SUMMARY OF THE WORK

PART I: A BRIEF REVIEW ON THE LITERATURE ON ELECTROPHILIC SUBSTITUTION OF INDOLE


PART II: ELECTROPHILIC SUBSTITUTION REACTION OF INDOLE WITH VARIOUS ELECTROPHILES

Chapter 2.1: Electrophilic Substitution Reaction of Indole with Acetone in Presence of Boron Trifluoride Etherate – a Fascinating Study for 95 years using Different Acids

The first report of the reaction of indole with acetone in the presence of HCl acid was made by M. Scholtz [M. Scholtz, Ber. Dtsch. Chem. Ges., 46, 1082, 1913]. Subsequently Noland et al [W. E. Noland; C. G. Richards; H. S. Desai; M. R. Venkiteswaran; J. Org. Chem; 26, 4254, 1961] carried out a reinvestigation of Scholtz’s reaction under identical condition and contradicted his work. He reported a new synthetic route to indolocarbazole [W. E. Noland et al; J. Org. Chem; 26, 4254, 1961]. This was possibly obtained by the double electrophilic substitution at C3 and C5 of two indole nuclei followed by double Plancher Rearrangement. This reaction, however, could not be stopped at the di(indolyl)methane stage. The investigation of the same reaction in our laboratory was started using the Lewis acid, BF3.Et2O, under mild conditions in an attempt to stop the reaction at the
di(indoly)methane stage. However working with BF$_3$.Et$_2$O in our laboratory it was found for the first time that new electrophilic species were generated, *in situ*, by the aldol condensation of acetone leading to the synthesis of new and fascinating heterocyclic systems [A. Chatterjee, S. Manna: J. Banerji: C. Pascard, T. Prangé, J. N. Shoolery. *J. Chem. Soc. Perkin Trans I* Organic and Bio Organic Chemistry, 2, 553, 1980 and J. Banerji, A. Chatterjee, S. Manna, C. Pascard, T. Prangé, J. N. Shoolery. *Heterocycles*, 15(1), 325, 1981] by interesting reaction pathways. However a compound termed as “Unstable Dimer” was reported from our laboratory in 1981. The structure could not be established due to the transformation of this compound rapidly in CDCl$_3$. The structure of the transformation product had been confirmed by X-ray crystallography. [J. Banerji, A. Chatterjee, S. Manna, C. Pascard, T. Prangé and J. N Shoolery. *Heterocycles*, 15(1), 325, 1981]. It was stable to a certain extent in d$_6$-DMSO. In the latter case only the $^1$H-NMR spectrum could be recorded in the 80 MHz CFT-20 NMR spectrometer before the compound began to decompose.

So the candidate reinvestigated the reaction of indole with acetone in presence of boron trifluoride etherate in methylene chloride as solvent with a view to isolating this “Unstable Dimer” scrupulously avoiding CHCl$_3$. A new compound A was isolated which was found to be identical with the reported “Unstable Dimer” (UV, IR, $^1$H-NMR and Mass spectral data).

Compound A, C$_{25}$H$_{28}$N$_2$O$_2$, M$^+$ 388, m.p. 155 °C (benzene), was obtained in 20% yield (isolated yield after purification). It showed ultraviolet absorption maxima $\lambda_{\text{max}}$$_{\text{ETH}}$ at 236 and 283.5 nm (log$e$: 3.98, 3.74 respectively). In the infrared spectrum (KBr pellet) peaks at 3518.8 (>NH), 3359.0 (−OH), 1610.7, 1455.5, 1075.5 (aromatic nucleus), 745.3 (o-disubstituted benzene ring) cm$^{-1}$ were discernible.

The 300 MHz $^1$H-NMR spectrum in 99.5% d$_6$-DMSO revealed the presence of two exchangeable protons at $\delta$ 9.81 and $\delta$ 5.91 thereby confirming the presence of a chelated indole >NH and an indoline >NH. Eight aromatic protons resonated in the region $\delta$ 7.34-6.47 as multiplet. Two pairs of non-equivalent methylene protons were discernible at $\delta$ 3.11 and $\delta$ 1.78 (d, 1H each, $J = 13.0$ Hz) and $\delta$ 2.87 and $\delta$ 2.20 (d, 1H each, $J = 13.0$ Hz). Two sharp singlets appeared at $\delta$ 5.27 and $\delta$ 4.93 (1H disappeared on D$_2$O, exchange with 20 sec. half
life) confirming the presence of two hydroxyl groups. Four methyls were observed at δ 1.40, 1.30, 1.10 and 0.56.

The 75.5 MHz $^{13}$C-NMR spectra (decoupled and DEPT-135°) in d$_6$-DMSO showed the presence of eight aromatic methine carbons at 117.8, 118.5, 117.6, 112.4, 124.1, 119.9, 128.7 and 109.3 ppm could be easily distinguished from the non-protonated signals. The most downfield signal at 149.8 ppm was assigned to C$_{2'}$, which was attached to two electronegative atoms. The signals at 30.7, 30.5, 28.5 and 25.4 ppm were consistent with the presence of two pairs of gem-dimethyl groups at C$_{3'}$ and C$_{5'}$. The C$_7$ appeared at 90.5 ppm due to the deshielding effect of the hydroxyl group. Of the three aliphatic quaternary signals those at 38.3, 43.1 and 55.9 ppm have been assigned to C$_5$, C$_3$ and C$_1$ respectively. On the basis of these data coupled with X-ray crystallographic analysis the structure of compound A was unambiguously established as I.

![Fig. 2.1: X-ray Crystallographic Structure of I [ORTEP Projection]](image)

Compound A was obtained as colourless crystals from benzene. Crystals of the compound were highly unstable in chloroform. The ORTEP projection has been shown in Fig. 2.1. The compound is an interesting (2:3) adduct of indole with acetone. The two five membered spiro rings are present in different planes but the two hydroxyl groups at C-2' and C-3' are on the same side.

Crystallographic details: Monoclinic
Space group: $P2_1$ (14)
Parameters: a = 9.272 (2) Å
b = 19.360 (3) Å
c = 11.789 (3) Å
β = 90.000°
z = 4
V = 2116.3 (8) Å$^3$
The mechanism of formation of this interesting product could be readily rationalised by the generation of an indolyl carbinol, followed by the elimination of water and formation of a 3,3-disubstituted indolenium cation. Subsequent Plancher Rearrangement followed by an Ene Reaction and Electrophilic Substitution with a second molecule of the indolenium cation (4) generated the novel skeleton. The plausible mechanism of the formation of compound (I) is given in scheme 2.1 and its ready conversion to the rearranged product (1a) in CDCl₃ has been shown in scheme 2.2. The elucidation of the structure of the "Unstable Dimer" is all the more important as it involves a fascinating molecular rearrangement in the NMR tube.

The molecular rearrangement of the "Unstable Dimer" is initiated by the elimination of water from the carbinolamine system generating an indoleninium cation.

Scheme 2.1: Formation of Compound (I)
Chapter 2.2: Electrophilic Substitution of Indole with Acetone in the Presence of Stannic Chloride

Reaction of indole with acetone was carried out by Chatterjee and Banerji et al [(a) A. Chatterjee, S. Manna, J. Banerji, C. Pascard, T. Prange' and J. N. Shoolery. *J. Chem. Soc. Perkin* 1(2), 1980. (b) J. Banerji, A. Chatterjee, S. Manna, C. Pascard, T. Prange' and J. N. Shoolery. *Heterocycles*, 15(1), 325, 1981] in the presence of the Lewis acid, boron trifluoride etherate. The remarkable feature of the reaction was that the aldol condensation of the simple electrophile acetone *in situ* was prevalent with this Lewis acid resulting in the generation of C₃-, C₆-, and C₉- units as observed in the reaction products.
These electrophilic species reacted with indole resulting in the synthesis of novel heterocyclic systems via Plancher Rearrangements. Earlier Noland et al. has studied this reaction with ethanolic hydrochloric acid and he reported the formation of indolocarbazole. This was later contradicted by Bergman et al. The formation of these reactive species in situ was not evident from Noland's work, published in 1961 but later confirmed by Bergmann in his work reported in 1989, and also by Noland in his later work reported in 1996.

The reaction with acetone was studied by the present investigator in presence of stannic chloride in order to see whether the reaction could be stopped at the di(indolyl)methane stage. The idea behind the use of this Lewis acid was based on the concept that Sn (IV) in SnCl₄ had the ability to expand it's valence shell. Although the valence shell of the Sn (IV) in stannic chloride is filled with eight electrons, Sn (IV) has two empty d-orbitals which can each accept a share of an electron pair. Thus a coordinate-covalent bond can be formed which would generate highly reactive electrophiles. These could then undergo various reactions and rearrangements.

