Synthesis of pyrazolo [3,2- c] cholest - 4 - ene derivatives from cholesterol

R K Tombisana Singh & L Warjeet Singh*
Department of Chemistry, Manipur University,
Canchipur 795 003, India

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Synthesis of pyrazolo [3,2- c] cholest - 4 - ene derivatives 3 and 5 from 2-ethoxymethylene-4-cholesten-3-one 2 and 2-bis (methylthio) methylene-4-cholesten-3-one 4, respectively, are reported.

Several ring modification studies of steroidal molecule by incorporation of heteroatom in the steroid skeleton and by annulation of heterocyclic ring have been reported. Many of these compounds, such as steroidal pyrazoles, are found to possess antimicrobial, antiinflammatory hypotensive, hypocholesterolemic and diuretic activities. In view of the therapeutic importance of these steroidal heterocycles, we report herein the synthesis of pyrazolo [3,2- c] cholest-4-ene 3 and 5 from 2-ethoxymethylene-4-cholesten-3-one 2 and 2-bis (methylthio) methylene-4-cholesten-3-one 4, respectively.

2-Ethoxymethylene - 4 - cholesten - 3 - one 2 was prepared by reacting 4 - cholesten - 3 - one 1 with ethyl orthoformate which was synthesized from cholesterol in four steps. The structure of 2 was assigned by the presence of a triplet at δ 1.30 and a quartet at δ 4.35 corresponding to the protons of the ethoxy group in its 1H NMR spectrum. It was further confirmed by the presence of a peak at δ 148.6 due to C-2 in its 13C NMR spectrum. The keten e dithioacet al 4 was obtained in 73% yield by reacting 1 and carbon disulfide in the presence of sodium tert - butoxide followed by alkylation. The structure of 4 was supported by the 1H NMR spectrum showing singlets at δ 2.39 and 2.43 due to the two SCH3 protons, 13C NMR spectrum and mass at m/z 489 (M+1). Compound 2 underwent dehydrative cyclization with hydrazine hydrate in ethanol affording the title compound 3 in 82% yield and its structure was supported by the absence of the carbonyl band and the presence of a band at 3386 cm-1 due to NH - stretching in its IR spectrum. It was further confirmed by the presence of a broad singlet at δ 8.62 due to NH group in its 1H NMR spectrum and by its 13C NMR spectrum.

Similarly, when 4 was reacted with hydrazine hydrate in refluxing ethanol, the corresponding pyrazole 5 was obtained in 64% yield. The structure was confirmed by its spectral data.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on a ATI Mattson Genesis Series FTIR by running the samples as a thin film (produced by evaporation of chloroform solution) on a sodium chloride plate. 1H NMR spectra were recorded on a Varian Unity 500 (500 MHz), Bruker Ac-300 or Varian XL (300 MHz) spectrometers and 13C NMR spectra on a Bruker AC-300 or Varian XL (75 MHz) spectrometer. Chemical Ionization and Electron Impact mass spectra were recorded on a Fisons TRIO 2000 quadrupole mass spectrometer or on a Jeol-D 300 mass spectrometer.

2- Ethoxymethylene - 4 - cholesten - 3 - one 2. A mixture of 1 (38.4 g, 0.1 mole) and ethyl orthoformate (400 mL, 3.0 mole) was refluxed (at 120 °C) for 17 h with continuous stirring. On cooling, the crude product obtained was filtered, washed with hexane, crystallized from benzene – pet. ether, yield 55 g (80%), m.p. 96 - 98°C as colourless solid; IR (CHCl3): 2945, 1676, 1614, 1462, 1231, 868 cm-1; 1H NMR (CDCl3):δ 0.72 (3H, s, C-18), 0.88 (3H, s, C-19), 0.92 (6H, d, J = 6.3 Hz, C-26 and C-27), 0.94 (3H, d, J = 7.6 Hz, C-21), 1.30 (3H, t, J = 7.5 Hz, OCH2CH3), 1.45 - 1.72 (10H, m, CH and CH2), 1.80 - 2.08 (10H, m, CH and CH2), 2.22 - 2.45 (6H, m, CH and CH2), 4.35(3H, q, J = 7.5Hz, OCH2CH3), 5.71 (1H, s, H-4), 8.64 (1H, s, CH); 13C NMR (CDCl3): δ 12.0, 17.4, 18.3, 20.8, 22.7, 22.9, 23.8, 24.2, 28.3, 28.5, 32.4, 33.1, 34.2, 35.1, 35.6, 36.2, 38.8, 39.3, 39.8, 41.8, 52.4, 54.6, 56.2, 122.6, 123.1, 133.4, 138.6, 148.6, 172.1, 198.3.

