CHAPTER 3

PHOTOCHEMISTRY OF
N-(2-FORMYL BENZOYL)-1,2,3,4- TETRAHYDROISOQUINOLINE
AND RELATED AMIDES
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N-(2-FORMYL BENZOYL)-1,2,3,4-TETRAHYDROISOQUINOLINE
AND RELATED AMIDES

Introduction: As already mentioned in preceding chapters the photochemistry of aldehydes and ketones has been extensively studied whereas the other carboxylic acid derivatives have received less attention. In aldehydes and ketones the replacement of a carbon, α to carbonyl function, by oxygen leads to the formation of esters. This results in a tremendous change in photochemistry of such compounds. Similar replacement of the α carbon with nitrogen gives amides which also show altered photochemical behaviour. Keeping in view our programme of studying photochemistry of nitrogen containing functional groups, some amides were investigated in the present work. Before describing this investigation a review of photoreactions of amides is appended here. Since the amides resemble esters in their reactions, the photochemistry of the latter is also mentioned briefly.

On irradiation esters undergo α and β-cleavage. The preferred course depends upon the factors of bond strength and stability of the radicals formed. α-Cleavage on
either side of the carbonyl group has been reported\textsuperscript{1} in case of saturated lactones.

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \]

\[ \text{1} \quad \text{2} \quad \text{3} \]

Photo-Fries rearrangement occurs in phenyl esters to give acetylated phenols. Flash photolysis studies\textsuperscript{2} on phenyl acetate (2) have revealed the intermediacy of phenoxy radicals and 2,4-cyclohexadienone intermediate in this reaction.

\[ \text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \]

\[ \text{2} \quad \text{3} \]

Esters also show inter and intramolecular hydrogen abstraction reactions, although these are not as extensive as in ketones and aldehydes. Photoreduction of 3 having electron
withdrawing groups in the aromatic ring has been reported\textsuperscript{3} to proceed by intermolecular hydrogen abstraction from toluene.

\[
\begin{align*}
\text{H}_3\text{COOC} & - \text{C-OC}_\text{H}_3 \\
+ \text{PhCH}_3 & \rightarrow \left( \begin{array}{c}
\text{H}_3\text{COOC} \text{C-OC}_\text{H}_3 \\
\text{PhCH}_2 \end{array} \right) \\
(26\%) \\
+ \\
\text{H}_3\text{COOC} & \text{C-OH} \\
\text{PhH}_2\text{C} & \text{C-CH}_2\text{Ph} \\
(40\%)
\end{align*}
\]

Intramolecular hydrogen abstraction by the ester carbonyl has been shown\textsuperscript{4} to give type-II elimination products in 4 with the cleavage occurring preferentially on the alcohol unit.

\[
\begin{align*}
\text{CH}_3\text{CO} & \text{O} \text{CH}_3 \\
\rightarrow \\
\text{H}_2\text{C} & \text{CHCH}_3 \\
(1\cdot0:0\cdot6) \\
\text{H}_2\text{C} & \text{=CH}_2 \\
+ \text{O} \text{CH}_3
\end{align*}
\]

Intramolecular hydrogen abstraction in ester 5 results in
photoenolization\textsuperscript{5} and the formed o-quinodimethane gets trapped with oxygen to finally give 6. It was also reported that deuterium incorporation occurs in the methyl group of 5 on irradiation in CD\textsubscript{3}OD. However, under similar conditions no deuterium uptake was noticed with 7.
Spangler et al. have reported the photoenolization of o-carboethoxybenzaldehyde (8) and trapping of the formed o-quinodimethane (9) with maleic anhydride to give adduct (10). In the absence of dienophile, cyclisation and dimerisation were noticed.

Like esters, amides also undergo α and β cleavage in the excited state. Simple amides have been shown to be either inactive photochemically or they undergo α cleavage of the (O=)C-N bond. Acetanalide on irradiation gave o- and p-acetylanilines along with aniline. The reaction is similar.
Hydrogen abstraction reactions in amides do not appear to be favoured and as such are not well documented. Some of the examples thought to involve hydrogen abstraction are discussed below. Irradiation of N-stearoylimidazole 11 gave\(^1\) the alkene 12 in 62\% yield. The reaction is said to
proceed by hydrogen abstraction from the acid chain to give the type-II elimination product. Irradiation\textsuperscript{11} of the 2-substituted pyridone 13 gave 14 as the major product and 15 as the minor product. The major product is thought to arise by $^\gamma$-hydrogen abstraction and subsequent cleavage. However, the other type-II product, the tetrahydropyridine (16), could not be detected. It is possible that the reaction involves a $\beta$-cleavage process which after radical reunion and hydrogen shift leads to 15.

Coyle and Kingston\textsuperscript{12} have reported that irradiation of N-alkylbenzamide 17 gave benzamide through $^\gamma$-hydrogen
abstraction. Quantum yield of the reaction was very low \( \phi, 0.0006 \) and appending a phenyl group in the alkyl chain (18) did not improve it. However, similar appendage of a dialkylamino group (19) led to considerable increase in quantum yield \( \phi, 0.053 \). An electron transfer mechanism was proposed for this reaction.

\[
\begin{align*}
\text{Ph-C-NHCH}_2\text{CH}_2\text{NR}_2 & \xrightarrow{hv} [19]^* \\
\text{Ph-C-NHCH}_2\text{CH}_2\text{NR}_2^+ & \xrightarrow{\text{OH}} \text{Ph-C=NH} + \text{H}_2\text{C=CHNR}_2 \\
\text{Ph-C-NH}_2 & \xrightarrow{\text{H}_2\text{C=CHNR}_2} \text{Ph-C-NH}_2
\end{align*}
\]
As compared to amides, hydrogen abstraction reactions in imides are relatively more pronounced. Some examples of this class are briefly mentioned below. Irradiation\textsuperscript{13} of phthalimide 20 in tert-butanol gave the cyclised product 21 which, on dehydration, led to 22.

\begin{center}
\begin{tikzpicture}

\node (A) at (0,0) {\includegraphics[height=1cm]{20.png}};
\node (B) at (2,0) {\includegraphics[height=1cm]{21.png}};
\node (C) at (4,0) {\includegraphics[height=1cm]{22.png}};
\draw[->] (A) -- (B) node[midway, above] {\text{hv}};
\draw[->] (B) -- (C) node[midway, above] {\text{t-BuOH}};
\end{tikzpicture}
\end{center}

Kanaoka et al.\textsuperscript{14} have reported the formation of 24 on irradiation of the N-\(\omega\)-arylalkylphthalimide 23. Charge transfer interaction between the aryl moiety and the phthalimide group was suggested to hold the molecule in a position favourable for cyclisation.
In another study, these workers have reported that irradiation of Mannich bases (25), with 'n' varying from 1 to 12, gives a variety of new ring systems (26).
Irradiation of bis(phthalimidomethyl)amine 27 has been reported\(^1\) to give the hexacyclic compound 28 in low yield.

