Chapter - Four

SYNTHESES OF STEROIDAL THIAZOLES
The five membered doubly unsaturated heterocyclic system containing one nitrogen and one sulphur atom is called thiazole. There are two possible heterocyclic rings (I) and (II), containing three carbon atoms, one sulphur atom and one nitrogen atom. The compounds containing sulphur and nitrogen at 1,2 positions are known as isothiazole. Isothiazole (I) has been studied very little and relatively few compounds containing this system are known. The thiazole (II) containing sulphur and nitrogen at 1,3 positions has been studied extensively and many compounds containing this heterocyclic system are of industrial and biological importance.

The dihydrothiazoles (III) and (IV) are designated as thiazolines. Tetrahydrothiazole or thiazolidone (V) constitutes a well known and important class of compounds. Many polycyclic and fused ring systems containing the thiazole nucleus are also known.
The history of thiazoles series began in 1874 with the work of Hofmann who prepared derivatives of benzothiazole, such as 2-chlorobenzothiazole and 2-phenylbenzothiazole. Compounds containing the simple thiazole nucleus were first reported by Hantzch and coworkers\textsuperscript{2} in the series of papers beginning in 1887. After this pioneer work, knowledge of the thiazole system developed steadily and many discoveries of commercial and biological interest gave impetus to the study. In 1888, Green\textsuperscript{3} described a yellow substance (primuline base) and dihydrothio-p-toluidine that were obtained by fusion of p-toluidine with sulphur. These substances were immediately recognised as benzothiazole derivatives and many related compounds were prepared. The investigations by Bogert and Collaborators\textsuperscript{4}, which greatly extended this field, were reported in a series of paper beginning in 1922. Also in 1922 Mill\textsuperscript{5} recognized the value of cyanine dyes containing thiazole ring as photographic sensitizers. At about the same time 2-mercaptobenzothiazole was developed as rubber vulcanization accelerator and many related compounds were investigated\textsuperscript{6}. Thus the early study of thiazole chemistry came from the practical importance of the benzothiazoles. Williams and coworkers demonstrated the existence of the simple thiazole ring in vitamin B (thiamine)\textsuperscript{7}. Shortly thereafter, the development of the sulpha drugs led to the usefulness of sulphathiazole (2-sulphanilamidothiazole) and several of its derivatives as chemotherapeutic agents for the treatment of bacterial infection\textsuperscript{8-10}. 
Miolati and Levi\textsuperscript{8-10} reported the preparation of 4-methyl 4-ethyl, 4-carbethoxymethyl-1-, 4-phenyl-2-mercaptothiazoles (VIIIa-d) by the condensation of the corresponding halomethyl ketones (VIa-d) with ammonium dithiocarbamate (VII).

\[
\text{RCOCH}_2\text{Cl} + \text{NH}_2\text{CSNH}_4 \rightarrow \begin{array}{c}
\text{S} \\
\text{N} \\
\text{SH}
\end{array}
\]

(VII)

<table>
<thead>
<tr>
<th>R</th>
<th>R</th>
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<tbody>
<tr>
<td>(VIa) CH(_3)</td>
<td>(VIIIa) CH(_3)</td>
</tr>
<tr>
<td>(VIb) C(_2)(_5)</td>
<td>(VIIIb) C(_2)(_5)</td>
</tr>
<tr>
<td>(VIc) CH(_2)COOC(_2)(_5)</td>
<td>(VIIIc) CH(_2)COOC(_2)(_5)</td>
</tr>
<tr>
<td>(VId) Ph</td>
<td>(VIIIId) Ph</td>
</tr>
</tbody>
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2-Methylthio-4-methylthiazole (IX) was prepared by the reaction of chloroacetone with dithiocarbamate (VII)\textsuperscript{11,12}.

\[
\text{CH}_3\text{C}\rightarrow\text{CH}_2\text{Cl} + \text{NH}_2\text{C}\rightarrow\text{S} \rightarrow \text{CH}_3 \rightarrow \begin{array}{c}
\text{S} \\
\text{N} \\
\text{SCH}_3
\end{array}
\]

(VIa) (VII) (IX)

Singh et al.\textsuperscript{13} reported the reaction of \(\omega\)-(6-methyl-4-pyridinylthio) acetophenone (X) and 2-(6-methyl-4-pyrimidinylthio) cyclohexanone (XI) with aqueous HCl/HClO\(_4\) or POC\(_3\) followed by hydrolysis provided 1-(4-aryl-2-thiazolyl)-2-propane (XII) and 4,5,6,7-tetrahydro-2-acetonyl benzothiazole (XIII), respectively.
Meakins et al.\textsuperscript{14} reported that reaction between N-benzoyl-N'-methyl-N'-phenylthiourea (XIV) and chloroacetone (VIA) gave 5-benzoyl-4-methyl-2-(N-methyl-N-phenylamino)thiazole (XV).

The reactions of dithiocyanates (XVI-XVIII) with p-methoxyaniline (XIX) in hot benzene afforded the dihydrothiazoles (XX-XII)\textsuperscript{15}. 
Condensation of 6-acetyl-7-methoxy-2,2-dimethylchroman, 6-acetyl-7-methoxy-2,2,8-trimethylchroman and 3,4,9,10-tetrahydro-2,2,8,8-tetramethyl-2H,8H-benzo[1,2-b:3,4-b]dipyran (XXIII-XXV) with thiourea in presence of iodine afforded corresponding 2-aminothiazole derivatives (XXVI-XXVII) respectively.\(^{16}\)
α-Bromo-α,β-dihydrochalcone derivatives (XXIX-XXXI) on condensation with thiourea afforded 2-amino-4-aryl-5-aryl-methylthiazole derivatives (XXXII-XXXIV).\(^{17}\)

Condensation of 2-chlorocyclohexanone (XXXV) with substituted thioamides (XXXVIa-g) in hot ethanol gave 2-substituted 4,5,6,7-tetrahydrobenzothiazole derivatives (XXXVIIa-g).\(^{18}\)

\[^{17}\text{Condensation of 2-chlorocyclohexanone (XXXV) with substituted thioamides (XXXVIa-g) in hot ethanol gave 2-substituted 4,5,6,7-tetrahydrobenzothiazole derivatives (XXXVIIa-g).}^{18}\]
The condensation of α-bromoketones (XXXVIIIa-e) with N-methyl thiourea (XXXIX) in neutral solvent afforded exclusively 2-N-methylamino-(4-substituted) thiazoles (XLa-e)\(^1\). (a, R = Me; b, Pri, c, But; d, Ph; e, 4-\(\text{C}_6\text{H}_4\)F).

