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NAME OF SUPERVISOR/NOM DU DIRECTEUR DE THÈSE J. W. ApSimon

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APPROACHES TOWARDS THE BIOGENETIC
TYPE SOLID PHASE SYNTHESIS
OF ALKALOIDS

by

Dilip M. Dixit

A thesis submitted to the Faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

Department of Chemistry

Carleton University

Ottawa, Ontario

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The undersigned recommend to the Faculty
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fulfilment of the requirements for the
degree of Doctor of Philosophy.

.....
Thesis Supervisor

.....
External Examiner

.....
Chairman, Department of Chemistry

Carleton University

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ABSTRACT

We were interested in the study of the oxidative coupling reactions of phenolic compounds, thereby leading to the biogenetic type synthesis of alkaloids. In plants the above oxidation proceeds smoothly to yield various products which are formed either by the intramolecular coupling of the phenolic substrates or via the intermolecular combination. Both processes occur with equal facility and through specific routes. In laboratory experiments the intermolecular oxidation predominates over the usually desired intramolecular mode and thus in various biogenetic type phenol oxidation studies of suitable substrates, the yields of alkaloids are generally low. In order to avoid intermolecular condensation reactions we decided to study the above oxidation reactions with the substrates anchored on the solid phase resin. The first two sections of this thesis deal with the solid phase synthesis of alkaloids while the last one is concerned with our approaches towards anodic oxidation of some norbelladine derivatives.

Firstly, we had to find a right anchoring functional group on the Merrifield's solid phase resin which would selectively hold the N-(4-hydroxyphenethyl)-3-hydroxybenzylamine and 1-(hydroxybenzyl)-1,2,3,4-tetrahydrohydroxy-isoquinoline derivatives used as our substrates. It was desirable to have the nitrogen atom protected and the phenolic groups left free to participate during the

subsequent oxidation stage. The anchoring function should be stable under oxidative reaction conditions but could easily be cleaved under mild conditions at the end of the synthesis.

Secondly, we carried out a large variety of oxidation reactions to induce intramolecular oxidative coupling to the substrates held on the solid phase resin. We also studied the photolytic coupling and dehydrobromination reactions on the bromine substituted derivatives. We were successful in achieving the synthesis of some novel Amaryllidaceae alkaloids in improved yields. The solid phase matrix appeared to have the ability to adopt the substrate molecules in different spatial orientations thus allowing the products to be formed via an alternative mode than that normally observed in other coupling reactions.

In the last section we report attempts to achieve anodic oxidations of some norbelladine derivatives with emphasis on the effect of the introduction of electron donating substituents in the aromatic rings on the facility of the oxidative coupling reaction.

INTRODUCTION

Alkaloids:

Alkaloids ^{1,2} are a large and structurally heterogeneous class of natural products. From ancient times man has utilized them as medicines, poisons and magical potions. Today, a little over two thousand alkaloids are known, and it is estimated that they are present in only 10-15% of all vascular plants. They are rarely found in cryptogamia (exception-ergot alkaloids), gymnosperms, or monocotyledons. They occur abundantly in certain dicotyledons and particularly in the families: APOCYNACEAE (dogbane, quebracho, pereiro bark), PAPAVERACEAE (poppies, chelidonium), PAPILIONACEAE (lupins, butterfly-shaped flowers), RANUNCULACEAE (aconitum, delphinium), RUBIACEAE (cinchona bark, ipecacuanha), RUTACEAE (citrus, fagara) and SOLANACEAE (tobacco, deadly nightshade, tomato, potato, thorn apple). Well-characterized alkaloids have been isolated from the roots, seeds, leaves or bark of some forty plant families and it is probable that the remaining families will provide only an occasional alkaloid-bearing plant.

Alkaloids have complex structures with one or more nitrogen atoms involved in the heterocyclic rings and often manifest significant pharmacological activity. Many widely distributed bases of plant origin, such as methyl, trimethyl and other open-chain simple alkyl amines, the cholines, the betaines and the purines are not classified as alkaloids. The distinction

between these biological amines (pseudoalkaloids) and the true alkaloids could be rationalized on the basis of the concept of biogenesis as follows.

Figure 1: Biogenesis of Alkaloids.

In general the alkaloids are classified either according to the plant genera in which they occur or on the basis of the similarity of molecular structure. Important classes of alkaloids containing generically related members are the aconitum, cinchona, ephedra, lupin, opium, rauwolfia, senecio, solanum and strychnos

alkaloids. Chemically derived alkaloids names are based on the skeletal feature which members of a group possess in common.

The indole alkaloids (e.g. psilocybin, the active principle of Mexican hallucinogenic mushrooms) contain an indole or modified indole nucleus and pyrrolidine alkaloids (e.g. hygrine) contain a pyrrolidine ring system. Other examples of this classification include the pyridine, quinoline, isoquinoline, imidazole, pyridine-pyrrolidine and piperidine-pyrrolidine type alkaloids.

Psilocybin (indole type)

Hygrine (pyrrolidine type)

Pseudopelletierine
(pyridine type)

Papaverine
(isoquinoline-type)

Pilocarpine
(imidazole type)

Atropine, Hyoscyamine
(piperidine-pyrrolidine type)

Nicotine
(pyridine-pyrrolidine type)

Quinine
(Quinoline type)

Figure 2. Some Representative Alkaloids

Biogenesis of Alkaloids:

The structural types found in the different classes of alkaloids are so diverse that it is impossible to develop a single biogenetic hypothesis to include all of them. As the structures of major groups of alkaloids were elucidated, it became apparent that their skeletons could be dissected visually into fragments whose carbon-nitrogen skeletons bore the features of various α -amino acids. The prominent among these were ornithine, lysine, phenylalanine, tyrosine, dihydroxyphenylalanine and tryptophan. These small fragments were reassembled into the complex product by

simple organic reactions. One reaction of particular importance was the Mannich reaction i.e. the condensation of an aldehyde with an amine, yielding an imine (or immonium salt) which may then be attacked by a nucleophilic carbon such as that of an enol or phenol to form a carbon-carbon bond.

Figure 3. Mannich Reaction

From biochemical studies, it is well known that the α -amino acids undergo decarboxylation to the amine as well as oxidative deamination and decarboxylation to the aldehyde in common metabolic situations. The α -amino acids supply the basic ingredients for the synthetic elaboration of alkaloid molecules in living tissue. The chief variants available in nature for affording diversity include the occasional involvement of small polyacetyl or $\text{C}_6\text{-C}_3$ fragments as in the acetogenins and several reactions such as N- and O- methylation, amine oxidation and the oxidative coupling of phenols in their ortho- and para-positions. In recent times radioactive tracer work has generally confirmed these speculations and added much solid detail as well.

The oxidative coupling of phenols plays an important role in the natural formation of wide varieties of compounds such as Pummerer's Ketone, usnic acid, tannins, bisnaphthols, bisanthraquinones, bisterpenoids, hypericin, thyroxine, picrolichenic acid, depsidones, xanthonones, grisans, geodin, erdin and 10% of estimated known alkaloids. Barton and Cohen³ proposed that the new carbon-carbon or carbon-oxygen bond is formed by radical pairing. This view imposes clear restrictions upon the nature of the substrate involved in the oxidative step.

(a) Amaryllidaceae alkaloids:

The alkaloids present in the Amaryllidaceae⁴ illustrate beautifully the varied operation of phenol coupling. These alkaloids may be considered to be three main skeletal types which can serve as the biogenetic precursors of all other bases in the family.

Figure 4 Skeletal Structures of Amaryllidaceae Alkaloids

Barton and Cohen ⁵ regarded all these structures to be derived from a single substance, norbelladine (1). The proposed biosynthetic pathways involve oxidation of suitably substituted norbelladine derivatives followed by rearrangement. The three main skeletal types may be regarded as arising by the following pathways ^{6,7}. (Figures 5 to 7).

Lycorine series:

Figure 5. Proposed Biogenetic Pathway Leading to Lycorine Type Alkaloids and C¹⁴ Labelling Patterns.

Haemanthamine and Crinamine series:

Figure 6. Proposed Biogenetic Pathway Leading to Haemanthamine and Crinamine Type Alkaloids and C¹⁴ Labelling Patterns.

Galanthamine series:

Figure 7. Proposed Biogenetic Pathway Leading to Galanthamine Type Alkaloids and C^{14} Labelling Patterns.

Norbelladine itself is biogenetically derived from phenylalanine and tyrosine as follows ^a (Figure 8).

Figure 8. Biogenesis of Norbelladine from Phenylalanine and Tyrosine (^{14}C Labelling).

These pathways are sustained by tracer evidence as indicated in the schemes above. The distribution of label found by unambiguous chemical degradation of the products was exactly as predicted on the basis of Barton's hypothesis. Specific entry of

the label from the O-methyl group of p'-O-methylnorbelladine into the methylenedioxy function of haemanthamine also provides experimental proof of the biosynthetic origin of this one-carbon function. N-Methylation of norbelladine blocks entry of the precursor into alkaloids of the lycorine and cgrinine series. It does not inhibit its incorporation into the galanthamine series. The methylation pattern of the precursor thus controls its entry into pathways leading to the different structural variants. Experiments with multiply labelled samples of p'-O-methyl- and N,p'-O-dimethylnorbelladine show that the methylation processes are specific and irreversible. Methylation at the m'-oxygen of norbelladine appears to inhibit the phenolic coupling as m'-O-methylnorbelladine was not incorporated into haemanthamine.

(b). 1-Benzylisoquinoline alkaloids:

Sir Robert Robinson ⁹ postulated that the alkaloids derived from 1-benzylisoquinolines are biosynthesized from a benzyl tetrahydroisoquinoline precursor, norlaudanosoline (3).

These classical biogenetic speculations not only served as a working hypothesis for biosynthetic investigations but correctly predicted many of the findings of recent tracer experiments. Norlaudanosoline is derived in the plants from the two $C_6 - C_2$ units of 3,4-dihydroxyphenylalanine (dopa), which in turn arises by the hydroxylation of tyrosine¹⁰ (Figure 9).

Figure 9. Biogenesis of Norlaudanosoline from Tyrosine
(C^{14} Labelling Patterns)

The alkaloids derived from norlaudanosoline (3) fall into two major subgroups as shown in subsequent figures. The first of

these includes the morphine, the aporphine and the aromatic erythrina bases; all of which contain the intact $C_{16}N$ nucleus of the norlaudanosoline, whereas a further carbon atom is required to complete the skeletons of the second group which includes the protoberberine, phthalideisoquinoline, protopine, and benzo-phenanthridine bases. This additional one carbon fragment is generated from a methyl group. Methionine serves as a one-carbon donor in many biochemical systems. The same source also supplies the peripheral one carbon units, the N-methyl, O-methyl and methylenedioxy carbons, which are found in alkaloids of both subgroups.

The use of optically pure precursors has yielded more detailed information of the final stages of biosyntheses of various alkaloids. Of various O-methylated derivatives of norlaudanosoline studied as a controlling factor in the biogenetic pathways, reticuline (serves as a precursor of the morphine alkaloids in the opium poppy ¹¹. It is the (-)-isomer which corresponds stereochemically to thebaine, codeine and morphine and is their precursor as indicated in the figure 10.

Figure 10. Biogenesis of Morphine from (-) Reticuline.

C¹⁴ Labelling Patterns .

The (+)-isomer of reticuline is preferentially incorporated into narcotine, stylophine, chelidonine as well as into berberine and protopine ¹² (figures 11 and 12).

Figure 11. Biogenesis of Narcotine, Stylophine and Chelidonine from (+)-Reticuline (C¹⁴ Labelling Patterns)

Figure 12. Biogenesis of Berberine and Protopine
from (+)-Reticuline
(C¹⁴ Labelling Patterns)

It appears that the berberine-bridged ($C_{17}N$) alkaloids are derived from one enantiomer of reticuline, and the non-berberine-bridged ($C_{16}N$) alkaloids from the other. An exception is sinomenine, a $C_{16}N$ alkaloid derived from (+)-reticuline.

(+)-Orientaline (5), the structural isomer of reticuline leads to the aporphine bases e.g. isothebaine¹³, while the erythrina alkaloids¹⁴ are derived from norprotosinomenine (6), yet another structural analog of reticuline. (Figures 13 and 14).

Figure 13. Biogenesis of Isothebaine from (+)-Orientaline.

(C^{14} Labelling Patterns)

Norprotosinomenine (6)

Figure 14. Biogenesis of Erythrina Alkaloids from Norprotosinomenine.

In each case enough evidence is available which provides experimental support for the validity of the proposed sequences. In addition to the use of multiply labelled, stereochemically resolved substrate which had been predicted as precursors, it has been demonstrated that these substrates are normally present in the experimental plants in many instances. The absolute stereochemistry of precursor and the product has been found to correspond and several of the intermediates e.g. salutaridine have been recognized as alkaloids in their own right. (Figure 10).

The mode of cyclization of the precursor is thus determined by the position of its free phenolic groups. It appears that the process of O-methylation directs cyclization by protection and consequent deactivation of the phenolic groups in a specific manner. The lack of incorporation of the wrongly or completely methylated precursor again indicated that the enzymic methylation processes are highly specific and that they are irreversible.

Hence the experimental studies in the biosynthesis of alkaloids derived from N-benzylphenethylamines, 1-benzyl-isoquinolines and various other bases have shown that the oxidative coupling of phenolic precursor plays a very important role in the biogenetic pathways.

(ii) Triterpenes are the most widespread terpenes in plants, where they are almost invariably pentacyclic compounds with few functional groups. They are biogenetically related to steroids and arise biosynthetically by cyclization of a folded squalene chain in a stereoselective fashion. Johnson and some other workers attempted to duplicate these cyclization processes in the laboratory and thus provide a nonenzymic and a stereoselective synthetic route to the tetra- and penta-cyclic triterpenes. An example of a Lewis acid catalysed cyclization of a tetraene acetal is as follows ¹⁷.

Figure 16. Biogenetic Type Synthesis of a Triterpene in a Highly Stereoselective Mode.

Biogenetic Type Syntheses of Alkaloids:

To demonstrate the validity of a biogenetic hypothesis some alkaloids have been chemically synthesized from suitably functionalized "cell-possible" fragments and in some cases even under the conditions assumed to resemble those of the cellular environment. Such "biogenetically modelled" syntheses generally involve Mannich and phenol coupling reactions and are an indirect evidence of the proposed biogenetic pathway.

(a) Amaryllidaceae Alkaloids:

With the ready availability of belladine derivatives, a considerable effort has been put into the synthesis of Amaryllidaceae alkaloids along the biogenetic pathways. Of the three possible alkaloid types obtained by phenolic oxidation of norbelladine (1), crinan- and galanthamine-type alkaloids have been successfully synthesized. Franck and Lubs¹⁸ oxidized a diphenolic precursor with ferric chloride to give a dienone in 12% yield.

