Present Work-Results and Discussion
The present study represents a part of our continuing investigative efforts aimed at developing a newer and convenient routes to furo(2,3-b)quinoline, its sulphur, selenium, tellurium, aza analogues. As discussed in the previous chapter, 3-(2'-hydroxyethyl)-2-quinolones (7) provided a basis for the construction of furo-90-93, thieno-117, selenolo-119, tellurolo-122, and 1H-pyrrolo-124 (2,3-b)quinoline systems, as summarised in the Chart I. The production of this alcohol from the 2-quinolone-3-acetic acids is a facile process but the preparation of the quinolone acetic acids suffer from certain limitations as stated under 'Objective'.

![Chemical Structures]

It was felt that if an alternative method is available for arriving at the synthesis of the quinolonyl-
ethanol (7), its utility to the synthesis of furoquinoline and its analogues could become more expedient and widely general.

One such method, that occurred to us was to proceed through the anilide 75 and subject it to a proper synthetic manipulation so as to yield the alcohol 7. A report has appeared on the transformation of 75 to 7 by sulphuric acid treatment but it was not extended to its derivatives.

We envisioned that the treatment of the anilide (75) with a Lewis acid like anhydrous Aluminium chloride might bring about a ready ring closure via the Zwitter ion (100) as envisaged below, to give rise to 7, on acidification.
CH₃CO₂H

SOLVENT: CDCl₃
NMR: 50 MHz

Fig. 1
With this anticipation, we stirred a mixture of the anilide 75 and anhydrous AlCl₃ in dry CH₂Cl₂ solution and monitored the reaction by t.l.c., Complete disappearance of anilide was observed after a period of 7 hr. Acidification of the reaction mixture, with ice cold dil. Hydrochloric acid furnished a colourless solid melting at 156-197°C in 61% yield. The product was found to be identical in all respects (m.p., mixture m.p., superimposable I.R. curve (fig. 1) and H-n.m.r. curve (fig. 1)) with the authentic sample of 7. When the same reaction was tried with Boron trifluoride etherate the yield was slightly better (67%) but with other Lewis acids like FeCl₃, SbCl₅, and ZnCl₂ the yields were only 48%, 20% and 16% respectively.

The possibility that the anilide 75 might behave as a triene system and undergo ready photocyclisation, on irradiation, to furnish 102 which may then lead or be exploited to give the desired alcohol 7 also appeared attractive.
In this context a brief survey may be made of the photocyclisation reactions of triene systems which have been well documented in stilbenes$_{126-129}$, azo-benzenes$_{130,131}$, anilides$_{133}$, enamides$_{134,135}$, 4-phenyl-3-vinylquinolones$_{136}$ etc.,

1. Mallory and co-workers$_{126-129}$ studied the photolysis of stilbenes in presence of oxidants like $O_2, I_2^-$, etc.,
2. Badger and co-workers\textsuperscript{130,131} obtained benzo(c)cinnolines (106) from azobenzenes by photolysis in sulphuric acid medium.

\[
\text{N} \quad \text{N} \quad \xrightarrow{\text{h}_\gamma} \quad \text{N} \\
\text{105} \quad \text{106} \\
\text{H}_2\text{SO}_4
\]

3. Cava and Schlesinger\textsuperscript{132} reported on the oxidative photocyclisation of Schiff base (107) which lead to 108.

\[
\text{107} \quad \xrightarrow{\text{h}_\gamma, \text{O}_2} \quad \text{108}
\]

4. Shanmugam et al\textsuperscript{136} reported the photocyclisation of 4-phenyl-3-vinyl-2-quinolones (109) under oxidative as well as under non-oxidative conditions to give 6-oxo-5,6-dihydrobenzo(k)phenanthradines (110) and 6-oxo-5,6,7,8-tetrahydrobenzo(k)phenanthradines (111) respectively.
5. It has been reported from this laboratory that the photolysis of 3-styryl-2-quinolones (112) under oxidative and non-oxidative conditions yielded respectively (113) and (114).
6. Anilides of $\alpha, \beta$-unsaturated acids were photolysed to give 3,4-dihydrocarbostyrils (116)\(^{133}\).

