Synthesis and Mechanistic Studies of Nitrogen, Oxygen and Sulphur Containing Organic Compounds

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BY

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Abstract

Steroids are a group of chemical substances which are found abundant in nature and show a wide range of characteristic. They include cholesterol, sex hormones, adrenal cortex hormones, bile salt, oestrogens, vitamin– D, sapogenin and some other important metabolites. These steroids have a close association or rather indispensable for various physiological phenomena of living world thus making themselves the focus of attention in the field of organic chemistry. The incentive feature of steroids is that they can be synthesized easily in laboratory on a large scale. The wide implication of these compounds and their association with life has made the field of steroids as an important research area. The discovery of testosterone which showed marked biological properties is most striking feature of this field Scientists diverted their interest towards the steroids and the work on isolation as well as on synthesis started with great enthusiasm. Thereafter, researchers diversified their efforts to evaluate the structural and stereo-chemical problems of steroidal skeleton. This particular area of research has proved to be of much interest because of the unique spatial requirements of the steroid molecule. Structure elucidation and the reaction mechanism of steroids became a matter of immense later on.

The fusion of any heterocyclic ring system to steroids or to introduce any hetero atom such as sulphur , oxygen , nitrogen or any of the halogen group members, was found to augment the biological and industrial revolution . Hence, innumerable methods started developing across the world to find the better substitutes for already existing steroids. As a matter of matter of fact, steroid chemistry has always proved to be

much inviting to chemists and industries and also fascinated us to undertake the work in the field.

Chapter One

Synthesis characterization and in vitro antibacterial activity of new Steroidal Thiosemicarbazones Derivatives

Some steroidal ketone thiosemicarbazone are prepared by the condensation of thiosemicarbazide with the steroidal ketones in the presence of few drops of conc. HCl, The structures of the synthesized compounds were confirmed by the elemental analysis, IR, ^{1}H NMR spectral analysis.

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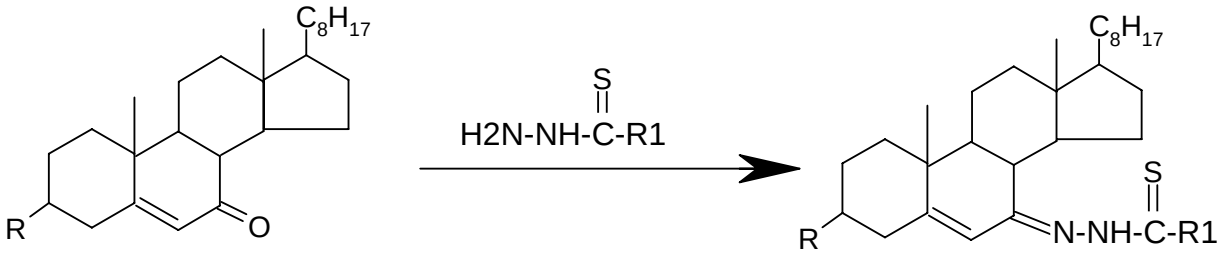
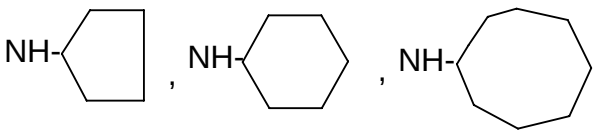


