STEREOSELECTIVE SYNTHESIS OF STEROIDAL SPIROAMINO-TRIAZINE THIONES

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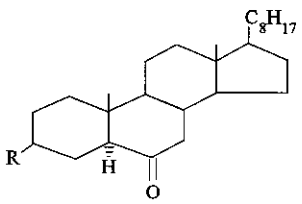
Abstract - Stereoselective transformations of some steroidal ketone thiocarbohydrazones (4)-(6) into the corresponding *R* - spiroaminotriazine thiones (7)-(9) by their oxidative cyclization with H_2O_2 at 0 °C are described.

Thiocarbohydrazides have been reported to show tuberculus activities[1] *in vitro* and its toxicity towards housefly was comparable to that of DDT.[2] They have also been investigated as antibacterials.[3,4] Prompted by the physiological properties of thiocarbohydrazides and related compounds[1-7] we undertook the systhesis of some steroidal spiroaminotriazinethiones (7)-(9) by the oxidative cyclization of thiocarbohydrazones (4)-(6) with H_2O_2 at 0 °C which is in continuation of our previous studies on thiosemicarbazones and their cyclization products.[8]

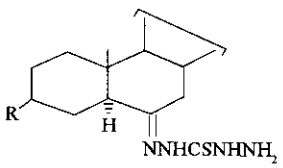
Here, we wish to report a simple and convenient stereoselective preparation of steroidal spiro aminotriazinethiones in quantitative yields by the reaction of steroidal thiocarbohydrazones (4)-(6) with H_2O_2 in chloroform.

To obtain the desired spiroaminotriazinethiones (7)-(9), steroidal thiocarbohydrazones (4)-(6)[9,10] were prepared by the treatment of thiocarbohydrazide with the steroidal ketones (1)-(3) in presence of traces of conc. HCl.[3]

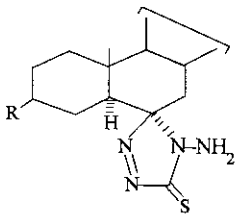
The reaction of 3β-acetoxy-5α-cholestan-6-one thiocarbohydrazone (4) with hydrogen peroxide in chloroform at 0°C afforded a diastereomer, 3β-acetoxy-5α-cholestan-6*R*-spiro-4'-amino-1',2',4'-triazine-3'-thione (7) as the only product. Under similar conditions 3β-chloro-5α–cholestan-6-one thiocarbohydrazone (5) and 5α-cholestan-6-one thiocarbohydrazone (6) provided selectively 3β-chloro-5α–cholestan-6*R*-spiro-4'-amino-1',2',4'- triazine-3'-thione (8) and 5α-cholestan-6*R*-spiro-4'-amino-1',2',4'-triazine-3'-thione (9), respectively.



(1 - 3)



(4 - 6)