7. Ninomiya et al\(^{140,141}\) irradiated $N$-cyclohexenoyl anilide (117) and observed a smooth cyclisation to a mixture of cis- and trans lactams (118). In a protic solvent (MeOH), the cis-lactam predominates while in an aprotic solvent the trans isomer is the main product.
8. Winterfeld and Aldtmann\textsuperscript{142} have reported on the photocyclisation of anilides of indole carboxylic acid like 119 and 120 to yield tetracycles like 121 and 122.

\[
\begin{align*}
119 & \xrightarrow{h\gamma} 121 \\
120 & \xrightarrow{h\gamma} 122
\end{align*}
\]

9. Kanaoka et al\textsuperscript{143-145} have extended the above photocyclisation reaction to furan and thiophene carboxylic acid anilides.

\[
\begin{align*}
123 & \xrightarrow{h\gamma} 124 \\
a) \ Y = O & \quad b) \ Y = S \\
124 & \quad a) \ Y = O & \quad b) \ Y = S
\end{align*}
\]
10. Ninomiya et al studied the photocyclisation of $\beta$-furoyl anilide (125) and obtained products as depicted below:

Besides the ready conrotatory ring closure expected in the photoreaction of 75 (Ref. page No. 43), we considered the feasibility that the photocyclised product 102 might undergo homolysis of the C-O bond to give rise to the diradical 129 followed by migration of the proximal cis hydrogen to give rise to quinolonylethanol (7) as depicted below.
With this anticipation we irradiated 75 in methanol using 253-7 nm lamp and monitored the reaction by t.l.c. Complete disappearance of the starting material was realised after irradiation for 25 hr. Evaporation of the solvent and purification of the residue over a column of silica gel furnished 7 identified in all aspects (m.p., mixture m.p., t.l.c., IR and $^1$H-n.m.r. spectra) with the authentic sample.92

In this context, it is considered relevant to give a brief survey of the reactions wherein such homolytic C-O bond fission, have been documented, for example, in ethers,147 lactones148, oxiranes149, oxetanes150, dioxan151 and several other heterocyclic systems including dihydrofurans152, benzofurans,153 oxepins156, etc.,. To quote a few...

1. In the photorearrangement of the furancompound (130), the reaction was postulated as proceeding
through the initial homolysis reaction to give the diradical (131)

2. Halovka et al. found the compound (132) to undergo an intriguing and interesting photoisomerisation combined with photo-degradation. The proposed mechanism proceeded via the diradical (134) formation in the initial step by the homolytic C-O bond fission.
3. The irradiation of dihydroflavone (138) has been reported to lead to a variety of products, presumably by an initial homolytic ring fission, as illustrated below: \(^1\)
4. The isomeric 4, 5-dihydro-oxepin (142) was found to yield three major aldehydic photo-products via the di-radical (143) as an intermediate.  

The following anilides were subjected to Lewis acid catalysed as well as photoinduced cyclisation, the yields of the alcohols are as tabulated below.

<table>
<thead>
<tr>
<th>Method A</th>
<th>Method B</th>
<th>Method C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AlCl₃)</td>
<td>(BF₃)</td>
<td>(hv)</td>
</tr>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>61</td>
<td>67</td>
<td>76</td>
</tr>
<tr>
<td>65</td>
<td>69</td>
<td>76</td>
</tr>
</tbody>
</table>
Since the photolytic method appeared to give a better yield of the alcohol, it was employed for the conversion of the other anilides as summarised in the Chart IV.
SOLVENT: CDCl₃
NMR: 60 MHz
Fig. 3

SOLVENT: CDCl₃ + DMSO-d₆

NMR: 60 MHz

ppm (6)
CHART - III

Starting compound

Product

Yield %

58
74.5
72
64.7
70
79
70
62

74.5
72
64.7
70
79
70
79
70
62
SOLVENT: CDC13
NMR: 90MHZ

COOCH3

N

ZO

CO

NH

H

0

H

COOCH3

SOLVE NT· CDC13
NMR: 90MHZ
It is pertinent to mention that the yield of the alcohol 7 from the anilide 75 is much greater than the overall yield of 7 from 2.

Eliminative photocyclisations involving ortho-substituents have been well documented in Stilbenes, Azo-benzenes, anilides, enamides, 4-phenyl-3-vinylquinolines etc., few examples.

1. Sargeant studied the photocyclisation of 2'-methoxy substituted stilbenes under non-oxidative conditions. The formation of (195) has apparently due to the elimination of elements of methanol in the photocyclisation.
2. Eliminative photocyclisation reactions in the case of 2-substituted azobenzenes were observed by Badger and co-workers.\textsuperscript{158}

\begin{equation}
\begin{aligned}
\text{197} & \overset{\text{h}^\lambda}{\longrightarrow} & \text{198} + \text{199}
\end{aligned}
\end{equation}

3. Kanaoka and Itoh\textsuperscript{159} have made an interesting observation in photolysing benzanilide \textsuperscript{200} which underwent an eliminative photocyclisation to yield phenanthridone (\textsuperscript{201}).