2- Bis (methylthio) methylene - 4 - cholesten - 3 - one 4. A solution of 1 (38.4 g, 0.1 mole) in dry
benzene (150 mL) was added to a cooled (0 °C) and stirred suspension of carbon disulphide (7.6 g, 10 mmole) and sodium tert-butoxide (20 mmole) in dry benzene (150 mL). The reaction mixture was further allowed to stir at room temperature for 8 hr. Methyl iodide (35.5 g, 25 mmole) was added dropwise at 0 °C and the reaction mixture was further stirred at room temperature for 8 hr. Methyl iodide (35.5 g, 25 mmole) was added dropwise at 0 °C and the reaction mixture was further stirred at room temperature for 8 hr (completion of the reaction was monitored by TLC). It was then poured into saturated aq. NH₄Cl solution (150 mL), extracted with chloroform (3×50 mL), dried (Na₂SO₄) and evaporated to give the crude 4 which was purified by flash chromatography (silica gel: pet. ether/ethyl acetate, 10 : 1); yield 26.2 g (73 %), m.p. 196 - 98°C; as colourless solid; IR (CHCl₃): 2924, 1659, 1457, 1339, 1258, 803, 753 cm⁻¹; ¹H NMR (CDCl₃): δ 0.74 (3H, s, C - 18), 0.86 (3H, s, C - 19), 0.90 (3H, s, C - 21), 0.92 (3H, d, J = 6.4 Hz, C - 26), 1.09 (3H, m, C - 27), 1.42 - 1.75 (10H, m, CH and CH₂), 1.86 - 2.20 (10H, m, CH and CH₂), 2.25 - 2.35 (6H, m, CH and CH₂), 2.39 (3H, s, SCH₂), 2.43 (3H, s, SCH₂) 5.71 (1H, s, H - 4); ¹³C NMR (CDCl₃): δ 12.5, 18.6, 18.8, 21.3, 22.5, 22.8, 23.7, 24.3, 27.9, 32.7, 33.1, 35.5, 35.7, 36.0, 36.2, 38.6, 38.9, 39.4, 40.2, 42.3, 43.4, 50.0, 55.1, 56.0, 125.2, 131.4, 139.6, 141.9, 168.7, 185.9; MS (m/z): 489 (M + 1, 60%), 443 (20), 385 (10).

Pyrazolo [3,2 - c] cholest - 4 - ene 3. A mixture of 2 (0.88 g, 2 mmole) in ethanol (25 mL), hydrazine hydrate (0.15 g, 3 mmole) and acetic acid (10 mL) was refluxed for 14 hr. The reaction mixture was concentrated, cooled and poured into ice-cold water. The solid thus obtained was dried and recrystallized from chloroform - methanol, yield 0.7 g (85 %), m.p. 196 - 98°C; as colourless solid; IR (CHCl₃): 3386, 2937, 2867, 1558, 1460, 1167, 1057, 880, 737 cm⁻¹; ¹H NMR (CDCl₃): δ 0.69 (3H, s, C - 18), 0.86 (3H, s, C - 19), 0.88 (3H, s, C - 21), 0.93 (6H, d, J = 6.7 Hz, C - 26 and C - 27), 1.12 - 1.20 (6H, m, CH and CH₂), 1.32 - 1.65 (10H, m, CH and CH₂), 1.74 - 2.32 (10H, m, CH and CH₂), 5.35 (1H, br s, H - 4), 8.15 (1H, s, CH = N), 8.62 (1H, br s, NH, exchangeable with D₂O); ¹³C NMR (CDCl₃): δ 12.13, 17.52, 18.63, 21.18, 21.53, 22.42, 22.90, 23.48, 24.57, 28.33, 28.55, 32.15, 33.12, 34.16, 34.78, 35.83, 36.02, 36.23, 38.93, 39.54, 42.43, 49.38, 54.22, 55.78, 56.43, 124.61, 129.31, 168.34.

[1'H] - 5' - (Methylthio) pyrazolo [3,2-c] cholest-4-ene 5. A solution of 4 (1.5 g, 3 mmole) in ethanol (30 mL) was refluxed with hydrazine hydrate (0.20 g, 4 mmole) for 3 hr. The solvent was removed in vacuo and the residue was diluted with ice-cold water (75 mL). The crude product, 5 was purified by flash chromatography (silica gel: pet. ether/ethyl acetate, 10 : 1) to afford a pale yellow solid; yield 0.92 g (64%), m.p. 159 - 60 °C; IR (CHCl₃): 3305, 2934,
2868, 1466, 1381, 757 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) : \(\delta\) 0.71 (3H, s, C - 18), 0.86 (6H, m, C - 19 and C - 21), 0.94 (6H, d, J = 5.7 Hz, C - 26 and C - 27), 1.32 - 1.64 (10H, m, CH and CH\(_2\)), 1.70 - 2.12 (10H, m, CH and CH\(_2\)), 2.20 - 2.38 (6H, m, CH and CH\(_2\)), 2.48 (3H, s, SCH), 6.26 (1H, s, H - 4), 8.54 (1H, br s, NH, exchangeable with D\(_2\)O); \(^1\)C NMR (CDCl\(_3\)) : \(\delta\) 11.88, 17.63, 18.57, 21.05, 21.23, 22.49, 22.75, 23.74, 24.14, 27.93, 28, 12, 30.42, 32.21, 35.19, 35.69, 36.05, 39.42, 39.70, 42.31, 51.57, 53.71, 55.95, 56.07, 123.81, 128.49, 132.43, 155.16, 162.54; MS (m/z) : 457 (M + 1, 5%), 399 (45), 384 (100).

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References