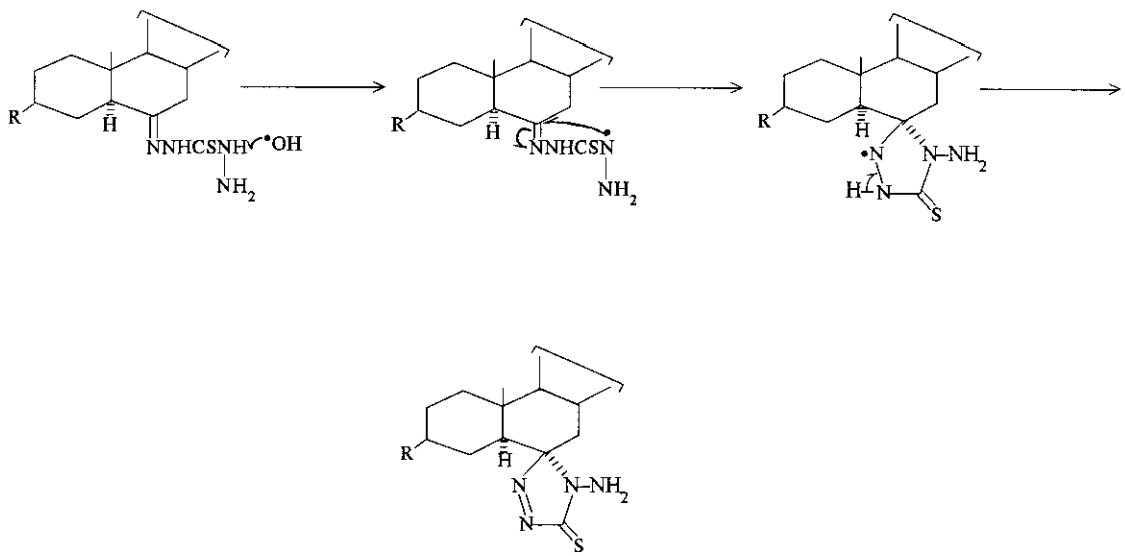


(7 - 9)

(1, 4, 7) R = OAc
(2, 5, 8) R = Cl
(3, 6, 9) R = H

Scheme 1

A free-radical mechanism (Scheme 2) has been proposed for the conversion of steroidal ketone thiocarbohydrazones (4) – (6) to the *R*-spiro aminotriazinethiones (7) – (9). The reaction is slowed down in the presence of free-radical inhibitor (HI) and this slowing down the reaction supports a free-radical process.



Scheme 2

These steroidal spiroaminotriazinethiones (7)-(9) have been characterized on the basis of their elemental analytical and spectral data[9,10] (Tables1 and 2). IR spectra of compounds (7)-(9) exhibited the characteristic absorption bands at 3320-3300 (NH_2), 1630-1620 (N=N) 1490-1460 (C-N) and 1160-1135 cm^{-1} (C=S). The NMR spectra of these aminotriazinethiones (7)-(9) showed a singlet at δ 2.65-2.4 for two protons (-NH_2). C-3α-Proton in compounds (7) and (8) appeared at δ 4.8 and 3.95, respectively as multiplets.

In this reaction one 6*R* stereoisomer was selectively obtained which might be explained on the basis of 1,3-diaxial interactions, mainly due to the steric repulsion between methyl and C6-NNH_2CS groups. In 6*R* isomer -NNH_2CS is equatorially (α) attached to C–6, so there should be less steric hinderance in comparison to that (6*S*)-isomer which has -NNH_2CS as axially (β) oriented at C-6. These 1,3-diaxial interactions cause less stability of 6*S*-isomer that results in the formation of 6*R* stereoisomer selectively which has minimum 1,3-diaxial interactions and hence should be more stable.

The selective formation of 6*R*-stereoisomer is further supported by the mechanism and the NMR spectra. The appearance of singlet for NH_2 protons at δ 2.65-2.4 clearly suggests that-NNH_2CS group is equatorially (α) oriented and in case of 6*S*-isomer which has-NNH_2CS group as axial (β), there should have been some distortion in the NH_2 signals due to the long-range coupling.

EXPERIMENTAL

IR spectra were recorded in KBr on a Perkin Elmer 782 Infrared Spectrophotometer and ^{1}H-NMR in $CDCl_3$on a Bruker BZH-200 instrument with TMS as internal standard.

Preparation of Ketone Thiocarbohydrazones. Reactions of Steroidal Ketones with Thiocarbohydrazide. General Procedure

To a boiling solution of steroidal ketone (1)[11] (2.0 g, 4.497 mmol) in methanol (35 mL) containing few drops of conc. HCl was added a solution of thiocarbohydrazide[3] (0.484 g, 4.567 mmol) in methanol (20 mL) with stirring. The reaction mixture was refluxed for 3 h and then cooled. The heavy precipitate thus obtained was collected by

Table 1 : Physical and Analytical Data for Compounds (4) - (9)