\begin{equation}
\begin{aligned}
\text{200} & \overset{\text{h}^\lambda}{\longrightarrow} & -\text{CH}_2\text{CH}
\end{aligned}
\end{equation}

4. Kessar\textsuperscript{161} has utilised eliminative photocyclisation of the ortho-bromo compound (\textsuperscript{202}) as a preliminary step in the preparation of benzo(c)phenanthridine alkaloids Nitidine and Avicine.
5. Shanmugam et al.\textsuperscript{162} have studied the irradiation of several 4-(2-substituted phenyl)-3-vinyl-quinolines (204) as well as o-substituted styrylquinolines (205) and have observed eliminative photocyclisations under non-oxidative conditions.

\[ X = \text{OCH}_3, \text{Cl} \]
\[ R = \text{OH, Cl} \]
Fig. 10

WAVE NUMBER (CM⁻¹)
Interestingly, in the photolysis of the ortho-substituted anilides, viz., 148-150, 153-159, 161 and 164 we did not observe any eliminative photocyclisation. The corresponding quinolone alcohols are obtained as the major product in all cases. With o-chloro anilide 149 photolysis was also done in the presence of few drops of \( \text{Et}_2\text{N} \) added to the solution, even then the eliminative cyclisation was not observed.

In the case of meta-substituted anilides, for eg. 165 the photocyclisation can be visualised to occur in two ways, that is to form 5- or 7- substituted quinolonyl-ethanols. With \( N-(3'\text{-methoxyphenyl})-4,5\text{-dihydrofuran-3-carboxanilide} \) 166 a mixture of two alcohols viz., 7-methoxy and 5-methoxy-2-quinolone-3-ethanols, resulted (191a) and (191b) as indicated by the NMR spectrum taken of the product. Efforts to separate the components either by fractional crystallisation or by column chromatography (silica gel) or by preparative t.l.c. were not successful. A similar situation prevailed in the case of isomeric quinolone alcohols derived from \( N-(3'\text{-chlorophenyl})-4,5\text{-dihydrofuran-3-carboxamide} \) (165) and \( N-(3'\text{-methylphenyl})-4,5\text{-dihydrofuran-3-carboxamide} \) (167).
Photolysis of the anilide 168 from 6-amino-coumarin gave a product, the I.R. spectrum of which revealed the presence of \(-\text{OH}(\gamma_{\text{max}} = 3450 \text{ cm}^{-1})\) and \(-\text{NH}_2\) (\(\gamma_{\text{max}} = 1640 \text{ cm}^{-1}\)) groups. Mass spectrum and elemental analysis showed the molecular formula to be \(C_{14}H_{11}O_4N\). So, the product was assigned the structure 193. The \(^1\text{H}-\text{n.m.r.}\) spectrum of the product could not be taken because of its poor solubility in usual spectral solvents.

The above structure for 193 was further attested by its conversion to a basic product upon treatment with PPA. I.R. (\(\gamma_{\text{max}} = 1720, 1645\) and \(1220 \text{ cm}^{-1}\)), Mass spectrum (\(M^+ = 239\)) and the elemental analysis confirmed the structure of the basic product to be 206. N.M.R. could not be taken due to its poor solubility.

The above system viz., 2,3-dihydrofuro(2,3-b)pyrano(5,6-f)quinoline is hitherto unknown.
CHART - V

Starting | Product | Yield %
---------|---------|--------
Br
H
O\(\text{OH}\)  | Br
N\(\text{O}\)
N\(\text{H}\)
O\(\text{OH}\)  | 75

Cl
O\(\text{CH}_3\)
O\(\text{CH}_3\)
| Cl
N\(\text{O}\)
N\(\text{H}\)
O\(\text{OH}\)  | 71.1

Cl
| Cl
N\(\text{O}\)
N\(\text{H}\)
O\(\text{OH}\)  | 90

Cl
| Cl
N\(\text{O}\)
N\(\text{H}\)
O\(\text{OH}\)  | 78

Cl
| Cl
N\(\text{O}\)
N\(\text{H}\)
O\(\text{OH}\)  | 72

Cl
| Cl
N\(\text{O}\)
N\(\text{H}\)
O\(\text{OH}\)  | 82
190a; $X = Cl, Y = H$
190b; $X = H, Y = Cl$

191a; $X = OMe, Y = H$
191b; $X = H, Y = OMe$

192a; $X = CH_3, Y = H$
192b; $X = H, Y = CH_3$

189
217
The anilide 164 from methyl anthranilate also readily underwent photocyclisation to give rise to alcohol(189).