Were R = AcO, Cl, H

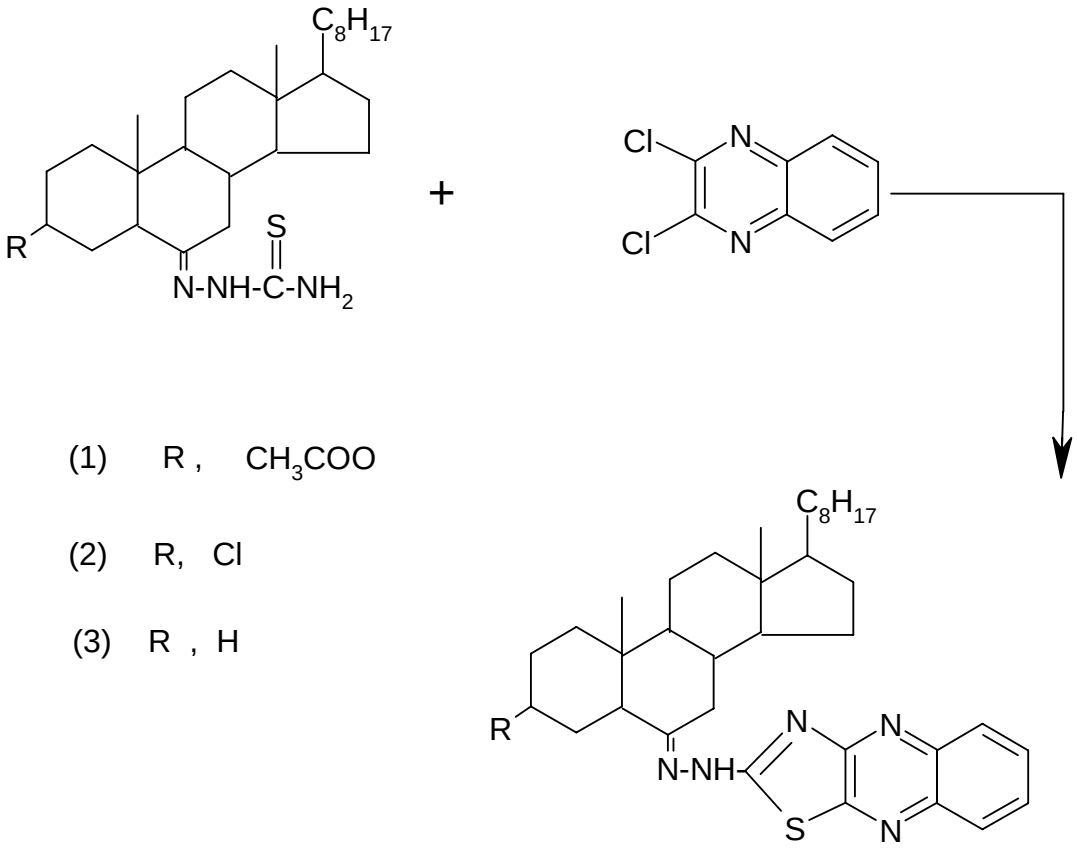
R 1 = 

The in vitro antibacterial activity of these compounds were evaluated by disk diffusion method against culture of *E. coli* and the results were compared with the standard drug Amoxicillin. The results showed that among all the compounds Acetoxy and Chloro Derivative of cyclo pentyl thiosemicarbazones Derivatives are better antibacterial agent as compared to Amoxicillin.

Chapter Two

Synthesis characterization and in vitro antibacterial activity of new Steroidal Thiazolo Quinoxaline Derivatives

Some steroidal thiazolo quinoxaline derivatives have been synthesized via the reaction of steroidal thiosemicarbazone with 2, 3- dichloroquinoxalines at 80 °C. The structures of the synthesized compounds were confirmed by the elemental analysis, IR, ^{1}H NMR and FAB mass spectral analysis.