Compound	m p (°C)	Yield (%)	Molecular Formula	Found (Calcd) (%) C	H	N
4	175	92	$C_{30}H_{52}N_4O_2S$	67.69 (67.62	9.78 9.84	10.57 10.52)
5	187	88	$C_{28}H_{49}N_4SCl$	66.08 (66.04	9.63 9.70	11.04 11.00)
6	159-160	78	$C_{28}H_{50}N_4S$	70.89 (70.84	10.57 10.62	11.83 11.80)
7	148-149	61	$C_{30}H_{50}N_4O_2S$	67.91 (67.88	9.43 9.49	10.56 10.56)
8	156-157	57	$C_{28}H_{47}N_4SCl$	66.34 (66.30	9.28 9.34	11.03 11.05)
9	131-132	54	$C_{28}H_{48}N_4S$	71.19 (71.14	10.17 10.23	11.86 11.85)

Table 2 : Spectral Data for Compounds (4) - (9)

Compound	I R (KBr) (cm^{-1})	^{1}H-NMR($CDCl_3$/TMS) δ_H(ppm, 200 MHz)[a]
4	3515 (NH_2), 3365 (NH), 1610 (C=N), 1135 (C=S), 1735, 1040 ($OCOCH_3$)	8.9 (s, 2H, 2xN*H*), 4.75 (m, 1H, C3α-*H*), 4.4 (s, 2H, NH_2)
5	3500(NH_2), 3380 (NH), 1605(C=N), 1140 (C=S), 720 (C-Cl)	8.8 (s, 2H, 2xN*H*), 4.35 (s, 2H, NH_2), 3.9 (m, 1H, C3α-*H*)
6	3490 (NH_2), 3320 (NH), 1590 (C=N), 1190 (C=S)	8.6 (s, 2H, 2xN*H*), 4.25 (s, 2H, NH_2)
7	3315 (NH_2), 1620 (N=N), 1490 (C-N), 1150 (C=S)	4.8 (m, 1H, C3α-*H*), 2.4 (s, 2H, NH_2)
8	3320 (NH_2), 1630 (N=N), 1480 (C-N), 1135 (C=S), 730 (C-Cl)	3.95 (m, 1H, C3α-*H*), 2.5 (s, 2H, NH_2)
9	3300 (NH_2), 1625 (N=N), 1460 (C-N), 1160 (C=S),	2.65 (s, 2H, NH_2)

[a]Angular and side-chain methyl protons appeared at δ 1.2-0.65

filtration. The crude solid was recrystallized from methanol to provide thiocarbohydrazone (4). Similar treatment of ketones (2)[12] and (3)[13] afforded thiocarbohydrazones (5) and (6), respectively. Yields, mp and spectral and elemental analytical data of the products (4)-(6) are given in the Tables 1 and 2.

Oxidative Cyclization of Steroidal 6-Ketone Thiocarbohydrazones (4)-(6). Steroidal 6*R*-Spiro-4'-amino-1',2',4'- triazine-3'- thiones (7)-(9). General Procedure

3β-Acetoxy-5α-cholestan-6-one thiocarbohydrazone (4) (1.066 g, 2.0 mmol) was taken in chloroform (40 mL) and treated with excess of 30% hydrogen peroxide (4 mL, 35.27 mmol) at 0°C and the reaction mixture was stirred for 3 h at 0 °C. After completion of reaction the organic layer was separated, dried over anhydrous sodium sulphate and evaporated to dryness. The crude product thus obtained was purified over silica gel column (petroleum ether : ether, 7:1) and then recrystallized from methanol to give 3β-acetoxy-5α-cholestan-6*R*-spiro-4'-amino-1',2',4'-triazine-3'-thione (7) as crystalline solid. Under similar reaction conditions thiocarbohydrazones (5) and (6) afforded 3β-chloro-5α-cholestan-6*R*-spiro-4'-amino-1',2',4'-triazine-3'-thione (8) and 5α-cholestan-6*R*-spiro-4'-amino-1',2',4'-triazine-3'-thione (9), respectively as crystalline solids. Yields, mp and spectral and elemental analytical data of the products (7)-(9) are given in the Tables 1 and 2.

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