When benzoyl isothiocyanate (XLII) was allowed to react with aminoacetoneitrile (XLI) under mild conditions, α-thiouriedo-nitrile (XLIII) was obtained, which on treatment with nitrous acid gave 5-amino-2-benzamidothiazole (XLIV)\(^2\).

\[
\begin{align*}
\text{CH}_2\text{-CN} + \text{C-Ph} & \rightarrow \text{CH}_2\text{-C=NH} \\
\text{NH}_2 & \rightarrow \text{CH}_2\text{-C=NH-C-Ph} \\
\text{S} & \rightarrow \text{S} \\
(\text{XLI}) & \rightarrow (\text{XLII}) & \rightarrow (\text{XLIII}) & \rightarrow (\text{XLIV})
\end{align*}
\]
α-Bromo methylacetate (XLVI) condensed with ethoxythiocarbonyl cyanamide salt (XLV) to form 4-amino-2-ethoxy-5-methoxycarbonylthiazole (XLVII).

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \quad \text{C}=\text{N}\text{-C}=\text{N} \\
\text{KS} & \quad \text{BrCH}_2\text{COOCH}_3 \\
(\text{XLV}) & \quad \text{(XLVI)} \quad \text{→} \\
\text{OCH}_3 & \quad \text{OC}_2\text{H}_5
\end{align*}
\]

In a similar manner, 1,3-dichloro-2-propanone (XLVIII) reacted with 2-equivalent of ethoxythiocarbonyl cyanamide salt (XLV) to give the bis(4-amino-2-ethoxy-5-thiazolyl) ketone (XLIX)\(^{21}\).

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \quad \text{C}=\text{N} \\
\text{KS} & \quad \text{C}_2\text{H}_5\text{O} \\
(\text{XLV}) & \quad \text{(XLVIII)} \quad \text{Et}_3\text{N} \\
\text{C}_2\text{H}_5\text{O} & \quad \text{OC}_2\text{H}_5 \quad \text{C}_2\text{H}_5\text{O}
\end{align*}
\]

\(\text{a-Bromoacetophenone (XXXVIIIa) readily reacted with potassium [ethoxy(thiocarbonyl)] cyanamide (XLV) to provide an open chain intermediate (L) which was converted into 4-amino-5-benzoyl-2-ethoxythiazole (LI)\(^{22}\) in high yield by treatment with a triethylamine at room temperature.}\)
The reaction of aldehydes (LII) and o-aminothiophenol (LIII) yielded either 2,3-dihydrobenzothiazoles (LIV) or benzothiazoles (LV) depending upon the aldehyde and the thiophenol employed. The reaction of 2-amino-4-chlorothiophenol with various aldehydes and ketones have been studied extensively.23,24
The reaction of thiourea on 2-bromo-β-hydroxyvinyl aryl ketones (LVIa-e) afforded 2-amino-5-aryltiazoles (LVIIa-e)\(^{25}\) [a, R=H; b, Cl, c, Br; d, CH\(_3\); e, OCH\(_3\)].

\[
\text{R} - \text{C} = \text{C} - \text{CH} - \text{OH} \xrightarrow{\text{H}_2\text{N-C-NH}_2} \text{R} - \text{C} - \text{NH}_2
\]

(LVIa-e) → (LVIIa-e)

Condensation of ethyl-2-(p-bromoacetylphenoxy)-propionate (LVIII) with thioacetamide (LIX) yielded ethyl-2[p-(2-methyl-4-thiazolyl)phenoxy]-propionate (LX) which on acidic hydrolysis generated 2[p-(2-methyl-4-thiazolyl)phenoxy]-propionic acid (LXI)\(^{26}\).

\[
\text{COCH}_2\text{Br} \quad \text{CH}_3\text{S-S-NH}_2 \quad \text{C}_2\text{H}_5\text{O}_2\text{C-HC-O} - \text{C}_2\text{H}_5
\]

(LVIII) + (LIX) → (LX)

(20% H\(_2\)SO\(_4\))

\[
\text{H}_3\text{C-HC-O} - \text{COOH}
\]

(LXI)
Cyclocondensation of 2,3-dichloro-1,4-napthoquinone (LXII) with thiourea and thioacetamide gave naptho[2,3-d]thiazole-4,9-diones (LXIVa-b) via intermediate 2-thiomido-3-chloro-1,4-napthoquinones (LXXIIa,b)\(^27\) \([a, R=\text{NH}_2; b = \text{CH}_3]\).

Addition of \(\text{H}_2\text{S}\) to piperidine carbonitrile (LXV) gave the thiocarboxamide (LXVI) which was cyclocondensed with \(\alpha\)-bromoacetophenone (LXVII) to give \(p(2\text{-phenylthiazolyl})\text{N-methyl piperidine (LXVIII)}\)\(^28\), which was potential bactericide and analgesic.
Thermal cyclization of N-phenylthiourea (LXIX) in sulphuric acid in the presence of sodium bromide provided 2-aminobenzothiazole (LXX)\textsuperscript{29}.

\[
\begin{align*}
\text{C}_{6}\text{H}_{5}\text{NH} & \text{C}\text{NH}_{2} \xrightarrow{\text{H}_{2}\text{SO}_{4} \text{NaBr}} \text{C}_{6}\text{H}_{5}\text{N} \text{S} \text{NH}_{2} \\
(\text{LXIX}) & \quad (\text{LXX})
\end{align*}
\]

\(p\text{-Acetamido-ω-chloroacetophenone (LXXI)}\) was cyclized with \(N\)-phenylthiourea to give \(p\)-(2-N-phenylamino-4-thiazolyl) aniline (LXXII)\textsuperscript{30}.

\[
\begin{align*}
\text{O} & \text{HN} \quad \text{C} \text{CH}_{2}\text{Cl} \xrightarrow{\text{PhNH-CNH}_{2}} \text{H}_{2}\text{N} \text{C}_{6}\text{H}_{5} \text{S} \text{NH}_{2} \text{Ph} \\
(\text{LXXI}) & \quad (\text{LXXII})
\end{align*}
\]

During the last few years a large number of steroidal thiazoles have been synthesized by different routes. When a mixture of \(o\)-toluidine-hydrochloride and \(2\alpha\)-thiocyanato-17\(\alpha\)-methylandrostan-3-on-17\(\beta\)-ol (LXXXIII) in ethanol was refluxed with ethyl acetate provided 17\(\alpha\)-methyl-17\(\beta\)-hydroxyandrostan-[3,2-\(d\)]-2',3'-disubstituted thiazolines (LXXIVa-c)\textsuperscript{31}.
Cyclocondensation\textsuperscript{32} of the $\alpha$-bromosolasonadane (\textit{LXXV}) with thiourea gave 2'-aminothiazolo [3,2-d] solasonadane (\textit{LXXVI}).

When 3\textbeta-acetoxy-5\alpha-androstane-16\alpha-bromo-17-one (\textit{LXXVII}) treated with thiourea provided 3\textbeta-acetoxy-5\alpha-androstane[17,16-d] 2'-aminothiazole (\textit{LXXVIII})\textsuperscript{33}.
Similar treatment of 17β-acetoxy-2α-bromo-5α-androstan-3-one (LXXIX) and 2α-bromo-5α-cholestan-3-one (LXXX) with thiourea in isopropyl alcohol provided 17β-acetoxy-5α-androstano[3,2-d]2'-aminothiazole (LXXXI) and 5α-cholestano[3,2-d]2'-aminothiazole (LXXXII)\textsuperscript{33}, respectively.