Compound B, C$_{19}$H$_{18}$N$_2$, m/z = 297 (M$^+$ + Na), m.p. 150 °C (white needles from petrol-benzene) was obtained in 80% yield (isolated yield after purification). It showed ultraviolet absorption maxima $\lambda_{max}^{\text{EtOH}}$ at 282.5 nm (logɛ: 4.00). In the infrared spectrum (KBr) peaks at 3404.2 (>NH), 1456.6, 1339.1 (aromatic nucleus), 739.9 cm$^{-1}$ were discernible.

The compound was found to be a symmetrical dimer. This was apparent from its molecular ion (M$^+$ + Na) peak at m/z 297 coupled with its $^1$H-NMR spectral data. The 300 MHz $^1$H-NMR spectrum of compound B in CDCl$_3$ revealed the presence of two >NH protons as a broad singlet at $\delta$ 7.86. Three doublets (two protons each) appeared at $\delta$ 7.45 (2H, d, $J = 8.1$ Hz) for C-4/C-4' protons, at $\delta$ 7.34 (2H, d, $J = 8.1$ Hz) for C-7/C-7' protons and $\delta$ 7.04 (2H, d, $J = 2.1$ Hz) for C-2/C-2'. Two triplets at $\delta$ 7.10 (2H, t, $J = 8.5$ Hz) appeared for C-5/C-5' protons and $\delta$ 6.89 (2H, t, $J = 7.5$ Hz) appeared for C-6/C-6' protons. A singlet at $\delta$ 1.94 (6H, s) indicated the presence of two methyl groups in the compound.

The structure was further confirmed from the 75.5 MHz $^{13}$C-NMR spectrum including DEPT-135° experiment in CDCl$_3$. The compound contained six aromatic sp$^2$-quaternary carbon atoms C-3/C-3', C-3a/C-3'a and C-7a/C-7'a which resonated at 125.5; 126.3 and 137.1 ppm respectively. One sp$^3$-quaternary carbon C-8 appeared at 34.9 ppm. Two methyl carbons C-9 and C-10 appeared at 30.2 ppm. From the above spectral analysis the structure of compound B could be definitely established to be the di indolyl system (II). The yield of this product was much higher than that observed with Montmorillonite Clay K-
Chapter 2.3: Dimerisation of Indole - Result of an Attempted Electrophilic Substitution of Indole with Benzophenone using Stannic Chloride as Catalyst

The reaction of indole with benzophenone was not studied earlier in presence of any kind of catalyst. The present investigator studied the reaction in presence of stannic chloride in methylene chloride as solvent under nitrogen atmosphere at 0 °C. Unfortunately, indole failed to react with benzophenone possibly due to deactivation of the carbonyl group by the aromatic ring. Rather it showed a stronger tendency to undergo dimerisation to give the indole dimer C in 78% yield. This was obtained earlier by G.F. Smith [G. F. Smith. Chem. and Ind., 1451, 1954] when he carried out the reaction with moderately strong hydrochloric acid. He obtained both the dimer and the trimer but with SnCl₄ only the former was obtained.

The stable dimer C, C₁₆H₁₄N₂, M⁺ 234 was isolated as a white solid, m.p. 118 °C in 78% yield from petrol: benzene (1:1) eluate (isolated yield after purification). It exhibited ultraviolet absorption maxima λ_max^pH at 465 nm (logε : 1.36). The characteristic bands which were observed in the IR spectrum (KBr) have been recorded.

The 300 MHz ¹H-NMR spectrum revealed the presence of one indole >NH at δ 7.79 while a second >NH appeared as a broad singlet (exchangeable with D₂O) at δ 6.95 thereby indicating the presence of a reduced indole system. The C-2 proton of the reduced indole
moiety resonated as a triplet at $\delta 4.67$ ($J = 7.5$ Hz) while the C-3 proton appeared as a doublet at $\delta 3.34$ ($J = 7.5$ Hz). Eight aromatic protons were found to be present in this molecule. Two aromatic protons resonated at $\delta 7.27$ (1H, d, $J = 8.1$ Hz) and $\delta 7.18$ (1H, d, $J = 8.1$ Hz). Three multiplets in the region $\delta 6.93-6.86$, $\delta 6.50-6.42$ and $\delta 6.82-6.69$ were assigned to six aromatic protons respectively at C-5H, C-5'H, C-7H, C-7'H and C-6H, C-6'H. A sharp singlet at $\delta 3.21$ was assigned to the C-2' proton.

The structure of compound C was established as (III) from its 75.5 MHz $^{13}$C-NMR spectral analysis including DEPT-135° experiment in $d_4$-methanol.

The C-2 and C-3 carbons of the indoline moiety were discernible at 36.0 and 38.3 ppm respectively. The two quaternary carbons of the indoline part, i.e C-3a and C-7a, appeared at 128.4 and 146.1 ppm respectively while the quaternary carbons of the indole moiety, i.e. C-3', C-3'a and C-7'a, resonated at 120.1, 128.3 and 138.4 ppm respectively. Eight aromatic methines, C-4, C-4', C-5, C-5', C-6, C-6', C-7 and C-7' appeared at 127.6, 120.3, 123.2, 119.9, 131.5, 119.2, 117.4 and 112.1 ppm respectively.

Chapter 2.4: Electrophilic Substitution of Indole with Cyclohexanone in Presence of Stannic Chloride

The reaction of indole with cyclohexanone was carried out earlier in our laboratory using boron trifluoride etherate. New heterocyclic systems were synthesised through fascination reaction pathways, aldol condensation playing a dominant role [J. Banerji, M. Saha, S. Kanar, A. Neuman and T. Prangé. J. Chem. Research(S), 518, 1996]. With stannic chloride only one product was obtained compound D.
Compound D, C_{22}H_{22}N_{2}, (eluate, petrol:benzene, 1:1) m.p. 72 °C, was obtained in 72% yield (calculated after purification) as light brown crystals from petrol. It exhibited UV absorption maxima $\lambda_{\text{max}}^{\text{EtOH}}$ at 281, 260 nm (log e: 4.13, 4.20 respectively). In the infrared spectrum using KBr pellet peaks at 3412.2 (>NH), 1454.8, 1337 (aromatic nucleus), 742.3 (o-disubstituted benzene ring) cm$^{-1}$ were discernible.

The symmetric bisindolyl nature of compound C was apparent from its molecular ion (M$^+$ + Na) peak at (m/z + Na) = 337 coupled with its $^1$H-NMR spectral data. The 300 MHz $^1$H-NMR spectrum in CDCl$_3$ revealed the presence of two > NH protons as a broad singlet at $\delta$ 7.91.

Two doublets at $\delta$ 7.57 (2H, d, $J = 8.1$ Hz) and $\delta$ 7.30 (2H, d, $J = 8.1$ Hz) and one sharp singlet at $\delta$ 7.26 (2H, s) were attributed to the C-4/C-4', C-7/C-7' and C-2/C-2' protons respectively. Two multiplets at $\delta$ 7.09-7.04 (2H, m) and $\delta$ 6.93-6.88 (2H, m) appeared for C-5/C-5' and C-6/C-6' protons. Four methylene protons resonated as a triplet at $\delta$ 2.55 (2H, t, $J = 5.6$ Hz) and six methylene protons as a multiplet in the region $\delta$ 1.67-1.60 (6H, m).

The structure of the compound was confirmed from the 75.5 MHz $^{13}$C-NMR spectrum including DEPT-135° experiment. Two aromatic sp$^2$ tertiary carbon atoms C-2 and C-2' resonated at 121.2 ppm. Six aromatic sp$^2$ quaternary carbon atoms C-3/C-3', C-3a/C-3'a and C-7a/C-7'a appeared at 123.7, 126.3 and 137.0 ppm respectively. Eight aromatic sp$^2$ tertiary carbons C-4/C-4', C-5/C-5', C-6/C-6', C-7/C-7' resonated at 121.4, 122.0, 118.5 and 111.0 ppm respectively. One sp$^3$ quaternary carbon C-8 appeared at 39.5 ppm. Five sp$^3$ secondary methylene carbons (C-9/C-13), (C-10/C-12) and C-11 resonated at 36.8, 23.0 and 26.7 ppm respectively. From the above spectral analysis the structure of D could be definitely established as the diindolyl system (IV).