Figure 17. Biogenetic Type Synthesis of a Crinan Derivative: Ferric Chloride Oxidation.

Schwartz ¹⁸ oxidized 0-methylnorbelladine (2) using vanadium oxytrichloride as an oxidant.

Figure 18. Biogenetic Type Synthesis of A Crinan Derivative: Vanadium Oxytrichloride Oxidation.

The yield of para-para coupled dienone had increased to 24%. This dienone on hydrolysis underwent a Michael addition involving the nitrogen atom to generate the crinan-type enone, which could be transformed into maritidine.

Narwedine was obtained in a poor yield by manganese dioxide oxidation of a belladine derivative, and was further reduced to galanthamine²⁰.

Figure 19. Biogenetic Type Synthesis of Galanthamine, Manganese Dioxide Oxidation.

Other oxidants such as potassium ferricyanide or lead dioxide did not lead to any improvement in the yields. Kametani²¹ reported improved yields involving bromoamide as a substrate for phenol oxidation. Amidation protected basic nitrogen against oxidation, and the bromine atom prevented oxidative coupling at an undesired position.

The yield of the o,p'-coupled product rose to 40%.

Figure 20. Potassium Ferricyanide Oxidation of a Belladine Derivative.

(b) 1-Benzylisoquinoline Alkaloids:

Many isoquinoline alkaloids have been synthesized using biogenetic-type reaction pathways. Majority of Aporphine bases were formed by phenolic coupling of appropriately protected derivatives of laudanosoline. First *in vitro* synthesis was accomplished by Franck²² who oxidized laudanosoline methiodide with ferric chloride.

Figure 21. Biogenetic Type Synthesis of Aporphines:
Ferric Chloride Oxidation.

The yields were 60%. The lone pair on the nitrogen atom was protected by methylation which facilitated carbon-carbon coupling.

Reticuline (4) had been oxidized with several oxidizing agents to afford isoboldine. The yields varied from 0.5 to 6%.

Figure 22. Biogenetic Type Synthesis of Aporphines.

Orientaline (5) which is isomeric to reticuline underwent phenolic oxidation with potassium ferricyanide in poor yields to afford orientalinone. Orientalinone on reduction with sodium borohydride gave orientalinol and the latter underwent dienol-benzene rearrangement to give isothebaine²⁴.

Orientaline

Figure 23. Biogenetic Type Synthesis of Aporphines:
Oxidation of Orientaline.

Morphinanedienone alkaloids are biogenetically derived from reticuline (4). Barton ²⁵ oxidized tritium labelled reticuline and the product was isolated using unlabelled salutaridine as a carrier. Oxidation was carried out with manganese dioxide, potassium ferricyanide, ferric chloride and Fremy's salt. The yields were very low. The salutaridine thus obtained was reduced to an epimeric mixture of diols

which were dehydrated under acidic conditions to give thebaine.

Figure 24. Biogenetic Type Synthesis of Morphinanediene
Alkaloids: Oxidations of Reticuline.

Another coupling mode of reticuline would give a second morphinanediene, pallidine. Franck²⁶ oxidized reticuline (4) with manganese dioxide on silica gel to

Other Approaches to the Biogenetic Type Syntheses of
Amaryllidaceae and 1-Benzyl-Isoquinoline Alkaloids:

(a) Photolytic Coupling

Another approach which involves the photolytic generation of diradicals leads to the synthesis of various isoquinoline and some Amaryllidaceae alkaloids ²⁹. The bromophenolic precursors were utilized for the intramolecular cyclization as it is well known that photolysis of aromatic halides in benzene results in the formation of biphenyl derivatives by the reaction of aryl radicals produced by the homolytic cleavage of the carbon-halogen bond ³⁰.

Figure 26. Photolysis of a Bromo-diphenol leading to the Synthesis of a Crinan-derivative.

This spirodienone, which was formed in low yields, could be transformed to maritidine via reduction.

Kametani cyclized the following diphenolic bromoamide to the narwedine-type analog which was reduced to yield galanthamine³¹.

Figure 27. Photolysis of a Diphenolic Bromoamide leading to the Synthesis of Narwedine-type Analog.

The photolysis of the 1-benzyl-8-bromotetrahydroisoquinoline gave a 7% yield of (+)- glaziovine³². Alternatively a 1% yield of the same compound was obtained by potassium ferricyanide oxidation.

Figure 28. Photolysis of 8-Bromotetrahydro-1-benzyl-isoquinoline Derivative leading to the Synthesis of Glaziovine.

The lone pair of electrons on the nitrogen atom had to be protected in order to permit the desired carbon-carbon photocyclization. Various other examples of similar syntheses are discussed in literature ²⁹.

(b) Benzyne Reaction

Kametani synthesized ($\pm$)-cryptaustoline and ($\pm$)-thaliporphine via the benzyne reaction of 1-(5'-bromo-benzyl)-tetrahydroisoquinoline derivative ³³.

Figure 29. Benzyne Reaction on a 1-(5'-Bromo-benzyl)-tetrahydroisoquinoline Derivative.

(c) Pschorr Reaction

The Pschorr reaction had also been applied to induce intramolecular coupling of phenolic radicals. The diazotized 1-benzyltetrahydroisoquinoline derivative cyclized under thermal conditions to yield morphinanedienone and an aporphine ³⁴.

Figure 30. Pschorr Reaction on a 1-(6'-Diazo-benzyl)-tetrahydroisoquinoline Derivative.

In general, most of the in vitro oxidative coupling reactions gave low yields of the desired products in the oxidation step. The under-lying cause might be the severity or the non-selectivity of the oxidant, which is reflected in the predominance of the dimeric or polymeric intermolecular condensation reaction over the desired intramolecular coupling. Phenolic precursors combine to form many different products arising from either carbon-oxygen or carbon-carbon coupling. Substitution products arising from coupling at benzylic positions are also possible in certain situations.

(d) Electro-oxidation

Electro-oxidation offered in itself a more promising oxidizing system ³⁵. By utilizing controlled electro-oxidation, one can use just enough oxidizing potential to carry out a desired, selective reaction without the fear of over-oxidation, and one can control this potential very accurately. This method works only as long as the product is less easily oxidized or reduced than the starting material. One can also control the rate of reaction by adjusting the electrode size and the potential, and thereby the current flow. Considerable work has been done in the studies of the electrolytic oxidations of simple phenols ³⁶.

Bobbitt ³⁷ studied the intermolecular coupling of 1-benzyltetrahydroisoquinoline derivative. The electrolytic oxidation of the sodium salt of ($\pm$)-N-ethoxycarbonyl-N-norarmepavine led to the dimeric mixtures in reasonable yields.

Figure 31. Electro-oxidation of the Sodium Salt of
(±)-N-Ethoxycarbonyl-N-norarmepavine.

The oxidation of the free nitrogen base under identical conditions led to the fragmentation of the tetrahydroisoquinoline system.

The intramolecular coupling of N-carbethoxy-N-norreticuline gave a dienone coupled in a para-para mode in about 18% yield³⁸.

Figure 32. Electro-oxidation of N-carbethoxy-N-norreticuline.

Miller ³⁹ had managed to couple nonphenolic derivative of 1-benzyltetrahydroisoquinoline at platinum electrode to afford O-methylflavinantine, a morphinandienone in 52% yield.

Figure 33. Electro-oxidation of a Nonphenolic 1-Benzyl-tetrahydroisoquinoline Derivative.

When the above oxidation was performed in the presence of bis (acetonitrile)-palladium (II)-chloride, the yield of the dienone was enhanced to 63%.

Comparison of Biological and Chemical Oxidation Processes

In nature, the biogenetic pathways by which different alkaloids are derived either by the intramolecular oxidative coupling or via the intermolecular mode from the same phenolic precursor, are specific and occur with an equal facility. The phenolic molecule is held on the enzyme surface in a proper orientation and location. During oxidative stage, it loses its electrons via the intermediacy of the acidic and basic functionalities on the surface. The three general classes of enzymes - peroxidases, laccases and tyrosinases, which are known to catalyze the oxidative coupling of phenols, contain metal atoms which can preferentially coordinate with the substrate ⁴⁰.

However in a chemical oxidation of a phenolic compound, the yields of intramolecularly coupled products are generally lower than the ones obtained via intermolecular condensations. As the phenolic precursor loses its electrons to the metal atom to form radicals or an equivalent species, it is under a strong influence of the neighbouring neutral phenolic molecules, radicals or charged species. Thus it exhibits a greater tendency to undergo intermolecular associations to

form di- or poly- radicals, which are also energetically more favoured. Further, the nature of metal atom present in the oxidant, its oxidation level and the type of ligands attached to it, do contribute to the product ratio of the intramolecular and intermolecular condensation reactions. Considering all these factors, it seems that the biological systems are more efficient to induce intramolecular oxidative coupling reactions of a phenolic substrate than the chemical analogs.

Application of the Principles of Solid Phase Synthesis to the Biogenetically Modelled Synthesis of Alkaloids.

In order to improve the yields of the alkaloids formed via the intramolecular oxidative coupling mode of a phenolic precursor, we set out to devise a synthetic method which might permit us to oxidize an appropriately functionalized phenolic compound selectively without allowing it to interact with its neighbours. The technique of the solid phase synthesis^{41,42} seemed to us to be a good choice as it incorporated all the requirements for a selective, high dilution oxidation reaction.

The solid phase synthesis was developed by R.B. Merrifield⁴³ for the synthesis of peptides. The fundamental premise of this method is that the amino acids can be assembled into a peptide of any desired sequence while one end of the chain

is anchored to an insoluble support. After the desired sequence of amino-acids has been linked together on the support, a reagent can be applied to cleave the chain from the support and liberate the finished product into the solution.

Figure 34. Principles of Solid Phase Synthesis.

The solid support, $(P)-$, is a synthetic polymer that bears reactive groups "X". These groups are made to react with the carboxyl group of an amino acid in such a way that the amino acid is bound covalently to the polymer. During this step, the amine group of the amino acid must be covered with a protecting group "Y", so that the amine will not react with the polymer. The protecting group must be such that it can be selectively removed without damage to the bond holding the amino acid to the support. After removal of this protecting group, a second N-protected amino acid can be caused to acylate the exposed amine group of the first amino acid, thus forming the first peptide bond. By repeating these two deprotection and coupling steps, using each time the proper N-protected amino acid, the peptide of a desired sequence is assembled on the polymer support. At the end of the synthesis, a different reagent is applied to cleave specifically the bond joining the first amino acid to the polymer, and free peptide is liberated into the solution.⁴ All the reactions involved in this synthesis can be brought to 100% completion, so that a homogeneous product can be obtained.

This method has since been modified by various workers and is at present a general procedure for the synthesis of medium length peptides. This method of repetitive "sequential-type" synthesis has also been applied to the synthesis of polynucleotides⁴⁴ and polysaccharides⁴⁵. Recently the

Insoluble polymers have been utilized for a wide variety of synthetic steps to solve specific problems in general organic synthesis. Various polymer bound reagents have been developed which are found to be more specific, easy to handle and lead to relatively clean reaction products ⁴².

The great advantage in using the solid phase method is that laborious purification at the intermediate steps in the synthesis is eliminated, and simple washing and filtration of the solid is substituted. Especially, for the synthesis of long chain enzymes and peptide hormones, the solid phase offers a very rapid and facile approach. Furthermore, this technique is also amenable to automation, which has proved to be a great timesaver, especially in the synthesis of long peptides.

The main limitations are due to the use of insoluble polymers, which lead to heterogeneous reaction mixtures, giving rise to lower yields in the condensation step or alternatively require longer than usual reaction times or more vigorous reaction conditions. The large excess of reagents are required to push the reaction closer to the completion. Even the release of the final product from the polymer support sometimes leads to great difficulty.

Considering all these problems involved, we attempted to develop a procedure for the application of the solid phase synthesis to the intramolecular oxidative coupling of phenols, thereby leading to a biogenetically modelled synthesis of alkaloids.

RESULTS AND DISCUSSION

This thesis describes the application of the principles of solid phase synthesis to the study of the intramolecular oxidative coupling of phenols with the view to the biogenetic type synthesis of alkaloids and some preliminary studies on anodic oxidations of some nonphenolic compounds. The discussion will be divided into three parts. The first chapter will deal with the study and application of various anchoring functional groups on the solid phase resin to the anchoring and deanchoring of some diphenolic substrates which are suitable for oxidative coupling. In the second part of the investigation, various attempts to oxidize these phenolic substrates on the solid phase resin will be discussed and finally the last section will deal with our experiments with the anodic oxidations of some norbelladine derivatives.

Chapter I

Investigation of Various Anchoring Functional Groups on the Solid Phase Resin for the Anchoring and Deanchoring of Some Diphenolic Substrates:

A suitable insoluble resin support and a satisfactory means of attaching the diphenolic precursor to it were of great importance for the successful solid phase synthesis. The solid support selected by us was "styrene-2% divinylbenzene copolymer resin (200-400 mesh)", which was specifically developed by R.B. Merrifield for the solid phase synthesis ⁴¹. It is in the form of fine beads (20-70 microns in diameter) and is commercially available. This polymer is composed of long alkyl chains bearing a phenyl group on every second carbon. These chains are crosslinked at approximately every fiftieth carbon by *p*-diethylphenyl residues derived from the divinylbenzene. This cross-linking causes the polymer to be completely insoluble in all ordinary solvents. The low degree of cross-linking gives a resin that swells extensively in organic solvents such as chloroform, dichloromethane, dioxane, *N,N'*-dimethylformamide and benzene, but swells much less in alcohols, ethyl acetate and acetic acid. The swelling in solvents is very important since substrate anchoring can take place within the pores and

interstices of the beads and it also permits the satisfactory penetration of solvents and reagents to the substrate anchored on the resin. This resin is also inert under normal chemical reactions.

Merrifield introduced the chloromethyl group as the first anchoring functional group on the resin, which was found very suitable for attaching the N-protected amino acid via its C-terminal (carboxyl group). The phenyl rings in the polystyrene-divinylbenzene resin can be conveniently chloromethylated in a Friedel-Crafts reaction with chloromethyl methyl ether and stannic chloride.

Figure 35. Chloromethylation of Styrene-2% Divinylbenzene Copolymer Resin.

The halogen thus introduced is in a reactive benzyl chloride type linkage and is susceptible to the facile nucleophilic displacement.

The phenolic substrates which are suitable for the oxidative coupling studies are of the type,

Where $n=2$ and $m=1$ or 2 .

