SYNTHESIS OF STEROIDAL DIAZOLIDINONE, DIAZOLIDINTHIONE AND DIAZOLES: REACTION OF STEROIDAL DIBROMOKETONES WITH NUCLEOPHILIC NITROGEN

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ABSTRACT

Reaction of 5,6β-dibromo-5α-cholestan-3-one 1 with thiourea, urea and guanidine hydrochloride provided 3-hydroxycholest-3-eno [5α,6α-d] 1′,3′-diazolidin-2′-thione 2, 3-hydroxycholest-3-eno [5α,6α-d] 1′,3′-diazolidin-2′-one 3 and 3-hydroxycholest-3-eno [5α,6α-d] 2′-amino-1′,3′-diazole 4 respectively. The structures of these products have been based on their elemental analysis and spectral data (IR, H NMR and MASS).

Keywords: Steroidal dibromoketone, Diazolidinone, Diazole, Thiourea, Urea, Guanidine hydrochloride.

INTRODUCTION

In the light of the reported biological activities of nitrogen containing heterocycles1-3 an attempt has been made to prepare steroidal compounds incorporating diazolidinone and diazole moieties in their frame work which is in continuation of our earlier studies of steroidal heterocyclic compounds.4,5 The chemistry of these heterocycles has become more important because of the discovery of the varied biochemical properties, industrial uses and analytical applications associated with them. Steroidal dibromoketones have been important starting materials for the construction of heterocycles and they can be easily prepared in good yields. The concept of nuclophilic reagent proposed, can be manipulated to yield heterocycles.

EXPERIMENTAL

General Remarks

The reactions were carried out in ethanol with urea, thiourea and guanidine hydrochloride. The starting steroidal dibromoketone was prepared in the laboratory by known method. All melting points were recorded on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were determined (KBr/Neat) by using CDCl3, as solvent on a Brucker 300 MHz spectrometer with TMS as an internal standard and its values are given in ppm (δ). The mass spectra were run on Jeol JMS D-300 spectrometer.

Synthesis of 3-hydroxycholest-3-eno [5α,6α-d] 1′,3′-diazolidin-2′-thione 2.

Steroidal dibromoketone 1 (1.0 g, 1.838 mmol) was taken in ethanol (30 ml) followed by thiourea2,12 (0.286 g, 3.763 mmol). The reaction mixture was refluxed for 2½ h. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was similarly worked up and purified by column chromatography (Petroleum ether-diethyl ether, 14:1) which provided a non-crystallizable oily compound 4, (yield 80 %). Anal. Found: C, 76.09; H, 10.68; N, 9.54 %. IR (Neat cm⁻¹): ν 3500 (NH), 3440 (NH), 3250 (OH), 1615 (C=O), 1540 (C-N), and 1045 cm⁻¹ (C-O). H NMR (CDCl3): δ 7.4 (s, 1H, NH, exchangeable with D2O), 0.95 and 0.90 (other methyl protons).

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compound exhibited a singlet (exchangeable with D$_2$O) for two (2 × NH) protons at δ 6.9 and another singlet for one protons at 5.6 for C$_2$-H. Hydroxyl proton appeared at δ 4.9 (exchangeable with D$_2$O) as a singlet and C$_β$β-proton at 3.87 ($J = 7.5$, 2.8 Hz) as a doublet. Angular and side-chain methyl protons were observed at δ 1.11 (C$_β$-CH$_3$), 0.71 (C$_γ$-CH$_3$), 0.93 and 0.81 (other methyl protons). The structure of the compound was further supported by its mass spectrum which showed the molecular ion peak at m/z (M$^+$ C$_{17}$H$_{13}$N$_3$O$_2$). The other important fragment ions were observed at m/z 414 (M-CO), 399 (M-NHCO), 384 (M-NHCONH), 328 (M-C$_7$H$_7$N$_3$O$_2$). Notice that the product of HBr elimination provided H$_2$O. The oily compound 4 was analyzed for C$_{28}$H$_{38}$N$_3$O (M$^+$ 441). The IR spectrum of the compound exhibited characteristic bands at 3500 (NH$_2$), 3440 (NH), 3250 (OH), 1618 (C=C), 1540 (C=N) and 1045 cm$^{-1}$ (C-O). The $^1$H NMR spectrum of the compound displayed characteristic peaks at δ 7.4 (s, 1H, NH, exchangeable with D$_2$O), 5.6 (br, s, 2H, NH$_2$, exchangeable with D$_2$O), 5.1 (s, 1H, C$_β$-H). Hydroxyl proton appeared at δ 4.7 (exchangeable with D$_2$O) and C$_β$-proton at 3.98 ($J = 7.8$, 3.2 Hz) as a doublet. Angular and side-chain methyl protons were observed at 1.15 (C$_β$-CH$_3$), 0.70 (C$_γ$-CH$_3$), 0.95 and 0.90 (other methyl protons). The structure of the compound was further supported by its mass spectrum, which showed the molecular ion peak at m/z 441 (M$^+$ C$_{17}$H$_{13}$N$_3$O). The other important fragments ions were observed at m/z 425 (M-NH$_2$), 399 (M-NH$_2$C=N), 384 (M-NHCNH$_2$), 328 (M-C$_7$H$_7$N$_3$O$_2$).

It is proposed that the reaction proceeds via nucleophilic attack of nitrogen at C$_N$ and C$_β$ position of steroid dibromomethone 1. The formation of cis product was supported by the proposed mechanism (Scheme 2) in which S$_{2}$2 inversion takes place at C$_N$. Notice that the product of HBr elimination provided 6β-bromocholest-4-en-3-one which is rate determining step with thiourea, urea and guanidine hydrochloride. It is also supported by Dreiding model which indicate that molecule is under less strain with a trans A/B ring junction as is commonly observed.

![Scheme 1](image1)

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![Scheme 2](image2)

**Scheme 2**

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**REFERENCES**