Montmorillonite Clay K-10 = 21%
Stannic Chloride = 72%
Chapter 2.5: Electrophilic Substitution of Indole with Mesityl oxide in Presence of Stannic Chloride

The reaction of indole with mesityl oxide was studied earlier in our laboratory in presence of boron trifluoride etherate. In this case indole failed to react with mesityl oxide. Rather it showed a stronger tendency to undergo dimerisation and trimerisation to give the indole dimer (1) and trimer (2).

The same reaction was reinvestigated by the candidate using stannic chloride in CH$_2$Cl$_2$ as solvent at 0 °C. Compound E, could be isolated from the reaction mixture in 85% yield (calculated after purification).

Two types of reactions appeared to be possible —

(i) 1,4 – addition
(ii) electrophilic substitution by indole on the carbonyl carbon.

Compound E, C$_{14}$H$_{17}$NO$_3$ (M$^+$ + Na) = 238, m.p. 78 °C (light yellow flake shape crystals from petrol) was obtained in 85% yield (isolated after purification). It showed ultraviolet absorption maxima $\lambda_{\text{max}}$ in EtOH at 282 nm ($\log e$: 3.75). In the infrared spectrum
(KBr) peaks at 3306.7 (>NH), 1690 (>C=O), 1432.3, 1349.9 (aromatic nucleus), 744.8 (o-disubstituted benzene ring) cm\(^{-1}\) were discernible.

The molecular ion peak (M\(^{+}\) + Na) at 238 and the 300 MHz \(^1\)H-NMR spectrum of compound E in CDCl\(_3\) revealed the monomeric nature of the compound. The one proton singlet at \(\delta\) 8.09 was assigned to > NH proton of the indole nucleus while five aromatic protons were discernible in the region \(\delta\) 6.93-7.83 [three one proton doublets appearing at \(\delta\) 7.83 (1H, d, \(J = 7.8\) Hz) for C-4 proton, \(\delta\) 7.38 (1H, d, \(J = 7.9\) Hz) for C-7 proton and \(\delta\) 6.93 (1H, d, \(J = 2.4\) Hz) for C-2 proton]. The remaining two aromatic protons at C-5 and C-6 resonated as two proton multiplets in the region \(\delta\) 7.26-7.11. Two methyl groups at C-10 appeared as six-proton singlet at \(\delta\) 1.56 whereas the third methyl group appeared as a three proton singlet at \(\delta\) 1.74. The presence of the carbonyl group was evident in the IR spectrum at 1690 cm\(^{-1}\). On the basis of these observations the structure of compound E could be established as (V).

The structure of compound E was further confirmed from its \(^{13}\)C-NMR data including DEPT-135° experiment. Three aromatic sp\(^2\)-quaternary carbon atoms C-3, C-3a, C-7a resonated at 123.6, 125.5, 137.2 ppm respectively and five aromatic sp\(^2\)-tertiary carbon atoms C-2, C-4, C-5, C-6, C-7 appeared at 120.8, 120.6, 121.7, 119.2 and 111.6 ppm respectively. The carbonyl carbon atom C-10 and one sp\(^3\)-quaternary carbon atom C-8 appeared at 209.2 and 34.4 ppm respectively. Three methyl carbon atoms C-11, C-12 /C-13 resonated at 31.7 and 28.8 ppm respectively.

From the above spectral studies it was observed that the reaction did not afford di(indolyl)methane but resulted in an indole-mesityl oxide 1:1 product, by exclusive 1:4 addition. The yield of the product was much higher than observed with Montmorillonite Clay K-10.

**Montmorillonite Clay K-10 = 18%**

**Stannic Chloride = 85%**
Chapter 2.6: Electrophilic Substitution of Indole with Acetylacetone in Presence of Stannic Chloride

The reaction of indole with acetylacetone was studied earlier in our laboratory in presence of borontrifluoride etherate. This resulted in the synthesis of a novel azapentacyclic compound incorporating a hemiacetal linkage (3) [J. Banerji, M. Saha, U. Dutta, P. Mukherjee, M. Chakrabarty, A. Chatterjee, Y. Harigaya, Y. Konda and A. Hatana. *J. Indian Inst. Sci.*; (Invited Paper-Special issue dedicated to Professor S.C. Bhattacharya on his 80th birth anniversary) 81,165,2001].

The candidate's study with SnCl₄ afforded the diindolyl methane system F.

Product F, C₂₁H₂₆N₂O, (M⁺ + Na) = 339, m.p. 196 °C (light yellow needles from petrol-benzene mixture) was obtained in 78% yield (after purification). It showed ultraviolet absorption maxima λₓₓₓₓₓₓₓₓ at 291, 285, 275, 268 nm (logɛ: 3.99, 3.96, 4.05, 3.99 respectively). In the infrared spectrum (KBr) peaks at 3399.6 (>NH), 1691.1 (>C=O), 1417.7, 1341.2 (aromatic nucleus) and 750.7 (o-disubstituted benzene ring) cm⁻¹ were discernible. Its ¹H-NMR spectrum in d₆-DMSO revealed the presence of two >NH protons as a singlet at δ 10.78. Two methyl groups appeared as three proton singlets each at δ 1.82, 1.46 and two methylene protons as a singlet at δ 3.38. The eight aromatic protons resonated in the region δ
7.24-6.63 [δ 7.24 (2H, d, J = 7.9 Hz) for C-4/C-4' protons, δ 7.09 (2H, d, J = 8.0 Hz) for C-7/C-7' protons, δ 6.87 (2H, t, J = 7.5 Hz) for C-5/C-5' protons, δ 6.63 (2H, t, J = 7.5) for C-6/C-6' protons]. Based on this observation the structure of compound F could be established as (VI) which was further supported by the $^{13}$C-NMR data including DEPT-135° experiment. Six aromatic sp$^2$ quaternary carbon atoms C-3/C-3', C-3a/C-3'a, C-7a/C-7'a resonated at 121.8, 125.8, 137.1 ppm respectively. Ten aromatic sp$^2$-tertiary carbon atoms C-2/C-2', C-4/C-4', C-5/C-5', C-6/C-6' and C-7/C-7' appeared at 121.6, 120.1, 120.5, 117.9 and 111.5 ppm respectively. The carbonyl carbon atom (C-10) and one sp$^3$-quaternary carbon atom (C-8) appeared at 208.2 and 37.0 ppm respectively. Two methyl carbons (C-11, C-12) and one methylene carbon atom (C-9) resonated at 31.7, 27.1 and 53.0 ppm respectively.

Montmorillonite Clay K-10 = 11%
Stannic Chloride = 78%

Chapter 2.7: Electrophilic Substitution of Indole with Cyclohexane 1,3-dione in Presence of Stannic Chloride

The reaction of indole with cyclohexane 1,3-dione was carried out in presence of stannic chloride in methylene chloride as solvent in nitrogen atmosphere at 0 °C which yielded two compounds G and H.

Compound G, C$_{14}$H$_{13}$NO, M$^+$ 211, m.p. 194 °C (petrol:benzene, 1:1), was obtained in 21% yield (isolated after purification). It showed ultraviolet absorption maxima $\lambda_{\text{max}}$ in EOH at 365, 345, 328 nm (logε: 4.01, 4.01, 3.94 respectively). In the infrared spectrum (KBr)
peaks were observed at 3226.3 (>NH), 1488, 1577.5, 1523.4, 1436.7, 1380.7 (aromatic nucleus), 737.9 cm$^{-1}$ (o-disubstituted benzene ring).

In the 300 MHz $^1$H-NMR spectrum in d$_6$-acetone, one singlet at $\delta$ 10.90 confirmed the presence of an indole >NH. Four aromatic protons resonated at $\delta$ 7.96-7.89 (1H, m) for C-4' proton, $\delta$ 7.53-7.47 (1H, m) for C-7' proton and $\delta$ 7.25-7.18 (2H, m) for C-5' and C-6' protons. A single olefinic proton appeared at $\delta$ 6.55 (1H, s) for C-2 proton and three pairs of methylene protons at $\delta$ 2.38 (2H, t, $J = 6.6$ Hz) for C-4 proton and $\delta$ 2.15-2.04 (4H, m) C-5 and C-6 Protons.