Coyle et al.\(^1\) have used this type of photocyclisation to synthesise products like the protoberberine 30 from the imide 29.
Photolysis of ketoamides is known\textsuperscript{18,19} to give cyclised products through intramolecular hydrogen abstraction. Thus, irradiation of the $\alpha$-ketoamide 31 afforded the $\beta$-lactam
Similarly, the β-ketoamide 33 gave the γ-lactam 34 in 88% yield.\(^{19}\)

![Chemical structure of 33 and 34](image)

However, these transformations may be attributed to the ketonic rather than the amidic function.

From the above review of literature, it appears that hydrogen abstraction reaction in the excited states of amides is not efficient. No instances of hydrogen abstraction from an o-substituent in a simple aryl amide of the type 35 seem to have been reported.

![Chemical structure of 35](image)
Present work: Although amides do not exhibit efficient hydrogen abstraction in the excited state, presence of an additional carbonyl group, in α or β position, has been shown\textsuperscript{18,19} to alter this situation. It was, therefore, of interest to investigate the photochemistry of the amide 36 in which a carbonyl group is placed γ to the amidic function. The objective of this work was two fold:

1) To see if any intramolecular hydrogen abstraction is shown by the amide function in 36.

2) To investigate the alternate possibility of hydrogen abstraction, via an 8-membered ring transition state, by the aldehydic function of amide 36. If successful, the methodology could be used to synthesise tetracyclic structures characteristic of ophiocarpine type alkaloids (36 $\rightarrow$ 37 $\rightarrow$ 38). This approach looked promising on the
basis of a recent report\textsuperscript{20} on $\varepsilon$-hydrogen (8-membered ring) abstraction by the ketonic carbonyl in 39. It was envisaged that on irradiation abstraction of a benzylic hydrogen (C$_1$-H) by aldehydic carbonyl in 36 would give 1,6-biradical 40 which could cyclise to give 37.

The synthesis of the amide 36 was planned along the following route.
The starting o-formylbenzoic acid (41) was prepared from naphthalene according to the procedure of Gardner and Naylor. Its $^1$H NMR spectrum exhibited a one proton singlet at $\delta$ 5.25, another broad singlet at $\delta$ 6.6-7.0 for one proton and a four proton multiplet at $\delta$ 7.5-8.1 for aromatic protons. The IR spectrum showed an absorption band at 1740 cm$^{-1}$ (C=O). This data is in agreement with cyclic structure of 41. Treatment of the acid 41 with thionyl chloride gave the acid chloride 42 in 80% yield m.p. 53-54°. Its IR spectrum showed an absorption band at 1800 cm$^{-1}$.

$^1$H NMR spectrum exhibited a one proton singlet at $\delta$ 7.2 (Ph-CHCl) and a four proton multiplet at $\delta$ 7.6-8.2 for
aromatic protons. Treatment of the acid chloride 42 with tetrahydroisoquinoline (43) gave amide 36 as a solid, m.p. 105-107\(^\circ\), in 59% yield. Its IR spectrum showed absorption bands at 1698 cm\(^{-1}\) (aldehyde) and 1654 cm\(^{-1}\) (amide). \(^1\)H NMR spectrum exhibited two pairs of triplets corresponding to two protons each at \(\delta\) 2.8, 3.1 (Ph-CH\(_2\)-CH\(_2\)-N) and \(\delta\) 3.5, 4.2 (Ph-CH\(_2\)-CH\(_2\)-N), two singlets corresponding to two protons at \(\delta\) 4.4 and 5.05 (Ph-CH\(_2\)-N). The aromatic protons (8H) appeared at \(\delta\) 7.2-8.2 and the aldehydic proton showed up as a split singlet at \(\delta\) 10.15-10.3. The MS gave the \(M^+\) peak at m/z 265 and the base peak at m/z 133 (M'-132). The UV spectrum (MeOH) showed absorption bands at 285, 255 and 235 nm. The characteristic appearance of various groups of equivalent protons at different chemical shifts (e.g. two singlets for Ph-CH\(_2\)-N; split singlet of -CHO) in \(^1\)H NMR spectrum may be ascribed to two rotamers with slow interconversion by rotation around the amidic bond.
Irradiation of a solution of amide 36 (0.2g, 0.75 mmol) in benzene (80 mL) for 2 h led to the complete disappearance of starting material. Removal of the solvent and crystallization of the residue from ethanol gave a solid, m.p. 177-78°, in 95% yield. Its $^1$H NMR spectrum exhibited a four proton multiplet at δ 2.8-3.25, a two proton singlet at δ 3.95, a one proton singlet at δ 6.5 and an eight proton multiplet at δ 7.2-8.2 (aromatic). MS gave peaks at m/z 265 (M$^+$) and 221 (M$^+$-44, base). The other prominent peaks were at m/z 133 and 132. IR spectrum showed an absorption band at 1742 cm$^{-1}$. On the basis of above spectral data, structure 44 was assigned to the photoproduct. This structure was confirmed by TLC, Co-TLC analysis and superimposable spectral data with an authentic sample of 44, prepared by thermal condensation of tetrahydroisoquinoline (43) and the ester obtained from 42.
The structure of lactone 44 was further supported by its chemical degradation to tetrahydroisoquinoline (43).

The smooth transformation of 36 to 44 may be postulated to take place through the intermediacy of 46 as shown below. It is interesting to note that the aldehydic hydrogen is being abstracted by the amidic carbonyl through a
6-membered transition state. The observation is noteworthy because, as mentioned in the introduction, such hydrogen abstraction by the excited state of amidic carbonyl group does not seem to have been observed earlier. It was, therefore, decided to investigate the synthetic scope, limitations and mechanism of the reaction.

It was argued that lactone 44 on reaction with a suitable anion may lead to the formation of a spiro system 47.