It contains two phenolic hydroxyl groups and a secondary amine function. During oxidation, the two phenolic hydroxyl groups, which are involved in radical (or equivalent species) formation should be free while the amino group must be protected. The lone pair of electrons on the unprotected nitrogen atom might be very reactive during oxidation and thus lead to unwanted side reactions. This substrate on condensation with the chloromethyl resin can form either an ether linkage at the phenolic oxygen atoms or a tertiary amine bond at the nitrogen atom. A typical oxidative coupling reaction on the solid phase utilizing a chloromethyl resin may be visualized as:

Figure 36. A Representative Oxidative Coupling Reaction on the Solid Phase.

The precursor belladine derivative, which is protected by a group "R" at the nitrogen atom, condenses with the chloromethyl resin to form an ether linkage at the phenolic oxygen atom, which is not involved in the phenolic oxidation step. This precursor anchored on the resin on oxidation should lead mainly to the intramolecular oxidative coupling. Each molecule of the precursor is held firmly via a covalent bond on the resin and thus cannot interact with its neighbours. The oxidized product is finally cleaved from the resin. The most commonly used procedure to remove the finished peptides from the chloromethyl resin support has been the nucleophilic displacement of the peptide by hydrogen bromide in an anhydrous trifluoroacetic acid medium. Other acidic or basic reagents can be used for the same purpose.

We attempted to anchor norbelladine (I) on the chloromethyl resin in a stepwise manner as follows,

Figure 37. Synthesis of Norbelladine on the Chloromethyl Resin.

The yields of deanchored norbelladine hydrobromide were negligible. The highly acidic deanchoring reaction medium might have destroyed most of the released material. Hence this procedure of the stepwise synthesis of substrate on the solid phase seemed not to be much of a preparative value to us.

We decided to synthesize the substrate first and then anchor it to the resin as a complete unit. This method would not leave any incomplete fragments on the resin. The main problem at this stage was to select the correct anchoring functional group on the resin which should exhibit some selectivity in its condensation reaction with the phenolic group or the secondary amine function of the substrate. Further, the reaction conditions to liberate the substrate (or the product) from the resin should be very mild in order to avoid decomposition.

The next anchoring functional group on the resin, which we studied for our purpose was the methyl chloroformyl resin. This function was developed by Letsinger ⁴⁶ and later utilized by Merrifield ⁴⁷ for the azide solid phase peptide synthesis. It was prepared via the action of phosgene on the hydroxymethyl resin.

Figure 38. Preparation of Methyl Chloroformyl Resin.

The methyl chloroformyl group should exhibit somewhat more preference to its electrophilic reaction with the secondary amino group rather than the phenolic hydroxyl groups. The synthetic procedure to anchor the substrate p'-O-Methylnorbelladine (2) on the methyl chloroformyl resin is represented as follows.

Figure 39. Anchoring of the substrate (2) on the Methyl Chloroformyl Resin.

We attempted to follow the course of the condensation reaction by observing the shift in the position and relative intensity of the carbonyl stretching band in the infrared spectrum of the resin. The reaction seemed to us to be non-selective and the yields of deanchored material were again very low.

A more selective anchoring functional group on the resin was found to be the carboxyl resin ⁴⁶. It was prepared by treating the resin with diphenylcarbonyl chloride and aluminum chloride in nitrobenzene followed by acidic hydrolysis of the resulting amide.

Figure 40. Preparation of the Carboxyl Resin.

The carboxyl chromophore exhibited a strong band at 1710 cm^{-1} in its infrared spectrum. When this resin was treated with the substrate (2) and dicyclohexylcarbodiimide in N,N'-dimethylformamide, the condensation mainly occurred at the nitrogen atom to form an amide bond on the resin.

Figure 41. Anchoring of the Substrate (2) on the Carboxyl Resin.

The tertiary amide bond absorption was indicated at 1635-1640 cm^{-1} . The phenolic hydroxyl groups of the substrate did not react with the carboxyl resin as shown by the complete absence of the aromatic ester band at the 1765 cm^{-1} . The rationale for this preferential and exclusive nucleophilic reaction leading to the formation of an amide bond on the resin might be due to the higher nucleophilicity of the secondary amino function as compared to the phenolic hydroxyl groups. This particular aspect of the condensation reaction was of a great advantage for our synthetic plan. The substrate was now bound to the resin via a very stable tertiary amide bond at the nitrogen atom. The resin thus acted as a protecting group for the secondary amino group and the unshared pair of electrons on the nitrogen atom would become localized preventing any side reactions during the oxidation step. The phenolic hydroxyl groups would be completely free to coordinate with the metal atom of the oxidant and undergo oxidative coupling. We had thus achieved our first goal of anchoring the substrate on the resin in an appropriate manner.

However the main disadvantage with the carboxyl resin arose during the deanchoring stage. The amide bond in general could be hydrolyzed under the both acidic and basic conditions. In the solid phase synthesis of peptides, the deanchoring of the product from the resin involved the hydrolysis of an ester bond. The most common methods employed to cleave the

peptide from the resin are the nucleophilic displacement of the peptide by hydrogen bromide in anhydrous trifluoroacetic acid medium, the acidic hydrolysis with anhydrous liquid hydrogen fluoride, saponification reaction using sodium hydroxide in aqueous para-dioxane, the transesterification with anhydrous methanol in the presence of triethylamine, the hydrazinolysis and the ammonolysis reactions of the ester bond ⁴¹. We attempted to hydrolyze the amide bond linking the substrate to the resin using all the above methods except the acidic hydrolysis with hydrogen fluoride. In most cases we even employed more vigorous reaction conditions using excess reagents and extended reaction periods. We found that it was nearly impossible to cleave the amide bond without the destruction of the substrate and the resin. We also utilized the nitrated form of the carboxyl resin for anchoring the substrate which should facilitate the nucleophilic displacement reactions in general but again the amide bond did not cleave satisfactorily.

Figure 42. Synthesis of the Nitrated form of the Carboxyl Resin.

We concluded that the unreactivity of the amide bond towards hydrolysis might be due to the higher steric and electronic requirements of the transition state. Usually the amide bond hydrolyzes with more difficulty than the ester bond. We decided to utilize the carboxymethyl resin for the anchoring-deanchoring studies ^{44-b}. This resin was prepared as follows:

Figure 43. Preparation of the Carboxymethyl Resin.

Here the carboxyl group was displaced by one more carbon atom from the polymeric phenyl groups and thus some of the steric strains which were involved in the transition state of the amide hydrolysis (or cleavage reaction) with the carboxyl resin might be relieved in this case. The carboxymethyl resin exhibited an equal facility to anchor the norbelladine

derivative (2) exclusively via the amide bond.

Figure 44. Anchoring of the Substrate (2) on the Carboxymethyl Resin.

The amide bond again could not be hydrolyzed under the same experimental conditions used to deanchor the substrate from the carboxyl resin. These results indicated that the electronic

factors might be playing a more important role in the transition state for the amide bond cleavage reaction. We also realized that it may be necessary to look for another anchoring functional group on the resin which would not necessitate the cleavage of an amide bond at the deanchoring step.

During the course of this work in searching for an anchoring functional group on the resin, which could cleave the anchored substrate easily and under mild conditions, some German workers ⁴⁸ were developing the use of some inorganic supports for the solid phase synthesis of peptides and oligonucleotides. These inorganic carriers were glass beads, silica gel and Sephadex, which could be represented as (P)-SiOH . The capacities of these polymeric supports were very low, but the rate of condensation reactions were quite fast and the deanchoring took place under very mild conditions. In order to examine the suitability of this system to our synthetic plan, we studied the following reaction sequence. We used silica gel (Merck, less than 0.08 mm. in diameter, finer than 200 mesh ASTM) as the carrier.

Figure 45. Anchoring of the Substrate (2) on the Functionalized Silica gel.

The progress of the sequence was followed by the infrared spectroscopy, although the resolution of the peaks in the spectra was very poor. The deanchoring was carried out by using 0.1M sodium hydroxide or hydrochloric acid solution. The yields were very low and the condensation appeared to be nonselective as the substrate was bound to the succinoyl residue both via the ester and amide bonds.

Yip and Tsou ⁴⁹ introduced a new anchoring functional group on the resin, which was prepared as follows:

Figure 46. Preparation of Succinoyl Resin.

In this system the anchoring took place at the free carboxyl group while the cleavage from the resin occurred at the carbonyl function. Thus the two functional groups which were involved in the anchoring and deanchoring processes were separate and of differing reactivities; while with the carboxyl and carboxymethyl resin, same functional group was responsible for both the steps. The cleavage from the resin occurred under very mild conditions. A typical reaction sequence is represented as

Figure 47. Anchoring and Deanchoring of the Substrate (2) on and from the Succinoyl Resin respectively.

Infrared spectroscopy indicated that the substrate (2) had been anchored via the amide bond to the succinoyl residue on the resin. This amide was not involved in the deanchoring process and we were able to hydrolyze the carbonyl bond quantitatively under the basic conditions. Thus for the first time, we were able to use a functional group on the solid phase resin which fitted well with our synthetic plan. The anchoring and deanchoring processes of the substrate from the resin occurred under mild conditions.

We encountered a major drawback with the succinoyl resin. During its preparation via acylation with succinic anhydride, aluminum chloride was used as a Lewis acid. All Lewis acids exhibited a strong tendency to get adsorbed or occluded and thus cross-polymerize the resin matrix. The occluded aluminum chloride could not be removed even under strong acidic conditions. As the anchoring processes occur within the pores and interstices of the resin beads, the presence of adsorbed aluminum chloride might hinder these "inside" reaction sites thereby reducing the anchoring capacity of the functional group on the resin. Also some undesirable side reactions or interaction might be induced by the presence of strong Lewis acid during subsequent oxidation step. Some workers⁵⁰ observed the resin occluded aluminum chloride to be a very stable acidic material which could be used selectively to catalyze some dehydration reactions. We decided to modify this succinoyl resin and

introduce the succinoyl residue on the resin without the use of a Lewis acid. We prepared the hydroxymethyl resin according to the Merrifield's procedure ⁴⁷ which was then acylated with succinic anhydride.

Figure 48. Preparation of the Modified Succinoyl Resin.

This modified succinoyl resin was clean, stable under normal reaction conditions and could easily anchor the substrate (2).

Figure 49. Anchoring of the Substrate (2) on the Modified Succinoyl Resin.

The infrared spectrum indicated the absorption at 1600, 1645 and 1730 cm^{-1} , which indicated that the anchoring of the substrate took place selectively at the nitrogen-atom to form a tertiary amide bond. The phenolic hydroxyl groups of the substrate remained free to take part in the

next oxidative coupling step.

The deanchoring of the substrate (2) from the modified succinoyl resin could be achieved under mild basic conditions. Sodium hydroxide (0.5M in water: p-dioxane, 1:1 ratio) at 80° C hydrolyzed both the ester and amide bonds in three hours to yield the free secondary amine (2). The reaction might involve internal nucleophilic displacement represented as follows.

Figure 50. Possible Mechanism for the Basic Hydrolysis of the Resin (14).

However we preferred milder transesterification reaction with potassium carbonate in methanol. The reaction mixture was heated with reflux for eighteen hours.

Figure 51. Transesterification of the Resin (14).

The succinoyl residue remained attached to the nitrogen atom of the substrate via the amide bond, which subsequently could be hydrolyzed to yield free amine (2). The microanalysis of this modified succinoyl resin anchored with the substrate (2) or resin (14) in the figure 50, indicated it to contain 0.96% of nitrogen which corresponded to 0.6858 mmole of the functional group per gram of the

resin. This capacity of the resin would be sufficient to carry out a successful solid phase synthesis.

The modified succinoyl resin could also be used for the stepwise synthesis of peptides, where the nitrogen-terminus (the amino group of an amino-acid) is linked first to the succinoyl chain on the resin. In order to examine the extent of racemization of an amino acid during the deanchoring process from the resin, we studied the following sequence with the l-tyrosine ethyl ester.

Figure 52: Anchoring-Deanchoring Studies with l-Tyrosine and Modified Succinoyl Resin.

The optical rotation of the deanchored amino acid residue was very close as compared with the one synthesized directly.

Figure 53. Synthesis of Ethyl succinoyl Derivative of L-Tyrosine Ethyl ester.

This experiment indicated the absence of any racemization during the deanchoring process. We also anchored L-menthol on the modified succinoyl resin which was recovered back on deanchoring with no racemization.

Similarly β -naphthol could be anchored to this resin via the ester bond and recovered back on the basic hydrolysis.

Thus the modified succinoyl resin can anchor alcohols, phenols, amines and amino-acids quantitatively and release them quantitatively under mild hydrolytic conditions. The resin is very stable under normal reaction conditions and can be used to study various synthetic transformations.

Finally we attempted to utilize the soluble polystyrene resin. The soluble polymer system should be superior to an insoluble resin because all the chemical reactions would be homogeneous in the former case. There would be a greater probability of a quantitative reaction at all the sites, since for Merrifield's insoluble resin⁴¹, the rate and extent of formation of new bonds or chemical transformations depended on the permeability of the resin. Polystyrene of molecular weight about 270,000 was chosen for the polymer support. It was soluble in most of the common organic solvents and insoluble in water and the lower molecular weight alcohols.

We decided to introduce a succinoyl chain on this polymer, so we had to follow the synthetic sequence which was utilized in the preparation of the modified succinoyl resin. However the problems arose in the first step where the polymer was chloromethylated with chloromethyl methyl ether in the presence of stannic chloride as a Lewis acid.

This reaction yielded a gelatinous insoluble material. The generation of this material was attributed to cross-polymerization by a stannic chloride-catalyzed intermolecular Friedel-Crafts reaction involving the benzyl chloride residues ⁵¹. As mentioned before, even Merrifield's insoluble resin exhibited a great affinity for occlusion by the Lewis acids ⁴¹. We tried to use various proportions of chloromethyl methyl ether and stannic chloride for chloromethylation but with no apparent success. We also substituted boron trifluoride as a Lewis acid, but it also led to the formation of the insoluble product. However, we were able to carry out the following sequence on a smaller scale using aluminum trichloride as a catalyst.

Figure 54. Synthesis of the Soluble Succinoyl Resin and Its Condensation with the Substrate (2).

We were unable to deanchor the substrate in satisfactory yields from this functionalized soluble polystyrene resin.

We also encountered difficulties in scaling up the synthetic sequence. The resin exhibited unpredictable solubilities in various organic solvents at the end of every synthetic step, which might be explained due to absorption of aluminum chloride and various other by-products in the resin matrix.

The table 1 summarizes the advantages and limitations of various anchoring functional groups on the resin, which we have studied so far.

Table 1. Scope and Limitation of Various Anchoring Functional Groups on the Resin.