The 75.5 MHz $^{13}$C-NMR spectrum in d$_6$-acetone, including DEPT-135° experiment confirmed the presence of fourteen carbons. Five aromatic quaternary carbons were evident for C-1, C-3, C-3', C-3'a and C-7'a. The most downfield signal at 198.2 ppm was attributed to the $\alpha,\beta$-unsaturated carbonyl carbon at C-1. However, the signal for the conjugated carbonyl system could not be detected in the infrared spectrum possibly due to the presence of intermolecular hydrogen bonding involving the carbonyl group of one molecule and the >NH group of another molecule. The C-3 carbon resonated at 155.6 ppm while the C-3', C-7'a and C-3'a appeared at 115.8, 138.5 and 125.6 ppm respectively. The olefinic protonated carbon C-2 was evident as 128.3 ppm while the aromatic protonated carbons C-2', C-4', C-5', C-6' and C-7' appeared at 121.6, 121.5, 123.1, 121.2 and 112.8 ppm respectively. The three methylene carbons C-4, C-5 and C-6 resonated at 28.2, 22.7 and 37.2 ppm respectively. On the basis of these data the structure of compound G could be established as (VII).

The second compound H, C$_{22}$H$_{20}$N$_2$O, M$^+$ 328, m.p. 234 °C (benzene: ethyl acetate, 4:1) was obtained in 65% yield (after purification). It showed a typical indole ultraviolet absorption spectrum $\lambda_{max}$$_{EtOH}$ at 341, 331, 323, 316.5 and 293.5 nm ($\log$ɛ: 4.12, 4.09, 4.13, 4.13, 4.09).
4.11 and 3.91 respectively). In the infrared spectrum (KBr) peaks at 3357.3 and 3293.5 (two >NH), 1577.3, 1522.9, 1487.5, 1436.6 (aromatic nucleus), 738 cm⁻¹ (o-disubstituted benzene ring) were discernible.

The 300 MHz ¹H-NMR revealed the presence of one chelated >NH at δ 9.48 and another indole >NH at δ 8.0. The single C-2' proton of one indole moiety appeared at δ 6.38 (1H, m). Eight aromatic protons resonated in the region δ 7.78-6.56 while two aromatic protons appeared at δ 7.78 (1H, m) and δ 7.17 (1H, m). A four hydrogen multiplet was discernible in the region δ 7.03-6.87 and a two proton multiplet was observed at δ 6.56. One doubly allylic aliphatic proton appeared at δ 5.38 as a doublet (C-11H) with coupling constant of 5.3 Hz. It is important to note that one non-equivalent methylene pair was discernible at δ 3.43 and δ 3.12. The proton at δ 3.12 showed only geminal coupling of 13.8 Hz and appeared as a doublet. The other proton of this non-equivalent methylene pair resonated at δ 3.43 as a doublet of doublet and underwent coupling with the methine proton (J = 6.1 Hz) in addition to the geminal coupling (J = 14.0 Hz).

The 75.5 MHz ¹³C-NMR spectrum, both decoupled and DEPT-135° of compound H, in d₆-acetone were investigated and showed the presence of twenty two carbons. The DEPT-135° spectrum confirmed the presence of—

(i) 4 sp³-methylene carbons  
(ii) 1 sp³-methine carbon  
(iii) 9 sp²-methine carbons and  
(iv) 8 sp²-quaternary carbons.

One sp²-quaternary carbon at 194.1 was attributed to the α,β-unsaturated carbonyl carbon at C-1. Two signals at 154.9 ppm and 137.5 ppm (both sp²-quaternary) were assigned to C-4a and C-11a respectively. The sp²-quaternary carbons of the 3-substituted indole moiety resonated at 116.4 (C-3'), 127.6 (C-3'a) and 130.2 (C-7'a). Two more signals at 141.3 and 118.7 ppm could be assigned to C-5a and C-9a respectively.

Four aromatic methines of the substituted aniline moiety appeared at 131.8 (C-9), 126.7 (C-7), 123.1 (C-8) and 118.1 ppm (C-6). Five more aromatic methine carbons resonated at 122.4 (C-2'), 121.4 (C-5'), 119.9 (C-4'), 119.7 (C-6') and 111.7 ppm (C-7') while
the aliphatic methine (C-11) appeared at 32.1 ppm. The four aliphatic methylene carbons C-2, C-3, C-4 and C-10 were discernible at 37.4, 22.6, 32.9 and 40.1 ppm respectively. The $^{13}$C-NMR spectrum unambiguously confirmed the structure of compound H as (VIII).

The formation of the compound has been rationalised in scheme 2.3.

This product was obtained with BF$_3$.Et$_2$O [J. Banerji, M. Saha, R. Chakrabarti, S. Kanrar, A. Chatterjee, H. Budzikiewicz, T. Prangé and A. Neuman. J. Chem. Research(S); 320, 1993] in 55% yield.

This was the only time that SnCl$_4$ showed its behaviour akin to BF$_3$.Et$_2$O. The indoleninium cation appeared to be the more powerful electrophile compared to cyclohexane 1,3-dione. It was only after the formation of the indole dimer, subsequent protonation of the aniline nitrogen and ring opening of the indoline system do we find that the enol form of cyclohexane 1,3-dione react as shown in scheme 2.3.
Chapter 2.8: Experimental

This chapter consists of the experimental section of the electrophilic substitution reactions of indole studied by the author.
PART III: A REVIEW ON 1,3-DIPOLAR CYCLOADDITIONS OF ACYCLIC NITRONES: MECHANISM, REACTIVITY AND SELECTIVITY. THEORETICAL CALCULATION AND SOME RECENT DEVELOPEMENTS

In connection with his studies on 1,3-dipolar cycloaddition reactions of nitrones the candidate thought it present to review the work carried out in his area from 2004 upto 2008.

PART IV: STUDIES ON 1,3-DIPOLAR CYCLOADDITIONS OF C,N-DISUBSTITUTED ALDONITRONES

Chapter 4.1: Cycloaddition of C-Aryl-N-(4-Methylphenyl) nitrones to Ethyl Crotonate

Cycloadditions of C-aryl-N-(4-methylphenyl) aldonitrones having different para-substituents on the C-aryl ring (varying from the electron-withdrawing p-nitro group to electron-donating p-methoxy group) with ethyl crotonate were studied earlier in the laboratory of one of my supervisors, Professor Avijit Banerji.

The present investigator has extended the scope of these reactions by studying the course of cycloadditions of several differently substituted C-aryl-N-(4-methylphenyl) nitrones to ethyl crotonate. The results are presented in chart 4.1. There were no previous reports in the literature regarding the cycloadditions of C-aryl-N-(4-methylphenyl) nitrones to ethyl crotonate.

The cycloadditions were performed in refluxing toluene under inert (nitrogen/argon) atmosphere varying from 4-12 hours. The reactions were monitored by TLC and 1H-NMR spectroscopy. At the end of the reaction period only small amounts of the nitrone survived. In some of the earlier reactions, approximately equimolar amounts of the dipole and dipolarophile were taken. Subsequently to enhance the reaction rates and yields, a 3-fold
molar excess of the dipolarophile was taken. Total yields were 61-70% for equimolar reactions but using excess of the dipolarophile the yields increased to above 80%.

The post-reaction mixture was worked up by removing the solvent under reduced pressure and the residue chromatographed over neutral alumina to resolve the components. The crude post-reaction mixture after removal of the solvent was analysed by $^1$H-NMR to assess the relative amounts of products formed.

The 3,4-trans-4,5-trans-4-carbethoxy-isoxazolidines (8,10,12,14) were the major products in all the reactions. The 3,4-cis isomers (9,11,13,15) were obtained as the minor cycloadducts.

The structure and stereochemistry of all the compounds were established by spectroscopic analysis, particularly NMR (300 MHz $^1$H-NMR, 75.5 MHz $^{13}$C-NMR; 500 MHz two dimensional $^1$H-$^1$H-COSY, carbon-hydrogen correlations and spectra simulation).
In the 300 MHz $^1$H-NMR spectra of the major products H-3 appeared as doublet and H-5 as multiplet, both being coupled to H-4. Their DQF-COSY spectra (compounds 8, 10, 12) confirmed this coupling pattern. Further, the H-5 protons exhibited coupling to the methyl doublet. Their DQF-COSY spectra showed long-range coupling between the ortho-protons and meta protons of both aromatic rings. This established the sequence $-\text{O-CH-(CH}_3\text{-CH(CO}_2\text{Et)}-\text{CH-(Ar)}$ in all the compounds.

The FAB-mass spectrum of compound (8) (Scheme 4.1), which belonged to the major series of cycloadducts, confirmed its regiochemistry. Compound (8) showed a (M$^+$) peak at m/z 370. Cycloreversion gave peaks at m/z 239 and m/z 131. The appearance of peaks at m/z 105 corresponded to simultaneous 1,2- and 2,3-cleavage and confirmed the 2-aryl disposition of the p-methyl phenyl group.

