Synthesis of steroidal thiazolidinone: 3-Diazo(4'-thiazolidinone) cholest-4-ene

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3-Diazo(4'-thiazolidinone) cholest-4-ene 3 with spiroheterocyclic system has been synthesized in quantitative yields by the treatment of cholest-4-en-3-one thiosemicarbazone 2 with chloroacetic acid and anhydrous sodium acetate in glacial acetic acid at reflux temperature for 17 hr. Thiosemicarbazone 2 is obtained by the condensation of cholest-5-en-3-one 1 with thiosemicarbazide in the presence of conc. HCl in ethanol. The products 2 and 3 are characterized by their physical, analytical and spectral (IR, 'H NMR, mass) data.

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The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. It is well-known that a number of heterocyclic compounds containing nitrogen and sulphur exhibit a wide variety of biological activities. Thiazolidinones possessing antimicrobial activity, antitubercular activity, antithyroid activity, amoebicidal activity and antihyperglycemic activity, as well as compounds exhibiting antiinflammatory activity, analgesic activity, anticonvulsant activity and antifungal activity, have been revealed.

They have also been utilized as hypolipidemic agents and hypcholesterolemic agents. Besides this they were used as Maillard reaction inhibitors and for treatment of diabetes complications. Thiazolidinone herbicides are the potent inhibitors of glucose incorporation into cell wall. Apart from this some of them showed oxytocic activity, catatonic activity, antibiotic activity and antiviral activity, some compounds were also used in the treatment of arthritis. Besides this they are proved as calcium antagonists with both calcium overload inhibition and antioxidant activity. Scanning of literature has revealed that little attention has been paid towards the synthesis of steroidal thiazolidinones.

The above importance of thiazolidinones prompted us to synthesize 3-diazo(4'-thiazolidinone)cholest-4-en-ene 3, which may exhibit pharmacological properties. Herein, we report the synthesis of steroidal thiazolidinone 3 in high yield by refluxing a mixture of cholest-4-en-3-one thiosemicarbazone 2, chloroacetic acid and anhydrous sodium acetate in glacial acetic acid (Scheme I) for 17 hr. Compound 2 was obtained by the condensation of cholest-5-en-3-one 1 with thiosemicarbazide in the presence of...
The formation of 3 from 2 can be rationalized on the basis of the proposed mechanism (Scheme II). The structures of the steroidal thiosemicarbazone 2 and thiazolidinone 3 have been established on the basis of their physical, analytical and spectral data.

The $^1$H NMR spectrum of compound 1 showed a multiplet centered at $\delta$ 5.58, which was assigned to C$_6$ olefinic proton, but in compound 2 a singlet was observed at $\delta$ 5.8, which was attributed to the C$_4$ olefinic proton. It suggests that during the course of reaction C-C double bond was shifted from C$_5$ to C$_4$.

The IR spectrum of compound 3 displayed characteristic bands at 3464 (NH), 1717 (C=O) and 680 cm$^{-1}$ (C=S-C) and its $^1$H NMR spectrum showed characteristic peaks as a one-proton singlet at $\delta$ 6.7 (exchangeable with D$_2$O) for N-H proton of the thiazolidinone ring and another two-proton singlet at $\delta$ 3.8 due to methylene protons of thiazolidinone ring, which further provided the evidence for the formation of compound 3.

**Experimental Section**

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr) were run on a Perkin-Elmer 1800 FTIR; $^1$H NMR spectra on a 300 MHz instrument using TMS as an internal standard (chemical shifts in $\delta$, ppm); and mass spectra on a Jeol JMS D-300 spectrometer. All the new compounds gave satisfactory C, H and N analysis.

**Synthesis of cholest-4-en-3-one thiosemicarbazone 2.** To a solution of cholest-5-en-3-one 1 (2.0 g, 5.19 mmole) in ethanol (35 mL) was added thiosemicarbazide (600 mg, 6.58 mmole) and conc. HCl (1.0 mL). The reaction mixture was refluxed for half an hour. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the solid left after removal of the solvent was dissolved in chloroform and extract was washed successively with water, sodium bicarbonate solution (5%) and water, and dried over anhydrous sodium sulphate. The solution was concentrated under reduced pressure and residue was crystallized from chloroform-methanol to give 2, yield 1.68 g (71%), m.p. 196-97°C. Anal. Found: C, 73.44; H, 10.36; N, 9.14. Calcd for C$_{20}$H$_{17}$N$_3$S: C, 73.46; H, 10.35; N, 9.18%; IR (KBr): 3450 (NH), 3150 (H$_2$), 1625 (C=C), 1435 (C=N), 1080 em$^{-1}$ (C=S); $^1$H NMR (CDCl$_3$): $\delta$ 6.5 (s, 1H, NH, exchangeable with D$_2$O), 6.2 (s, 2H, NH$_2$, exchangeable with D$_2$O), 5.8 (s, 1H, C$_4$-H), 1.15, 0.91, 0.85 and 0.65 (angular and side-chain methyl protons).

**Synthesis of 3-diazo(4'-thiazolidinone) cholest-4-ene 3.** A mixture of 2 (1.0 g, 2.26 mmole), chloroacetic acid (2.0 mL) and anhydrous sodium acetate (800 mg, 12.1 mmoles) in glacial acetic acid (25 mL) was refluxed for 17 hr. The reaction mixture was then cooled and poured into crushed ice. The solution was extracted with diethyl ether and the extract was washed successively with water, sodium bicarbonate solution (5%) and water, and dried over anhydrous sodium sulphate. The solvent was evaporated and the residue was chromatographed on
silica gel column using light petroleum - diethyl ether (7:3) as eluant, which provided compound 3 as solid, yield 0.70 g (64.36%), m.p. 137 °C. Anal. Found: C, 72.36; H, 9.52; N, 8.45. Calcd for C_{30}H_{47}N_{3}O_{5}: C, 72.38; H, 9.51; N, 8.44%; IR (KBr): 3464 (NH), 1717 (C =O), 1621 (C =C), 1482 (C =N), 680 (C-S-C); 1H NMR (CDCl₃): 6 6.7 (s, 1H, NH, exchangeable with D₂O), 5.75 (s, 1H, C₄-H), 3.8 (s, 2H, methylene protons of thiazolidinone ring), 1.21, 0.92, 0.80, 0.73 (angular and side-chain methyl protons); MS: m/z 497 (M⁺), 423 (M-COCH₂S), 384 (M-C₅H₁₂).

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References