PART C
CHAPTER VIII
SYNTHESIS OF SOME NEW CHROMENO[2,3-d] PYRIMIDINE DERIVATIVES
CHAPTER VIII

Synthesis of some new chromeno[2,3-d]pyrimidine derivatives

Introduction:

Pyrimidine derivatives when fused with oxygen heterocycles, have resulted in the synthesis of many bicyclic and tricyclic heterocyclic systems possessing a variety of useful biological properties.

Amongst the various oxygen heterocyclic systems fused to pyrimidine, furan and benzofuran derivatives have been of considerable importance.

Sangapure and Agasimundin\(^1\) reported the synthesis of Benzofuro[3,2-d]pyrimidine derivatives by the reaction of 3-amino-2-carbethoxy benzofuran with urea and formamide as shown below.

\[
\begin{align*}
\text{NH}_2 & \quad \text{COOC}_2\text{H}_5 \\
\text{Urea} & \quad \text{NH} \\
\text{Formamide} & \quad \text{NH} \\
\text{NH}_2 & \quad \text{COOC}_2\text{H}_5 \\
\end{align*}
\]

Hossini et al.\(^2\) reported the synthesis of many pyrano pyrimidines by the reaction of heterocyclic β-enamino ester (A).

\[
\begin{align*}
\text{CN} & \quad \text{COOC}_2\text{H}_5 \\
\text{Ph} & \quad \text{Ph} \\
\text{NH}_2 & \quad \text{C}_6\text{H}_5\text{N}=\text{C}=\text{S} \\
\text{CHCH}_2\text{COOEt} & \quad \text{NH} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{NC} \\
\end{align*}
\]
Ibrahim et al. reported the synthesis of pyrano[3,2-d]pyrimidines by the reaction of nitriles with heterocyclic active methylene compounds viz. thiobarbituric acid.

\[
\text{Ar-CH}=\text{C-CN} + \text{CN} \rightarrow \text{Ar-}\text{C}=\text{O-N=S} \text{NH}_2 \text{O}
\]

Malik et al. reported the synthesis of 4-hydroxypyrimidines fused to benzofuran nucleus by the reaction of amidines with 2-carboxybenzofuran-3-ones.

\[
R^1 = R^2 = H, \text{Cl}; R^3 = \text{Me, Et.}
\]

Tricyclic heterocyclic systems derived from tetrahydrobenzofurans were synthesised as new pharmaceutical leads by Remers and Jones.

In another study of polycyclic heterocyclic compounds naphthopyranylpyrazoles were reported by Italian workers.
Cannabinols contain the chromene skeleton and other chromenes like cyanomaclurin and Evodinol have been naturally occurring.  

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{OCH}_3 \\
\text{H}_3\text{COC} & \quad \text{O}
\end{align*}
\]

2-Aryl-3-substituted chromenes and their reactions were investigated by Clark-Lewis et al.  

\[
\begin{align*}
R & = \text{CHO, CN etc.}
\end{align*}
\]

During their study on the hydration of acetylenic ketones Thyagarajan et al. reported the synthesis of chromenes with exocyclic double bond.  

\[
\begin{align*}
\text{R} & = \text{R}^1 = \text{H, Cl, Me}
\end{align*}
\]

In the light of the hitherto discussion on fused pyrimidines with oxygen heterocycles and chromenes it was thought of considerable interest to use the chromene ester to construct the pyrimidine nucleus fused at C(2) and C(3) positions of the chromene ring system. The crystal structure of the chromene ester has recently been reported by Kokila, Puttaraja and Kulkarni.
During the present investigation attempts have been made to synthesise chroinenopyrimidines by the reaction of (I) with various compounds like urea, thiourea and formamide. The products obtained are expected to be accompanied by dehydrogenation or elimination of either HCN or HCO₂Et.

