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

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ABSTRACT

An efficient synthesis of steroidal indole in one operation by reaction of steroidal ketones with phenylhydrazine in acetic acid, using BF3-etherate as catalyst. Compounds obtained are purified by column chromatography and their structure supported by IR, 1H NMR, 13C NMR and MS spectral studies.

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

INTRODUCTION

The synthesis of indoles is very active field due to their widespread occurrence in nature and their wide ranging biological activities. These compounds are found to possess antitumor, anti-HIV metabolites and antibacterial activity. Invitably they may be used in 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, 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).

RESULTS AND DISCUSSION

The easily accessible steroidal ketones (I, II, and III) were synthesized by the reported method. 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, 1H NMR, 13C NMR 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 support the presence of indole moiety attached at the 6.7 position of the cholestane skeleton B ring. The 1H NMR spectrum displayed signals in the downfield region at δ 7.1 to 7.6 integrating for four protons which could be assigned to aromatic protons. A broad signal appeared as a singlet at δ 6.7 (exchangeable with deuterium), which was assigned to –NH proton. A multiple band at δ 2.81 and δ 2.22 assigned to C5-αH, however angular (C10-CH3), (C13-CH3) and side chain methyl (C21-CH3), (C25-CH3) groups were observed at δ 1.1, 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-cholestanol [6,7-b] indole (iv) indoel. Product (v) was also characterized on the basis of similar account. Moreover, 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-cholestanol-3-eno [6,7-b] indole (vi) with OCOCH₃ 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 OCOCH₃ around δ2.1 and a one proton multiplet around δ4.7-4.9 due to C₃α-H in its PMR spectrum. However its ¹H-NMR 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-cholestanol-3-eno [6,7-b] indole (v).

The compound (iii) also follows the mechanism as other product (iv & v) except during the formation, the ecetoxo 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) ¹H(300MHz) & ¹³C(75MHz)NMR spectra were recorded on a CDCl₃ solvent chemical shifts are reported with reference to the δ7.27 signal of CHCl₃ ¹H(NMR) AND δ77.23 Signal of CDCl₃ ¹³C(NMR) as an internal standard. These values are given in ppm (s-singlet, d-doublet, t-triplet, b-broad, m-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 2:
Table 1: Physical, spectral and analytical data for the products IV to VI

<table>
<thead>
<tr>
<th>Compound</th>
<th>State</th>
<th>Formula</th>
<th>Found (required)</th>
<th>$v_{\text{max/cm}^{-1}}$</th>
<th>$^1\text{HNMR}(\delta)_{\text{ppm}}$</th>
<th>$^{13}\text{CNMR}(\delta)_{\text{ppm}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>oil</td>
<td>C$<em>{35}$H$</em>{51}$N</td>
<td>86.21 (86.11), 10.72 (10.27), 3.13 (3.11)</td>
<td>1600 (aromatic), 1582 (C=C), 3407 (C-H stretch aromatic) and 3497 (-NH)</td>
<td>7.1-7.6 mc (4H, aromatic protons), 3.8 br (NH), 2.8 cm (C$_5$-α-H) 2.2 mc (C$_6$-H) 1.1, 1.0, 0.93, 0.91, 0.86 and 0.62 (Me)</td>
<td>145.6 (C=C) 141.0, 136.3, 128.4, 118.2, 110.5, 107.5 (aromatic)</td>
</tr>
<tr>
<td>V</td>
<td>oil</td>
<td>C$<em>{34}$H$</em>{50}$NCl</td>
<td>81.50 (81.41), 10.45 (10.26), 5.72 (5.43)</td>
<td>1658 (aromatic), 1589 (C=C) 2919-3060 (C-H stretch aromatic) 3272 and 735 (C-Cl)</td>
<td>9.8-7.5 cm (4H, aromatic protons), 4.73 br (-NH) 3.8 cm (C$_5$-α-H) 2.28 mc (C$_3$-α-H) 2.0 (C$_5$-H) 1.2, 1.0, 0.97 and 0.85 (Me)</td>
<td>143.8 (C=C) 161.4, 133.5, 129.5, 120.2, 141.9 (aromatic)</td>
</tr>
<tr>
<td>VI</td>
<td>oil</td>
<td>C$<em>{34}$H$</em>{49}$N</td>
<td>83.74 (83.90), 11.63 (11.89), 3.27 (3.29)</td>
<td>1655 and 1624-1594 C=C-C=C- 2492-3060 (C-H stretch aromatic) 3320-3400 (-NH)</td>
<td>7.1-7.5 m (4H, aromatic protons), 7.7-7.9 br (-NH) 5.6-5.9 br (NH) 5.6-5.9 br (vinyllic protons) 2.2 br (C$_5$-α-H) 1.25, 1.21, 1.18 and 0.9 (Me)</td>
<td>145.3 and 123.7 (C=C) 1542, 142.5 131.1, 128.5, 111.3 110.8, 107.0 and 100.5 (aromatic)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>M$^+$ calculated</th>
<th>M$^+$ observed</th>
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</thead>
<tbody>
<tr>
<td>IV</td>
<td>485.3374</td>
<td>485.3385</td>
</tr>
<tr>
<td>V</td>
<td>507.5869</td>
<td>507.5884</td>
</tr>
<tr>
<td>VI</td>
<td>471.3556</td>
<td>471.3582</td>
</tr>
</tbody>
</table>
The residue thus obtained was extracted with ether. The ethereal layer was washed with several times with water and sodium bicarbonate solution \( \text{NaHCO}_3 \) (5%) and dried over anhydrous sodium sulphate. (\( \text{NaSO}_4 \)) 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[6,7-b] indole (v) (170mg: 0.36mmol), 3β-chloro-5α-cholestano[6,7-b] indole (vi) (110mg: 0.33mmol).

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**REFERENCES**