Type of Resin	Ease of Anchoring	Stability of the Resin	Ease of Deanchoring
(1) Chloromethyl resin	Difficult	Stable	Very difficult
(2) Chloroformyl resin	Non-selective	Less Stable	Difficult

Type of Resin	Ease of Anchoring	Stability of the Resin	Ease of Deanchoring
(3) Carboxyl resin	Easy and selective	Stable	Very difficult
(4) Carboxymethyl resin	Easy and selective	Stable	Very difficult
(5) Silica gel succinoyl resin	Non-selective	Not very stable	Very easy
(6) Succinoyl resin	Easy and selective	Stable	Very easy
(7) Modified succinoyl resin	Easy and selective	Stable	Very easy and under mild conditions
(8) Soluble succinoyl resin	Selective but difficult	Unstable	Difficult and incomplete

The succinoyl and modified succinoyl resins on deanchoring led to the quantitative recovery of the substrate, as the infrared spectrum of the deanchored resin exhibited a complete absence of the ester and amide bands.

Thus at this stage the modified succinoyl resin was best suited to anchor various diphenolic precursors and study their intramolecular oxidative coupling reactions on the resin.

Chapter II

Investigation and the Use of Various Oxidizing
Agents to Induce Intramolecular Oxidative Coupling in
Some Diphenolic Substrates Anchored to Solid Phase Resin.

The chemical oxidation of phenols ⁴⁰ is quite complex. Usually a mixture of products are formed and sometimes the same phenol can yield different product mixtures with different oxidants. In general, in the presence of a variety of chemical and biological oxidizing agents, phenolic molecules combine to form either carbon-carbon or carbon-oxygen coupling. Simple phenols are linked at positions ortho and/or para to the hydroxyl group to yield several possible dimers, these can be further oxidized to produce trimers, polymers and quinoid-structures. Intramolecular as well as intermolecular coupling may occur in more complex polyhydroxy aromatic compounds. Substitution products and compounds resulting from coupling at benzylic positions are also observed in some oxidation reactions.

Oxidative coupling as it is commonly conceived is a two electron oxidation. However, two general modes of overall coupling; external and internal oxidation, are possible. In the former process, electrons are transferred from the phenolic moieties to an external oxidizing agent,

whereas in the latter process an internal oxidation-reduction occurs, in which one moiety is oxidized and the other reduced during the coupling step. There is no net change in the overall oxidation state during this reaction and this last process may be termed as "non-oxidative coupling" (NOC).

Plausible mechanisms for external oxidative coupling can be grouped into two broad classes, each of which may be further divided into several general mechanistic types. (figure 55.)

1. Mechanisms involving free-radical intermediates.
 - (i) Direct coupling of two phenoxy radicals (FR1)
 - (ii) Homolytic aromatic substitution (FR2)
 - (iii) Heterolytic coupling preceded by two successive one electron oxidations (FR3)
2. Mechanisms which are nonradical in character.
 - (i) Heterolytic coupling preceded by a single two electron transfer (NR1)
 - (ii) Concerted coupling and electron transfer (NR2)

FR1, FR2 and FR3 Mechanisms:

R = Alkyl group

NR1 Mechanism:

NR2 Mechanism:

Figure 55. Mechanism for the Oxidative Coupling of Phenols.

With two-electron oxidants ⁵² such as lead tetraacetate, benzoyl peroxide and possibly alkaline persulphate, the dominant reaction is electrophilic attack on the aromatic ring i.e. mechanism FR3. However, one-electron oxidants such as potassium ferricyanide, ferric chloride and other oxidants yield aryloxy radicals, detectable by ESR spectroscopy, which may dimerize either by carbon-carbon or carbon-oxygen coupling and often yield polymeric rather than dimeric final products. These reactions will fall under the mechanisms FR1 and FR2.

The aryloxy cations will exist mainly as carbonium ions, whereas the aryloxy radicals are neutral but dipolar species with a higher electron density on the oxygen-atom than on the aromatic ring.

Figure 56. Electron Density Distribution on Aryloxy Cation and Radical.

On account of this dipolar character the dimerization of radicals should preferably proceed by carbon-oxygen-carbon coupling to give dimers and eventually polymers though some concurrent carbon-carbon coupling should occur.

Figure 57. Dimerization and Polymerization of the Aryloxyl Radicals.

In contrast aryloxyl cations should be very reactive species for effecting the electrophilic nuclear substitution of even un-ionized phenols to yield the dimers and then the quinones.

Figure 58. Dimerization of the Aryloxyl Cations.

Experimental evidence indicates that in acid solution or with reagents of high potential, the quinones and diphenquinones are formed in preference to carbon-oxygen-carbon dimers or polymers, while with reagents such as alkaline ferricyanide an increase in alkalinity favours polymer formation.

Thus the reaction mechanism which involves the formation of aryloxyl radicals is not applicable to those biogenetic

syntheses in which carbon-carbon coupling occurs between two different aryloxy-groups. For homolytic oxidations effective carbon-carbon coupling of unsymmetrical molecules HO-Ar-X-Ar'-OH (where X is a nonconjugative linking group) would require the kinetically improbable condition that the stage (ii) of the following sequence (Figure 59) should be very much faster than the stage (i) for otherwise the monoradical $\cdot\text{O-Ar-X-Ar'-OH}$ would have ample time to dimerise to a carbon-oxygen-carbon coupled product.

Figure 59. Homolytic Oxidation of Unsymmetrical Molecules

So the biochemical oxidative carbon-carbon coupling of phenols and biphenols HO-Ar-X-Ar'-OH would preferentially take place via the reaction mode which involves the formation of an aryloxy cation. The electrophilic substitution is a reaction between an active cation and a phenol molecule. This cation should attack very effectively a phenol of

different structure to its own precursor and in the case of biphenol HO-Ar-X-Ar'-OH , this unsymmetrical cross linking (coupling) would be particularly favourable. The route of this crosslinking should depend on the relative oxidation potentials of HOAr and HOAr' , for these factors should determine the particular aromatic ring at which the oxidative attack first occurs.

Since these two distinct reaction mechanisms may be operative, it does account for the fact that the routes of enzymic oxidative coupling of plant phenols are varied and yet biologically selective.

In the initial stage, we decided to utilize the oxidizing agents which were previously found to induce oxidative coupling in various biogenetic type syntheses of alkaloids. Potassium ferricyanide and ferric chloride are the most commonly employed oxidants⁴⁰. They are both one electron oxidants and involve the intermediacy of phenoxy radicals. However in various oxidations of phenols, the ferricyanide produces carbon-oxygen coupled products, whereas the use of ferric chloride promotes carbon-carbon coupling. This anomalous behaviour can be rationalized on the basis of the coordination capabilities of the metal complex.

Ferricyanide is a substitution inert transition metal complex and it does not exchange its ligands at a rate fast enough to compete with rapid electron transfer (oxidation-

reduction) reactions. Therefore oxidations by ferricyanide occur through nonbonded or an outer-sphere process, whereby an electron is transferred from the substrate to the metal ion via the cyano ligand. Each phenoxy radical so produced is then free to react as it chooses; and carbon-oxygen coupling becomes probable. Most ferricyanide oxidations of phenols are carried out in an alkaline medium, so the phenoxy anion is better able to transfer an electron to ferricyanide by an outer-sphere process.

Ferric chloride in neutral or acidic aqueous solution exists as various chloro-aquo complexes. Exchange of the various ligand molecules from the ferric ion occurs easily and thus the electron transfer from the substrate to the metal ion probably occurs directly through a metal-substrate bond. Iron has a great affinity for the ligands coordinating through oxygen. This inner-sphere electron transfer mechanism explains the predominance of carbon-carbon coupling if the phenoxy radicals produced remain complexed through oxygen to the respective iron atoms during the coupling step.

Our first attempts were to oxidize N-(4-hydroxyphenethyl)-3-hydroxy-4-methoxybenzylamine (compound 2) on the solid phase resin using ferric chloride dissolved in a mixture of N,N'-dimethylformamide and water in 1:1 proportion.

Figure 60. Oxidation Experiments with Compound (2) on the Solid Phase Resin.

The former solvent was used to swell the resin, thus allowing the oxidant to have an access to coordinate with as many resin bound substrate molecules as possible. We utilized varying concentrations of ferric chloride at different temperatures for extended periods of reaction time, but the yields of the expected coupled product were none to very minute. Similarly the oxidations with potassium ferricyanide which were carried out in a mixture of N,N'-dimethylformamide, and water with some ammonium acetate or sodium bicarbonate, did not lead to the formation of coupled product even with a large excess of oxidant, longer than usual reaction periods and higher

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temperatures were utilised. We also attempted to oxidize 1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (compound 15) on the solid phase resin with ferric chloride and potassium ferricyanide under similar reaction conditions

Figure 61. Oxidation Experiments with Compound (15) on the Solid Phase Resin.

and again we had no success. In all the above experiments the deanchoring of the substrate from the resin was carried out either with 0.5M sodium hydroxide in a mixture of water and *p*-dioxane or potassium carbonate in methanol. The substrate was recovered quantitatively either as free

secondary amine or a succinoyl amide derivative.

The next oxidant studied, was vanadium oxytrichloride. Here the reactive species is vanadium (V) and it has been used to oxidize phenols in aprotic solvents to give good yields of para-para coupled products. Schwartz ¹⁹ had oxidized a norbelladine derivative to crinan type compound in 24% yield (figure 18). He ⁵³ postulated a simple mechanism involving the formation of a vanadium-phenolate compound, followed by decomposition of this species to give a phenoxy radical and a vanadium species of one lower valence unit and then dimerization of the radicals to give the product. However this simple explanation does not satisfy all the experimental evidence. Although the course of the phenolic coupling reactions is not clear, the existence of a metal-phenol derivative has been established and a nonradical, two electron oxidation pathway might be possible. A simplified version of a NR2 mechanism ⁴⁰ for these reactions may be represented as follows:

Figure 62. Mechanism for the Vanadium Oxytrichloride Oxidation of Phenol.

In our experiments to oxidize the compound (2) or (15) on the solid phase, we stirred a mixture of the substrate on the resin with vanadium oxytrichloride (5mmoles of the oxidant per gram of the resin) in dry methylene chloride at -78°C for six hours followed by heating with reflux for the next forty hours. Surprisingly we observed the oxidative decomposition of the resin material. Normally

the resin itself is very stable against many corrosive reagents. We repeated the above experiment at room temperature but still could not avoid the loss of resin.

At this stage we decided to use strong oxidizing agents which were not used in the oxidative coupling reactions of various phenolic compounds. We attempted the oxidation of our substrates on the solid phase with potassium dichromate in a 1:1 mixture of acetic acid and N,N'-dimethylformamide or in 3M sulphuric acid, 3M nitric acid mixed with *p*-dioxane in a 1:1 ratio and neutral and weakly acidic or basic solutions of potassium permanganate. These acidic reagents should facilitate the formation of aryloxy cation from the substrate and thus promote the intramolecular cross-coupling. In the oxidation of simple phenols, these strong oxidants did oxidize some 2,6-disubstituted phenols to 3,3',5,5'-tetra substituted diphenokynones but with most phenols extensive decomposition of the organic material occurred. We reasoned that the substrate while anchored on the resin should be less sensitive to the strong oxidizing agents due to the heterogeneous nature of the reaction. The rate and extent of the oxidation reaction would depend on the accessibility of the oxidant to reach and coordinate with the substrate through the resin matrix. Thus by adjusting suitable reaction medium, we might be able to get some oxidative coupling of the substrate without the concurrent decomposition.

We used the following substrates for the oxidation experiments.

Figure 63. Substrates used for the Oxidative Coupling Experiments.

We again utilized varying concentrations of above oxidants in the reaction medium at different temperatures and reaction periods. However, the majority of these experiments either led to no oxidation under mild conditions or partial (or complete) decomposition of the precursor when the strength of the oxidation medium was raised. We

were unable to have a precise control over the desired intramolecular oxidative coupling reactions.

In the oxidation of the substrate (7) on the solid phase resin with 3M nitric acid in *p*-dioxane at room temperature, we obtained a coupled derivative as a very minor component to which we tentatively assigned the following structure..

Figure 64. Nitric Acid Oxidation of the Substrate (7)
on the Solid Phase.

This lactam (22) was possibly formed via the ortho-para coupling of the two phenolic rings followed by benzylic oxidation. The succinoyl chain was lost from the nitrogen atom under the transesterification conditions. Franck¹¹ (figure 17) had oxidized a derivative of compound (7) with ferric chloride and obtained an enone which was formed via the para-para coupling of the phenolic rings. The structure of the lactam (22) was based on the following spectral properties.

IR: ν max (CHCl_3) 1770 (aryl ester), 1690 (lactam),
1605, 1510 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) *213 ($\log \epsilon = 4.8983$), 232 ($\log \epsilon = 3.9746$),
285 nm ($\log \epsilon = 0.9289$).

NMR (CDCl_3) δ : 2.0 (6H,s,Ar-O-C(=O)-CH₃), 3.5 (6H,s,Ar-O-CH₃),
6.4 (4,m,aromatic protons)

MS $m/e = 399$ (absent) (M^+), 356 (17.4%) ($399 - \text{H} - \text{COCH}_2$),
314 (22.1%) ($356 - \text{COCH}_2$), 297 (20.9%) ($356 - \text{OCOCH}_3$),
284 (19.76%) ($314 - \text{CH}_2\text{O}$), 272 (49%) ($356 - \text{CO} - \text{CONH}=\text{CH}$),
271 (31%) ($356 - \text{CHO} - \text{CONH}=\text{CH}$), 255 (61.6%) ($271 - \text{CH}_3$),
241 (57%) ($271 - \text{CH}_2\text{O}$), 179 (15%), 137 (base peak) ($179 - \text{COCH}_2$)

The presence of biphenyl structure was indicated by the low intensity of the mass peak at $m/e = 179$, which was the base peak in the mass spectrum of the diacetate of the substrate (7).

Figure 65. Base Peak in the Mass Spectrum of the Diacetate of the Compound (7).

The lactam unit was lost as $m/e = 56$ during a fragmentation process. The other products of the oxidation reaction were formed via the overoxidation of the substrate molecule. We could not improve the yields of the dienone (22) on subsequent experiments and we thus abandoned this route.

The next oxidizing agent which we studied, was ceric sulphate in 10% sulphuric acid. This reagent is usually used as a visualizing aid on analytical silica gel plates for various organic compounds. Kupchan⁵⁴ observed that some monophenolic 1-benzyl isoquinoline compounds did cyclize to quinonoid derivatives on the silica gel plates, when the latter were sprayed with 3% ceric sulphate in 3N sulphuric acid. On subsequent preparative experiments they improved the yields of cyclized material to about 25%. We attempted to cyclize the compounds (2), (7), (15) and (16) (figure 63) anchored on the solid phase resin, but with many trials we were unable to induce any intramolecular coupling reaction.

