.S,Atsushi. S, Tessuya. K, Atsushi.S,O. Satoshi, O, Hisashi. O and Osamu. O, *Bioorg. & Med. Chem. Lett*. **13**: 3569 (2001).
3. Scheiek L.W, Kuna. K, Frank W, Albert A, Asche C. and Kucklaender U, *Bioorg.& Med. Chem*. **14**: 3599 (2006)
4. Marminor C, Pierre A, Peraz, V, Leonie S, Jouber A. *J. Med. Chem* **46**: 68 (2003)
5. Kuethe J.T, Wong A, Xiang C, Smitroric Q.J. Davies. I.W. and Hughes D.L, *J.Org. Chem*. **70**: 5328 (2000).
6. Park A, Moor R.E. and Patterson G.M.L. *Tetrahedron Letters*, **33**: 3257(1992)
7. S.Ravi & M. sarwaramoosthy, *Orient. J. Chem*, **16**(3): 521 (2000).
8. Ch. Sridevi, K.Balaji, A.Naidu and R.Suthakaran, *Orient. J.Chem*. **25**(1): 325 (2009).
9. Nguyen C.H. Marchand C, Stephane D, Sheng S.J.Garestier T, Helene C and Bisagul E, *J.Am. Chem. Soc*, **120**: 2501 (1998).
10. Meragelman K.M. West L.M. Northcote P.T. Pannell L.K.Mckee T.C. and Boyd M.R. *J.Org. Chem*.**67**: 6671 (2001)
11. Moore R.E, Clerk C, Lu G.Y. Qiang. And Patterson G.M.L. *J.Org.Chem*. **52**: 1036 (1987).
12. Sachin K.Singh R.Saxena and Shamim Ahmed *Org. J.Chem.* **25**(2): 433 (2009).
13. A.Siddiqui, S.A.Iqbal and S.Qureshi *Org. J. Chem*. **20**(4) 655,(2004).
14. Finlay M.J. Honda T and Gribble G.W. Arkivoe, **12**: 38 (2002).
15. Doson R.M. and Reigel B.J. *Org.Chem*. **13**: 42 (1948)
16. Windaus A and Dalme O.*Chem.Ber,* **52**: 162 (1919).