Possible eliminations in the side chain during the reaction of 4-substituted 2-amino-3-carbethoxy chromene can be depicted as follows:

The experimental conditions employed in this work correspond to those reported in the literature¹ which involve only mixing the equimolar quantities of the reactants and heating at higher temperatures. No acidic or basic reagents have been used in the present synthesis.
**Present work**

Reaction of salicylaldehyde with two equivalents of ethylcyanoacetate afforded the 2-amino-3-carbethoxy-4-(1-carbethoxy-1-nitrilomethyl)-4[H]chromene\(^{12}\) (I). Attempts have been made to react (I) with urea, thiourea and formamide with a view to construct the pyrimidine ring fused to C(2) to C(3) positions of the chromene nucleus. The structures of the products obtained correspond to (II), (III) and (IV) which have been proved by spectral and analytical techniques, (scheme 1).

**Scheme 1**

![Scheme 1](image-url)
When the above sequence of reactions was tried on 2-hydroxy-1-naphthaldehyde 2-amino-3-carbethoxy-4-(1-carbethoxy-1-nitrilo methyl) 5,6-benzo-4[H] chromene (Ia) was obtained (scheme 2). The product obtained in the reaction of (Ia) with urea was characterised as (IIa) indicating the elimination of HCN. The reaction of (Ia) with thiourea resulted in the formation of (IIIA) which was accompanied by dehydrogenation. The product obtained in the reaction of (Ia) with formamide was consistent with structure (IVA) indicating the elimination of HCOOEt. All the structures were confirmed by spectral and analytical data.

Scheme 2
Results and discussion:

The product (II) obtained in the reaction of (I) with urea exhibited strong band in IR spectrum (spectrum no. 62) around 2200 cm\(^{-1}\) indicating the presence of C=N. A broad band around 1700 cm\(^{-1}\) was assigned for C=0 stretching vibrations whereas NH stretching band was observed around 3200 cm\(^{-1}\). The PMR spectrum (spectrum no. 63) showed a three proton triplet (CH\(_3\)) at 1.2 \(\delta\) ppm and a two proton quartet at 4.2 \(\delta\) ppm due to O-CH\(_2\) protons. The aromatic protons were observed around 7.4-7.8 \(\delta\) ppm. The NH protons were observed around 8.4 and 9.00 \(\delta\) ppm.

The thiourea condensation product (III) also exhibited a sharp band 2200 cm\(^{-1}\) (C=N) and two bands due to C=0 groups at 1700 and 1680 cm\(^{-1}\) (spectrum no.64). The band at 3400 cm\(^{-1}\) is due to NH stretching vibration. The PMR spectrum indicated a triplet at 1.2 \(\delta\) ppm and a quartet at 4.2 \(\delta\) ppm. The aromatic protons were observed around 7.4-7.8 \(\delta\) ppm and the NH protons resonated at 8.4 and 9.00 \(\delta\) ppm.

Product (IV) obtained by the reaction of formamide showed the presence of NH, C=N and C=0 groups at 3400, 2210 and 1710 cm\(^{-1}\) respectively (spectrum no. 65). The PMR spectrum (spectrum no. 66) indicated the aromatic protons around 7.4-7.8 \(\delta\) ppm as multiplet whereas two singlets at 8.8 and 8.9 \(\delta\) ppm were assigned to C(2)-H of pyrimidine, -CHCN and -NH protons.

Reaction of 2-hydroxy-1-naphthaldehyde with ethyl cyanoacetate gave 2-amino-3-carbethoxy-4-(1-carbethoxy-1-nitrilomethyl)5,6-benzo,4[H]chromene (Ia). Condensation of (Ia) with urea afforded a product which was characterised as (IIa). This is supported by its IR spectrum (spectrum no. 67) which showed the absence of C=N. The three bands around
1730, 1700 and 1660 cm$^{-1}$ are due to carbonyl functions. The NH stretching band was observed around 3390 cm$^{-1}$. The PMR spectrum (spectrum no. 68) showed a three proton triplet at 1.4 $\delta$ppm and a quartet at 4.00 $\delta$ppm. A singlet at 8.3 $\delta$ppm was assigned to -CHCOOEt proton where as the two NH protons were observed as broad peaks around 8.2 and 8.8 $\delta$ppm. The six aromatic protons were observed as four doublets and two triplets. The skeletal structure of the benzochromene pyrimidines indicating the protons in aromatic region is shown in below fig.