Treatment of the epiminopregnenonehydrazone (LXXXIII) with thioacetic acid gave the pregnenothiazoline (LXXXIV) and the hydrazone (LXXXV)\textsuperscript{34}. 

\[ \text{R} \quad \text{OAc} \quad \text{C}_8\text{H}_{17} \quad \text{R} \quad \text{OAc} \quad \text{C}_8\text{H}_{17} \]
Cyclocondensation\textsuperscript{35} of 2α-bromodihydrosdiosgenone (\textit{LXXXVI}) with benzathiosemicarbazone (\textit{LXXXVII}) gave 2'-substituted thiazolo[4,5-d]diosgenin (\textit{LXXXVIII})\textsuperscript{35}. 
3β-Methoxy-5-pregnen-20(21)-en-20-ol silyl trimethyl ether (LXXXIX) was oxidised by N-methylmorpholine N-oxide monohydrate and OsO₄ to give the hydroxyketone (XC) which underwent methylation and bromination to give (XCI). Hantzsch reaction of the (XCI) with ethyl thioxamate gave 17β-[4′-(2′-ethoxy-carbonyl-1′,3′-thiazolyl)]-3β-hydroxy-5-androstane (XCII) which was converted to 17β-[4′-(2′-ethoxycarbonyl-1′,3′-thiazolyl)]-3β-hydroxy-5-androstene-3-carboxypropanoate (XCIII)³⁶.

Reaction of 7α-bromo-6-oxo-5α-cholestane (XCIV), its 3β-chloro (XCV) and 3β-acetoxy (XCVI) analogues with thiourea afforded 2′-amino-5α-cholest-6-en(6,7-d)thiazole (XCVII) its 3β-chloro (XCVIII) and 3β-acetoxy (XCIX) analogues respectively³⁷.
2'-Methyl-5α-cholest-6-eno[6,7-d]thiazole (CIII) its 3β-chloro (CIV) and 3β-acetoxy (CV) analogues were obtained by the reaction of respective steroidal bromoketones (C-CII) with thioacetamide.
V.K. Ahluwalia et al. reported that 2-thiobarbituric acid (CVI) on reaction with N-bromosuccinimide, benzoylperoxide and thiourea at reflux temperature in benzene gave 5-amino-1,2,3,7-tetrahydro-7, oxo-2-thioxothiazolo[4,5-d]-pyrimidine (CVII). Similar condensation of 1,3-diarylthiobarbituric acids (CVIII-CXII) afforded 1,5-diaryl-b-amino-1,2,3,7-tetrahydro-7-oxo-2-thioxothiazolo[4,5-d]-pyrimidines (CXIII-CXVII).
Discussion

The non steroidal substituted thiazoles have been reported to possess biological activities such as antimicrobial, antihistaminic, fungicidal, antibacterial and antiinflammatory. Motivated by these biological and therapeutic properties of thiazole derivatives, an attempt has been made to synthesize these steroidal thiazoles. Different investigators use different routes to synthesize steroidal thiazoles. Most commonly it was synthesized by the reaction of α-bromoketones with thiourea and thioacetamide.

In the present study an attempt has been made to synthesize steroidal thiazoles (CXXI-CXXVI) from easily accessible steroidal hydroxy ketones (CXVIII-CXX) with the reaction of thiourea, and thioacetamide in the presence of N-bromosuccinamide (NBS) and benzoylperoxide.

![Diagram showing the synthesis of steroidal thiazoles](image-url)
REACTION OF HYDROXY KETONES WITH THIOUREA

Reaction of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) with thiourea, NBS and benzoylperoxide (catalytic amount)

A mixture of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) and NBS was refluxed with thiourea and benzoylperoxide in benzene at room temp. for 8 hrs. The solvent was distilled off under reduced pressure and the residue was treated with crushed ice and extracted with ether. The ethereal layer was washed with water, potassium carbonate solution (5%) and again with water. The removal of the solvent gave an oily product which was chromatographed over silica gel column to afford a compound, as semisolid.

\[
\begin{align*}
\text{HO} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{C}_{2} \text{H}_{5} & \\
\text{HO} & \quad \text{H} \\
\text{HO} & \quad \text{C} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{C}_{8} \text{H}_{17} & \\
\text{H}_{2} \text{N} & \quad \text{S} & \quad \text{C} & \quad \text{NH}_{2} & \text{NBS} & \text{Benzoylperoxide} & \text{Benzene} \\
\text{HO} & \quad \text{H} & \quad \text{H} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{NH}_{2}
\end{align*}
\]

(CXVIII) (CXX)
Characterization of the compound, semisolid as 3β,5-dihydroxy-2'-amino-5α-cholest-6-eno[6,7-d]thiazole (CXX):

The elemental analysis of the compound, semisolid corresponded to the molecular formula $\text{C}_{28}\text{H}_{46}\text{N}_{2}\text{O}_{2}\text{S}$. The IR spectrum of the compound exhibited bands at 3400 (OH), 3255, 3160 (NH$_2$), 1630 (C=C), 1600, 1520 (C=N), 1455, 1375 (C-N) and 660 cm$^{-1}$ (C-S). These values suggest the presence of thiazole moiety fused with steroidal nucleus. The $^1$H-NMR spectrum of the compound displayed two broad singlets at $\delta$ 4.75 and 3.41 (exchangeable with deuterium) and were assigned to NH$_2$, C5α-OH and C3β-OH respectively. A multiplet appeared at $\delta$ 4.48 (W1/2 = 17Hz, axial) integrating for one proton and was assigned to C3α-H. Methyl protons were observed at $\delta$ 1.2 (C10-CH$_3$), 0.72 (C13-CH$_3$), 0.91 and 0.81 (other methyl protons). The mass spectrum of the compound (CXX) gave molecular ion peak at $M^+$ 474 ($\text{C}_{28}\text{H}_{46}\text{N}_{2}\text{O}_{2}\text{S}$) followed by significant ion peaks at m/z 459, 456, 438, 414, 361, 252, 234 and other fragment ion peaks. The tentative mechanism for the formation of some of the salient fragment ions has been shown in scheme-1.
Reaction of 3β-acetoxv-5-hydroxy-5α-cholestan-6-one (CXIX) with thiourea NBS and benzoylperoxide (catalytic amount):

A mixture of 3β-acetoxv-5-hydroxy-5α-cholestan-6-one (CXIX) and NBS when refluxed with thiourea and benzoylperoxide (catalytic amount) under the conditions as described earlier. The reaction mixture after usual work up and column chromatographic separation afforded, the compound, m.p. 205°.
Characterization of the compound, m.p. 205° as 3β-acetoxy-5-
hydroxy-2′-amino-5α-cholest-6-eno[6,7-d]thiazole (CXXII):

The compound, m.p. 205° was analysed correctly for
C_{30}H_{48}N_{2}O_{3}S. The IR spectrum of the compound showed weak
absorption bands at 3450, 3300, 3150 cm^{-1} and strong absorp-
tion bands at 1730, 1265 cm^{-1} which are due to the presence
of NH_{2}, OH and acetate groups. Other bands observed at 1630
(C=\pi), 1525 (C=N), 1460, 1375 (C-N) and 665 cm^{-1} (C-S). These
values indicate the presence of thiazole moiety in the steroid
nucleus. The {^1}H-NMR spectrum of the compound displayed a broad
multiplet at δ 5.01 (W1/2 = 18Hz, axial) integrating for one
proton and was assigned to C3α-H. Two broad singlets \( \text{at} \ δ 4.92 \text{ and} \ δ 3.42 \) (exchangeable with deuterium) integrating
for one proton and two protons each were assigned \( \text{to} \ C2α-\text{H} \)
and NH_{2} respectively.