![Reaction Scheme](image)

To test this hypothesis it was planned to treat the lactone 44 with anion 48 which could be obtained from amine 49 using the BF$_3$ complexation methodology for generation of $\alpha$-azacarbanions. The amine 49 was prepared by the following known route.
Treatment of amine 49 (0.43 mmol) with BF$_3$.Et$_2$O (0.45 mmol) in THF at -20° followed by addition of sec-butyllithium (2.2M, 0.52 mmol) at -78° gave a deep red solution. This was quenched with a solution of lactone 44 (0.43 mmol) in THF. The reaction mixture after basic workup followed by purification using centrifugal chromatography gave the spirocompound 51 in 25% yield, m.p. 159-61°. Its
\(^1\text{H} \text{ NMR} \) spectrum exhibited a three proton singlet at \(\delta \) 2.4 (N-CH\(_3\)), a broad singlet equivalent to three protons at \(\delta \) 2.72 for Ph-CH\(_2\)-CH\(_2\)-N and -OH (D\(_2\)O exchangeable), and a three proton singlet at \(\delta \) 3.6 for a methoxy group. The other methoxy and the methylene (Ph-CH\(_2\)-CH\(_2\)-N) protons appeared together as a multiplet (5H) at \(\delta \) 3.86. The Ph-CH-OH proton showed up as a singlet at \(\delta \) 5.29. The six aromatic protons showed up differently at \(\delta \) 6.19 (singlet, C\(_1\)-H), 6.66 (singlet, C\(_4\)-H) and as a multiplet at \(\delta \) 7.4-8.1 (4H). The Mass spectrum gave the M\(^+\) ion as a base peak at m/z 339 and other prominent peaks at m/z 324, 206 and 204. The IR spectrum displayed absorption bands at 1704 cm\(^{-1}\) (carbonyl) and 3406 cm\(^{-1}\) (hydroxyl).

The facile transformation of substrate 44 into the spiro system is proposed to take place by the following reaction mechanism.
No effort was made to maximise the yield or to synthesise the actual alkaloids since this was not the main objective of the present investigations. However, it may be noted that this methodology may also be applicable for the synthesis of fredericamycin A (52) which contains such a spiro system and is a potent anticancer drug\(^2\). Reaction of an indanyl anion (53) with substrate 44 should give the spiro compound 54 which has the necessary basic spiro skeleton of fredericamycin.
To explore the generality of the photocyclisation of aldehydic amides, 55 was synthesised by the condensation of diethylamine and acid chloride 42 in 50% yield. Its $^1$H NMR
spectrum exhibited two triplets of three protons each at δ 1.00 and 1.30 (2x -CH₃), two quartets of two protons each at δ 3.15 and 3.6 (2x -CH₂-), a multiplet for four aromatic protons at δ 7.3-8.1 and a downfield singlet for the aldehydic proton at δ 10.2.

Irradiation of the amide 55 (0.29g, 1.42 mmol) in benzene (45 mL) for 2 h gave the lactone 56, as an oil, in quantitative yield. Its ¹H NMR spectrum showed a six proton multiplet at δ 1.2 (2x -CH₃), a four proton multiplet at δ 3.0 (2x -CH₂-), a singlet at δ 6.5 (1H, Ph-CH< ) and a four proton multiplet at δ 7.3-8.2 (aromatic). It should be noted that in 55 γ hydrogen is available on the N-alkyl as well as the aldehydic carbon, but the latter seems to get abstracted preferentially in the excited state.

To study the reaction in secondary amides, amide 57 was synthesised. The treatment of n-butylamine with acid
chloride 42, followed by purification with elution chromatography gave an oil in 17% yield. Its $^1$H NMR spectrum exhibited a three proton multiplet at $\delta$ 1.0 (-CH$_3$), two multiplets equivalent to two protons each at $\delta$ 1.5 and 2.2 (N-CH$_2$-CH$_2$-CH$_2$-CH$_3$), two multiplets of one proton each at $\delta$ 3.2 and 3.9 (>N-CH$_2$-), one proton singlet at $\delta$ 5.45 and another one proton broad singlet at $\delta$ 1.9 (D$_2$O exchangeable). The four aromatic protons appeared at $\delta$ 7.35-8.0. MS gave the M' peak at m/z 205 and other prominent peaks at m/z 204 (M' -1), 188 (M' -17) and 133 (base). On the basis of above spectral data structure 58 was assigned to this compound. The formation of 58 can occur from 57 in the following manner.
A solution of this amide (0.08g, 0.39 mmol) in benzene (45 mL) was irradiated and the course of reaction was followed by TLC analysis. It indicated no change in starting material at different intervals of time and even after 3 h. The result is not unexpected if the equilibrium lies almost entirely in favour of the cyclic compound 58.

Some work was then undertaken to ascertain the postulated intermediacy of the o-quinodimethane 46. Similar
o-quinodimethane intermediates have been reported in photolysis of o-phthalaldehyde (59) and these could be trapped with maleic anhydride to give 61. A solution of amide 36 (0.1g, 0.38 mmol) in benzene (80 mL) containing maleic anhydride (0.1g, 1.0 mmol) was irradiated for 140 min. TLC analysis as well as $^1$H NMR spectrum of the mixture indicated the presence of lactone 44 as the major product ($\approx 75\%$) and there was no evidence of adduct formation. After the failure of intermolecular trapping of o-quinodimethane 46 its intramolecular trapping was attempted. For this purpose the
substrate 62 having dienophile as part of the molecule was synthesised by the reaction of styryl amine 63 with acid chloride 42. It is interesting to note that if successful, this reaction could open up a facile route to ring C oxygenated benzo[C]phenanthridine alkaloids (64).
The styryl amine 63 required for the purpose was synthesised by the following route.

\[
\begin{align*}
\text{3,4-dihydroisoquinoline} & \rightarrow \text{3-vinylbenzaldehyde (65)} \\
\text{65} & \rightarrow \text{N-methyl-2-vinylbenzylamine (63)}
\end{align*}
\]

Treatment of 3,4-dihydroisoquinoline with dimethyl sulphate and NaOH at 110-120° afforded the known\textsuperscript{27} 2-vinylbenzaldehyde (65) in 80% yield (Lit\textsuperscript{27} yield 60%). Its \textsuperscript{1}H NMR spectrum exhibited a two proton multiplet at δ 5.2-5.9 (-CH=CH\textsubscript{2}), a five proton multiplet at δ 7.2-8.1 (-CH=CH\textsubscript{2}; 4H, aromatic) and a one proton singlet at δ 10.4 (CHO). The aldehyde 65 on treatment with methylamine in ethanol, followed by reduction with sodium borohydride furnished N-methyl-2-vinylbenzylamine (63) in 68% overall yield. Its \textsuperscript{1}H NMR spectrum showed a broad singlet at δ 1.0 (1H, >NH), a three proton singlet at δ 2.47 (N-CH\textsubscript{3}), a two
proton singlet at δ 3.76 (Ph-CH$_2$-N), a two proton multiplet at δ 5.26-5.77 (-CH=CH$_2$) and a five proton multiplet at δ 7.0-7.6 (1H, -CH=CH$_2$; 4H, aromatic).