Scheme 4.1: Mass Fragmentation of Compound (8)
The 500 MHz $^1$H-NMR analysis of compound (8), a typical member of the Type I cycloadduct series, was studied as a marker for the remaining compounds in this series. The H-3 proton appeared at $\delta$ 5.26 as doublet, $J_{3,4} = 6.6$ Hz. The low-field positions of the H-3 ($\delta$ 5.26) and H-5 ($\delta$ 4.46) were commensurate with their attachment with a carbon atom adjacent to a heteroatom. Both were coupled to the H-4 proton at $\delta$ 3.11. Thus the skeletal pattern of (8) could be unambiguously settled. The H-4 and H-5 protons showed a trans-relationship to each other, retaining the relative stereochemistry of the dipolarophile.

The $^1$H-NMR and $^{13}$C-NMR of compounds (10), (12) and (14) were similar to (8), taking into account the small (and expected) changes due to the change in substituents. Hence, they all belonged to the Type I cycloadducts.

The corresponding minor products (9), (11), (13) and (15) were assigned the 3,4-cis-4,5-trans structures (Type II). Decoupling and two-dimensional $^1$H-$^1$H correlations of compound (9), showed a similar sequence of substituent groups on the isoxazolidine ring system as in the major Type I cycloadducts. However, the chemical shifts of H-3, H-4 and H-5 and their mutual coupling constants were different. The H-5 proton resonated at $\delta$ 4.75 as a multiplet while the H-3 proton appeared at $\delta$ 4.87 ($J_{3,4} = 10.0$ Hz). The large $J_{3,4}$ was in agreement with the cis-disposition of the 3,4-substituents. In this case compound (9) was taken to be a typical member of the Type II adducts.

The 500 MHz $^1$H-NMR and 125.5 MHz $^{13}$C-NMR of (8) and 300 MHz $^1$H-NMR and 75.5 MHz $^{13}$C-NMR of (9) are given in Table 4.1 and Table 4.2.

The NMR characteristics of compounds (11), (13) and (15) were similar to those of (9). Thus the structural and stereochemical assignments of these followed logically.

**Ratio of Cycloadducts Formed**

In all the four reactions studied (Scheme 4.1) the major product was invariably the 3,4-trans-4,5-trans-2-(4-methylphenyl)-3-aryl-4-carboxy-5-methyl isoxazolidine. The minor diastereoisomeric product had the 3,4-substituents cis- to each other. The ratio of the 3,4-trans : 3,4-cis isomer was 89-87 : 11-13. No regioisomeric product was obtained.
### Table 4.1: 300 MHz $^1$H-NMR Assignments of Compounds (8) and (9)

<table>
<thead>
<tr>
<th>Proton No.</th>
<th>8$^\dagger$ (chemical shift and multiplicity)</th>
<th>9$^\ast$ (chemical shift and multiplicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3</td>
<td>5.26, d (6.6)</td>
<td>4.87, d (10.0)</td>
</tr>
<tr>
<td>H-4</td>
<td>3.11, dd (8.9, 6.6)</td>
<td>3.39, t (9.7)</td>
</tr>
<tr>
<td>H-5</td>
<td>4.46, m</td>
<td>4.75, m</td>
</tr>
<tr>
<td>-CH$_2$</td>
<td>1.52, d (6.0)</td>
<td>1.47, d (6.0)</td>
</tr>
<tr>
<td>-CO$_2$CH$_3$CH$_2$</td>
<td>4.18, q (7.1)</td>
<td>3.88, m</td>
</tr>
<tr>
<td>-CO$_2$CH$_3$CH$_3$</td>
<td>1.25, t (7.1)</td>
<td>1.0, t (7.2)</td>
</tr>
<tr>
<td>-PhCH$_2$</td>
<td>2.28, s</td>
<td>2.33, s</td>
</tr>
<tr>
<td>Ring A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-2,6</td>
<td>7.07, d (8.4)</td>
<td>7.02, d (8.4)</td>
</tr>
<tr>
<td>H-3,5</td>
<td>6.88, d (8.4)</td>
<td>6.83, d (8.4)</td>
</tr>
<tr>
<td>Ring B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-2,6</td>
<td>7.74, d (8.8)</td>
<td>7.67, d (8.6)</td>
</tr>
<tr>
<td>H-3,5</td>
<td>8.23, d (8.8)</td>
<td>8.19, d (8.6)</td>
</tr>
</tbody>
</table>

$^1$H-NMR chemical shift in $\delta$, ppm, coupling constant $J$ in Hz in brackets.

$^\dagger$In CDCl$_3$ solution (500 MHz)  $^\ast$In CDCl$_3$ solution (300 MHz)

### Table 4.2: 75.5 MHz $^{13}$C-NMR Assignments of Compounds (8) and (9)

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>8 (chemical shift)$^\ddagger$</th>
<th>9 (chemical shift)$^\ast$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-3</td>
<td>73.1</td>
<td>71.5</td>
</tr>
<tr>
<td>C-4</td>
<td>65.7</td>
<td>61.0</td>
</tr>
<tr>
<td>C-5</td>
<td>78.0</td>
<td>75.3</td>
</tr>
<tr>
<td>C-6</td>
<td>170.3</td>
<td>168.6</td>
</tr>
<tr>
<td>C-7</td>
<td>18.0</td>
<td>17.7</td>
</tr>
<tr>
<td>-CH$_2$</td>
<td>62.1</td>
<td>59.7</td>
</tr>
<tr>
<td>-CO$_2$CH$_3$CH$_3$</td>
<td>14.5</td>
<td>13.8</td>
</tr>
<tr>
<td>-CO$_2$CH$_3$CH$_3$</td>
<td>20.9</td>
<td>20.6</td>
</tr>
<tr>
<td>-PhCH$_2$</td>
<td>149.9</td>
<td>147.7</td>
</tr>
<tr>
<td>Ring A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-1</td>
<td>149.9</td>
<td>147.7</td>
</tr>
<tr>
<td>C-2,6</td>
<td>114.6</td>
<td>116.3</td>
</tr>
<tr>
<td>C-3,5</td>
<td>130.1</td>
<td>129.3</td>
</tr>
<tr>
<td>C-4</td>
<td>131.9</td>
<td>132.6</td>
</tr>
<tr>
<td>Ring B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-1</td>
<td>149.0</td>
<td>147.1</td>
</tr>
<tr>
<td>C-2,6</td>
<td>127.8</td>
<td>129.1</td>
</tr>
<tr>
<td>C-3,5</td>
<td>124.5</td>
<td>123.5</td>
</tr>
<tr>
<td>C-4</td>
<td>147.9</td>
<td>145.5</td>
</tr>
</tbody>
</table>

$^\ddagger$In CDCl$_3$ solution (125.5 MHz)

$^\ast$In CDCl$_3$ solution (75.5 MHz)
Chapter 4.2: Cycloaddition of C-(4-Chlorophenyl)-N-(4'-Methylphenyl) Nitrones to Ethyl Crotonate Catalysed by Ytterbium Triflate [Yb(OTf)₃] and Lithium Triflate [Li(OTf)]

As of now, very little information exists on ytterbium triflate and lithium triflate catalysed reaction of 1,3-dipolar cycloaddition reactions. Hence the present investigator decided to study the effect of ytterbium triflate and lithium triflate (20 mol % of nitrone) as a catalyst on the following cycloaddition reactions.

The result with ytterbium triflate and lithium triflate have been discussed in Chart 4.2.

A mixture of C-(4-chlorophenyl)-N-(4'-methylphenyl) nitrone (2) (0.2 g, 0.00081 mol) and ethyl crotonate (6) (0.17 g, 1.5 x 0.00081 mol) and Yb(OTf)₃ (20 mol % of nitrone, 0.1 g, 0.00016 mol) were refluxed in an oil bath at 80 °C in dry toluene under nitrogen atmosphere. The reaction was studied by taking the ¹H-NMR spectrum of the crude reaction mixture at 4 hrs interval. The 300 MHz ¹H-NMR analysis of the post reaction mixture showed the presence of two stereoisomers which were the same as those obtained without the catalyst. However, using the catalyst the reaction was found to be 6 times faster than that normal reaction without the catalysts. The reaction was completed almost in 4 hours. Up to 8 hours the yield of the major product increased and the minor product decreased. After 8 hours
the yield of the major product decreased and the minor product increased. The total yields of
the product were 80.6, 91.6, 74.3 and 77.8 after the completion of 4, 8, 12 and 16 hours of the
reaction respectively.