A singlet appeared at δ 2.05 integrating for three protons
was due to acetate methyl. Angular and side chain methyl protons
were observed at δ 1.2 (C10-CH₃), 0.78 (C13-CH₃) and 0.91 and 0.81. These values suggested the structure of the compound, m.p. 205° as 3β-acetoxy-5-hydroxy-2'-amino-5α-cholest-6-eno[6,7-d]thiazole (CXXII). This structure was further supported by mass spectral studies. The mass spectrum of the compound (CXXII) gave the intense molecular ion peak at M⁺ 516 (C₃₀H₄₈N₂O₃S) followed by other important peaks at m/z 501, 474, 456, 438, 414, 403, 396, 234, 216 and 192 and lower mass peaks. The fragmentation pathway of important fragment ions has been rationalized according to scheme-2.

Scheme-2

![Scheme-2 Diagram](image-url)
Reaction of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CXX) with thiourea, NBS and benzoylperoxide (catalytic amount):

A mixture of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CXX) and NBS when refluxed with thiourea and benzoylperoxide (catalytic amount) under the conditions as mentioned earlier. After the usual work up and column chromatographic separation, the reaction mixture afforded a compound as an oil.

![Chemical structure](image)

Characterization of the oily compound as 3β-chloro-5-hydroxy-2'-amino-5α-cholestan-6-eno[6,7-d]thiazole (CXXIII):

The oily compound was analysed correctly for C_{28}H_{45}ClN_{2}OS...
(positive Beilstein test). The IR spectrum of the compound exhibited bands at 3430, 3300, 3150 (NH₂, OH), 1638 (C=C), 1530 (C=N), 1470, 1380 (C-N) and 655 cm⁻¹ (C=S). These values suggest the presence of thiazole moiety on steroid nucleus and 780 cm⁻¹ for (C-Cl). The ¹H-NMR spectrum of the compound exhibited two broad singlets centred at δ 4.71 and 3.41 (exchangeable with deuterium) integrating for two protons and one proton each assigned to -NH₂ and C5α-OH. A multiplet was observed at δ 4.03 (J₁/₂ = 17Hz, axial) for one proton and was assigned to C3α-H. Angular and side chain methyl protons were observed at δ 1.2 (C10-CH₃), 0.75 (C13-CH₃), 0.9 and 0.8 (other methyl protons). These values suggested the compound to be 3β-chloro-5-hydroxy-2'-amino-5α-cholest-6-eno[6,7-d]thiazole. This structure was further supported by its mass spectral studies. The mass spectrum of thiazole (CXXIII) gave the molecular ion peak at M⁺ 492/494 (C₂₈H₄₅ClN₂O₅), followed by other significant fragment ion peaks at m/z 477/479, 474/476, 450, 438, 432/434, 414, 396, 379/381, 234, 216, 192 and other lower mass peaks. The formation of the some of the fragment ions has been rationalized according to the scheme-3.
Scheme-3

\[
\text{m/z 379/381} \xrightarrow{-\text{C}_8\text{H}_{17}} \quad \text{m/z 474/475} \quad \text{m/z 477/479} \quad \text{m/z 432/434}
\]

\[
\text{m/z 492/494} \quad \text{m/z 456} \quad \text{m/z 438} \quad \text{m/z 396}
\]

\[
\text{m/z 234} \quad \text{m/z 216} \quad \text{m/z 192}
\]

\[
\text{m/z 414} \quad \text{m/z 396}
\]
REACTION OF HYDROXY KETONES WITH THIOACETAMIDE

Reaction of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) with thioacetamide, NBS and benzoylperoxide (catalytic amount):

A mixture of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) and NBS was refluxed with thioacetamide and benzoylperoxide (catalytic amount) in benzene at room temperature for 8 hrs. The solvent was distilled off under reduced pressure and the residue treated with crushed ice and extracted with ether. The ethereal layer was washed with water, potassium carbonate solution (5%) and again with water. The removal of the solvent gave an oily residue which was chromatographed over silica gel column to afforded a compound as an oil.
Characterization of the oily compound as 3β,5-dihydroxy-2'-methyl-5α-cholest-6-eno[6,7-d]thiazole (CXXIV):

The oily compound was analysed correctly for $C_{29}H_{47}N_2O_2S$. The IR spectrum of the compound exhibited bands at 3400 cm$^{-1}$ for -OH absorption. Other absorption bands at 1630 (C=C), 1530 (C=N), 1470, 1380 (C=N) and 655 cm$^{-1}$ (C-S) were observed due to the presence of thiazole moiety on steroid nucleus. The $^1$H-NMR spectrum of the compound exhibited a multiplet at $\delta$ 4.48 (W1/2= 18Hz) integrating for one proton and was assigned to C3α-H. A singlet at $\delta$ 3.21 integrating for two protons was observed for C3β-OH and C5α-OH (exchangeable with deuterium). A singlet at $\delta$ 2.51 integrating for three protons was assigned to -N=C-CH$_3$. Angular and side chain methyl protons were observed at $\delta$ 1.2 (C10-CH$_3$), 0.75 (C13-CH$_3$), 0.9 and 0.8. On the basis of above discussion the structure of the oily compound was assigned as 3β,5-dihydroxy-2'-methyl-5α-cholest-6-eno[6,7-d]thiazole (CXXIV). This structure was further supported by its mass spectral studies. The mass spectrum of thiazole (CXXIV) gave the molecular ion peak at $M^+$ 473 ($C_{29}H_{47}N_2O_2S$) followed by other significant peaks at m/z 458, 455, 437, 421, 403, 395, 360 and other lower mass fragment ion peaks. The tentative mechanism for the formation of some of the salient fragment ions has been shown in scheme-4.
Reaction of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CXIX) with thioacetamide, NBS and benzoylperoxide (catalytic amount)

A mixture of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CXIX) and NBS was refluxed with thioacetamide and benzoylperoxide (catalytic amount) in benzene for 8 hrs. Reaction mixture after usual workup and column chromatographic separation afforded, the compound, m.p. 178°.
Characterization of the compound, m.p. 178° as 3β-acetoxy-5-hydroxy-5α-cholest-6-eno[6,7-d]2'-methyl thiazole (CXXV):