The quinolonyl alcohols, thus prepared were cyclized with PPA to the corresponding 2,3-dihydrofuro(2,3-b) quinolines. In the case of carbomethoxy alcohol 189, the cyclisation was effected by treatment with p-toluene-sulphonyl chloride in pyridine. The hitherto unknown dihydrofuroquinolines are 203-213 and 217 (Chart V).

In the case of mixture of isomers 5-chloro- and 7-chloro-, and 5-methoxy- and 7-methoxy-, and 5-methyl and 7-methyl- dihydrofuroquinolines, only 7-substituted derivatives could be obtained in the pure state.

In the case of nitroanilides (218, 219 and 220) the photolysis, did not proceed to the appreciable extent. Prolonged treatment gave only tarry material.

Thieno(2,3-b)quinolines

Having obtained 3-quinolonyl-2-ethanols by the photolytic method, it was an easy matter for us to convert them by heating with P4S10 in pyridine into dihydrothieno-(2,3-b)quinolines. The overall yield of the dihydro-compound amounts to 60.8% which is higher than obtainable by the earlier two methods (A and B) reported from this laboratory.
It is thus evident that the above photolytic technique provides a neat entry in the thienoquinoline system also (Chart VI).

Overall yield: Method A: 22.6%
Method B: 17%

<table>
<thead>
<tr>
<th>Compound</th>
<th>R⁴</th>
<th>R⁵</th>
<th>R⁶</th>
<th>R⁷</th>
<th>R⁸</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>170</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>176</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>
The dihydro-thienoquinoline 13 has been converted into thieno(2,3-b)quinoline by Kuwayama et al. by treating it with perphthalic acid and then boiling the resulting s-oxide 14 with acetic anhydride. But in the S-oxide formation other products like S,S-dioxide, S,S,N-trioxide and N-oxide were also reported to be found.

It was felt that with the use of another oxidant the yield of the S-oxide could be enhanced. Of the various reagents known in the literature viz., nitric acid, hydrogen peroxides, dinitrogen tetroxide, chromic acid, ozone, peracids, hydroperoxides, manganese(II) dioxide, Iodobenzenedichloride, sodium metaperiodate, t-butylhypochlorite, Iodobenzenedichloride.
bromine\(^{177}\), 2,4,4,6-tetrabromocyclohexa-dienone\(^{178}\), ceric ammonium nitrate\(^{179}\), sulphuryl chloride\(^{180}\), chloramin-T,\(^{181}\) ruthenium tetroxide\(^{182}\), air, in the presence of vanadyl acetyl acetonate\(^{183}\), \(N\)-bromo-\(\varepsilon\)-caprolactam\(^{184}\) etc., we chose sodium metaperiodate for it has been reported\(^{185}\) to yield sulfoxides in high yields uncontaminated with by products like sulfones.

When \(13\) was stirred with an equivalent of NaIO\(_4\) in ethanol/water at ice-cold temperature, a colourless product was isolated in 82\% yield. It was identified to be the S-oxide \(14\) (M.P., N.M.R., I.R. and Mass spectrum). The experiment was repeated with two fold excess or more of the oxidant, only the S-oxide was found to be formed in 85-89\% yield.

The improvement thus effected in the yield of S-oxide formation was tested with a number of derivatives of \(13\).
Note: The $R^4$-substituted dihydrothieno(2,3-b) quinolines were prepared from the corresponding 3-(2'-hydroxy ethyl)-2-quinolones which in turn were obtained from 4-substituted-2-quinolone-3-acetic acids.
Kuwayama had used acetic anhydride for converting the S-oxide into the thienoquinoline. Though it gave a good yield (88%) of the thieno compound, yet we wanted to try other reagents for bringing the desired conversion. One such reagent we tried was POCl₃ in pyridine in the use of which we expected the following mechanistic outcome leading to 3.

When a mixture of 14, POCl₃ and pyridine was heated at reflux for 6 hours, the product on work up was found contain 3 as well as 13 in the yield ratio 67% : 17.4%. The acetic-anhydride procedure was indeed quite productive and the sulfoxides were dehydrated to the corresponding thieno(2,3-b)quinolines.
It is to be mentioned here that earlier workers from this laboratory found that 2,3-dihydro-5,3-dimethoxythieno-(2,3-b)quinoline (224) could not be converted into thienoquinoline (239) by NBS/DBU reaction;
Overall yields are denoted in the brackets

*
Overall yields are given for path I(*1) and path II(*2) below the final products.

Path I starts from N-phenylacetonamide.

Path II starts from N-aryl-4,5-dihydropyran-3-carboxamide.