The aromatic protons are assigned as follows.

<table>
<thead>
<tr>
<th>Proton</th>
<th>$\delta$ppm</th>
<th>Splitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_5$</td>
<td>7.95</td>
<td>Doublet</td>
</tr>
<tr>
<td>$H_6$</td>
<td>7.2</td>
<td>Triplet</td>
</tr>
<tr>
<td>$H_7$</td>
<td>7.3</td>
<td>Triplet</td>
</tr>
<tr>
<td>$H_8$</td>
<td>7.7</td>
<td>Doublet</td>
</tr>
<tr>
<td>$H_9$</td>
<td>7.6</td>
<td>Doublet</td>
</tr>
<tr>
<td>$H_{10}$</td>
<td>7.1</td>
<td>Doublet</td>
</tr>
</tbody>
</table>

Reaction of benzochromene (Ia) with thiourea gave a product which was assigned to the structure (IIla). The IR spectrum (spectrum no. 69) showed
a sharp band at 2200 cm\(^{-1}\) and the two bands around 1730 cm\(^{-1}\) and 1665 cm\(^{-1}\) are due to carbonyl groups. The NH stretching band was observed around 3385 cm\(^{-1}\). The PMR spectrum (spectrum no. 70) showed a triplet at 1.4 (CH\(_3\)) and a quartet at 4.3 (O-CH\(_2\)) indicating the presence of an ethoxy group. The aromatic pattern was consistent with the two triplet four doublet pattern observed in the case of (IIa). The two NH protons were observed at 8.9 and 9.4 \(\delta\text{ppm}\) respectively. The aromatic protons are assigned as follows:

<table>
<thead>
<tr>
<th>Proton</th>
<th>(\delta\text{ppm})</th>
<th>Splitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_5)</td>
<td>8.4</td>
<td>Doublet</td>
</tr>
<tr>
<td>H(_6)</td>
<td>7.8</td>
<td>Triplet</td>
</tr>
<tr>
<td>H(_7)</td>
<td>7.7</td>
<td>Triplet</td>
</tr>
<tr>
<td>H(_8)</td>
<td>8.2</td>
<td>Doublet</td>
</tr>
<tr>
<td>H(_9)</td>
<td>8.0</td>
<td>Doublet</td>
</tr>
<tr>
<td>H(_{10})</td>
<td>7.5</td>
<td>Doublet</td>
</tr>
</tbody>
</table>

Condensation of formamide with benzochromene ester (Ia) gave product (IVA) which is in agreement with earlier observed product (IV) in the case of chromene ester (I). In the IR spectrum the product (IVA) exhibited a band around 2210 cm\(^{-1}\) to C=N stretching. The band around 1705 cm\(^{-1}\) is due to C=O stretching and the NH stretching band was observed at 3370 cm\(^{-1}\). In the PMR spectrum (spectrum no. 71) the aromatic protons were observed in the range of 7.00 to 7.8 \(\delta\text{ppm}\). The two singlets around 8.2 and 8.6 \(\delta\text{ppm}\) were
assigned to =CHCN and C(2)-H of pyrimidine moiety. The aromatic protons are assigned as follows.