The compound, m.p. 178° was analysed for C_{31}H_{49}NO_{3}S. Its IR spectrum had bands at 3400 (OH), 1735, 1240 (CH₃COO⁻), 1530 (C=N), 1470, 1385 (C-N) and 665 cm⁻¹ (C-S). These IR values indicate the presence of hydroxyl acetoxy groups and thiazole moiety in the compound. The $^1$H-NMR spectrum of the compound displayed a broad multiplet at $\delta$ 5.01 ($\omega \lambda /2 = 18$Hz, axial) integrating for one proton and was assigned to (C3α-H). The hydroxyl proton (exchangeable with deuterium) was appeared at $\delta$ 3.41. A sharp singlet was observed at $\delta$ 2.53 for three protons ascribable to thiazole ring methyl protons. The angular and side chain methyl signals were seen at $\delta$ 1.23 (Cl₀-CH₃), 0.76 (Cl₃-CH₃), 0.9 and 0.8. From the above data, it is evident that the structure of compound (CXXV) is confirmed as 3β-acetoxy-5-hydroxy-5α-cholest-6-eno[6,7-d]2'-methylthiazole (CXXV). This structure was further supported by its mass spectral studies. The mass spectrum
of the compound (CXXV) showed intense molecular ion peak at \( M^+ 515 \) \((C_{31}H_{49}NO_3S)\) followed by other significant fragment ions at \( m/z \) 500, 497, 474, 456, 455, 437, 402, 396 and other lower mass ion peaks. Genesis of some of the fragment ions is shown in Scheme-6.

Scheme-6

Reaction of 3\(^\beta\)-chloro-5-hydroxy-5\(^\alpha\)-cholestan-6-one (CXX) with thioacetamide, NBS and benzoylperoxide (catalytic amount):

A mixture of 3\(^\beta\)-chloro-5-hydroxy-5\(^\alpha\)-cholestan-6-one (CXX) and NBS was refluxed with thioacetamide and benzoylperoxide (catalytic amount) in benzene for 8 hrs. After usual worked up and column chromatographic separation an oily compound was isolated.
Characterization of the compound oil as $3\beta$-chloro-$5$-hydroxy-$5\alpha$-cholest-$6$-eno[6,7-d]-$2\prime$-methylthiazole (CXXVI):

The oily compound was analysed for $C_{29}H_{46}$NSOCI (positive Beilstein test). The IR spectrum showed band at 3450 and 780 cm$^{-1}$ for hydroxyl and halogen group. Other absorption bands at 1535 (C=N), 1465, 1385 (C-N) and 655 cm$^{-1}$ (C-S) confirm the presence of thiazole moiety. The $^1$H-NMR spectrum exhibited a broad multiplet centred at $\delta$ 3.85 ($\nu_1/\nu = 18$Hz, axial)$^{46}$ integrating for one proton assigned to C3a-H. A singlet was observed at $\delta$ 3.21 for C5a-OH (exchangeable with deuterium). The thiazole ring methyl and acetate methyl protons appeared as a sharp singlet at $\delta$ 2.53 and 1.96 respectively. The angular and side chain methyl protons were observed at $\delta$ 1.25 (C10-CH$_3$), 0.75 (C13-CH$_3$) and 0.93, 0.83. The above data led to the structure of the compound (CXXVI) as $3\beta$-chloro-$5$-hydroxy-$5\alpha$-cholest-$6$-eno[6,7-d]-$2\prime$-methyl thiazole. This structure was
further supported by its mass spectral studies. The mass spectrum of the compound (CXVI) showed intense molecular ion peak at $M^+ 491/493 (C_{29}H_{46}NOSCl)$ followed by other significant fragment ions at $m/z 476/478$, $473/475$, $455$, $430/432$, $432/434$, $414$, $378/380$, $215$, and other lower mass peaks. The formation of the fragment ions is shown in Scheme-6.

**Scheme-6**

$m/z 378/380$

$m/z 476/478$  
$\rightarrow$ -C$_8$H$_{17}$  
$\rightarrow$ -CH$_3$  
$\rightarrow$ -H$_2$O  
$\rightarrow$ M.$^+ 491/493$ (CXVII)

$m/z 455$  
$\rightarrow$ -HCl  
$\rightarrow$ -C$_{16}$H$_{30}$  
$m/z 215$

$m/z 473/475$  
$m/z 432/434$

$m/z 414$  
$m/z 432/434$

$m/z 450/452$
3β,5,6β-Trihydroxy-5α-cholestane

A mixture of cholesterol (20 g) and formic acid (20 ml; 88%) was heated on a water bath at 70-80° for 5 minutes and then allowed to attain room temperature. Hydrogen peroxide (20 ml; 30%) was added to the mixture and it was kept at room temperature for 12 hrs. with occasional shaking. Boiling water (300 ml) was added to the mixture with stirring and the reaction mixture was allowed to attain room temperature when a white solid separated which was filtered under suction and air dried. The solid was dissolved in methanol (600 ml) and the solution was heated with sodium hydroxide solution (20 ml; 25%) for 10 minutes on a steam bath. It was acidified with hydrochloric acid and diluted with boiling water (300 ml). The triol obtained on cooling was collected by filtration and recrystallized from methanol to give 3β,5, 6β-trihydroxy-5α-cholestan (18 g) m.p. 237° (reported 47, m.p. 237-239°).

3β,5-Dihydroxy-5α-cholestan-6-one (CXVIII)

To a solution of 3β,5,6β-trihydroxy-5α-cholestan (10 g) in dioxane (90 ml) was added N-bromosuccinimide (4.5 g) at
about 25°. After 15 minutes, the reaction mixture was cooled in an ice bath and the solid which crystallized out was collected by filtration under suction and washed thoroughly with 50% methanol to give dihydroxyketone (CXVIII) (6.5 g), m.p. 231° (reported\textsuperscript{47}, 231-233°).

**Reaction of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) with thiourea, NBS and benzoylperoxide (catalytic amount): 3β,5-dihydroxy-2'-amino-5α-cholest-6-eno[6,7-d]thiazole (CXXI)**

A mixture of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) (1.0 g, 2.39 m mol) and NBS (0.500 g, 2.39 m mol) was refluxed with thiourea (0.178 g, 2.39 m mol) and benzoylperoxide (catalytic amount) in benzene (40 ml) at reflux temperature for 8 hrs. After completion of the reaction, the solvent was distilled off under reduced pressure and the residue treated with crushed ice and extracted with ether. The ethereal layer was washed with water, potassium carbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was chromatographed over silica gel (20 g) column. Elution with a mixture of light petroleum ether and ether (5:1) provided 3β,5-dihydroxy-2'-amino-5α-cholest-6-eno[6,7-d]thiazole (CXXI) as a semi solid (0.723 g, 1.6 m mol).
Analysis found: C, 70.89; H, 10.25; N, 6.09

C$_{28}$H$_{46}$N$_2$O$_2$S requires: C, 70.88; H, 10.22; N, 6.05%.

**IR:** $\nu_{\max}$: 3400 (-OH), 3255, 3160 (NH$_2$), 1630 (C=C), 1600, 1520 (C=N), 1455, 1375 (C-N) and 660 cm$^{-1}$(C-S).