A mixture of C-(4-chlorophenyl)-N-(4'-methylphenyl) nitrone (2) (0.2 g, 0.00081
mol) and ethyl crotonate (6) (0.17 g, 1.5 x 0.00081 mol) and Li (OTf) (20 mol % of nitrone,
0.025 g, 0.00016 mol) were refluxed in an oil bath at 80 °C in dry toluene under nitrogen
atmosphere. The reaction was studied by taking the $^1$H-NMR spectrum of the crude reaction
mixture at 4 hrs interval. The 300 MHz $^1$H-NMR analysis of the post reaction mixture
showed the presence of two stereoisomers which were identical with those obtained without
using the catalyst. The reaction was faster by 6 times. In this case the reaction was also
completed within 4 hours. Up to 8 hours yield of the major product increased and the minor
product decreased. After 8 hours the yield of the major product decreased and the minor
product increased. The total yields of the product were 82.1, 93.4, 96.8 and 97.3 after the
completion of 4, 8, 12 and 16 hours of the reaction respectively. Here the maximum yield of
the product (10) was observed after 16 hrs.

Chapter 4.3: Cycloaddition of C,N-Diaryl Nitrones to Diethyl Aryl Methylene
Malonates

Cycloadditions of nitrones to diethyl aryl methylene malonates occur with very high
selectivity to furnish 3,5-trans-2,3,5-triaryl-4,4-dicarbethoxy isoxazolidines. This is in
contrast to the nitrone cycloadditions to other α,β-conjugated carbonyl derivatives where two
diastereoisomerio (and occasionally regioisomeric) cycloadducts are generally obtained.

Cycloaddition reactions of nitrones to diethyl aryl methylene malonates were studied
earlier in our laboratory using different electron withdrawing group (viz. –Cl, NO$_2$) at the p-
position of C-aryl ring in the nitrone. The candidate studied a model reaction with m-nitro
group at C-aryl ring in the nitrone to invigas whether there would be any change in the
product formation as there would be no change in electron-withdrawing effect on the nitrone
with respect to the p-nitro group at C-aryl ring in the nitrone. However the resonance effect
would be absent. The same type of product as with p-nitro substituent was obtained but in lower yield.

The cycloaddition of C-m-nitrophenyl-N-phenyl nitrone (5) having meta- substituent on the C-aryl ring (containing electron-withdrawing nitro group) with diethyl benzylidene malonate has been studied (Chart 4.2).

The reaction was carried out in refluxing toluene under nitrogen atmosphere for 24 hours. At the end of this period only small amount of the nitrone survived. To enhance the reaction rate a 3-fold molar excess of the dipolarophile was taken. Exclusive formation of the 3,5-trans-2,3,5-triaryl-4,4-dicarbethoxy isoxazolidine occurred in 83% yield. The solvent was removed under reduced pressure and the post-reaction mixture was chromatographed over neutral alumina. No other product was detected within the limits of ¹H-NMR analysis in the reaction mixture.

The structure and relative configurations of the product was established on the basis of spectroscopic data and X-ray analysis.

The IR spectrum of the cycloadduct showed the expected bands for an unconjugated ester at 1728.2 cm⁻¹. The 500 MHz ¹H-NMR assignment for the product was confirmed by two-dimensional NMR experiments. The 500 MHz ¹H-NMR spectrum of (16) showed two singlets at δ 5.62 (H-3) and 6.22 (H-5). The H-3 and H-5 protons showed the expected long-range coupling to the ortho protons of the aryl rings attached to the respective carbons in the COSY-LR spectrum. Similar correlations were apparent in their two dimensional C-H correlation spectrum. The two methylene protons in both the carbethoxy groups in the cycloadduct could be differentiated in (16) as one set of methylene protons appeared at δ 3.82
and 3.39, while the other set appeared at δ 3.84 and 3.38. These were coupled to the methyl groups appearing at δ 0.81 and 0.69 respectively. This could be concluded from the two-dimensional COSY experiment.

The relative configuration of the aryl substituent could be settled only from X-ray crystallographic analysis. The LURE DCI Synchrotron facility in Orsay, France, was used to record the data. An image Plate system (MAR 345) was used as the detector. Recording was done under cryotemperature conditions. The crystal was monoclinic, with space group P2₁/c. The cell parameters and the ORTEP projection have been shown. The structure featured an all-trans stereochemistry for the N-lone pair/H-3/H-5 atoms. The nitro group on the phenyl ring at CC3 is highly agitated with a main component for 033b normal to the phenyl ring. Thus the structure and stereochemistry of the product could be unambiguously confirmed as (16).

Mass spectral fragmentation patterns were same as the previous compound. The 500 MHz ¹H-NMR and 125.5 MHz ¹³C-NMR assignments of (16) have been given in Tables 4.3 and 4.4.

![Fig. 4.1: X-ray Crystallographic Structure of 16 [ORTEP Projection]](image)

| Table 4.3: 500 MHz ¹H-NMR Assignment of Compound (16) |
|---------------------|------------------|
| Proton No.          | 16 (chemical shift and multiplicity) |
| H-3                 | 5.62, s           |
| H-5                 | 6.22, s           |
| -CO₂CH₂CH₂ (I)      | 3.38, 3.84, m     |
| -CO₂CH₆CH₆ (I)      | 0.69, t (7.5)     |
\(-\text{CO}_2\text{CH}_2\text{CH}_3\) (II) & 3.39, 3.82, m \\
\(-\text{CO}_2\text{CH}_2\text{CH}_3\) (I!) & 0.81, t (7.5) \\
**Ring A** \\
H-2,6 & 7.08, d (7.5) \\
H-3,5 & 7.23, t (7.9) \\
H-4 & 7.04, t (7.4) \\
**Ring B** \\
H-2 & 8.40, s \\
H-4 & 8.18, dd (8.2, 1.2) \\
H-5 & 7.54, t (8.0) \\
H-6 & 7.95, d (7.5) \\
**Ring C** \\
H-2,6 & 7.49, d (8.6) \\
H-3,4,5 & 7.34, m \\

1H-NMR chemical shift $\delta$ in ppm, coupling constant $J$ in Hz (in CDC\(_3\)).

Table 4.4: 125.5 MHz $\text{^{13}C}$-NMR Assignment of Compound (16).

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>16 (chemical shift)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-3</td>
<td>74.7</td>
</tr>
<tr>
<td>C-4</td>
<td>75.0</td>
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<tr>
<td>C-5</td>
<td>83.6</td>
</tr>
<tr>
<td>-\text{CO}_2\text{CH}_2\text{CH}_3) (I!)</td>
<td>13.8</td>
</tr>
<tr>
<td>-\text{CO}_2\text{CH}_2\text{CH}_3) (I!)</td>
<td>13.6</td>
</tr>
<tr>
<td>&gt;\text{CO} (I!)</td>
<td>62.4</td>
</tr>
<tr>
<td>&gt;\text{CO} (I!)</td>
<td>62.0</td>
</tr>
<tr>
<td><strong>Ring A</strong></td>
<td></td>
</tr>
<tr>
<td>C-1</td>
<td>148.6</td>
</tr>
<tr>
<td>C-2,6</td>
<td>118.9</td>
</tr>
<tr>
<td>C-3,5</td>
<td>129.2</td>
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<tr>
<td>C-4</td>
<td>124.7</td>
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<tr>
<td>C-1</td>
<td>148.6</td>
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<td>C-2</td>
<td>124.4</td>
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<td>C-3</td>
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<td>C-4</td>
<td>123.9</td>
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<td>129.9</td>
</tr>
<tr>
<td>C-6</td>
<td>135.4</td>
</tr>
<tr>
<td><strong>Ring C</strong></td>
<td></td>
</tr>
<tr>
<td>C-1</td>
<td>135.2</td>
</tr>
<tr>
<td>C-2,6</td>
<td>127.6</td>
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<tr>
<td>C-3,5</td>
<td>129.2</td>
</tr>
<tr>
<td>C-4</td>
<td>128.6</td>
</tr>
</tbody>
</table>

$\text{^{13}C}$-NMR chemical shift in CDC\(_3\).
Chapter 4.4: Rationalisation of the Course of the Cycloadditions on the Basis of Frontier Molecular Orbital Interactions and Density Functional Theory

The regio- and stereoselectivities of the cycloaddition process can be correctly predicted considering frontier-orbital interactions. Sustman [R. Sustman, *Tetrahedron Letters.*, 12, 2721, 1971] analysed these in detail for 1,3-dipolar cycloaditions. He classified 1,3-dipolar cycloaddition into three types, viz.

(i) Type I: Dipole HOMO-dipolarophile LUMO interaction predominated in case of electron-donating or conjugating substituents on the dipole and electron-withdrawing or conjugating substituents on the dipolarophile.