Synthesis of amide 62 was accomplished by condensation of amine 63 with acid chloride 42 in 60% yield. Its $^1$H NMR spectrum exhibited a pair of singlets at δ 2.6 and 3.03 corresponding to three protons (N-CH$_3$), a pair of singlets at δ 4.4 and 4.9 corresponding to two proton (Ph-CH$_2$-N), a two proton multiplet at δ 5.3-5.9 (-CH=CH$_2$), a nine proton multiplet at δ 7.4-8.1 (1H, -CH=CH$_2$; 8H, aromatic) and a downfield singlet at δ 10.2 (CHO). Its UV spectrum (MeOH) showed absorption maxima at 255, 285 and 295 nm. MS gave the M' peak at m/z 279 and the base peak at m/z 105. Other prominent peaks were seen at m/z 162 and 133.

Irradiation of a solution of amide 62 (0.14g, 0.5 mmol) in benzene (45 mL) for 2.25 h showed complete disappearance of the starting material. The formation of one major product along with some minor products was evident from TLC analysis. Removal of the solvent followed by purification of the residue through elution chromatography furnished an oil in 43% yield. Its $^1$H NMR spectrum showed a three proton singlet at δ 2.23 (N-CH$_3$), two doublets corresponding to two
protons at \( \delta 3.86-4.2 \) (Ph-CH\(_2\)-N), a two proton multiplet at \( \delta 5.33-5.9 \) (\(-\text{CH} = \text{CH}_2\)), a one proton singlet at \( \delta 6.2 \) (Ph-CH\(<\)) and a nine proton multiplet at \( \delta 7.13-8.1 \) (1H, \(-\text{CH} = \text{CH}_2\); 8H, aromatic). MS gave the M\(^+\) peak at m/z 279 and other prominent peaks at m/z 235 (M\(^+\)-44), 133 and 105 (base). The above spectral data is in agreement with structure 67. The formation of lactone under the conditions suitable for intramolecular trapping of the o-quinodimethane suggests that either this intermediate is not formed or its lactonisation is faster than reaction with the dienophile.

It is interesting to note that Scaiano et al.\(^{28}\) have proposed that photoconversion of phthalaldehyde (59) to phthalide (69) occurs through the intermediate 68 and not through the quinodimethane 60. This pathway was found to be independent of the other process which involves the triplet...
excited state reverting back to 59 via the biradical 71 and the stereoisomeric enol(s) 60.
Using laser flash photolysis techniques these workers have shown that the yield of 68, and the photoproducts, is not affected by the presence of triplet quenchers. Therefore, they exclude the involvement of any triplet precursors in the generation of 68 which has been proposed to arise by a concerted mechanism. Further, the intermediate 68 could be scavenged by TFA, 2,5-dimethylhexa-2,4-diene and dimethyl acetylenedicarboxylate whereas maleic anhydride failed to produce the desired effect.

It is possible that a similar intermediate 72 may be involved in the photoconversion of 36 to 44. The failure of maleic anhydride to give any adduct on irradiation with 36 and the negative results in intramolecular trapping support this view.
Reverting back to the objective of hydrogen abstraction through an eight membered ring, photochemistry of the ketoamide 73 was investigated. It was hoped that in the absence of aldehydic proton, abstraction from position 1 of isoquinoline may occur to give the tetracyclic compound 74.

Amide 73 was synthesised according to the following route.

Acid 75 was prepared by treatment of phthalic anhydride with malonic acid in 14% yield, m.p. 118° (CH₂Cl₂) (Lit²⁹ m.p. 114-115°). Its ¹H NMR spectrum exhibited a three proton singlet at δ 2.05 (CH₃), one proton singlet at δ 4.85 (D₂O exchangeable, -OH) and a four proton multiplet at δ 7.5-8.1
(aromatic). MS gave the M+ peak at m/z 164 and other prominent peaks at m/z 149 (M+ -15), 147 (M+ -17) and 120 (M+ -44). This data indicated that acid 75 exists in cyclic form. Treatment of 75 with thionyl chloride furnished 76 in 84% yield. Its IR spectrum showed an absorption band at 1790 cm⁻¹ (C=O). ¹H NMR spectrum exhibited two singlets at δ 1.9 and 3.1 corresponding to three protons (-CH₃) and a multiplet at δ 7.4-8.1 for four aromatic protons. The above spectral data indicates that the acid chloride 76 exists in both forms, open and cyclic. Condensation of 76 with amine 43 gave the amide 73 in 38% yield, m.p. 113-115° (EtOH). Its IR spectrum showed absorption bands at 1690 cm⁻¹ (ketone) and
1640 cm\(^{-1}\) (amide). \(^1\)H NMR spectrum exhibited a three proton multiplet at \(\delta\) 2.6 (-CH\(_3\)), two pairs of triplets corresponding to two protons each at \(\delta\) 2.8, 3.05 (Ph-CH\(_2\)-CH\(_2\)-N) and \(\delta\) 3.45, 4.1 (Ph-CH\(_2\)-CH\(_2\)-N), a pair of singlets corresponding to two protons at \(\delta\) 4.35, 5.00 (Ph-CH\(_2\)-N) and an eight proton multiplet at \(\delta\) 6.8-8.00 (aromatic). MS exhibited the M\(^+\) peak at m/z 279 and other prominent peaks at m/z 147 (M\(^+\)-132, base) and 132 (M\(^+\)-147). The foregoing \(^1\)H NMR spectral data suggests the presence of two rotamers of 73.

\[ \text{73} \]

A solution of amide 73 (0.1g, 0.36 mmol) was irradiated in benzene (45 mL) for 8 h. The TLC analysis indicated the presence of two new spots other than the starting amide. The solvent was removed and the residue triturated with ether. A polymeric solid (15mg) separated out which was filtered off. Evaporation of the filtrate
furnished an oil (80mg) which was subjected to preparative TLC. The band at Rf 0.8 was isolated as an oil (16mg). Its 
$^1$H NMR spectrum exhibited a three proton doublet at $\delta$ 1.65, a 
one proton quartet at $\delta$ 5.8 and a four proton multiplet 
at $\delta$ 7.4-8.1. On the basis of the spectral data this compound 
was identified as 2-methylphthalide (77). The structure was 

![Chemical Structure](image)

further supported by TLC and Co-TLC comparison with an 
authentic sample prepared by treating acid 75 with sodium 
borohydride.