**$^1$H-NMR:** $\delta$ 4.75 (brs, NH$_2$-exchangeable with deuterium), 4.48 (m, $\omega$/2 = 17Hz, C3$\alpha$-H, axial), 3.41 (brs, CH, exchangeable with deuterium), 1.2 (ClO-CH$_3$), 0.72 (Cl$_3$-CH$_3$), 0.91 and 0.81 (other methyl protons).

**MS:** $M^+$ 474 (30.00, C$_{28}$H$_{46}$N$_2$O$_2$S), 459 (20.00, C$_{27}$H$_{43}$N$_2$O$_2$S), 457 (10.00), 456 (10.00), 441 (2.50), 438 (3.20), 433 (2.0), 432 (12.50, C$_{27}$H$_{44}$O$_2$S), 427 (2.50), 414 (3.50), 396 (3.75), 393 (7.5), 388 (5.00), 387(36.25), 386 (8.75), 385 (8.75), 384 (12.50), 372 (7.5), 371 (18.75), 370 (2.5), 369 (5.00), 368 (3.75), 361(5.00, C$_{20}$H$_{39}$N$_2$O$_2$S), 350 (4.50), 348 (2.50), 345 (3.45), 343 (2.50), 341 (3.20), 330 (2.50), 329 (5.00), 328 (2.5), 326 (2.1), 320 (5.4), 317 (2.15), 313 (3.45), 274 (11.25), 273 (43.75), 263 (5.00), 252 (2.50), 246 (7.50), 245 (17.50), 244 (7.50), 234 (3.45), 233 (17.5), 232 (27.50), 231 (82.50), 220 (6.25), 218 (2.5), 216 (8.75), 205 (3.75), 204 (2.50), 203(5.00), 190 (2.50), 189 (5.00), 178 (2.50), 177 (11.25), 176 (2.50), 165 (7.5), 164 (12.50), 163 (10.00), 161 (2.50), 152 (7.50), 150 (6.25), 149 (10.25), 147(5.00),
3β-Acetoxy-5,6β-dihydroxy-5α-cholestane

3β-Acetoxy-5,6α-epoxy-5α-cholestan-6-one (CXIX)
in acetone (30 ml) and was kept in ice bath. To this solution Jone's reagent (35 g of chromium trioxide in 100 ml of water + 30 ml of H₂SO₄) was added dropwise with stirring till the colour of the solution persisted. The solution was further stirred for 30 minutes. The reaction mixture was diluted with water and the precipitated solid was filtered, dried and recrystallized from acetone to give the ketone (CXIX) (3.0 g) m.p. 232° (reported 232-233°).

II A mixture of 3β,5-dihydroxy-5α-cholestan-6-one (CXVIII) (10 g) pyridine (15 ml, freshly distilled over KOH) and acetic anhydride (10 ml) was heated under reflux for 2 hrs. The reaction mixture was allowed to cool at room temperature and treated with water. The reaction product consisting of colourless needles was filtered, washed with a little methanol and air dried. Recrystallization from methanol gave the hydroxy ketone (CXIX) (6.5 g), m.p. 232° (reported 232-233°).

Reaction of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CXIX) with thiourea, NBS and benzoylperoxide (catalytic amount):

3β-Acetoxy-5-hydroxy-2'-amino-5α-cholest-6-enol[6,7-d]thiazole (CXXII):

A mixture of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one
(1.0 g, 2.17 m mol) and NBS (0.385 g, 2.17 m mol) was refluxed with thiourea (0.164 g, 2.17 m mol) and benzoylperoxide (catalytic amount) in benzene (40 ml) at reflux temperature for 8 hrs. After usual work up and evaporation of the solvent gave an oil which was chromatographed over silica gel column.

Elution with petroleum ether - ether (8:1) provided an oil which was crystallized from hexane to afford 3β-acetoxy-5-hydroxy-2'-amino-5α-cholest-6-eno[6,7-d]thiazole (CXXII) (0.625 g, 1.21 m mol), m.p. 205°C.

Analysis found : C, 69.75; H, 9.38; N, 5.39

C_{30}H_{48}N_{2}O_{3}S requires : C, 69.72; H, 9.36; N, 5.42%.

IR : ν_{max} 3450 (-OH), 3300, 3150 (-NH$_2$), 1730, 1265 (CH$_3$COO), 1630 (C=C), 1525 (C=N), 1460, 1375 (C-N), and 665 cm$^{-1}$ (C-S).

$^1$H-NMR : δ 5.01 (brm, W1/2 = 18Hz; C3α-H, axial), 4.92 (brs, NH$_2$, exchangeable with deuterium), 3.42 (brs, C5α-OH, exchangeable with deuterium), 2.05 (s, -O-C-CH$_3$), 1.2 (C10-CH$_3$), 0.78 (C13-CH$_3$), 0.91 and 0.81 (other methyl protons).

MS : M$^+$ 516 (30.25; C$_{30}$H$_{48}$N$_2$O$_3$S), 501 (2.35; C$_{29}$H$_{45}$N$_2$O$_3$S), 498 (2.39), 474 (3.25), C$_{28}$H$_{44}$N$_2$OS), 456 (12.31), 438 (2.14), 414 (2.53), 403 (4.25), 396 (100.00), 391 (5.00), 390 (2.45), 386 (0.97), 385 (1.74), 384
(2.90), 383 (1.10), 371 (2.10), 370 (2.50), 369 (1.50), 368 (1.45), 365 (2.50), 363 (2.40), 362 (3.40), 361 (1.25), 360 (3.53), 332 (5.00), 329 (5.15), 301 (3.75), 292 (1.25), 294 (2.51), 276 (4.35), 252 (2.12), 240 (3.20), 239 (1.35), 238 (3.25), 237 (2.15), 235 (2.15), 234 (2.25), 230 (1.51), 224 (2.51), 223 (3.21), 222 (1.25), 221 (0.75), 220 (2.50), 219 (2.50), 218 (12.00), 202 (5.00), 191 (2.50), 189 (12.50), 176 (2.50), 165 (2.50), 163 (2.50), 151 (2.50), 109 (2.50), 107 (2.50), 95 (3.75), 94 (2.50), 93 (10.00), 90 (2.50), 83 (1.25), 81 (3.75), 79 (1.25), 71 (2.50), 68 (2.50), 66 (3.75), 57 (6.25), 56 (2.50), 55 (10.00), 43 (40.00), 42 (2.50), 41 (13.75).

3β-Chloro-5α,6β-dihydroxy-5α-cholestan  

Finely powdered 3β-chlorocholest-5-ene (28 g) was dissolved in hot glacial acetic acid (300 ml) and treated with hydrogen peroxide (60 ml; 30%). The reaction mixture was kept at 95° for 1 hr. After removal of the solvent, the oily product was extracted with ether and the ethereal layer was washed successively with water, sodium bicarbonate solution (10%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil (~12 g) which was chromatographed over silica gel column (240 g) and eluted in 50 ml (portions). Elution with petroleum ether - benzene (7:3) gave the unreacted 3β-chlorocholest-5-ene (2 g), m.p. 96° (reported, m.p. 96°). Further elution with benzene - chloroform (9:1) gave 3β-chloro-5α-hydroxy-
6β-acetoxy-5α-cholestan (3.31 g), m.p. 148° (reported, 150-151°).