(ii) Type II: Dipole LUMO-dipolarophile HOMO interaction predominated. In this case electronic demands of the substituents are reversed as compared to Type I.

(iii) Type III: Both pairs of FMO interactions are of comparable importance.

The orbital coefficients for ethyl crotonate were calculated earlier by Joucla et al. [M. Joucla, F. Tonnard, D. Greé and J. Hamelin. *J. Chem. Res.* (S) 240, 1978]. The HOMO-LUMO interactions for the cycloaddition of ethyl crotonate to C,N-diaryl nitrones is represented in Fig. 4.2.

![Fig. 4.2](image)

Qualitatively, the HOMOs and LUMOs of all the diaryl nitrones have similar shapes with C₂ > C₁ in the HOMO and C₂ < C₁ in the LUMO and for the dipolarophile C₂ > C₃ in the HOMO and C₃ > C₂ in the LUMO in case of ethyl crotonate. For most of
these aldonitrone, both types of interaction, dipole-HOMO controlled (Sustmann Type I) and dipole-LUMO controlled (Sustmann Type II) would favour the formation of the same regioisomeric transition state which would lead to the formation of the 5-methyl-4-carbethoxy cycloadducts. This can therefore explain the overwhelming regioselectivity observed in most of these reactions. Electron-withdrawing substituents on both the dipole as well as dipolarophile directly conjugating with the ring cause a decrease in the difference in magnitude of the terminal orbital coefficients leading to a loss of regioselectivity. Thus a p-nitro substituent on the C-nitrone carbon reduces the regioselectivity, while a m-nitro substituent, which cannot enter into direct conjugation increases the regioselectivity.

**Theoretical Calculations using Density Functional Theory:**

Geometry optimizations were performed for all reactions and products using DFT/B3LYP/6-31G as implemented in Gaussian 03. All stationary points were characterised with frequency calculations.

In this work the candidate has presented a theoretical study (by means of BL3YP/6-31G) to establish the relative reactivity of all conformations of reactants in 1,3-dipolar cycloaddition reactions. Special interest was paid to the ethyl crotonate reactions. Counterparts often used in experimental studies: ethyl crotonate and C,N-diaryl nitrone for the 1,3-dipolar cycloaddition. Furthermore, the reaction of ethyl crotonate with the parent nitron has also been drawn in comparison with other theoretical studies. Both endo and exo approaches have been considered, whereas approaches leading to 4,5-disubstituted isoxazolidines have been considered for the 1,3-dipolar cycloaddition reactions.

The source of the preference for the 4-regio isomers in 1,3-dipolar cycloaddition reactions between nitrones and moderately electron deficient dipolarophiles has been a matter of debate. Thus, a possible explanation has been attributed to the control of the regioselectivity by $\text{HOMO}_{\text{dipolarophile}} - \text{LUMO}_{\text{dipole}}$ interactions. However, the calculations on efficient $\pi$-frontier molecular orbitals show a significantly lower energy gap for the $\text{HOMO}_{\text{dipole}} - \text{LUMO}_{\text{dipolarophile}}$ interaction (-0.292 ev) in comparison with that for the $\text{HOMO}_{\text{dipolarophile}} - \text{LUMO}_{\text{dipole}}$ interaction (-0.194 ev). Such results would predict the favoured formation of the 4,5-cycloadduct.
The different energy state (HOMO – LUMO) of nitrone, ethyl crotonate and the corresponding product in terms of ev have been shown in Table 4.5.

Table 4.5: HOMO-LUMO energies of nitrone, ethyl crotonate and the cycloadduct.

<table>
<thead>
<tr>
<th>Nitrono</th>
<th>Ethyl Crotonate</th>
<th>Cycloadduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMO (ev)</td>
<td>LUMO (ev)</td>
<td>HOMO (ev)</td>
</tr>
<tr>
<td>-0.268 (61*)</td>
<td>-0.074 (65*)</td>
<td>-0.264 (31*)</td>
</tr>
<tr>
<td>-0.263 (62*)</td>
<td>-0.018 (66*)</td>
<td>-0.268 (30*)</td>
</tr>
<tr>
<td>-0.243 (63*)</td>
<td>-0.013 (67*)</td>
<td>-0.290 (29*)</td>
</tr>
<tr>
<td>-0.209 (64*)</td>
<td>-0.007 (68*)</td>
<td>-0.341 (28*)</td>
</tr>
</tbody>
</table>

* denotes orbital number

From the comparison of the different HOMO-LUMO orbital energies of nitrone and ethyl crotonate we can conclude that orbital 65 of nitrone i.e. LUMO and orbital 30 of ethyl crotonate i.e. HOMO are more compatible and form the corresponding cycloadduct.

Chapter 4.5: Experimental

This chapter consists of the experimental section of the cycloaddition reactions studied by the author.

PART V: REVIEW ON THE CHEMICAL CONSTITUENTS OF MURRAYA KOENIGHI SPRENG (RUTACEAE)

In connection with his studies on Murraya koenigii Spreng (Rutaceae) the candidate thought it present to review the work carried out on this species till date.

PART VI: CHEMICAL INVESTIGATION OF MURRAYA KOENIGHI SPRENG (RUTACEAE)

Chapter 6.1: Isolation and Structure Elucidation of a New Carbazole Alkaoid

Murraya koenigii Spreng. (Rutaceae) locally called “curry patta” grows throughout India and the Andaman Islands. It is non-toxic and is highly valued for its characteristic aroma and medicinal importance in the indigenous system of treatment. The root bark of the
plant relieves renal pain while the leaves exhibit antioxidant and hypoglycemic action. Also the leaves of the plant are used to cure dysentery. [A. Chatterjee. *The Treatise on Indian Medicinal Plants, Vol.3*, National Institute of Science Communication, (CSIR) New Delhi p.108, 1997].

*M. koenigii* Spreng., is a rich source of carbazole alkaloids which have significant biological activities: anti-inflammatory, anti-diarrhoeal, anti-viral and also effect the central nervous system. Carbazole alkaloids, e.g. mahanimbine, murrayanol and mahanine, obtained from bioassay guided fractionation of the acetone extract of fresh leaves of *M. koenigii* Spreng showed mosquitocidal, antimicrobial activities and also exhibited topoisomerase I and II inhibition activities [R. S. Ramsewak, M. G. Nair, G. M. Strasburg, D. L. Dewitt, J. L. Nitiss. *Journal of Agricultural and Food chemistry*, 47(2), 444, 1999]. Beside these, murrayanol exhibited anti-inflammatory activity while mahanimbine showed anti-oxidant property. Anti-oxidants have gained much importance in recent years due to their anti-ageing properties. These compounds act as scavengers in removing the peroxy radicals, produced during our metabolism, which bring about ageing. Murrayanine, girinimbine, mahanine have anti-fungal property and in addition, mahanimbine also showed larvicidal activity. All these studies promoted the candidate to re-investigate the seeds of this plant. A new carbazole alkaloid, 8-hydroxy (2',2',3)-trimethyl (5,6)-dimethoxy pyrano carbazole, was obtained. The structure of this compound was elucidated on the basis of spectral data (IR, $^1$H and $^{13}$C-NMR, HMBC) and mass spectral analysis.

The n-hexane extract of seeds of *M. koenigii* on column chromatography over silica gel (60-120 mesh) afforded one known carbazole alkaloid Koenimbine (II) and a new carbazole alkaloid Kurryam (I), C$_{20}$H$_{21}$NO$_4$ (M$^+$ 339), m.p. 206 °C. The UV spectrum of this new compound showed ultraviolet absorption maxima: $\lambda_{\text{max}}^\text{EtOH}$ at 342, 299.5, 289.5 nm (log $\varepsilon$ 3.94, 4.34, 4.28 respectively) thereby indicating the presence of a carbazole unit. In the IR spectrum the peaks $v_{\max}^\text{KBr}$ at 3424.2 cm$^{-1}$ indicated the presence of a -OH and >NH group which has also been confirmed from the $^1$H-NMR signals at $\delta$ 7.78 and $\delta$ 7.55. The $^1$H-NMR spectrum of the compound also indicated the presence of two methoxy groups at $\delta$ 3.91 (3H, s, C-6aH) and $\delta$ 3.97 (3H, s, C-7aH). It also showed the two peaks for the gem-dimethyl group at $\delta$ 1.61 and $\delta$ 1.47. The signal at $\delta$ 2.32 indicated the presence of one aromatic methyl
The signals for the olefinic protons were obtained as a doublets at $\delta$ 5.67 (1H, d, $J = 9.9$ Hz, H-3') and 6.59 (1H, d, $J = 9.9$ Hz, H-4').