![Chemical Reaction](image)

The second band, Rf 0.65, from preparative TLC 
afforded a solid (20mg) which was identified as unreacted 
amide 73 by mixture m.p. and $^1$H NMR data. The third
component, isolated as an oil (8mg) from the band at Rf 0.5, was found to be 3,4-dihydroisoquinoline (78) by TLC and Co-TLC comparison with an authentic sample.

Formation of phthalide 77 and imine 78 on irradiation of amide 73 may be rationalised in the following manner.

$$\begin{align*}
73 & \xrightarrow{\text{hv}} 79 & \xrightarrow{} 78 + 80 \\
77 & \xrightarrow{} 82 & \xrightarrow{} 81
\end{align*}$$

It seems that the envisaged hydrogen abstraction through 8-membered ring transition state is taking place to give the
biradical 79. At this stage radical coupling would have generated the expected cyclic product 74. However, the biradical 79 gets cleaved, in Norrish type-II manner, to o-quinodimethane 81 and imine 78. An alternate reaction path\textsuperscript{30} envisages $\alpha$-cleavage as the first step as shown below.

These results may be compared with an earlier study on $\alpha$-ketoamides (83) carried out in this laboratory.\textsuperscript{31} The formation of 84 has been explained as shown below.
In an alternate thermal approach for the synthesis of the tetracyclic skeleton 37, it was envisaged that a base might pick up a proton from position-1 and the generated anion may cyclise to give the desired product. In the event, treatment of the amide 36 (0.87 mmol) with LDA (2.6 mmol)
followed by work up indicated the formation of a complex mixture of products (TLC). In view of the close Rf values of various components in this mixture separation was not attempted.

The studies in this chapter show that amides in the excited state can abstract hydrogen from a suitably placed formyl group as in 36. Abstraction of aldehydic hydrogen is, in fact, preferred over that of other γ-hydrogens available in the molecule. Further, if the aldehydic hydrogen is replaced by a methyl group, (73), the course of the photoreaction is governed by the ketonic chromophore rather than the amidic function. In this situation hydrogen abstraction through an 8-membered ring probably takes place but it does not lead to cyclohexanol formation due to rapid Norrish type-II cleavage.
EXPERIMENTAL
AND
REFERENCES
2-Formylbenzoic acid (41):

A 500 mL two necked round bottom flask fitted with a reflux condenser, an addition funnel and magnetic stirring bar was charged with sodium hydroxide solution (95 mL, 0.5N) and naphthalene (6.0g, 47 mmol). The mixture was heated to boiling and hot KMnO₄ solution (40.0g, 250 mmol in 280 mL water) was added in portions over a period of 1.5 h with vigorous stirring. During the addition of KMnO₄ solution external heating was slowed. Occasionally steam was passed through the condenser jacket to return the sublimed naphthalene to reaction flask. After the last addition of KMnO₄ solution the mixture was boiled for additional 45 min. To reduce the unchanged permanganate, alcohol (3.5 mL) was added and the reaction mixture was cooled and filtered. The filtrate was acidified with HCl (27 mL) concentrated to one fifth of its original volume, cooled and filtered. The filtrate was neutralized with sodium hydroxide solution (20%) and NaHSO₃ (9.37g, 90 mmol) was added. The mixture was evaporated to dryness on a steam bath. The residue was stirred with HCl (25 mL) and evaporated to dryness. The treatment with HCl followed by evaporation was repeated twice. The residue was thoroughly extracted with benzene and
the extract was evaporated to dryness. The solid was crystallised from hot water, m.p. 95-97° (Lit21 m.p. 96-96.5°), yield 2.94g, 42%; 'H NMR (CDCl₃): δ 5.25 (s, 1H, Ph-CH<), 6.6-7.0 (bs, 1H, -OH), 7.5-8.1 (m, 4H, ArH); IR (Nujol): 1740 cm⁻¹ (C=O).

2-Formylbenzoyl chloride (42):

A solution of 2-formylbenzoic acid (41) (0.8g, 5.33 mmol) and thionyl chloride (10 mL) was refluxed for 4 h. Excess of reagent was distilled off to give an oil which solidified on standing, m.p. 53-54°, yield 0.72g (80%), 'H NMR (CDCl₃): δ 7.2 (s, 1H, Ph-CH<), 7.6-8.2 (m, 4H, ArH); IR (Nujol): 1800 cm⁻¹ (C=O).

1,2,3,4-Tetrahydroisoquinoline (43):

This was prepared from 3,4-dihydroisoquinoline by reduction with NaBH₄ in methanol. Yield 80%, b.p. 100-105°/5 mm.

N-(2-formylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (36):

To a stirred solution of acid chloride (42) (0.75g, 4.45 mmol) in benzene (5 mL) at room temperature was added
dropwise a solution of 1,2,3,4-tetrahydroisoquinoline (43) (0.6 g, 4.5 mmol) and pyridine (0.36 g, 4.5 mmol) in benzene (95 mL). After the addition was complete, the reaction mixture was stirred for 12 h. The solid (pyridinium chloride) separated was removed by filtration and the filtrate was treated with sodium hydroxide solution (20%) and HCl (20%). This was washed with water and dried. Evaporation of solvent gave a solid (0.7 g, 59%), m.p. 105-107°. IR (Nujol): 1698 cm⁻¹ (aldehyde), 1654 cm⁻¹ (amide); ¹H NMR (CDCl₃): δ 2.8, 3.1 (triplets, 2H, Ph-CH₂-CH₂-N), 3.5, 4.2 (triplets, 2H, Ph-CH₂-CH₂-N), 4.4, 5.05 (singlets, 2H, Ph-CH₂-N), 7.2-8.2 (m, 8H, ArH), 10.15-10.3 (split s, 1H, CHO); Mass spectrum (70 eV) m/z (rel. intensity): 265 (1, M⁺), 264 (4), 133 (100, base peak), 132 (17); UV (MeOH): 285, 255, 235 nm. Anal. Calcd for C₁₇H₁₃NO₂: C, 76.98; H, 5.66; N, 5.28. Found: C, 76.74; H, 5.74; N, 5.3.