The other oxidants which we studied were manganese dioxide, lead dioxide, lead tetraacetate and benzoyl peroxide and we were again unsuccessful. Finally we decided to try to apply thallium (III) trifluoroacetate for our purpose. Taylor⁵⁵ oxidized some simple phenolic derivatives to para-quinones with this reagent and Schwartz⁵⁶ extended this approach to the synthesis of ($\pm$)-oxocrine in about 20% yield. Recently⁵⁷ he oxidized ($\pm$) N-nor-reticuline derivative at low temperatures to give a

salutaridine derivative and isoboldine analog in 11 and 7% yields respectively. These compounds were formed via the ortho-para coupling of the two phenolic rings.

Figure 66. Thallium (III) trifluoroacetate Oxidation
of a Norbelladine and Norreticuline Derivative.

We attempted to oxidize the substrate (2) on the solid phase resin using various proportions of the oxidant in dry methylene chloride. However this reagent destroyed the substrate when the oxidation was carried out at room temperature; although the resin itself remained unaffected

under these conditions. We repeated the oxidation at -55°C for 24 hours and still the overoxidation of the substrate could not be prevented. Thus thallium (III) trifluoroacetate seemed not to be very satisfactory as an oxidant for the solid phase coupling reactions.

At this stage we had studied a wide variety of inorganic oxidizing agents which were known to induce intramolecular oxidative coupling reactions with various phenolic compounds. We were thus far unable to apply these reagents to oxidize our substrates on the solid phase resin in a reasonable yield. We decided to look for other approaches to solve this problem. We prepared the bromo-derivatives of compounds (2) and (7) and decided to study their photocyclization on the solid phase resin.

Kametani ³⁰ had photolysed the compound (23) to produce an enone in low yields, which was further converted to a crinan derivative, maritidine (figure 26). We repeated the above photolysis with the compound (23) anchored on the solid phase resin. The photolysis was carried out in a medium consisting of para-dioxane and water (ratio 1:1) and containing 2% sodium hydroxide to polarize the phenolic groups thus activating them to undergo oxidative cyclization. We used Hanovia 73 A 36 mercury lamp with a pyrex filter. However the major reaction under these conditions seemed to be the deanchoring of the substrate from the resin. We reduced the concentration of sodium hydroxide to one milligram per millilitre of the solution and also the irradiation period, but still considerable deanchoring of the uncyclized substrate was observed. We also carried out some photolysis experiments without the addition of base in the reaction medium, but we could not observe any increase in the yields of the coupled product. The photolysis of compound (24) anchored on the solid phase resin produced a coupled compound (25) in very low yield, whose tentative structure might be represented as

The spectral data for this compound is

IR: $\nu_{\max}$ (CHCl_3) 1725 (ester), 1665 (amide) 1565, 1515 cm^{-1} .

UV: $\lambda_{\max}$ ($\text{C}_2\text{H}_5\text{OH}$) 210 ($\log \epsilon = 4.5115$), 238 ($\log \epsilon = 4.1506$),
285 nm ($\log \epsilon = 1.3161$).

The mass spectrum of this compound indicated the absence of the mass peaks at $m/e = 215$, 217 or 137. These peaks would be the base peaks in the mass spectra of noncoupled compounds (24) and (7).

(7) $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{H}$. $m/e = 137$ $\text{R}_2 = \text{H}$

(24) $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{Br}$ $m/e = 215, 217$ $\text{R}_2 = \text{Br}$

Figure 67. Base Peaks observed in the Mass Spectra of the Compounds (7) and (24).

In order to improve the yields of coupled product, we decided to study the Pschorr reaction on the solid phase resin. This reaction involves diazotization of a primary amine derivative of a diphenolic compound thereby generating an unstable aromatic carbonium ion which should cyclize readily to form the coupled compounds. This procedure had been utilized by Kametani ³⁴ to synthesize some aporphine derivatives in low yields (figure 30). We decided to substitute the bromine atom in compounds (23) and (24) with a primary amino group and then study its diazotization reaction on the solid phase. We anchored compound (23) on the modified succinoyl resin and treated it with sodium amide in liquid ammonia for 12 hours. To check the identity of the amino derivative, we deanchored the solid phase held material via transesterification with methanol-potassium carbonate and followed it by methylation of free phenolic groups with diazomethane. We obtained the following compounds.

Figure 68. Solid Phase Synthesis of Lycorine Type Alkaloids:
Intramolecular Coupling of a Benzyne Intermediate.

The spectral evidence supporting the structure of (28) is

IR: ν max (CHCl_3) 1730 (ester), 1668 (amide), 1615, 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 203 ($\log \epsilon = 4.6101$), 223 ($\log \epsilon = 4.0692$),
278-282 nm ($\log \epsilon = 1.0012$).

NMR (CDCl_3) : 3.69 (6H,s,- OCH_3), 3.86 (6H;d,- OCH_3), 4.5 (2H,
d, $\text{Ar-CH}_2\text{-N}$), 6.65 (m, aromatic protons).

The mass spectrum of this compound indicated the presence of the molecular ion at $m/e = 413$ (40%).

The compound (28) was formed via the ortho-para-coupling of the two phenolic rings and thus should be the member of Lycorine family (figure 5). When the compound (23) was treated with ten-fold excess of sodium amide in liquid ammonia for eighteen hours, the products (26), (27) and (28) were formed in the yields of 38, 49 and 13 percent respectively. Similarly when the compound (24) anchored on the solid phase resin was subjected to sodium amide-liquid ammonia treatment for twelve hours, the compounds (29), (30) and (31) were formed in the ratio 28:67:4.5 respectively.

Figure 69. Solid Phase Coupling of Compound (24) through the Intermediate formation of Benzyne.

The mass spectrum of the compound (31) indicated the presence of the molecular ion $m/e = 443$ as the base peak.

The other peaks were $m/e = 412$ (21%) ($443 - \text{OCH}_3$), 328 (78%) ($443 - 115$), 313 (26%) ($328 - \text{CH}_3$), 285 (14%) ($313 - \text{CO}$) and 270 (16%) ($285 - \text{CH}_3$)

The mass peak at $m/e = 328$ was interesting as it was formed due to the loss of succinoyl chain from the compound (31).

The infrared and ultraviolet spectra of this compound were in accord with the assigned structure.

In our previous experiments with vanadium oxytrichloride as an oxidant, we observed a considerable loss of the substrate and resin material when the oxidations were carried out in ice bath or at room temperature. We repeated above experiments at -55°C . The compound (2) anchored on the solid phase resin was mixed with 5 to 10 mole equivalents of vanadium oxytrichloride in dry methylene chloride under the atmosphere of nitrogen. The oxidation reaction was carried out in a Dewar flask using Cryo Cool to maintain the low temperature for 36 to 48 hours. There was no loss of substrate from the resin during oxidation and the resin itself remained intact. It was deanchored with usual procedure with methanol and potassium carbonate followed by methylation with diazomethane. We obtained a coupled biphenyl derivative which was not identical on thin layer chromatography with the compound (28) which was obtained via sodium amide-liquid ammonia treatment with the compound (24) on the solid phase resin (figure 68).

Figure 70. Solid Phase Coupling of the Compound (2)
via Vanadium Oxytrichloride Oxidation.

The formation of compound (32) could be explained via the ortho-ortho-coupling of the two phenolic rings. The spatial geometry with the two phenolic hydroxyl groups lying face to face over each other and in coordination with vanadium (V) ion appeared to be more favoured in the transition state of the oxidation reaction. This unusual and sterically strained mode of coupling might be due to the formation of very stable bidentate vanadyl complex (or organometallic intermediate) as influenced by the resin matrix. The intramolecular concerted electron transfer to the metal atom would lead to the formation of biphenyl derivative (figure 70). During the methylation reaction of the deanchored reaction mixture with diazomethane, the predominant product appeared to be the trimethyl derivative in addition to minor quantity of the tetramethyl compound (32). The former compound could be crystallized out from its concentrated ethereal solution to form globular crystals with a melting point of 132-133°C. This trimethyl derivative could be represented by either of the two structures (33-a) or (33-b), but (33-a) seemed to be more favoured on the basis of steric factors.

The intramolecular hydrogen bonding present in the compound (33-a) or (33-b) appeared to be quite strong as it could be converted to compound (32) only under forced methylation reaction conditions. The spectral

characteristics of partially methylated derivative
(33-a) or (33-b) were as follows.

IR: ν max (CH_2Cl_2) 3420 (-OH), 1730 (ester), 1640 (amide),
1600, 1520 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 205 ($\log \epsilon = 4.1231$), 227 ($\log \epsilon = 3.3240$),
277.5 nm ($\log \epsilon = 1.0727$).

NMR (CDCl_3) δ : 3.715 (6H,m,- OCH_3), 3.93 (3H,d,- OCH_3),
4.76 (2H,d, Ar- CH_2 -N), 6.2-7.1 (5H,m, aromatic protons).

MS: m/e = 399 (base peak) (M^+), 368 (27.6%) ($\text{M}^+ - \text{OCH}_3$),
284 (44.8%) ($\text{M}^+ - 115$), 255 (31%) (284-CHO), 241 (84.8%)
(284- CH_3 -CO), 151 (24.1%), 115 (48.3%).

The high resolution mass spectrum indicated the molecular
ion at 399.1697 (the calculated mass based on the composition
of $\text{C}_{22}\text{H}_{25}\text{O}_6\text{N} = 399.1682$). The NMR spectrum showed diamagnetic
shift of the absorption of aromatic protons as compared to
the substrate (2) and completely methylated derivative (32).
The spin-spin splitting patterns were quite complex
indicating existence of more than one conformer.

The compound (32) had following spectral properties.

IR: ν max (CH_2Cl_2) 1730 (ester), 1645 (amide), 1605, 1510 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 207 ($\log \epsilon = 3.3998$), 226 ($\log \epsilon = 3.7013$),
283, ($\log \epsilon = 1.2131$).

NMR (CDCl_3) : 3.66 (3H, s, $-\overset{\text{O}}{\parallel}{\text{C}}-\text{OCH}_3$), 3.9 (9H, t, $-\text{OCH}_3$),
5.25 and 3.1 (2H, dd, $\text{Ar}-\text{CH}_2-\text{N}$), 6.7 to 7.4 (5H, m,
aromatic protons).

MS: $m/e = 413$ (base peak) (M^+), 382 (19.4%) (M^+-OCH_3),
298 (25.4%) (M^+-115), 283 (22.4%) ($298-\text{CH}_3$), 282 (26.9%)
($298-16$), 270 (49.25%) ($298-\text{CO}$), 269 (98.5%) ($298-\text{CHO}$)
or ($298-\text{CH}_2\text{NH}$), 255 (71.64%) ($298-\text{CH}_3\text{CO}$), 115 (28.35%).

The high resolution mass spectrum revealed the
molecular ion at 413.1855 (the calculated mass based on
the composition of $\text{C}_{23}\text{H}_{27}\text{O}_6\text{N} = 413.1838$).

The total yield of coupled biphenyl derivatives (33-a)
or (33-b) and (32) were in the range of 50-60%. Similarly
the compound (7) on vanadium oxytrichloride oxidation on
the solid phase resin produced cyclised biphenyl derivative
(34).

Figure 71. Vanadium Oxytrichloride Oxidation of the Compound (7) on the Solid Phase Resin.

The compound (34) had following spectral properties.

IR: ν max (CH_2Cl_2) 1725 (ester), 1635 (amide), 1600 and 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 203 ($\log \epsilon = 4.0193$), 225 ($\log \epsilon = 3.7640$), 280 nm ($\log \epsilon = 1.0014$).

MS: $m/e = 443$ (24%) (M^+), 412 (23%) ($\text{M}^+ - \text{OCH}_3$), 368 (base peak) ($\text{M}^+ - \text{CH}_3 - \text{COOCH}_3$), 328 (61.5%) ($\text{M}^+ - 115$).

This derivative was not identical with the compound (31) which was formed via a benzyne intermediate indicating ortho-ortho coupling of the two phenolic rings in the substrate (7).

We also applied the vanadium oxytrichloride oxidation procedure to N-nororientaline (compound 16) and N-norreticuline (compound 17) on the solid phase resin. Our preliminary oxidations were carried out on a small scale. However the major reaction seemed to be the chlorination of tetrahydroisoquinoline nucleus, which prevented any further oxidative coupling process.

It became obvious to us that the 1-benzyl-tetrahydroisoquinoline substrates are more bulky and less nucleophilic as compared to norbelladine derivatives and thus the anchoring process of the former on the solid phase resin is much less efficient. As we used the same amount of oxidant per gram of resin in both cases, the ratio of oxidant to substrate on the resin became too high with compounds (16) and (17) leading to undesired side reaction. When we repeated the oxidation of compound (16) on large scale, we obtained following reaction mixture.

Figure 72. Vanadium Oxytrichloride Oxidation of Compound (16) on the Solid Phase Resin.

The compounds (36) ⁶⁰ and (37) were present as minor components. By sheer coincidence, the base peaks in mass spectra of the compounds (35) and (36) have same m/e value.

Figure 73. Base Peaks in the Mass Spectra of the Compounds (35) and (36).

It became very difficult to measure correctly the molecular ion at $m/e = 340$ with high resolution mass spectroscopy.

In future we have decided to use vanadium oxytri-fluoride as an oxidant instead, and reduce the ratio of oxidant to substrate on the resin to a much lesser value in order to eliminate undesirable halogenation reaction.

Thus at this stage solid phase approach towards the biogenetic type syntheses of various alkaloids appears to be quite encouraging. The yields of the oxidatively coupled products are better than those carried out under normal solution reaction conditions and the possibility of formation of dimeric and polymeric coupled compounds is completely avoided. Another advantage seems to be in the capability of the solid phase resin matrix to influence the substrate to adopt a specific orientation in coordination with the oxidant during the coupling step. The biphenyl compounds (28) and (31) were formed via the ortho-para coupling mode of the two phenolic rings in the norbelladine derivatives (23) and (24) and thus were the members of the lycorine series.

The biogenetic type syntheses of lycorine alkaloids, are difficult under normal circumstances, in fact no example of such a synthesis has been reported in the literature. Further, the coupled compounds (32) and (33) obtained through the vanadium oxytrichloride oxidation of the norbelladine derivatives (2) and (7) were formed via the ortho-ortho coupling of the two phenolic groups.

This mode of coupling constitutes a new biogenetically possible class of Amaryllidaceae alkaloids which has not yet been found in nature.

The aromatic rings in the coupled product could further be transformed into alicyclic rings common to various naturally occurring alkaloids via simple chemical reactions. The concept of solid phase synthesis could also be applied to the synthesis of Erythrina and Colchicine alkaloids or in general any naturally occurring compound whose biogenetic pathway involves oxidative coupling of

phenols could be synthesised by our procedure. In addition Pschorr reaction and photolytic coupling-reaction could further be developed and adopted to solid phase synthesis as a means to induce coupling of phenolic moieties.

