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

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ABSTRACT

Reaction of 5,6 β -dibromo-5 α -cholestan-3-one **1** with thiourea, urea and guanidine hydrochloride provided 3-hydroxycholest-3-eno [5 α ,6 α -d] 1',3'-diazolidin-2'-thione **2**, 3-hydroxycholest-3-eno [5 α ,6 α -d] 1',3'-diazolidin-2'-one **3** and 3-hydroxycholest-3-eno [5 α ,6 α -d] 2'-amino-1',3'-diazole **4** respectively. The structures of these products have been established on the basis of their elemental analysis and spectral data (IR, ¹H 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.⁴⁻⁶ 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 nucleophilic 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 method⁷. All melting points were recorded on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were determined (KBr/Neat) with Perkin Elmer 1600 FTIR spectrophotometer. The ¹H NMR spectra were recorded by using CDCl₃ as solvent on a Bruker 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 [5 α ,6 α -d] 1',3'-diazolidin-2'-thione **2**.

Steroidal dibromoketone **1** (1.0 g, 1.838 mmol) was taken in ethanol (30ml) followed by thiourea⁸⁻¹² (0.286 g, 3.763 mmol). The reaction mixture was refluxed for two h. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was concentrated under reduced pressure and the residue was taken in diethyl ether. The ethereal solution was washed with water and dried over anhydrous sodium sulphate. The crude product obtained after removal of solvent was purified by column chromatography over silica gel column (Petroleum ether-diethyl ether, 19:1). The compound was recrystallized from methanol, m.p 63-64 °C, Yield 83 % (Beilstein negative). Anal. Found: C, 73.28; H, 10.06; N, 6.12 %. C₂₈H₄₆N₂OS required: C, 73.30; H, 10.10; N, 6.10 %. IR (KBr, cm⁻¹): ν 3450 (NH), 3300 (OH), 1680 (NHCS), 1610 (C=C), and 1040 cm⁻¹ (C-O). ¹H NMR (CDCl₃): δ 7.3 (s, 2H, 2 $\times$ NH, exchangeable with D₂O), 5.7 (s, 1H, C₄-H), 4.8 (s, 1H, OH, exchangeable with D₂O), 3.9 (dd, 1H, J = 8.4, 3.6 Hz, C β -H), 1.10 (C₁₀-CH₃), 0.71 (C₁₃-CH₃), 0.93 and 0.81 (other methyl protons). MS: m/z 458 (M⁺ C₂₈H₄₆N₂OS), 414 (M-CS), 399 (M-NHCS), 384 (M-NHCSNH), 345 (M-C₈H₁₇).

Synthesis of 3-hydroxycholest-3-eno [5 α ,6 α -d] 1',3'-diazolidine-2'-one **3**.

To a solution of steroidal dibromoketone **1** (1.0 g, 1.838 mmol) in ethanol, urea⁹⁻¹² (0.22 g, 3.666 mmol) was added and the reaction mixture was refluxed for 1½ h. Progress of the reaction was monitored by TLC. After completion of reaction it was usually worked up and purified by column chromatography (Petroleum ether-diethyl ether, 15:1) provided a non-crystallizable oily

compound **3** (yield 70 %). Anal. Found: C, 75.92; H, 10.44; N, 6.34 %. C₂₈H₄₆N₂O₂ required: C, 75.96; H, 10.47; N, 6.32 %. IR (Neat, cm⁻¹): ν 3445 (NH), 3210 (OH), 1690 (NHCO), 1616 (C=C) and 1045 cm⁻¹ (C-O). ¹H NMR (CDCl₃): δ 6.9 (s, 2H, 2 $\times$ NH, exchangeable with D₂O), 5.6 (s, 1H, C₄-H), 4.9 (s, 1H, OH, exchangeable with D₂O), 3.87 (dd, 1H, J = 7.5, 2.8 Hz, C β -H), 1.11 (C₁₀-CH₃), 0.71 (C₁₃-CH₃), 0.93 and 0.81 (other methyl protons). MS: m/z 442 (M⁺ C₂₈H₄₆N₂O₂), 414 (M-CO), 399 (M-NHCO), (M-NHCONH), 329 (M-C₈H₁₇).

Synthesis of 3-hydroxycholest-3-eno [5 α ,6 α -d] 2'-amino-1',3'-diazole **4**.

Steroidal diromoketone **1** (1.0 g, 1.838 mmol) was similarly treated with guanidine hydrochloride¹³⁻¹⁵ (0.22 g, 3.666 mmol) in ethanol (30 ml). 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 (NH₂), 3440 (NH), 3250 (OH), 1618 (C=C), 1540 (C=N), and 1045 cm⁻¹ (C-O). ¹H NMR (CDCl₃): δ 7.4 (s, 1H, NH, exchangeable with D₂O), 5.6 (br, s, NH₂, exchangeable with D₂O), 5.1 (s, 1H, C₄-H), 4.7 (s, 1H, OH, exchangeable with D₂O), 3.98 (dd, 1H, J = 7.8, 3.2 Hz, C β -H), 1.15 (C₁₀-CH₃), 0.70 (C₁₃-CH₃), 0.95 and 0.90 (other methyl protons). MS: m/z 441 (M⁺ C₂₈H₄₇N₃O), 425 (M-NH₂), 399 (M-NH₂CN), 384 (M-NHCNNH₂), 328 (M-C₈H₁₇).