Elution with chloroform gave 3β-chloro-5,6β-dihydroxy-5α-cholestan, recrystallized from methanol (2.3 g), m.p. 124° (reported, 126°, positive Beilstein test for halogen).

3β-Chloro-5-hydroxy-5α-cholestan-6-one (CXX)

3β-Chloro-5,6β-dihydroxy-5α-cholestan (2 g) was dissolved in ether (40 ml), methanol (10 ml) and water (10 ml) and treated with N-bromosuccinimide (1 g). After 1 hr, ether (50 ml) was added and the solution was washed with water, sodium metabisulphite solution (10%) and water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the crude ketone (CXX) which was recrystallized from acetone to afford 3β-chloro-5-hydroxy-5α-cholestan-6-one (CXX), (1.4 g), m.p. 181° (reported, 182°).

Reaction of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CXX) with thiourea, NBS and benzoylperoxide (catalytic amount): 3β-Chloro-5-hydroxy-2′-amino-5α-cholestan-6-eno[6,7-d]thiazole (CXXIII)

A mixture of 3β-chloro-5-hydroxy-5α-cholestan-6-one (1.0 g, 2.10 m mol) and NBS (0.373 g, 2.10 m mol) was refluxed with thiourea (0.149 g, 2.10 m mol) and benzoyl peroxide (cata-
lytic amount) in benzene (40 ml) was refluxed under similar reaction conditions as described earlier. Usual work up of the reaction mixture followed by evaporation of the solvent yielded a residue which was chromatographed over silica gel (20 g) column. Elution with petroleum ether - ether (18:1) afforded 3β-chloro-5-hydroxy-2'-amino-5α-cholest-6-eno[6,7-d] thiazole (CXXIII) (0.615 g, 1.43 m mol) as an oil.

Analysis found: C, 67.42; H, 9.43; N, 5.83

C_{28}H_{45}ClN_{2}OS requires: C, 67.40; H, 9.42; N, 5.82%.

IR: ν_{max} 3430 (–OH), 3300, 3150 (NH₂), 1638 (C=C), 1530 (C=N), 1470, 1380 (C−N), 780 (C−Cl) and 655 cm⁻¹ (C=S).

¹H-NMR: δ 4.71 (brs, NH₂, exchangeable with deuterium), 3.41 (brs, C5α−OH, exchangeable with deuterium), 4.03 (m, W/2 = 17Hz; C3α−H, axial), 1.2 (C10−CH₃), 0.75 (C13−CH₃), 0.9 and 0.8 (other methyl protons).

MS: \( M^+ \) 492/494 (10.35/3.53; \( C_{28}H_{45}ClN_{2}OS \)), 477/479 (3.72/1.25, \( C_{27}H_{43}ClN_{2}O_{2}S \)), 474/476 (6.75/2.25; \( C_{28}H_{45}ClN_{2}S \)), 457 (2.5), 456 (12.50), 438 (0.25), 432/434 (7.25/2.65, \( C_{27}H_{41}ClS \)), 314 (4.25), 400 (13.25), 399 (10.35), 398 (3.25), 379 (0.87), 385 (1.74), 384 (2.90), 383 (1.10), 382 (2.50), 379/381 (12.25/4.07), 371 (1.10), 370 (1.45), 369 (3.25),
Reaction of 3β-5-hydroxy-5α-cholestan-6-one (CXVIII) with thioacetamide, NBS, Benzoylperoxide (catalytic amount). 3β-5-Dihydroxy-2'-methyl-5α-cholest-6-eno[6,7-d]thiazole (CXXIV)

A mixture of 3β,5-hydroxy-5α-cholestan-6-one (1 g, 2.39 m mol) and NBS (0.500 g, 2.39 m mol) was refluxed with thioacetamide (0.179 g, 2.30 mmol) and benzoylperoxide (catalytic amount) in benzene (40 ml) for 6 hrs.
in benzene (40 ml) under similar reaction conditions as described earlier. After usual workup and evaporation of the solvent gave an oil which was chromatographed over silica gel (20 g) column and eluted with petroleum ether - ether (12:1) to provide an oil which was crystallized from hexane to afford 3β-acetoxy-5-hydroxy-5α-cholest-6-eno(6,7-d)-2'-methylthiazole (CXXV) (0.165 g, 0.320 m mol), m.p. 178°.

Analysis found: C, 71.85; H, 9.76; N, 2.74

C₃₁H₄₉NO₃S requires: C, 71.84; H, 9.75; N, 2.73%

IR: \( \nu_{\text{max}} \): 3400 (-OH), 1735, 1240 (CH\(_2\)-COO), 1530 (C=N), 1470, 1385 (C-N) and 665 cm\(^{-1}\) (C-S).

\(^1\)H-NMR: \( \delta \): 5.01 (brm, \( W_{1/2} = 18 \text{Hz} \), C3\(\alpha\)-H, axial), 3.21 (s, C5\(\alpha\)-OH, exchangeable with deuterium), 2.53 (s, \(-N=C-\text{CH}_3\)), 1.96 (s, \(-O-C-\text{CH}_3\)), 1.25 (C10-CH\(_3\)), 0.75 (C13-CH\(_3\)), 0.93 and 0.83 (remaining side chain methyl protons).

MS: \( M^+ \): 515 (25.15; C₃₁H₄₉NO₃S), 500 (12.35; C₃₀H₄₆NO₃S), 497 (2.35), 498 (2.35), 474 (4.25; C₂₈H₄₄OS), 457 (4.20), 456 (3.25), 455 (2.12), 438 (1.25), 437(1.25), 413 (2.53), 402 (4.25), 396 (1.25), 390 (5.00), 389 (2.45), 387 (0.85), 386 (0.97), 385 (1.74), 384(2.90), 383 (1.12), 372 (2.10), 371 (3.15), 370 (1.45), 365 (2.40), 364 (1.25), 363 (1.25), 362 (2.40), 361 (1.50), 360 (4.53), 346 (1.25), 345 (0.78), 328 (0.78), 327
(2.50), 368 (5.00), 367 (3.75), 360 (5.00; C_{21}H_{42}NO_2S), 349
(4.50), 347 (2.50), 344 (3.45), 342 (2.50), 340 (3.20), 329
(2.50), 328 (5.00), 327 (2.50), 325 (2.10), 319 (5.40), 316
(2.15), 312 (1.50), 274 (11.25), 273 (43.75), 262 (5.00), 251
(2.50), 246 (7.50), 245 (17.50), 244 (7.50), 234 (3.75), 232
(5.00), 231 (82.50), 220 (6.25), 218 (1.50), 216 (8.75), 205
(4.75), 204 (2.75), 203 (5.15), 190 (2.50), 179 (3.75), 178
(3.75), 176 (10.00), 166 (2.50), 165 (2.50), 163 (3.75), 159
(7.50), 153 (3.75), 152 (7.50), 151 (2.50), 150 (3.75), 149
(6.25), 147 (0.85), 137 (1.50), 136 (2.75), 135 (15.00), 124
(3.25), 123 (6.25), 122 (3.75), 121 (7.50), 119 (4.25), 110
(5.00), 109 (28.00), 108 (27.00), 107 (17.50), 105 (12.50), 97
(10.00), 95 (37.50), 94 (12.40), 93 (27.50), 91 (16.25), 83
(10.00), 82 (1.25), 81 (7.50), 80 (7.50), 79 (27.50), 77 (8.75),
71 (15.00), 70 (7.50), 69 (25.00), 68 (1.50), 67 (30.00), 57
(27.50), 56 (15.00), 55 (45.00), 53 (10.00), 44 (1.25), 43
(95.00), 42 (100.00), 41 (50.00).