Some of the problems which we had to encounter in solid phase reactions were the formation of dicyclohexylurea and poor nucleophilicity of 1-benzyl-tetra-hydroisoquinoline substrates. The coupling reaction between the modified succinoyl resin and the substrate, using dicyclohexylcarbodiimide as a condensing agent ⁶² could be visualized as follows.

Figure 74. Dicyclohexylcarbodiimide Induced Coupling
Reaction between the Modified Succinoyl Resin
and Substrate.

The first step involved the formation of O-acylisourea on the resin. This reactive intermediate could now undergo a nucleophilic displacement reaction with the secondary amino function of the substrate and thus lead to the anchoring of the latter compound on the resin via a tertiary amide bond. The dicyclohexylurea was the by-product and could be washed away. However any leftover O-acylisourea derivative on the resin which could not be attacked by the substrate due to steric factors or poor nucleophilicity, would produce additional urea mixed with desired compounds in the deanchoring step. Another frequently found by-product was N-acylurea which could be produced by an O $\rightarrow$ N acyl migration.

The solubilities of urea and N-acylurea are rather similar to our reaction products and thus it led to additional difficulties in the purification step. However these purification problems could be overcome with the use of water soluble diimides ⁶³.

We also observed that 1-benzyl-tetra hydroisoquinoline derivatives were considerably less nucleophilic in their reaction with the modified succinoyl resin in the presence of dicyclohexylcarbodiimide than the norbelladine derivatives. Thus the amount of substrate anchored on the resin was limited. As the O-acylisourea derivative on the resin (figure 74) could not be consumed, additional quantity of urea was produced at the end of deanchoring step thereby making the purification of final products more difficult. The secondary amino function in the norbelladine derivatives appeared to be easily accessible because of the conformational mobility of the two aryl side chains. These derivatives could readily anchor on the modified succinoyl resin, but the same ease of mobility might be the cause of the low yields of intramolecularly oxidized products since this process involves the adoption of suitable conformation in coordination with the oxidant. The 1-benzyl tetra hydroisoquinoline derivatives were more bulky and sterically hindered for the anchoring process, but once anchored on the resin, they should easily coordinate with the oxidant in proper orientation leading to higher yields of cyclized aporphines.

In order to improve the problems of low nucleophilicity of the substrates and to avoid the formation of undesired dicyclohexylurea, we decided to employ following alternative approach towards the anchoring process.

Figure 75. Alternative Procedure to Anchor the Substrates on the Solid Phase Resin.

This procedure eliminated the use of dicyclohexylcarbodiimide as a condensing agent and the whole anchoring sequence became analogous to normal solid phase peptide synthesis.

We observed that the norbelladine derivatives could be anchored on the solid phase resin much more efficiently and the product mixture became easily separable. The anchoring of 1-benzyl-tetra-hydroisoquinoline compounds on the resin also took place in better yields.

In general the use of succinoyl derivatives of the precursor molecules in the synthetic scheme should make the biogenetic type synthesis of alkaloids on the solid phase to be more facile and preparatively advantageous.

Summary:

The preliminary results on the solid phase synthesis of alkaloids based on biogenetic pathways seems to be encouraging. Novel alkaloidal derivatives have been prepared in improved yields. The following biphenolic compounds have been oxidatively coupled to the products as indicated.

(1)

(2)

(3)

$\text{R}_3 = \text{H or OCH}_3$

(4)

(5)

Chapter III

Anodic Oxidation of Some Norbelladine Derivatives

Of all the various aromatic ring systems which occur in natural products, especially secondary metabolites, none are so easily oxidized as the phenol system. Electrolytic oxidation of phenols ³⁵ may follow a very complex pathway but in general, a phenol (I) may lose a proton and an electron to give a phenoxide radical (II) in which the radical is localized on the oxygen and in the ortho- and para- positions. When an alkyl group is present in the ortho- or para- position, some radical character may be developed on the benzyl carbon (IV). These radical species generally dimerize to yield products. Loss of a second electron leads to a phenoxonium ion (III) in which the positive charge is mainly on the ortho- or para- positions or, in appropriate conditions, on a benzyl carbon ortho or para to the phenol (V). Such phenoxonium ions generally stabilize by reacting with any available nucleophile (even another phenol ring) or by losing a proton. Both the radical and the positive ion can take part in various abstraction processes.

Figure 76. General Scheme for Oxidation of Phenols

It is not completely correct to call these reactions as "phenol oxidations" since the hydroxyl group of the phenol frequently emerges from the reaction unchanged.

Actually, it is the aromatic ring which is made susceptible to oxidation by the strongly electron donating phenol group. When additional electron donating groups are present on the ring, oxidation becomes easier and with electron withdrawing groups, it becomes more difficult. Half-wave potentials of para-substituted phenols have been correlated with Hammett functions ⁵⁸.

We were interested in studying the anodic oxidations of the norbelladine system and especially the effect of introduction of electron donating substituents in the aromatic rings towards the facility of the oxidative coupling reaction. We utilized a three compartment cell as shown in the figure 77. The platinum cathode, anode and silver-silver nitrate reference electrodes were separated by ceramic frits. The anodic oxidations were carried out in dry acetonitrile with tetramethylammonium tetrafluoroborate as an electrolyte. The initial current was in the range of 80 to 90 mA at the electrode potential of 0.5 to 1.5 V, which dropped slowly to about 40 mA in about 3 to 5 hours and then it remained constant at that value. The anodic solution was evaporated to dryness which was followed by the addition of chloroform and water. The chloroform soluble products were separated by preparative TLC on silica gel and then spectrally analysed.

Figure 77: Three Compartment Cell.

We used following norbelladine substrates for the anodic oxidation studies.

The compounds (38) to (41) had increasing number of electron donating methoxyl groups attached to the aromatic rings thereby activating them towards oxidation. Methyl ethers were used instead of the free phenolic groups to prevent overoxidation of the substrate. The nitrogen atom was protected as a trifluoroacetyl derivative which could easily be removed via mild alkaline hydrolysis at the end of oxidation reaction.

From the anodic oxidation of the compound (38), we did not observe any indication of intermolecular or intramolecular coupling. Majority of the substrate was recovered back unchanged. We attempted to vary the

experimental conditions by changing the anodic potential and the electrolysis duration. Under stronger conditions the solvent acetonitrile itself polymerized to yield various different products. This undesirable side reaction could be suppressed to a considerable extent by pulsing the potential between the electrodes thereby blocking the chain lengthening processes. We also examined the anodic oxidation of the nonmethylated phenolic substrate i.e. the N-trifluoroacetyl derivative of the substrate (2) but were unable to achieve any coupling reaction.

The compound (39) which possessed two methoxyl groups in each phenyl ring would be expected to be more reactive for the anodic oxidation. Anodic oxidation in the range of +0.5 to +1.5V followed by usual work up led

approximately 5% of the substrate to be dimerized. This dimer seemed to have one of its monomeric units coupled intramolecularly. On the basis of mass spectrometry this compound could be tentatively represented as follows.

Figure 78. Anodic Oxidation of Trifluoro-acetyl-N-(3,4-dimethoxyphenethyl)-3,4-dimethoxybenzylamine (39).

The substrate molecule appeared to have undergone an ortho-para-coupling to form a diphenyl derivative which recondensed with another unoxidized substrate molecule via an oxygen ether linkage in a free ortho- or para-position to produce the dimer. The presence of the diaryl ether bridge was indicated by the presence of following fragments in its mass spectrum.

Figure 79. Mass Spectrum Analysis of the Dimer Arising From the Anodic Oxidation of Compound (39).

We could not improve the yields of this dimer on subsequent experiments. Bobbitt ^{35,61} had submitted similar compounds to electro-oxidation under various conditions.

Figure 80. Bobbitt's Experiments of the Anodic Oxidations of Some Norbelladine Derivatives.

In cases where the nitrogen atom was not protected, no products were isolable. When the nitrogen was trifluoroacetylated, only dimers were obtained in yields of about 10%. Mass spectrometry of the dimers indicated that they were joined at the position marked with an arrow on the structures (figure 80).

However Tobinaga and coworkers ⁵⁹ reported the anodic oxidation of the compound (38) to form the dienone in 62% yield, which was then converted to ($\pm$)-oxomaritidine on alkaline hydrolysis.

Figure 81. Tobinaga's Experiment on the Anodic Oxidation of the Norbelladine Derivative (38).

We repeated above anodic oxidation under the specified experimental conditions in our laboratory and we could not observe the formation of any enone derivative.

The compounds (40) and (41) which contain additional electron donating methoxyl groups exhibited a preference to intermolecular additions.

Compound (40) R = H

Compound (41) R = OCH₃

Figure 82. Anodic Oxidation of the Compounds (40) and (41).

The above tentatively assigned dimerization process might involve the head to tail coupling of two substrate units. We did not observe any indication of intramolecular coupling in any of the monomeric units. The mass spectrum of the dimer obtained from the oxidation of the compound (41) was quite complex but did reveal the presence of following mass fragments.

DIMER $\longrightarrow$

And

Figure 83. Mass Spectrum Analysis of the Dimer Arising From the Anodic Oxidation of Compound (41).

The yields of the dimer were in the range of 5 to 8%. Considerable oxidative decomposition of the substrate did occur during the anodic oxidation.

Thus the norbelladine derivatives indicated a preferred tendency towards intermolecular associations on anodic oxidation. This might be due to their inability to adopt a right spatial orientation which would be a desired prerequisite for an intramolecular cross-linking. Miller ³¹ used bis (acetonitrile)-palladium (II) chloride to enhance the yields of the coupled dienone in the anodic oxidation of a nonphenolic derivative of 1-benzyl-tetrahydro-isoquinoline. This reagent was shown to have an ability to complex with tertiary amines. We also studied the influence of palladium (II) chloride in the anodic oxidation of the compound (39) but it was not very effective in bringing about the intramolecular oxidative coupling.

Summary:

In the anodic oxidation of various norbelladine derivatives, the introduction of electron donating groups in the aromatic rings has a pronounced effect on the nature of coupling reactions. The presence of one methoxyl group in the phenethyl aromatic ring and two methoxyl groups in the benzyl aromatic ring did not activate the substrate enough to undergo oxidative coupling in either intramolecular or intermolecular mode. Some Japanese workers claimed to obtain intramolecularly coupled enone in very high yield under similar electrolytic conditions. We and Bobbitt's group could not observe similar results with the repetition of above experiments.

The introduction of another methoxyl group in the phenethyl benzene ring leads to intramolecular cross-linking of the substrate followed by intermolecular association with another unoxidized substrate molecule. Further introduction of methoxyl groups in either aromatic ring leads mainly to intermolecular condensations. Bis (acetonitrile)-palladium(II) chloride which is capable of complexing with tertiary amine, has apparently no influence on the course of the anodic oxidation reaction.

EXPERIMENTAL

Infrared spectra were determined on Perkin Elmer -257 and 237:B-grating infrared spectrophotometers using nujol mull, chloroform solutions and potassium bromide discs.

Ultraviolet spectra were determined in 95% ethanol. The Perkin Elmer -202 ultra-violet-visible spectrophotometer and Perkin Elmer-Coleman:124 double beam spectrophotometer were used.

Nuclear magnetic resonance spectra were determined on 60 MHz Varian T-60 NMR spectrometer and 100 MHz Varian XL-100 NMR spectrometer. Chemical shifts are given in delta (δ) units relative to the tetramethylsilane as an internal standard. The following abbreviations are used to describe the signals:

s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Only signals deemed to be of any interest in assigning structure have been quoted. Deuteriochloroform, polysol and DMSO-D₆ were used as solvents.

Carbon and 100 MHz proton NMR spectra of a very small quantity of an important product was kindly run by Prof. K. Nakanishi of Columbia University.

Melting points are uncorrected $^{\circ}$ and were determined on a Fischer-Johns melting point apparatus.

Mass spectra were determined on a AEI, MS 12 mass spectrometer through the courtesy of Mr. J.M. Cashmore, Trent University, Peterborough. We also are indebted to Dr. Blair of Ottawa University, Ottawa for some low and high resolution mass spectra.

Microanalyses were determined by A. Spang, Ann Arbor, Michigan.

The experimental section will be divided into three parts. The first part will deal with the description of the syntheses of some diphenolic precursors and experiments to study the anchoring and deanchoring of these compounds on the solid phase resin. The second part will deal with the attempts to induce intramolecular oxidative coupling into these resin bound substrate molecules. The last part would be associated with our anodic oxidation experiments.

PART ISynthesis of N-(4-hydroxyphenethyl)-3-hydroxy-4-methoxybenzylamine (2).

An equimolecular mixture of isovanillin (1.5 g) and tyramine, the free base was obtained from the aqueous solution of its hydroxhloride salt at pH 10.2 as a precipitate (1.4 g) was dissolved in absolute ethanol (100 ml) and the solution was refluxed for two hours under an atmosphere of nitrogen. The formation of Schiff's base was followed by the infrared spectroscopy. The mixture was allowed to cool in ice and sodium borohydride (1.5 g) was added carefully to prevent the exothermic evolution of hydrogen. The mixture was heated under reflux for another two hours. Ethanol was removed under reduced pressure and the residue thus obtained was dissolved in 3M HCL. The acidic solution was made basic with aqueous ammonia. The crude (2) solidified in the aqueous solution was filtered, dried under vacuum and was extracted with ethyl acetate in a soxhlet extractor. The concentrated ethyl acetate solution was diluted with petroleum ether (B.P. 60 C) to induce crystallization. The crystals were further purified by recrystallization in the ethanol-ether mixture to give needles (2.3 g).

m.p. 186° C. (Calc. for $C_{16}H_{19}O_3N$: C. 70.31; H. 7.004; N. 5.125. Found C. 70.34; H. 7.62; N. 5.11%).

N-(4-Hydroxy-3-methoxyphenethyl)-3-hydroxy-4-methoxybenzylamine (7) was prepared in a similar manner.

Synthesis of 1-(4-hydroxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline (15).

This compound was prepared according to the experimental procedure cited before in the literature ^{51,31}. An equimolecular mixture of 4-benzyloxy-phenylacetic acid and 4-benzyloxy-3-methoxy-phenethylamine was heated at 180° under an atmosphere of nitrogen. The amide thus obtained was cyclised with phosphoryl chloride in refluxing dry benzene and the dehydro- compound was reduced with sodium borohydride in methanol at room temperature to yield isoquinoline base. This base was purified as its hydrochloride salt and the free base was debenzylated via hydrogenolysis with 10%-palladium on charcoal in ethanol-acetic acid (95:5) mixture. The compound (15) was crystallized from chloroform to give needles. M.P. 231° C.

IR: ν max (nujol) 3400 (NH), 3300 (OH), 1600, 1525 cm^{-1} .

NMR (CDCl_3 + polysol) δ : 6.7 (6H, m, aromatic protons), 3.8 (3H, s, $-\text{OCH}_3$).