The 75.5 MHz $^{13}$C-NMR spectrum, including DEPT-135° experiment, revealed the presence of twenty carbon atoms, of which one gem-dimethyl and one aromatic methyl carbon appeared at 16.1 and 27.5 ppm respectively. Two methoxy carbons were discernible at 56.1 and 56.5 ppm. Eleven quaternary carbons at 120.1, 150.1, 134.0, 148.6, 115.2, 102.1, 144.2, 148.1, 133.9, 129.2 and 75.7 ppm were assigned to C-1, C-2, C-3, C-4, C-4a, C-4b, C-6, C-7, C-8a, C-9a and C-2' respectively. The new carbazole alkaloid has an aromatic methyl, one phenolic –OH and two methoxy groups. The $^1$H-NMR spectrum (CDCl$_3$) exhibited two singlets in the aromatic region at $\delta$ 6.88 and 7.38. These observations conjointly with the $^{13}$C-NMR spectral data allowed the only arrangement of the substitutions as shown in Fig. 6.1. The $^1$H-NMR assignments for the two protons in para position to each other in ring A are similar to the respective proton resonances in Koenidine [N. S. Narasimhan, M. V. Paradkar, V. P. Chitguppi, S. L. Kelkar. Indian Journal of Chemistry, 13, 993, 1975], another carbazole alkaloid. Moreover in the $^{13}$C-NMR spectrum the two –OCH$_3$ carbons resonated at 56.1 and 56.5 ppm which indicated that both the methoxyls are adjacent to at least one proton otherwise they would have resonated at ~ 60 ppm. The $^1$H-$^{13}$C HMBC correlation study also unequivocally supported the structure, which has been shown in Fig. 6.2. Again from the comparison of the spectral data of compound (I) with various literature data, [N. S. Narasimhan, M. V. Paradkar, V. P. Chitguppi, S. L. Kelkar. Indian Journal of Chemistry, 13, 993, 1975; A. Patra, P. K. Mukhopadhyay. Journal of Indian Chemical Society, LX, 265, 1983; M. Shamma, D. M. Hindenlang. Plenum Press, New York, p. 120, 1979; S. Mandel, P. C. Das, P. C. Joshi. Journal of Indian Chemical Society, 69, 611, 1992; N. A. Begum, D. N. Choudhury, J. Banerji, B. P. Das. Journal of Indian Chemical Society, 82, 165, 2005], it could be confirmed that the structure of compound (I) must be 4-hydroxy (2',2',3)-trimethyl (6,7)-dimethoxy pyrano carbazole, a new alkaloid isolated from the seeds of M. koenigii Spreng (Rutaceae), bearing an –OH group at C-4, hitherto unknown in this series of alkaloids.
Diarrhoea is caused by gastrointestinal infections which kill around 1.8 million people globally each year, mostly children in developing countries. The main cause of death from diarrhoea is dehydration, which results from loss of electrolytes in diarrhoeal stools.

During the last decade oral dehydration therapy has contributed greatly to the reduction of diarrhoeal mortality in children and elderly. However, diarrhoeal attack rate has remained unchanged and dehydration treatment often fails in high stool output state. Symptomatic therapy with antimortality agents is restricted to non-dehydrated patients without features of systematic infection. Moreover, there is an increasing threat of drug resistance, side effects of treatment with antibiotics, supra infection when normal symbiotic bacteria producing vitamins are eradicated. Despite the success of development of modern medicines, plant remedies have gained vast popularity over the recent years as cure for treatment of diarrhoea. A number of medicinal plant preparations have been recognised for treating diarrhoea, although their mode of action in elimination of organism remains unclear.
In our present study we have isolated and purified Kurryam (I) and Koenimbine (II) from *Murraya koenigii* Spreng and studied the effect of the compound on castor oil induced diarrhoea in rat model and compared their activity with standard antidiarrheal medicine diphenoxylate.

**Test animals:**

Wister rats weighing between 150 and 200 gms of either sex were used. The rats were housed in standard environmental conditions and provided with food and water ad libium.

**Castor oil-induced diarrhoea in rats:**

Rats of either sex were fasted for 18 hrs and randomly assigned to five groups of six animals each. The doses of Koenimbine (II), selected on trial basis, were administered orally (10, 50 and 100 mg/kg suspended in 2% v/v aq. tween 80) to three groups of animals. The fourth group received 5 mg/kg of diphenoxylate orally as a standard drug. The fifth group which served as control received 2% v/v aq. tween 80 suspension only. One hour after treatment each animal received 1 ml of castor oil orally by gavages and then defection was observed upto 4 hrs. The presence of characteristic diarrhoeal doping was noted. The same experiment was done with Kurryam (I).

**Chapter 6.3: Experimental**

In this chapter the candidate has discussed the isolation of the alkaloids from *Murraya koenigii* Spreng and study of the antidiarrheal properties.

**PART VII: CHEMICAL INVESTIGATION OF PAEDERIA FOETIDA AUCT. NON. L. (RUBIACEAE)**

*Paederia foetida auct. non L.* (Rubiaceae), known “Gandhabhadulia” in Bengali, grows in tropical parts of India, as well as in Central and Eastern Himalayas. The stem of the plant has a reputation in folklore medicine and exhibits anti-inflammatory, antimicrobial, antioxidative and hepatoprotective properties.
The occurrence of a number of iridoid glycosides and lactones (paederinin, paederoside and paederia lactone) in the stem of this species has been reported. The candidate undertook a detailed chemical investigation of the stem from which one new compound, i.e. an amide, N-(4-methylphenyl) benzopropanamide, was isolated.

The ethereal extract of the stem was fractionated between n-hexane and ethyl acetate. The ethyl acetate fraction of the extract was subjected to column chromatography over silica gel (60-120 mesh) and afforded the amide, C_{16}H_{17}NO [(m/z + Na) = 262.1203], m.p. 128 °C. In the infrared spectrum the peak at 3299.8 and 1655.2 cm⁻¹ indicated the presence of >NH and >C=O group. The presence of the amide carbonyl has also been confirmed from the $^{13}$C-NMR peak at 170.2 ppm. In the 300 MHz $^1$H-NMR spectrum, two triplets at δ 2.65 and δ 3.06 have been assigned to two adjacent methylenes, the latter being adjacent to a carbonyl group as it resonated in a comparatively downfield region. A three proton singlet at δ 1.71 was due to the p-methyl substituent at C-4.

The 75.5 MHz $^{13}$C-NMR spectrum showed the presence of twelve carbon atoms in the molecule. Comparison of the $^{13}$C-NMR spectrum with DEPT 135° clearly indicated the presence of one methyl at 20.8 ppm, two methylenes at 39.4 and 31.6 ppm, nine aromatic methines and four quarternary carbons at 170.2, 140.7, 135.2 and 133.9 ppm in the molecule, among which the signal at δ 170.2 was assigned to the carbonyl carbon.

All these spectral data indicated compound (I) to be N-(4-methylphenyl)-benzopropanamide, the first report of the isolation of an amide from the genus Paederia.

The structure of amide was further confirmed from X-ray crystallographic analysis (Fig. 7.1). The crystals of this compound are monoclinic, space group P2₁/c, with parameters a = 14.706 (3); b = 4.870 (4); c = 18.965 (4) Å; β = 98.14 (4) °.
The n-hexane eluent afforded white needle-like crystals, C_{30}H_{52}O (M^+ 428), m.p. 287-289 °C (n-hexane-ethyl acetate mixture). The IR spectrum showed the characteristic band for an aliphatic hydroxyl group at 3413.9 cm\(^{-1}\).

The 300 MHz \(^1\)H-NMR spectrum of the compound in CDCl\(_3\) showed the presence of one hydroxyl proton at \(\delta 2.07\) (1H, br. s.), one methine proton adjacent to the hydroxyl group at \(\delta 3.71\) (1H, d, \(J = 2.1\) Hz). Four methine and eleven methylene protons appeared in the region \(\delta 1.18-1.88\). Eight methyl groups were discernible in the \(^1\)H-NMR spectrum at \(\delta 0.83, 0.90, 0.92, 0.94, 0.96, 0.97, 0.98\) and 1.14 respectively.

The 75.5 MHz \(^{13}\)C-NMR spectrum including DEPT-135° were studied.

From the analysis of all the spectral data it could be confirmed that the triterpene isolated was 3β-friedelinol (II) (Fig. 7.2) which was further confirmed by comparison with an authentic sample obtained from the candidate's laboratory.