Irradiation of N-(2-formylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (36):

A solution of amide 36 (0.2 g, 0.75 mmol) in dry benzene (80 mL) was irradiated with pyrex filtered light from 125W lamp for 2 h. The solvent was removed under reduced
pressure to give a solid which was crystallised from ethanol, yield 0.19g, 95%, m.p. 177-78°. IR (Nujol): 1742 cm⁻¹; ¹H NMR (CDCl₃): 5 2.8-3.25 (m, 4H, Ph-CH₂-CH₂-N), 3.95 (s, 2H, Ph-CH₂-N) 6.5 (s, 1H, Ph-CH<), 7.2-8.2 (m, 8H, ArH); Mass spectrum (70 eV) m/z (rel. intensity): 265 (22, M⁺), 264 (8), 221 (100, base peak), 133 (51), 132 (42). High-resolution MS (70 eV): m/z 265.1096 (M⁺); Calcd for C₁₇H₁₅NO₂ 265.1103.

Ethyl-2-formylbenzoate:

A mixture of acid chloride 42 (0.3g, 1.8 mmol), absolute ethanol (10 mL) and pyridine (0.25g, 3.2 mmol) was refluxed on a steam bath for 8 h. Excess of ethanol was removed by distillation, the residue taken in water and extracted with ether. Ether extract was dried and the solvent was evaporated to give an oily residue (0.3g, 94%).

Thermal synthesis of 3-[2-(1,2,3,4-tetrahydroisoquinolyl)] phthalide (44):

To a solution of above ester (288mg, 1.62 mmol) in benzene (5 mL) was added amine 43 (215mg, 1.62 mmol) and the mixture was heated under reflux for 10 h. Benzene was
evaporated to give a solid which was crystallised from ethanol to afford 44, (60mg, 14%), m.p. 179°. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.8-3.2 (m, 4H, Ph-CH\(_2\)-CH\(_2\)-N), 4.0 (s, 2H, Ph-CH\(_2\)-N), 6.6 (s, 1H, Ph-CH\(_2\)), 7.2-8.2 (m, 8H, ArH).

**Hydrolysis of 3-[2-(1,2,3,4-tetrahydroisoquinolyl)] phthalide (44):**

To a solution of lactone 44 (50mg, 0.19 mmol) in glacial acetic acid (0.5 mL) was added hydrochloric acid (1.5 mL, 40%) and the mixture was kept at room temperature for 60 h. It was neutralised with solid sodium bicarbonate and extracted with ether. The ether layer was washed with water, dried and evaporated to give an oil (15mg, 60%). The TLC and Co-TLC analysis showed it to be identical with an authentic sample of 1,2,3,4-tetrahydroisoquinoline. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.6 (s, 1H, NH), 2.75 (t, 2H, Ph-CH\(_2\)-CH\(_2\)-N), 3.15 (t, 2H, Ph-CH\(_2\)-CH\(_2\)-N), 4.00 (s, 2H, Ph-CH\(_2\)-N), 6.9-7.25 (m, 4H, ArH).

**6,7-Dimethoxy-3,4-dihydroisoquinoline:**

It was prepared from homoveratryl amine in 85% yield, b.p. 161°/2 mm (Lit\(^2\) b.p. 155-160°/1 mm).
6,7-Dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide:

It was prepared from 6,7-dimethoxy-3,4-dihydroisoquinoline and methyl iodide by standard procedure in 70% yield, m.p. 201-202°.

6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (49):

It was prepared from 6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium iodide by reduction with sodium borohydride according to the known procedure in 79% yield, m.p. 77-78°. (Lit m.p. 65°).

2,3-Dimethoxy-8-hydroxyochotensone-13 (51):

To a stirred solution of amine 49 (90mg, 0.43 mmol) in THF (2.5 mL) was added BF₃.Et₂O (0.06 mL, 0.45 mmol) at -20° and the contents were stirred for 10 min. The temperature was then lowered to -78° and sec-butyllithium in n-pentane (2.2M, 0.22 mL, 0.52 mmol) was added. A deep red solution was obtained which was stirred for 1 h at -78°. The reaction mixture was quenched with lactone 44 (115mg, 0.43 mmol) in THF (1.5 mL) and the temperature was raised gradually to 0° in 1 h. The contents were stirred at 0° for 30 min. After this HCl 5% (5 mL) was added and reaction
mixture washed with ether to remove non-basic material. It was then basified with solid NaHCO₃ and again extracted with ether. The organic layer was dried and evaporated to give a solid residue (100mg). This was purified by centrifugal chromatography (ethyl acetate-methanol, 3:1) to give 51 (37mg, 25%); m.p. 159-161°C. IR (Nujol): 1704 cm⁻¹ (C=O), 3406 cm⁻¹ (-OH); ¹H NMR (CDCl₃): δ 2.4 (s, 3H, N-CH₃), 2.72 (bs, 3H, Ph-CH₂-CH₂-N and -OH, exchangeable), 3.6 (s, 3H, -OCH₃), 3.86 (m, 5H, -OCH₃ and Ph-CH₂-CH₂-N), 5.29 (s, 1H, Ph-CH-OH), 6.19 (s, 1H, C₁-H, ArH), 6.66 (s, 1H, C₄-H, ArH), 7.4-8.1 (m, 4H, ArH); Mass spectrum (70 eV) m/z (rel. intensity): 339 (100, M⁺), 324 (22), 206 (26), 204 (61); High-resolution MS (70 eV): m/z 339.1461 (M⁺); Calcd for C₂₀H₂₁NO₂ 339.1470.

N,N-diethyl-2-formylbenzamide (55):

To a stirred solution of acid chloride 42 (500mg, 3.0 mmol) in dry benzene (5 mL) was added dropwise diethylamine (220mg, 3.0 mmol) and pyridine (240mg, 3.0 mmol) in dry benzene (5 mL). After complete addition the reaction mixture was stirred for 12 h. The separated pyridinium chloride was removed by filtration and the benzene layer successively treated with NaOH (20%), HCl (20%) and brine.
After evaporation of the solvent amide 55 was obtained as a liquid (300mg, 50%). $^1$H NMR (CDCl$_3$): $\delta$ 1.0 (t, 3H, -CH$_2$-CH$_3$), 1.3 (t, 3H, -CH$_2$-CH$_3$), 3.15 (q, 2H, -CH$_2$-CH$_3$), 3.6 (q, 2H, -CH$_2$-CH$_3$), 7.3-8.1 (m, 4H, ArH), 10.2 (s, 1H, CHO).