MS: m/e = 284 (2.9%) (M^+-1), 178 (base peak) (M^+-107), 163 (47.7%) ($178-\text{CH}_3$) 107 (18.6%).

1-(4-Hydroxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxyisoquinoline or N-nororientaline (16) and 1-(3-hydroxy-

4-methoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy isoquinoline or N-norreticuline (17) were prepared in a similar manner.

Synthesis of chloromethyl resin:

Styrene - 2% divinylbenzene copolymer resin (200-400 mesh) was chloromethylated according to the Merrifield's procedure ⁴¹.

Synthesis of 3-acetoxy-4-hydroxy-benzaldehyde (8):

Protocatachualdehyde (5 g) was dissolved in acetic anhydride (3.4 g) and pyridine (5 ml). The solution was heated overnight, cooled and dissolved in ether (75 ml).

The ethereal solution was washed with a saturated solution of sodium bicarbonate in water and water respectively. The ethereal layer was dried, evaporated under reduced pressure and the oil thus obtained was crystallized in ethyl acetate-hexane mixture to give needles (3 g) M.P. 110°C.

Attempted synthesis of N-(4-hydroxyphenethyl)-3,4-dihydroxybenzylamine on the resin.

Chloromethyl resin (5 g) was mixed with the substrate (8) (1 g) and pyridine (2 ml) in ethyl acetate (75 ml) and was heated with reflux for 48 hours. The resin was filtered and washed with methanol and ether and dried

under vacuum. The unreacted substrate was recovered from the combined filtrate and washings and its yield indicated the anchoring of the benzaldehyde derivative on the resin to be less than 1 mmol per gram of the resin. In the next step, the above resin was mixed with tyramine (0.7 g) and dicyclohexylcarbodiimide (1 g) in N,N'-dimethylformamide (75 ml) and was heated at 80° C for 48 hours under an atmosphere of nitrogen. The resin was filtered, washed with water, ethanol, acetone and ether respectively and dried under vacuum. It was finally reduced with sodium borohydride (1 g) in methanol (100 ml) at 60° C for 36 hours. The resulting substrate anchored resin was filtered, washed with methanol and ether respectively and dried under vacuum.

Deanchoring of N-(4-hydroxyphenethyl)-3,4-dihydroxy-benzylamine from the resin.

The above resin (1 g) was suspended in anhydrous trifluoroacetic acid (10 ml) and anhydrous hydrogen bromide gas was bubbled for 90 minutes at room temperature. It was filtered and washed with more trifluoroacetic acid (10 ml) and methanol respectively. The combined filtrate was evaporated to dryness under reduced pressure. The amount of recovered amine-hydrobromide was very low, as indicated by infrared and NMR spectra.

Synthesis of methylchloroformyl resin.

Chloromethyl resin (10 g) was converted into methylchloroformyl resin according to the procedure of R.B. Merrifield ⁴⁷.

Anchoring of the substrate (2) on the methylchloroformyl resin.

Methylchloroformyl resin (5 g) was mixed with the substrate (2) (1 g), triethyl amine (20 ml) and N, N'-dimethyl formamide (75 ml). This mixture was heated at 80° C for 48 hours. The resin (9) thus obtained was filtered, washed successively with ethanol, acetone, ether and dried under vacuum.

Deanchoring of the substrate (2) from the resin (9).

Resin (9) (1 g) was treated with trifluoroacetic acid and hydrogen bromide gas according to the procedure to deanchor N-(4-hydrophenethyl)-3,4-dihydroxybenzylamine from the resin (mentioned previously). The yield of deanchored amine salt was very low.

Synthesis of carboxyl resin.

Copolystyrene -2% divinylbenzene resin (200-400 mesh) beads (25 g) were converted into the carboxyl resin according

to the procedure of Letsinger.⁴⁶

Anchoring of the substrate (2) on the carboxyl resin.

Carboxyl resin (10 g) was mixed with the substrate (2) (1 g), dicyclohexylcarbodiimide (1.5 g) in N,N'-dimethylformamide (75 ml) which was heated at 80 °C for 2 days under an atmosphere of nitrogen. The resin (10) thus obtained was washed with water, ethanol, acetone, ether respectively and dried in vacuo. The resin (2.5 mg) was mixed with dry potassium bromide (100 mg) and pressed into a pellet. The infrared spectrum of this pellet indicated the presence of the 1645 cm^{-1} band of the tertiary amide function. The aryl ester band at 1760 cm^{-1} was absent.

Deanchoring studies with the resin (10).

The hydrolysis of the amide function of resin (10) was attempted by using hydrogen bromide-trifluoroacetic acid, sodium hydroxide in aqueous para-dioxane, transesterification with methanol and triethylamine, methanol and ammonia and hydrazinolysis in N,N'-dimethylformamide according to the experimental procedures described to deanchor peptides from the solid phase resin⁴¹. The substrate (2) could not be deanchored under these conditions as indicated by infrared spectroscopy.

Synthesis of carboxymethyl resin.

Carboxymethyl resin was prepared from copolystyrene -2% divinylbenzene resin (200-400 mesh) beads (10 g) according to the procedure of T. Kusama and H. Hayatsu ^{4a-b}.

Anchoring of the substrate (2) on carboxymethyl resin.

Carboxymethyl resin (5 g) was mixed with the compound (2) (0.75 g), dicyclohexylcarbodiimide (0.9 g) in N,N'-dimethylformamide (75 ml). The experimental procedure used was the same as that for the anchoring of the compound (2) on the carboxyl resin. The resin (11) exhibited an infrared absorption at 1640 cm^{-1} indicating complete conversion of the carboxyl group to a tertiary amide function.

Deanchoring studies with the resin (11).

The hydrolysis of the amide bond was attempted by using similar methods as used for the resin (10). The substrate again could not be deanchored as indicated by infrared spectroscopy.

Use of silica gel as a polymer support.

Silica gel (Merck, 0.08 mm. in diameter, finer than 200 mesh ASTM) (10 g) was mixed with thionyl chloride (50 ml) and dry benzene (100 ml). The mixture was stirred

mechanically and heated with reflux for 4 hours. It was then cooled, filtered, washed thoroughly with benzene and ether respectively and finally dried under vacuo. This chlorinated derivative was mixed with succinic acid (5 g), N,N'-dimethylformamide (50 ml) and pyridine (5 ml). The mixture was stirred mechanically at 80° C for 12 hours. It was then cooled, filtered, washed with more N,N'-dimethylformamide and benzene respectively and dried under vacuum. Infrared analysis of this succinoyl derivative of the silica gel showed a poor absorption at 1725 cm^{-1} indicating an ester chromophore. The succinoyl derivative (9 g) was condensed with the substrate (2) (1 g) and dicyclohexylcarbodiimide (1.5 g) in N,N'-dimethylformamide (50 ml) at 80° C and the mixture was stirred mechanically for 15 hours. It was then cooled, filtered, washed with more N,N'-dimethylformamide and ether respectively and dried under vacuum. The infrared spectrum of this silica gel derivative (12) was very poor and exhibited mainly the ester chromophore at 1725 cm^{-1} .

Deanchoring of the substrate from the silica gel derivative (12).

The silica gel derivative (12) (8 g) was mixed with 0.1M hydrochloric acid (100 ml) and was stirred at room temperature for $\frac{1}{2}$ hour. It was then filtered, washed with water (50 ml) and the combined aqueous solution was extracted with ethyl acetate. The ethyl acetate solution was dried over anhydrous magnesium sulphate and evaporated. The oily

residue thus obtained was separated on a preparative silica gel thin layer plate. The plate was first developed in ethyl acetate, dried and redeveloped in a mixture of chloroform and methanol (ratio 95:5). The infrared spectrum of the ~~more~~ polar fraction indicated it to be the succinoyl ester of the compound (2) ν max (CHCl_3) 1750 (ester), 1700 (acid), 1510 cm^{-1} (12.3 mg) whereas the less polar fraction appeared to be the succinoyl amide derivative of the compound (2) ν max (CHCl_3) 1700 (acid), 1640 (amide), 1515 cm^{-1} (6.8 mg).

Synthesis of succinoyl resin.

The succinoyl resin was prepared from copolystyrene -2% divinylbenzene (200-400 mesh) beads (25 g) according to the procedure of Yip and Tsou ⁴⁹.

Anchoring of the compound (2) on the succinoyl resin.

The succinoyl resin (10 g) was mixed with the compound (2) (1 g), dicyclohexylcarbodiimide (2 g) in N,N'-dimethylformamide (100 ml). The reaction mixture was stirred at 80°C for 48 hours. It was then cooled, filtered, washed with ethanol, acetone, ether respectively and dried under vacuo.

The infrared spectrum of this resin (13) indicated that the substrate (2) was anchored to the succinoyl residue on the resin exclusively via an amide bond.

ν max (KBr) 1700, 1650, 1601 cm^{-1} . The yield of the resin (13) was 10.4 g.

Deanchoring of the compound (2) from the resin (13).

The resin (13) (2 g) was treated with 0.5M sodium hydroxide in a mixture of water and para-dioxane in the ratio 1:1 (50 ml) for 48 hours at room temperature. The reaction mixture was filtered and washed with water (50 ml). The infrared spectrum of the resin indicated the loss of absorption at 1700 and 1650 cm^{-1} . The aqueous solution was acidified with 3M hydrochloric acid to pH 5 and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate and evaporated. The oily residue thus obtained was separated on a preparative silica gel thin layer plate, which was first developed in ethyl acetate, dried and redeveloped in a mixture of chloroform and methanol (ratio 95:5). The major aromatic fractions were the compound (2) (21.4 mg) and its succinoyl amide (30.1 mg). The spectral characteristics of the succinoyl amide were IR: ν max (CHCl_3) 1700 (acid), 1640 (amide) and 1515 cm^{-1} ; UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 208 ($\log \epsilon = 4.1968$), 225 ($\log \epsilon = 4.0753$) and 280 nm ($\log \epsilon = 1.8905$) nm.

Synthesis of modified succinoyl resin.

Hydroxymethyl resin (25 g) was prepared according to the procedure of R.B. Merrifield ⁴¹. It was suspended in N,N'-dimethylformamide (100 ml) and was mixed with succinic anhydride (5 g) and pyridine (10 ml). The mixture was

stirred mechanically for 48 hours at 80° C. It was cooled, filtered and the resin was washed with ethanol, acetone and ether respectively and was finally dried under vacuum. Infrared spectrum of the resin indicated ν_{max} (KBr) 1730, 1715 and 1600 cm^{-1} .

Anchoring of the compound (2) on the modified succinoyl resin.

Modified succinoyl resin (10 g) was mixed with the compound (2) (1 g), dicyclohexylcarbodiimide (2 g) in N,N'-dimethylformamide (100 ml). The reaction mixture was stirred at 80° C for 48 hours. The progress of the condensation reaction was followed by infrared spectroscopy. The resin was filtered, washed with ethanol, acetone and ether respectively and finally dried under vacuum. The infrared spectrum of this resin (14) showed the complete conversion of the carboxyl chromophore to a tertiary amide group. IR: ν_{max} (KBr) 1730, 1645, 1600 cm^{-1} . The microanalysis indicated the resin (14) contained 0.96% of nitrogen which corresponded to 0.6858 mmole of functional group per gram of the resin.

Deanchoring studies with the resin (14).

The resin (14) (2 g) was mixed with sodium hydroxide (0.5M in para-dioxane and water, 1:1 ratio, 50 ml) and was heated at 80° C for 3 hours. The infrared spectrum of the resin indicated a complete deanchoring. The resin was

filtered, washed with water and the total aqueous solution was acidified to pH 5 with 3M hydrochloric acid. It was then extracted with ethyl acetate, the extract was dried over anhydrous magnesium sulphate and evaporated to dryness. The oily residue was separated on a silica gel column. The elutant with CHCl_3 - CH_3OH (95:5) gave a solid as a major component. It was succinoyl amide of compound (2) (28 mg). The spectral data of this compound were as follows.

IR: ν max (CHCl_3) 1710 (acid), 1640 (amide), 1600 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 207 ($\log \epsilon = 5.9851$), 223 ($\log \epsilon = 5.7275$), 281 nm ($\log \epsilon = 1.1835$).

NMR (CDCl_3 + polysol) δ : 2.6 (4H, m, $-\text{N}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{O}-$), 3.8 (3H, s, $-\text{OCH}_3$), 6.8-7 (8H, m, aromatic protons).

This succinoyl amide was acetylated with acetic anhydride (5 ml) and pyridine (1 ml) at room temperature for 12 hours. The diacetyl derivative thus obtained exhibited M^+ peak at $m/e = 471$ in its mass spectrum.

The resin (14) (2 g) was also deanchored with methanol and potassium carbonate. The resin was heated with reflux with a mixture of potassium carbonate (2 g) and methanol (75 ml) for 18 hours. The solvent was removed under reduced pressure and the oily residue was acidified with 3M hydrochloric acid to pH 5. This acidic solution was extracted with ethyl acetate and the extract was dried over anhydrous magnesium sulphate and evaporated to dryness. The oil thus obtained was chromatographed over a silica gel

column. The elutant with CHCl_3 - CH_3OH (97:3) gave an oil (34 mg) as a major component, whose spectral properties were as follows.

IR: ν max (CHCl_3) 1730 (ester), 1625 (amide), 1600 and 1505 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 210 ($\log \epsilon = 5.8364$), 225 ($\log \epsilon = 5.5659$) and 280 nm ($\log \epsilon = 1.0992$).

NMR (CDCl_3) δ : 2.6 (4H,m, $-\text{N}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}_2-\text{CH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-$), 3.65 (3H,s, $\text{C}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{OCH}_3$), 3.8 (3H,s, ArOCH_3), 6.8 (8H,m, aromatic protons).

This oil was methylated with diazomethane in methanol to give a tetramethyl derivative. MS M^+ at $m/e = 415$.

Anchoring of l-tyrosine ethyl ester on the modified succinoyl resin.

The modified succinoyl resin (3 g) was mixed with l-tyrosine ethyl ester (0.7 g), dicyclohexyl carbodiimide (0.8 g) in dry methylene chloride and the solution was heated with reflux for 30 hours. The progress of the anchoring reaction was followed by infrared spectroscopy. The resin was filtered, washed with ethanol, acetone and ether respectively and dried under vacuum. The infrared spectrum of the resin indicated ν max (KBr) 1730 (ester), 1660 (amide), 1601 cm^{-1} .

Deanchoring of l-tyrosine ethyl ester anchored on the solid phase resin.

Above resin (3 g) was mixed with potassium carbonate (1.5 g) in ethanol (40 ml). The mixture was heated with reflux for 18 hours. The solvent was removed under reduced pressure and the residue was extracted with methylene chloride. The extract was dried over anhydrous magnesium sulphate and evaporated. The oil thus obtained was purified over silica gel column to yield ethyl succinoyl amide of tyrosine ethyl ester (40 mg). Spectral properties of this compound were as follows.