Chemical shifts

<table>
<thead>
<tr>
<th>Proton</th>
<th>δppm</th>
<th>Splitting</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₅</td>
<td>7.75</td>
<td>Doublet</td>
</tr>
<tr>
<td>H₆</td>
<td>7.2</td>
<td>Triplet</td>
</tr>
<tr>
<td>H₇</td>
<td>7.35</td>
<td>Triplet</td>
</tr>
<tr>
<td>H₈</td>
<td>7.65</td>
<td>Doublet</td>
</tr>
<tr>
<td>H₉</td>
<td>7.55</td>
<td>Doublet</td>
</tr>
<tr>
<td>H₁₀</td>
<td>7.00</td>
<td>Doublet</td>
</tr>
</tbody>
</table>

Formation of the exocyclic double bond in structures (II), (III), (IV), (IIIa) and (IVa) was also supported by the C≡N stretching which appeared around 2250cm⁻¹ in (I) where as in the condensation products the stretching frequency was reduced to 2200cm⁻¹ due to conjugation.
Spectrum No. 62
IR spectrum of compound (II).

Medium: KBr

Wave numbers (cm⁻¹)

Instrument: Perkin-Elmer IR spectrometer

Transmittance (%)
Spectrum No. 63

PMR spectrum of compound (II).

Solvent: DMSO-d6

§ (ppm)

Instrument Varian 300MHz NMR spectrometer

Spectrum No. 63
PMR spectrum of compound (II).
Solvent: DMSO-d6
§ (ppm)
Instrument Varian 300MHz NMR spectrometer
Spectrum No. 64

IR spectrum of compound (III).

Medium: KBr

Wave numbers (cm⁻¹)

Transmission (%)
Spectrum No. 65

IR spectrum of compound (IV).

Medium: KBr

Instrument: Perkin-Elmer IR spectrometer
Spectrum No. 66

PMR spectrum of compound (IV).

Solvent: DMSO-d$_6$

Instrument: Varian 300 MHz NMR spectrometer
Spectrum No. 67
IR spectrum of compound (IIa).

Medium: KBr
Instrument: Perkin-Elmer IR spectrometer
Spectrum No. 68

PMR spectrum of compound (IIa).

Solvent: CDCl₃ + DMSO-d₆

Instrument: Varian 300MHz NMR spectrometer
Spectrum No. 69
IR spectrum of compound (IIia).

Medium: KBr

Wave numbers (cm⁻¹)

Instrument: Perkin-Elmer IR spectrometer

Transmission (%)
Spectrum No. 70

PMR spectrum of compound (IIIa).

Solvent: CDCl₃ + DMSO-d₆

Instrument: Varian 300 MHz NMR spectrometer
Spectrum No. 71
PMR spectrum of compound (IVa).
Solvent: DMSO-d.
Instrument Varian 300MHz NMR spectrometer
EXPERIMENTAL:

This part deals with the preparation of starting compounds and synthesis of some new chromeno pyrimidines. Commercial samples of salicylaldehyde and 2-hydroxy-1-naphthaldehyde were used after purification.

1. 2-\textit{Amino}-3-carbethoxy-4-(1-carbethoxy-1-nitrilomethyl)-4[H]chromene (I).

Salicylaldehyde (5ml, 0.04M) and ethylcyano acetate (9ml, 0.08M) were taken in a conical flask. To this catalytic amount of piperidine was added and the reaction mixture was kept in ice chest for four hours. Solid separated was repeatedly washed with cold ethanol, filtered and crystallised from ethanol. (Yield 80%, M.P 142-3°C)

2. 2,4-Di hydroxy,5-(1-carbethoxy-1-nitrilomethylene) cromeno (2,3-d) pyrimidine. (II)

Chromene ester (I) (1gm, 0.003M) and urea (0.36gm ; 0.006M) were taken in a R.B flask and heated for four hours at 150-160°C in an oil bath. The reaction mixture was cooled and washed with water. The solid separated was filtered, dried and crystallised from DMF-water (Yield 75%, M.P 268°C, Mol.formula C_{16}H_{11}N_{3}O_{5}; Analysis (%) C : 60.01, H : 3.53, N:13.12; calcd C:59.07, H:3.38 N:12-92).