(1) R , CH_3COO

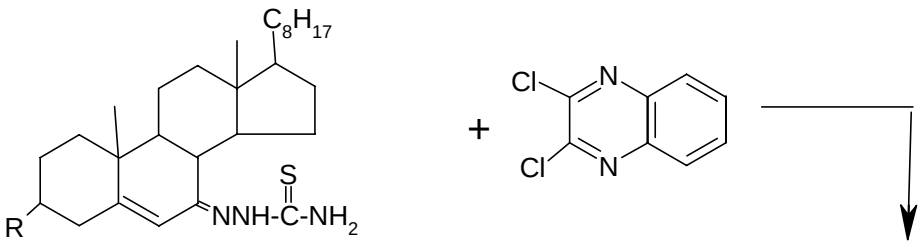
(2) R, Cl

(3) R , H

(4) CH_3COO

(5) , Cl

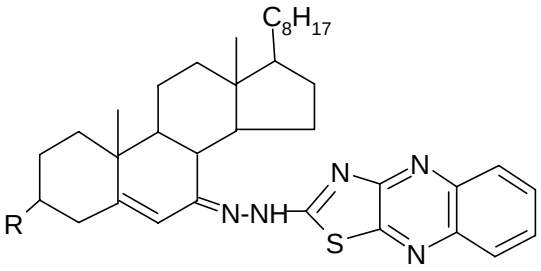
(6), H



(7), R , CH_3COO

(8) R , Cl

(9) R , H



(10) R , CH_3COO

(11) R , Cl

(12) R , H

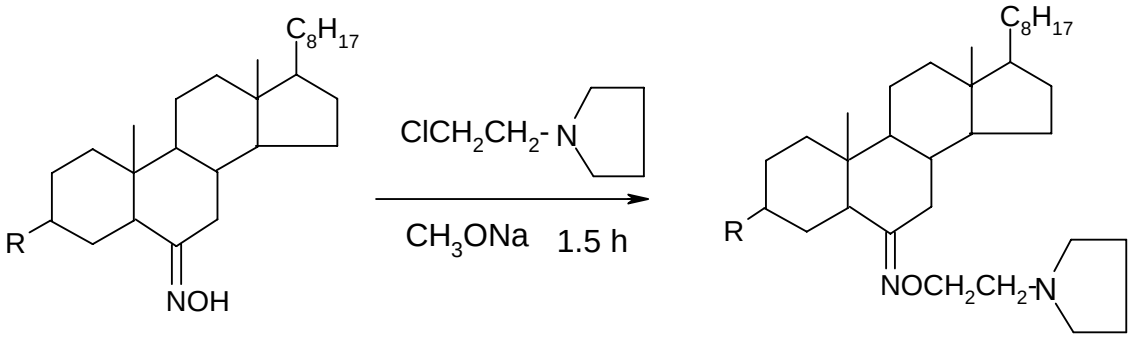
The in vitro antibacterial activity of these steroidal thiazolo quinoxaline compounds were evaluated by disk diffusion method against culture of *E. coli* and the results were compared with the standard drug Amoxicillin. The results showed that among all the six compounds, Acetoxy and Chloro derivative of thiazolo quinoxaline are better antibacterial agent as compared to Amoxicillin.

Chapter Three

Synthesis characterization and in vitro antibacterial activity of new Steroidal Oxime-Ether Derivatives

Recently oxime – ether derivative have been reported as potential anti- bacterial drugs which prompted us to undertake the synthesis of some steroidal oxime- ether derivatives (4, 5, 6) from easily accessible steroidal oximes (1, 2,, 3) .

Treatment of 3β- acetoxycholestan-6-one oxime(1),3β-chlorocholestan-6-one oxime(2), and 5α cholestan-6-one oxime(3), in methanol with 1-(2-chloroethyl) pyrrolidine hydrochloride in the presence of base (CH_3ONa) afford 3β-Acetoxy-6-(2-pyrrolidino ethoxy imino)-cholestane,(4) 3β-chloro-6-(2-pyrrolidino ethoxy imino)-cholestane,(5) 6-(2' -prrolidino ethoxy imino) cholestane (6).The structures of the synthesized compounds were confirmed by the elemental analysis, IR, ^1H NMR and FAB mass spectral analysis.



(1) R = OAc

(2) R = Cl

(3) R = H

(4) R = OAc

(5) R= Cl

(6) R = H

The in vitro antibacterial activity of these steroidal Oxime – Ether derivatives were evaluated by disk diffusion method against culture of *E. coli* and the results were compared with the standard drug Amoxicillin. The results showed that all the three compounds showed better antibacterial agent as compared to Amoxicillin.

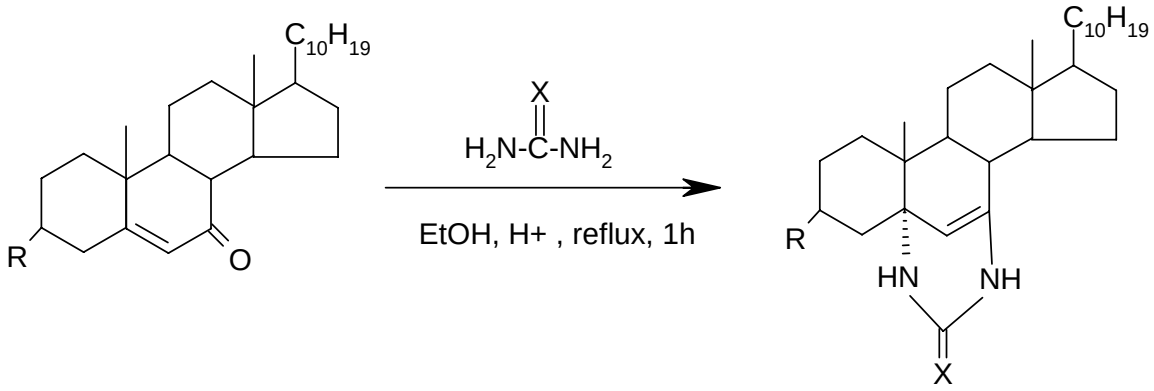
Chapter Four

Synthesis characterization and in vitro antibacterial activity of Urea and Thiourea Derivatives of Steroids

In this part some α, β- unsaturated steroidal ketones (1-3) were subjected to react with urea and thiourea in absolute ethanol and in the presence of few drops of conc. HCl in view to obtain the urea and thiourea derivatives of steroids.