Irradiation of N,N-diethyl-2-formylbenzamide (55):
A solution of amide 55 (290mg, 1.42 mmol) in dry benzene (45 mL) was irradiated with pyrex filtered light from a 125W lamp for 2 h. Removal of the solvent under reduced pressure gave an oil (280mg, 96.5%). $^1$H NMR (CDCl$_3$): $\delta$ 1.2 (m, 6H, 2x -CH$_2$-CH$_3$), 3.0 (m, 4H, 2x -CH$_2$-CH$_3$), 6.5 (s, 1H, Ph-CH<), 7.3-8.2 (m, 4H, ArH).

n-Butyl-2-formylbenzamide (57):
Acid chloride 42 (500mg, 3.0 mmol) and n-butylamine (740mg, 10 mmol) were taken in benzene (10 mL) and the mixture was refluxed for 6 h. Water was added to the reaction mixture and the benzene layer was separated. It was treated with NaOH (20%) and HCl (20%) and washed with brine. Evaporation of benzene gave an oily residue which was purified by column chromatography on silica gel using gradient elution with petroleum ether-ether as eluant to give
amide 57 (100mg, 17%) as a liquid. $^1$H NMR (CDCl$_3$): $\delta$ 1.0 (m, 3H, $-\text{CH}_3$), 1.5 (m, 2H, $-\text{CH}_2-\text{CH}_3$), 1.9 (bs, 1H, exchangeable, $-\text{OH}$), 2.2 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$), 3.2 $\delta$ 3.9 (m, 1H each, $\text{N-CHH-C}_3\text{H}_7$), 5.45 (s, 1H, Ph-$\text{CH}<$), 7.35-8.0 (m, 4H, ArH); Mass spectrum (70 eV) m/z (rel. intensity): 205 (12, M'), 204 (41), 188 (66), 133 (100, base peak).

Irradiation of n-Butyl-2-formylbenzamide (57):

Amide 57 (80mg, 0.39 mmol) in dry benzene (45 mL) was irradiated with pyrex filtered light from a 125W lamp. TLC analysis after 1 h, 2.5 h and 3 h of irradiation indicated only unreacted starting material. The irradiation was then discontinued.

Irradiation of N-(2-formylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (36) in presence of maleic anhydride:

A solution of amide 36 (100mg, 0.38 mmol) and maleic anhydride (100mg, 1.0 mmol) in dry benzene (80 mL) was irradiated with pyrex filtered light from 125W lamp for 2 h and 20 min. A solid separated in the vessel was removed by filtration (10mg), m.p. 165°(dec.). From the filtrate benzene was removed under reduced pressure and the residue was
taken in ether. Its TLC analysis indicated the presence of lactone 44 as the major product along with other minor components. Ether was evaporated to give an oil (180mg) 1H NMR (CDCl3): δ 2.8-3.2 (m, 4H), 4.0 (m, 2H), 4.8 (bs, 1H), 6.5 (m, 1H), 6.8-8.2 (m, 12H), 8.2-8.5 (bs, 2H).

2-Vinylbenzaldehyde (65):

3,4-Dihydroisoquinoline (10g, 0.077 mol) was mixed with a stirred solution of sodium hydroxide (60g, 1.5 mol) in water (240 mL) at 70°, under nitrogen atmosphere. To this was added dimethyl sulphate (60 mL, 80.0g, 0.635 mol) slowly and after the addition was complete the reaction contents were heated at 110-120° for 2 h, cooled and extracted with ether. The ether layer was treated with HCl (10%), washed with water and dried. Evaporation of ether followed by distillation under reduced pressure afforded 65 (8g, 80%), b.p. 95°/4 mm (Lit27 b.p. 113-115°/18 mm, yield 60%). 1H NMR (CCl4): δ 5.2-5.9 (m, 2H, -CH=CH₂), 7.2-8.1 (m, 5H, -CH=CH₂ and ArH), 10.4 (s, 1H, CHO).

N-methyl-2-vinylbenzylamine (63):

To a solution of aldehyde 65 (5.0g, 0.038 mol) in
ethanol (25 mL) was added aqueous methylamine (40%, 7 mL) and the mixture was stirred at room temperature for 20 h. Solid sodium borohydride (2.0 g, 0.053 mol) was added and the contents were kept under stirring for another 4 h. Ethanol was removed under reduced pressure and water was added to the residue. This was extracted with ether and the ether layer was treated with HCl (10%). The latter was then basified with sodium hydroxide (20%) and extracted with ether. This ether extract was washed with water, dried and evaporated to give amine 63 as an oil (3.8 g, 68%). $^1$H NMR (CDCl$_3$): δ 1.0 (bs, 1 H >NH), 2.47 (s, 3 H, N-CH$_3$), 3.76 (s, 2 H, Ph-CH$_2$-N), 5.26-5.77 (m, 2 H, -CH=CH$_2$), 7.0-7.6 (m, 5 H, -CH=CH$_2$ and ArH).

$N$-methyl-$N$-(2-vinylbenzyl)-2-formylbenzamide (62):

To a stirred solution of acid chloride 42 (1.1 g, 6.5 mmol) in dry benzene (15 mL) was added a solution of amine 63 (1.0 g, 6.8 mmol) and pyridine (0.6 mL, 580 mg, 7.4 mmol) in dry benzene (5 mL) and the mixture was stirred at room temperature for 16 h. Water was added to the reaction mixture and the organic layer was separated. This was treated successively with sodium hydroxide (20%), HCl (20%) and
brine. Benzene was evaporated and the residue was subjected to column chromatography using gradient elution with ether-petroleum ether to give amide 62 as an oil (1.1g, 60%).

$^1$H NMR (CDCl$_3$): δ 2.6, 3.03 (singlets, 3H, -CH$_3$), 4.4, 4.9 (singlets, 2H, Ph-CH$_2$-N), 5.3-5.9 (m, 2H, -CH=CH$_2$), 7.4-8.1 (m, 9H, -CH=CH$_2$ and ArH), 10.2 (s, 1H, CHO); Mass spectrum (70 eV) m/z (rel. intensity): 279 (15, M$^+$) 162 (38), 133 (86), 105 (base peak); UV (MeOH): 255, 285, 295 nm.