RESULTS AND DISCUSSION

Steroidal dibromoketone **1** on treatment with thiourea⁸⁻¹² in ethyl alcohol afforded a solid compound which was analyzed for C₂₈H₄₆N₂OS (M⁺ 458). Negative Beilstein test, elemental analysis, MS and absence of C-Br absorption band in the IR spectrum clearly suggested the absence of bromine in the product. The IR spectrum exhibited characteristic absorption bands at 3450 (N-H), 3300 (OH), 1680 (NHCS), 1610 (C=C) and 1040 cm⁻¹ (C-O). The ¹H NMR spectrum of the compound displayed a singlet (exchangeable with D₂O) for two (2 $\times$ NH) protons at δ 7.3, another singlet for one proton at δ 5.7 assignable to C₄-olefinic proton. Hydroxyl proton appeared at δ 4.8 (exchangeable with D₂O), a doublet for one proton was observed at δ 3.9 (J = 8.4, 3.6 Hz) which was assignable for C β -proton. Angular and side-chain methyl protons were observed at δ 1.10 (C₁₀-CH₃), 0.71 (C₁₃-CH₃), 0.93 and 0.81 (side-chain methyl protons). Additional support to the structure **2** was provided by its mass spectrum which gave a prominent molecular ion peak at m/z 458 (M⁺ C₂₈H₄₆N₂OS) along with M+2 peak. Other significant peaks were observed at m/z 414 (M-CS), 399 (M-NHCS), 384 (M-NHCSNH), 345 (M-C₈H₁₇).

The same steroidal ketone **1** on similar treatment with urea⁹⁻¹² and guanidine hydrochloride¹³⁻¹⁵ provided 3-hydroxycholest-3-eno [5 α ,6 α -d] 1',3'-diazolidine-2'-one **3** and 3-hydroxycholest-3-eno [5 α ,6 α -d] 2'-amino-1',3'-diazole **4**, respectively. Both the products showed negative Beilstein test. Compound **3** was analyzed for C₂₈H₄₆N₂O₂ (M⁺ 442). The IR spectrum of the compound showed absorption bands at 3445 (NH), 3210 (OH), 1690 (NHCO), 1616 (C=C) and 1045 cm⁻¹ (C-O). The ¹H NMR spectrum of the

compound exhibited a singlet (exchangeable with D₂O) for two (2 × NH) protons at δ 6.9 and another singlet for one protons at 5.6 for C₄-H. Hydroxyl proton appeared at δ 4.9 (exchangeable with D₂O) as a singlet and C₆ β -proton at 3.87 (J = 7.5, 2.8 Hz) as a double doublet. Angular and side-chain methyl protons were observed at δ 1.11 (C₁₀-CH₃), 0.71 (C₁₃-CH₃), 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⁺ C₂₈H₄₆N₂O₂). The other important fragment ions were observed at m/z 414 (M-CO), 399 (M-NHCO), 384 (M-NHCONH), 329 (M-C₈H₁₇).

The oily compound **4** was analyzed for C₂₈H₄₇N₃O (M⁺ 441). The IR spectrum of the compound exhibited characteristic bands at 3500 (NH₂), 3440 (NH), 3250 (OH), 1618 (C=C), 1540 (C=N) and 1045 cm⁻¹ (C-O). The ¹H NMR spectrum of the compound displayed characteristic peaks at δ 7.4 (s, 1H, NH, exchangeable with D₂O), 5.6 (br, s, 2H, NH₂, exchangeable with D₂O), 5.1 (s, 1H, C₄-H). Hydroxyl proton appeared at δ 4.7 (exchangeable with D₂O) and C₆ β -proton at 3.98 (J = 7.8, 3.2 Hz) as a double doublet. Angular and side-chain methyl protons were observed at 1.15 (C₁₀-CH₃), 0.70 (C₁₃-CH₃), 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⁺ C₂₈H₄₇N₃O). The other important fragments ions were observed at m/z 425 (M-NH₂C=N), 399 (M-NH₂C=N), 384 (M-NHCNNH₂), 328 (M-C₈H₁₇).

Scheme 1

It is proposed that the reaction proceeds via nucleophilic attack of nitrogen at C₅ and C₆ position of steroidal dibromoketone **1**. The formation of *cis* product was supported by the proposed mechanism (Scheme 2) in which S_N2 inversion takes place at C₆. Notice that the product of HBr elimination provided 6 β -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.¹⁷

Scheme 2

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