Treatment of 3β-acetoxystigmest-5-en-7-one(1) and 3β-chlorostigmest-5-en-7-one(2) with urea in absolute ethanol in presence of few drops conc. HCl provided the corresponding urea derivatives 3β-acetoxystigmest-6-en-7, 5α–urea (4) and 3β-chlorostigmest-6-en-7, 5α–urea (5) in high yields. Stigmest-5-en-7-one(3) on reaction with urea under identical conditions remained unchanged.

Steroidal ketones (1,2) on reaction with thiourea under similar reaction condition provided 3β- acetoxystigmest -6- en-7, 5α- thiourea (6) and 3β- chlorostigmest-6-en-7,5α- thiourea (7) in high yields while ketone (3) remained unchanged in identical reaction conditions**.** The structures of the synthesized compounds were confirmed by the elemental analysis, IR, ^{1}H NMR spectral analysis.



(1) R=OAC

(2) R=Cl

(3) R=H

(4) R=OAC; X=S

(5) R=Cl;X=S

(6) R=OAC; X=O

(7) R=Cl;X=O

The in vitro antibacterial activity of these steroidal urea and thiourea derivatives were evaluated by disk diffusion method against culture of *E. coli* and the results were compared with the standard drug Amoxicillin. The results showed that all the four compounds, thiourea derivatives and uria derivatives showed better antibacterial agent as compared to standard drug Amoxicillin.

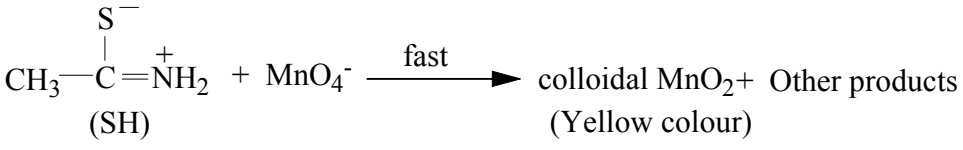
Chapter Five

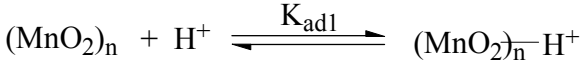
Kinetic and mechanistic study of the oxidation of sulphur containing compounds by permanganate

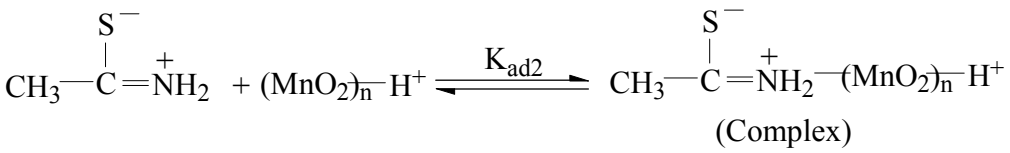
The kinetic and mechanistic studies of organic compounds have been the scope of interest of many investigators. Sulphur containing compounds have attracted much attention on account of their pharmacological activities. There is an increasing interest in the reactivity patterns of such compounds due to the non-linear kinetic behavior shown by them on oxidation by various metal oxidants. Kinetic studies provide a better understanding of this complex behavior.

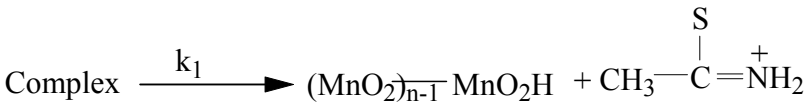
The kinetic study of thioacetamide and thiourea was carried out under varied conditions. On the basis of the results observed the following mechanisms are proposed for the oxidation of the thioacetamide and thiourea.