Irradiation of N-methyl-N-(2-vinylbenzyl)-2-formylbenzamide (62):

A solution of amide 62 (140mg, 0.5 mmol) in dry benzene (45 mL) was irradiated with pyrex filtered light from a 125W lamp for 2 h and 15 min. The reaction contents were filtered to remove some solid particles (20mg). Benzene was evaporated under reduced pressure and the residue was taken in ether. A solid separated, which was removed by filtration (20mg). The appearance, solubility and handling of the solid indicated its polymeric nature. Ether was evaporated from the filtrate and the residue was subjected to column chromatography. The elution with petroleum ether-ether gave an oil (60mg, 43%). $^1$H NMR (CDCl$_3$): δ 2.23 (s, 3H, N-CH$_3$),
3.86-4.2 (doublets, 2H, Ph-CHz-N), 5.33-5.9 (m, 2H, -CH=CH2), 6.2 (s, 1H, Ph-CH<), 7.13-8.1 (m, 9H, -CH=CHz and ArH); Mass spectrum (70 eV) m/z (rel. intensity): 279 (13, M'), 235 (5), 133 (76), 105 (100, base peak).

2-Acetylbenzoic acid (75):

This was prepared by known procedure24 from phthalic anhydride (13.0g, 0.09 mol), malonic acid (11.0g, 0.11 mol) and pyridine (10 mL, 9.8g, 0.12 mol) in 14% yield, m.p. 118° (CH2CL2) (Lit29 m.p. 114-115°). 1H NMR (CDCl3): δ 2.05 (s, 3H, -CH3), 4.85 (s, 1H, exchangeable, -OH), 7.5-8.1 (m, 4H, ArH); Mass spectrum (70 eV) m/z (rel. intensity): 164 (8, M'), 149 (48), 147 (100, base peak), 120 (60).

2-Acetylbenzoyl chloride (76):

To a stirred solution of acid 75 (225mg, 1.4 mmol) in dichloromethane-benzene (20 mL, 1:1) was added thionyl chloride (0.15 mL, 240mg, 2.0 mmol) at 5°. After 30 min the contents were allowed to attain room temperature and the stirring was continued for 15 h. The solvent was removed under reduced pressure to give an oil (210mg, 84%). IR (neat): 1790 cm⁻¹ (C=O); 1H NMR (CDCl3): δ 1.9, 3.1
(singlets, 3H, -CH₃), 7.4–8.1 (m, 4H, ArH).

N-(2-acetylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (73):

To a stirred solution of acid chloride 76 (650mg, 3.6 mmol) in dry benzene (5 mL) was added dropwise a solution of amine 43 (480mg, 3.6 mmol) and pyridine (0.3 mL, 290mg, 3.7 mmol) in benzene (5 mL). The stirring was stopped after 4 h, pyridinium chloride separated was removed by filtration and the organic layer was treated with sodium hydroxide (20%) and HCl (20%). This was washed with water and dried. Evaporation of solvent gave an oil which was triturated with ethyl acetate-petroleum ether (94:6) mixture to give a solid (380mg, 38%), m.p. 113–115° (EtOH). IR (Nujol): 1690 cm⁻¹ (ketone), 1640 cm⁻¹ (amide); ¹H NMR (CDCl₃): 5 2.6 (m, 3H, -CH₃), 2.8, 3.05 (triplets, 2H, Ph-CH₂-CH₂-N), 3.45, 4.1 (triplets, 2H, Ph-CH₂-CH₂-N), 4.35, 5.00 (singlets, 2H, Ph-CH₂-N), 6.8–8.00 (m, 8H, ArH); Mass spectrum (70 eV) m/z (rel. intensity): 279 (1, M⁺), 147 (100, base peak), 132 (69). Anal. Calcd for C₁₈H₁₇NO₂: C, 77.42; H, 6.09; N, 5.02. Found: C, 77.55; H, 6.2; N, 4.95.
Irradiation of N-(2-acetylbenzoyl)-1,2,3,4-tetrahydro isoquinoline (73):

A solution of amide 73 (100mg, 0.36 mmol) in benzene (45 mL) was irradiated with pyrex filtered light from a 125W lamp. The course of the reaction was monitored by TLC analysis which did not indicate the complete disappearance of the starting material even after 8 h. The irradiation was then discontinued, the solvent removed under reduced pressure and the residue taken in ether. A solid separated was removed by filtration (15mg) m.p. 140°(dec.). The appearance, solubility and TLC of the solid indicated its polymeric nature. The filtrate was evaporated to give an oil (80mg) which was subjected to preparative thick layer chromatography using ether-ethyl acetate (6:4) as eluant. The band at Rf 0.8 on separation gave 2-methylphthalide (77) (16mg). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.65 (d, 3H, -CH\(_3\)), 5.6 (q, 1H, Ph-CH\(_2\)), 7.4-8.1 (m, 4H, ArH). The band at Rf 0.65 was separated to give amide 73 (20mg), m.p. 114°. Mixture m.p. 112-114°. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.55 (m, 3H, -CH\(_3\)), 2.75, 3.00 (triplets, 2H, Ph-CH\(_2\)-CH\(_2\)-N), 3.4, 4.00 (triplets, 2H, Ph-CH\(_2\)-CH\(_2\)-N), 4.3, 4.9 (singlets, 2H, Ph-CH\(_2\)-N), 6.8-8.0 (m, 8H, ArH). Separation of the band at Rf 0.5 gave an oil
(8mg). TLC and Co-TLC comparison indicated this oil to be identical with an authentic sample of 3,4-dihydroisoquinoline (78).

Preparation of authentic 2-methylphthalide (77):

A solution of acid 75 (200mg, 1.22 mmol) in ethanol (10 mL) in presence of NaBH₄ (500mg, 13 mmol) was refluxed for 6 h. The excess of ethanol was evaporated off and the residue was taken in water and extracted with ether. The ether layer was washed with brine and the solvent removed to give 77 as an oil (145mg, 80%). ¹H NMR (CDCl₃): δ 1.65 (d, 3H, -CH₃), 5.5 (q, 1H, Ph-CH<), 7.4-8.2 (m, 4H, ArH).

Attempted cyclisation of N-(2-formylbenzoyl)-1,2,3,4-tetrahydroisoquinoline (36):

To a stirred solution of diisopropylamine (0.4 mL, 290mg, 2.86 mmol) in dry THF (25 mL) under nitrogen atmosphere was added a solution of butyllithium (1.95M in n-hexane, 1.34 mL, 166mg, 2.6 mmol) at -70°. After stirring the contents for 0.5 h a solution of amide 36 (230mg, 0.87 mmol) in dry THF (10 mL) was added slowly. After 1.25 h the contents were allowed to attain room temperature at which the
REFERENCES