3. 2-Mercapto-4-hydroxy-5-(1-carbethoxy-1-nitrilomethylene)-chromeno(2,3-d)pyrimidine (III).

Chromene ester (I) (1gm ; 0.003M) and thiourea (0.45gm ; 0.006M) were taken in a R.B flask and heated for four hours at 150-160°C in an oil bath. The reaction mixture was cooled and washed with water. The solid separated was filtered, dried and crystallised from DMF-water (Yield 80%;
M.P. 273°C, Mol.formula C16H11N3O4S; Analysis (%) C: 56.82, H: 3.41, N: 12.52; calcd C: 56.30, H: 3.23 N: 12.31).

4. 4-Hydroxy-5-(1-nitrilomethylene)chromeno(2,3-d)pyrimidine (IV)

Chromene ester (I) (1g; 0.003M) and formamide (0.3ml; 0.006M) were taken in a R.B flask and heated for four hours at 150-160°C in an oil bath. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered, dried and crystallised from DMF-water (Yield 82%; M.P 263°C, Mol.formula C13H7N3O22; Analysis (%) C: 66.02, H: 3.12, N: 17.60; calcd C: 65.82, H: 2.95 N: 17.72).

5. 2-amino-3-carbethoxy-4-(1-carbethoxy-1-nitrilomethyl)5,6-benzo,4[H]chromene (Ia).

2-Hydroxy-1-naphthaldehyde (1g; 0.007M) and ethylcyanoacetate (1.6ml; 0.014M) were taken in a conical flask. To this, catalytic amount of piperidine was added and the reaction mixture was kept in an ice chest for four hours. Solid separated was repeatedly washed with cold ethanol, filtered and crystallised from ethanol (Yield 73%; M.P. 135°C).

6. 2,4-Dihydroxy-5-(1-carbethoxy methylene) 6,7-benzo- chromeno(2,3-d)pyrimidine (IIa).

Benzochromene ester (Ia) (1g; 0.0026M) and urea (0.31g; 0.0052M) were taken in a R.B flask and heated for four hours at 150-160°C in an oil bath. The reaction mixture was cooled and washed with water. The separated solid was filtered, dried and crystallised from ethanol (Yield 78%, M.P. 268°C, Mol.formula C19H14N2O5; Analysis (%) C: 64.89, H: 3.23 N: 7.68; calcd C: 65.14, H: 4.00 N: 8.00).
7. 2-Mercapto-4-hydroxy-5-(1-carbethoxy-1-nitrilomethylene) 6,7-benzo-chromeno(2,3-d)pyrimidine (IIIa).

Benzochromene ester (Ia) (1gm ; 0.0026M) and thiourea (0.4gm ; 0.0052M) were taken in a R.B flask and heated for four hours at 150-160°C in an oil bath. The reaction mixture was cooled and washed with water. The separated solid was filtered, dried and crystallised from ethanol (Yield 78%, M.P. 250°C, Mol.formula C$_{20}$H$_{13}$N$_{3}$O$_{4}$S; Analysis (%) C : 60.89, H : 3.52, N:10.05; calcd C:61.38, H:3.32 N:10.74).

8. 4-Hydroxy-5-(1-nitrilomethylene)6,7-benzo-chromeno(2,3-d)pyrimidine (IVa)

Benzochromene ester (Ia) (1gm ; 0.0026M) and formamide (0.234gm ; 0.0052M) were taken in a R.B flask and heated for four hours at 150-160°C in an oil bath. The reaction mixture was cooled and poured into the ice cold water. The separated solid was filtered, dried and crystallised from ethanol. (Yield 80%, M.P 256°C, Mol.formula C$_{17}$H$_{9}$N$_{3}$O$_{2}$; Analysis (%) C : 69.83, H : 3.02, N:14.50; calcd C:70.58, H:3.11, N:14.53).
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