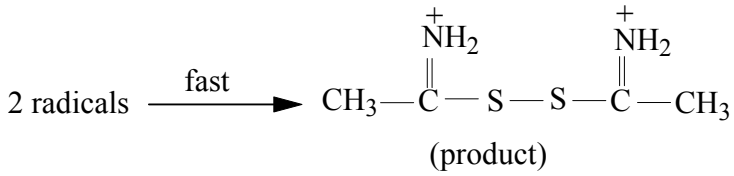
A- oxidation of thioacetamide

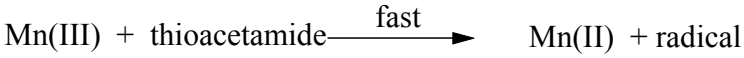




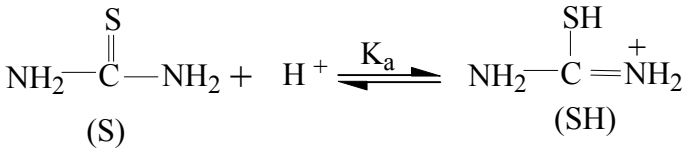


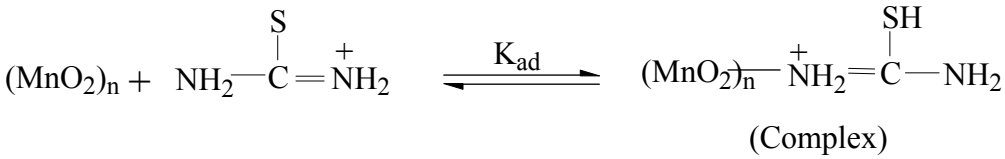


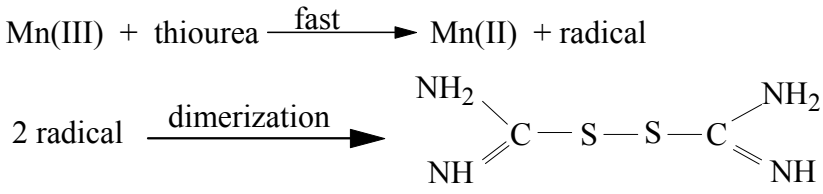




B- Oxidation of thiourea







This scheme represents the adsorption of thiourea on the surface of colloidal MnO_2 through the electrostatic interaction. There is a one-step, one electron oxidation-reduction, rate determining step. This reaction results in the formation of other

intermediate i.e. Mn(III). The rate law consistent with Scheme may be expressd by eq.

$$k_{obs} = \frac{kK_a K_{ad} [H^+] [\text{thiourea}]_T}{(1 + K_a [H^+])}$$

if $1 >> K_a [H^+]$, eq. (7) becomes

$$k_{obs} = kK_aK_{ad} [H^+] [\text{thiourea}]_T$$

According to this eq. the plots of k_{obs} versus [thiourea] should be linear passing through the origin with positive slope at constant $[H^+]$. Such plots have been realized in the present study (Fig.B2).

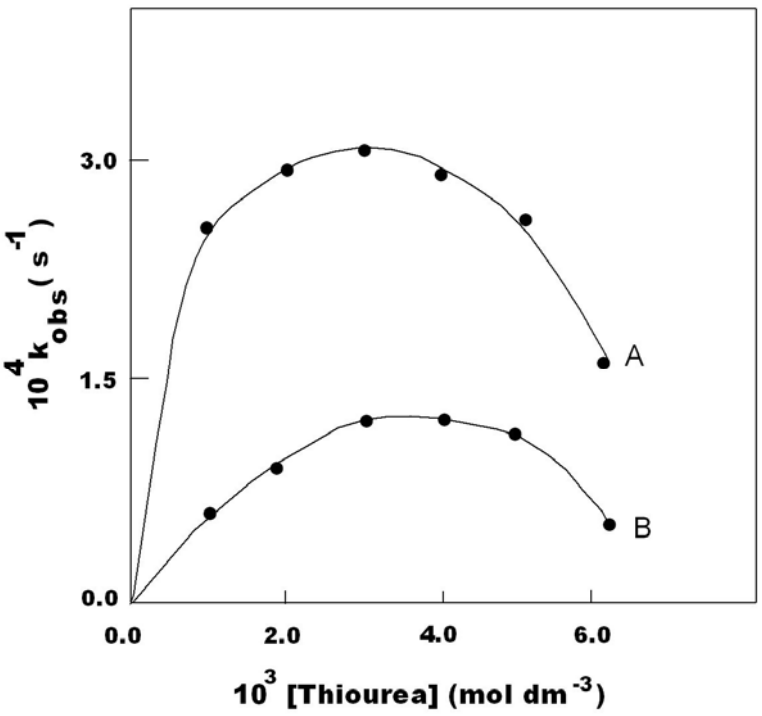


Fig. B2- Effect of [thiourea] on k_{obs} for the MnO_4^- oxidation of thiourea. $[MnO_4^-]$ = 2.0 x 10^{-4} mol dm^{-3}; $[HClO_4]$ = 1.86 x 10^{-4} mol dm^{-3}; temp. = 50 (A), = 40 ^oC (B).