**Reaction of 3β-Acetoxy-5-hydroxy-5α-cholestan-6-one (**CXIX**) with thioacetamide, NBS and benzoylperoxide (catalytic amount):**

3β-Acetoxy-5-hydroxy-5α-cholesten-6-eno[6,7-d]-2'-methylethiazole
(**CXXV**):

A mixture of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (1.0 g,
2.17 m mol) and NBS (0.385 g, 2.17 m mol) was refluxed with thio-
urea (0.164 g, 2.17 m mol) and benzoylperoxide (catalytic amount).
After completion of the reaction, the solvent was distilled off under reduced pressure and the residue treated with crushed ice and extracted with ether. The ethereal layer was washed with water, potassium carbonate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was chromatographed over silica gel (~20 g) column. Elution with a mixture of petroleum ether and ether (10:1) provided 3β-5-dihydroxy-2'-methyl-5α-cholest-6-eno[6,7-d]thiazole (CXXIV) as an oil (0.625 g, 1.32 mmol).

Analysis found: C, 73.19; H, 10.18; N, 2.93
C_{29}H_{48}NO_2S requires: C, 73.21; H, 10.17; N, 2.92%.

IR: \( \gamma_{\text{max}} \): 3400 (–OH), 1630 (C=C), 1530 (C=N), 1470, 1380 (C–N) and 655 cm\(^{-1}\) (C–S).

\(^1\)H-NMR: \( \delta \): 4.48 (m, \( \omega l/2 = 18\text{Hz} \); C3α–H; axial), 3.21(s, C5α–OH, C3β–OH, exchangeable with deuterium), 2.51 (s, –N=C–CH\(_3\)), 1.2 (C10–CH\(_3\)), 0.75 (C13–CH\(_3\)), 0.9 and 0.8 (other methyl protons).

MS: M\(^+\) 473 (30.00; C_{29}H_{47}NO_2S), 458 (10.50; C_{28}H_{44}NO_2S), 456 (2.50), 455 (13.50), 440 (2.50), 437 (3.20), 432 (12.00), 431 (10.50; C_{28}H_{44}O_2S), 426 (2.50), 395 (3.75), 392 (7.50), 387 (5.00), 386 (36.25), 385 (8.75), 384 (8.74), 383 (12.50), 371 (7.50), 370 (18.75), 369
Reaction of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CXXIII) with thioacetamide, NBS and benzoylperoxide (catalytic amount): 3β-Chloro-5-hydroxy-5α-cholest-6-eno[6,7-d]-2′-methylethiazole (CXXVI):

A mixture of 3β-chloro-5-hydroxy-5α-cholestan-6-one (1.0 g, 2.1 m mol) and NBS (0.373 g, 2.1 m mol) was refluxed with thioacetamide (0.123 g, 2.1 m mol) and benzoylperoxide (catalytic amount) in benzene (40 ml) was refluxed under similar reaction conditions as described earlier. Usual workup of the reaction mixture followed by evaporation of the solvent yielded an oily residue which was chromatographed over silica gel (20 g) column. Elution with petroleum ether - ether (20:1) afforded 3β-chloro-
5-hydroxy-5α-cholest-6-eno[6,7-d]-2'-methylthiazole (CXXVI)
(0.585 g, 1.19 m mol) as an oil.

Analysis found : C, 75.93; H, 10.32; N, 3.29

C₂₉H₄₆NOSCl requires : C, 75.92; H, 10.33; N, 3.28%.

IR : ν_max. 3450 (-OH), 1535 (C=N), 1465, 1385 (C-N), 780 (C-Cl) and 655 cm⁻¹ (C-S).

¹H-NMR : δ 3.85 (brm, W₁/₂ = 20Hz, C₃α-H, axial), 3.41 (s, C₅α-OH, exchangeable with deuterium), 2.53 (s, -N=C-CH₂), 1.23 (C₁₀-CH₃), 0.76 (C₁₃-CH₃), 0.9 and 0.8 (other methyl protons).

MS : M⁺ 491/493 (3.49/1.16; C₂₉H₄₆NOSCl), 476/478 (10.45/3.45; C₂₈H₄₆NO₃Cl), 473/475 (5.75/1.25), 455 (5.00), 450/452 (7.25/2.25), 432/434 (10.45/3.45), 403 (1.12), 400 (2.45), 399 (3.45), 383 (3.75), 382 (2.15), 378/380 (6.25/2.07), 377 (1.10), 370 (1.45), 369 (3.25), 368 (1.25), 367 (3.25), 364/366 (10.35/3.75), 350 (1.50), 349 (0.87), 348 (0.45), 347 (1.12), 346 (2.15), 345 (2.15), 343 (1.25), 342 (2.01), 341 (1.25), 340 (0.25), 339 (1.61), 338 (2.15), 330 (1.25), 324 (3.75) 323 (1.05), 305 (0.87), 303 (1.45), 282 (1.16), 279 (3.49), 236 (1.50), 228 (1.74), 227 (4.06), 226 (3.49), 225 (1.74), 219 (2.32), 215 (1.45), 212 (1.74),
211 (6.39), 201 (1.87), 200 (0.85), 199 (3.25), 198 (1.45),
197 (0.45), 196 (1.25), 195 (2.25), 194 (1.75), 193 (1.25),
192 (2.25), 191 (1.51), 190 (1.25), 189 (4.12), 180 (2.01),
179 (1.05), 178 (0.35), 177 (0.45), 176 (0.25), 158 (1.25),
159 (2.31), 150 (2.32), 149 (19.17), 134 (5.81), 133 (2.32),
132 (5.22), 131 (5.22), 130 (4.64), 123 (2.32), 122 (6.97),
121 (3.77), 120 (6.97), 119 (3.19), 118 (6.68), 112 (3.48),
111 (9.29), 110 (9.87), 109 (9.87), 108 (4.06), 107 (12.78),
106 (11.63), 105 (37.21), 74 (32.55), 70 (11.63), 69 (32.50),
67 (16.28), 58 (4.65), 57 (37.21), 56 (12.79), 55 (12.79), 55
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