IR: ν max (CH_2Cl_2) 1730 (ester), 1648 (amide), 1600, 1510 cm^{-1} .

NMR (CDCl_3) δ : 1.22 (3H,t, $\text{Ar}-\text{C}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-\text{C}-\text{CH}_3$), 1.28 (3H,t, $-\text{C}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{O}-\text{C}-\text{CH}_3$), 2.6 (4H,m, $-\text{N}-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}_2-\text{CH}_2-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$), 4.2 (2H, m, $-\text{C}-\text{O}-\text{CH}_2-\text{C}$), 6.9 (4H,m, aromatic protons).

The specific rotation in methanol: $\alpha_D^{22} = +15.73$.

Synthesis of ethyl succinoyl amide of l-tyrosine ethyl ester.

l-Tyrosine ethyl ester (1 g) was mixed with succinic anhydride (0.75 g) in dry pyridine (50 ml) and the solution was heated at 80° C for 12 hours. The solvent was removed under reduced pressure and the residue was mixed with absolute ethanol (10 ml) and conc. sulphuric acid (5 drops). The above solution was heated with reflux for 10 hours, cooled and evaporated to dryness. The residue was dissolved in

methylene chloride, washed with minimum quantity of a saturated aqueous solution of sodium bicarbonate, dried over anhydrous magnesium sulphate and evaporated. The oily residue was purified via passage through a silica gel column using methylene chloride as an eluant. The compound (188 mg) was similar in its spectral properties and TLC behaviour to the one obtained via solid phase synthesis. The specific rotation in methanol was $\alpha_D^{22} = +16.69$.

Anchoring of 1-menthol and β -Naphthol on the Modified succinoyl resin.

The modified succinoyl resin (5 g) was mixed with 1-menthol (0.8 g) or β -naphthol (0.75 g) and dicyclohexylcarbodiimide (1 g) in N,N'-dimethylformamide (50 ml), and heated at 80° C for 2 days. The mixture was cooled, filtered and the resin was washed with ethanol, acetone and ether respectively and dried under vacuum. The infrared spectra of the resins were $\nu_{\max}$ (KBr) 1730 (ester), 1601 cm^{-1} (for 1-menthol on the resin) and $\nu_{\max}$ (KBr) 1765 (ester), 1601 cm^{-1} (for β -Naphthol on the resin).

Deanchoring of resin bound 1-menthol and β -Naphthol.

The resin (5 g) was mixed with 0.5M sodium hydroxide in para-dioxane and water in 1:1 ratio (100 ml) and was heated at 80°C for 3 hours. The solution was cooled,

filtered and the resin was washed with more water (25 ml) and ethyl acetate (50 ml). The infrared spectrum of the resin indicated a complete absence of ester chromophore. The total aqueous solutions were acidified to pH 5 with 3M hydrochloric acid and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulphate, evaporated to dryness. 1-Menthol or β -naphthol could be obtained in pure state from this residue by passing them through a silica gel column using chloroform and chloroform-methanol (98:2) as eluant. The 1-menthol thus obtained had the same specific rotation as the starting material, $\alpha_D^{23} = -48.14$.

Synthesis of soluble succinoyl resin.

The polystyrene resin (mol. wt. about 270,000) (10 g) was dissolved in nitrobenzene (48 ml), and the solution was cooled to 0° C. Benzoyl chloride (1 ml) and anhydrous aluminum chloride (0.57 g) were added to above solution which was stirred mechanically for 3 hours at about 0 to 5° C. The reaction solution was mixed with cold 3M hydrochloric acid (25ml) and the resin material precipitated out of the solution. This resin lump was stirred in water (100 ml) and ethanol (100 ml) respectively to remove unreacted material and dried under vacuum. The thin film infrared spectrum of the resin revealed the carbonyl

chromophore at 1650 cm^{-1} . The resin was now dissolved in diglyme (55 ml) and cooled to 0°C . A solution of sodium borohydride (0.5 g) in diglyme (10 ml) was added to the resin solution slowly and the whole reaction solution was stirred mechanically at 60°C for 16 to 20 hours or until the infrared spectrum of the resin indicated the reduction of carbonyl chromophore. The solution was cooled and ethanol (about 150 ml) was added to precipitate the resin out of the solution. It was washed with more ethanol, dried under reduced pressure and finally under vacuum. It was redissolved in N,N'-dimethyl formamide (75 ml) and succinic anhydride (1 g) was added to the solution which was stirred at 80°C for 24 hours. The solution was cooled and the resin was precipitated out of the solution by the addition of ethanol. The resin was washed with ethanol, methanol and dried. The resin indicated the presence of the chromophore at 1725 and 1710 cm^{-1} in its infrared spectrum. This succinoyl resin was condensed with compound (2) (0.75 g) and dicyclohexylcarbodiimide (1 g) in N,N'-dimethylformamide (75 ml) and the solution was stirred at 80°C for 1.5 days. After cooling the resin was precipitated out with the addition of ethanol, washed with more ethanol, methanol and dried under reduced pressure. Its infrared spectrum revealed the chromophore at 1725 and 1645 cm^{-1} .

Deanchoring of the substrate from the soluble succinoyl resin bound with compound (2).

Above soluble succinoyl resin anchored with compound (2) (about 2 g) was suspended in 0.5M sodium hydroxide in para-dioxane and water (ratio 1:1) (50 ml) and enough para-dioxane (25 ml) was added to dissolve the resin into the solution (by heating if necessary). The solution was heated at 80° C for two hours. A part of the solution was withdrawn in a test tube and enough water was added to it to complete the precipitation of the resin. The resin was washed in methanol and dried. Its infrared spectrum indicated the presence of the chromophores at 1725 and 1645 cm^{-1} and thus there was no deanchoring. We continued the hydrolysis for another six hours by withdrawing a sample every hour and checking its infrared spectrum. At the end, we observed a very minimal deanchoring and the resin partially precipitated out of the solution. It could not be redissolved in hot para-dioxane. We attempted to hydrolyze the resin by using stronger basic conditions but still we could not completely deanchor the substrate and we could not avoid the formation of insoluble resin.

PART II

Preliminary oxidation experiments

The compound (2) anchored to the modified succinoyl resin was used as a substrate. For the oxidation with ferric chloride, the resin (14) (2 g) was added to a solution containing ferric chloride (3.5 g) in a mixture of water and N,N'-dimethylformamide (ratio 1:1) (50 ml). It was stirred at 80° C for 2 to 4 days. After cooling the mixture was filtered and the resin was washed with water, ethanol and acetone respectively and dried under vacuum. The infrared spectrum of the resin revealed the presence of the chromophores at 1730 and 1645 cm^{-1} . The potassium ferricyanide oxidations were carried out using same procedure except ammonium acetate (2 g) or sodium bicarbonate (1.5 g) was added to the reaction mixture. The deanchoring of the resin (after oxidation) was done via transesterification with methanol and potassium carbonate using the same experimental procedure as used to deanchor the resin (14). Unreacted substrate as methyl ester of its succinoyl amide derivative was recovered.

The oxidation with manganese dioxide was done by using the same procedure as with ferric chloride. The oxidations with benzoyl peroxide were carried out with the resin suspended in chloroform and mixed with 5 mole

equivalents of oxidant. The reaction mixture was heated with reflux for two days. As for the use of lead dioxide and lead tetracetate, the resin (14) (2 g) was suspended in glacial acetic acid or a mixture of glacial acetic acid and *N,N'*-dimethylformamide (ratio 1:1) (50 ml) and the oxidant (1.5 g). The reaction mixture was heated at 60° C for 2 days. The resin was filtered, washed with ethanol, acetone and ether respectively and dried under vacuum. The transesterification of the resin with methanol and potassium carbonate gave mainly the methyl ester of succinoyl amide of compound (2). Some side products were also observed in low yields which were formed via oxidative fragmentation of the substrate.

The oxidation with potassium dichromate was carried out either in a mixture of glacial acetic acid and *N,N'*-dimethylformamide or in 3M sulphuric acid. The procedure used was the same as above. The potassium permanganate oxidations were carried out either in neutral aqueous or with 6M sulphuric acid. The resin (14) was suspended in a solution containing the oxidant (1 g) in either water or 6M sulphuric acid (50 ml) and the reaction mixture was stirred at room temperature for 40 hours. The resin was filtered, washed with water, ethanol and acetone respectively and dried under vacuum. On transesterification the resin yielded unreacted compound (2) as the methyl ester of its succinoyl amide and some

oxidative fragmentation products. When the above reaction mixtures were heated at 60-80° C, near complete oxidative decomposition of the substrate occurred. Similarly, some oxidations were carried out with potassium permanganate in 6M sodium hydroxide at room temperature but no intramolecularly coupled products were observed after transesterification of the oxidized resin.

Oxidation with 3M nitric acid.

The resin (21) or the compound (7) anchored on the modified succinoyl resin (5 g) was added to a mixture of 3M nitric acid and para-dioxane (ratio 1:1) (75 ml) and the mixture stirred at room temperature for 3 to 4 days. The resin was filtered, successively washed with water, ethanol and acetone and finally dried under vacuum. the infrared spectrum of the resin indicated absorption at 1730 and 1650 cm^{-1} , although their intensities were reduced. Thus some deanchoring of the substrate had apparently occurred during the oxidation.

The resin was transesterified with methanol and potassium carbonate in the usual manner and the reaction product was separated on a silica gel preparative TLC plate. The TLC plate was developed first with ethyl acetate, dried and redeveloped in a mixture of chloroform and methanol (ratio 10:2). The visualization of the com-

ponents was done with iodoplatinic acid or 3% ceric sulphate in 3M sulphuric acid. The products were obtained via soxhlet extraction of the silica gel portions. The major component was unreacted methyl ester of the succinoyl amide of compound (7) and its overoxidized derivatives. A minor component (about 4%) (9 mg) seemed to be a lactam. It was an oil and its infrared spectrum revealed $\nu_{\max}$ (CHCl_3) 1690 (lactam), 1625, 1590 and 1510 cm^{-1} .

This compound was mixed with acetic anhydride (0.5 ml) and pyridine (2-3 drops). The reaction mixture was stirred overnight at room temperature. It was dissolved in ether and washed with saturated aqueous sodium bicarbonate solution. The ethereal solution was dried over anhydrous magnesium sulphate and evaporated to dryness. The acetylated derivative was further purified by sublimation under vacuum (0.25mm Hg, 60° C). The yield of the product was 6.7 mg. Its spectral properties were as follows.

IR: $\nu_{\max}$ (CHCl_3) 1770 (aryl ester), 1690 (lactam), 1605, 1510 cm^{-1} .

UV. $\lambda_{\max}$ ($\text{C}_2\text{H}_5\text{OH}$) 213 ($\log \epsilon = 4.8983$), 232 ($\log \epsilon = 3.9746$), 285 nm ($\log \epsilon = 0.9289$).

NMR (CDCl_3) : 2.0 (6H,s,Ar-O-C-CH₃), 3.5 (6H,s,Ar-O-CH₃), 6.4 (4H,m,aromatic protons).

MS: $m/e = 399$ (absent) (M^+), 356 (17.4%) (399-H-COCH₂), 314 (22.1%) (356-COCH₂), 297 (20.9%) (356-OCOCH₃),

284 (19.76%) (314-CH₂O), 272 (49%) (356-CO-CONH=CH),
 271 (31%) (356-CHO-CONH=CH), 255 (61.6%) (271-CH₃),
 241 (57%) (271-CH₂O), 179 (15%), 137 (base peak)
 (179-COCH₂).

The oxidation experiment gave unreliable results when it was subsequently repeated. The yields of the lactam (22) were variable, sometimes dropping to zero. The compounds (2) and (15) anchored on the modified succinoyl resin were also oxidized with 3M nitric acid in para-dioxane under identical conditions. The only products obtained were unreacted substrates (as their methyl ester of succinoyl amides) and their over-oxidized derivatives.

Oxidations with ceric sulphate in 10% sulphuric acid and with thallium trifluoroacetate.

The resin (14) (2 g) was mixed with ceric sulphate (2.8 g) in 10% sulphuric acid (25 ml) and the reaction mixture was heated at 80° C for 3 days. The resin was filtered, successively washed with water, ethanol, acetone and dried under vacuum. The infrared spectrum of the resin indicated the absence of any deanchoring of the substrate during oxidation. The resin was transesterified with methanol and potassium carbonate in a usual procedure and the reaction product was acetylated with acetic anhydride.

and pyridine. The acetylated product mixture was separated over silica gel preparative TLC plate. The plate was developed first in ethyl acetate, dried and redeveloped in a mixture of chloroform and methanol (ratio 10:2). The visualization of the components was done with 3% ceric sulphate solution in 3M sulphuric acid and the products were obtained via soxhlet extraction. The major product was unreacted substrate (2) as its methyl ester of succinoyl amide. The other minor products were formed from the oxidative decomposition of the substrate. This oxidant was also used with the compound (7) and (16) but there was no indication of any intramolecular oxidative coupling.

For the oxidation with thallium trifluoroacetate, the resin (14) (2 g) was suspended in dry methylene chloride (25 ml) and a solution of thallium trifluoroacetate (0.3 g) in dry methylene chloride (15 ml) was added to it. The weighing and transfer of the oxidant was done in a dry box under nitrogen. The oxidation was carried out at room temperature under the atmosphere of dry nitrogen. After every two hours a sample of resin was quickly withdrawn from the reaction mixture, filtered and washed with methylene chloride and methanol respectively. The infrared spectra of resin indicated the decrease in intensity and a shift of -25 to -30 cm^{-1} of the ester bond from its original position at 1730 cm^{-1} while the intensity of the

amide bond increased to a larger extent with a shift of -25 cm^{-1} from its original position of 1645 cm^{-1} , as the complexation and oxidation with the reagent progressed. However when the resin was transesterified with methanol and potassium carbonate after 6 to 8 hours, and the reaction mixture was separated on silica gel preparative TLC plates using ethyl acetate and chloroform: methanol:: 10:2 in succession as developer, there was no evidence of oxidative intramolecular coupling. All the substrate was completely destroyed due to overoxidation. We reduced the amount of the oxidant and reaction period, but with no useful results. Finally the oxidation was carried out at -55°C in a dewar flask using Cryo-Cool to maintain the low temperature for 24 hours and still the overoxidation of the substrate could not be prevented.

Synthesis of N-(4-hydroxyphenethyl)-6-bromo-3-hydroxy-4-methoxybenzylamine (23).

Isovanillin was brominated according to the procedure ⁶⁶ to yield 2-bromoisovanillin and 6-bromoisovanillin which were separated by fractional crystallization. An equimolecular mixture of 6-bromoisovanillin (2.3 g) and tyramine (1.4 g) were heated together in absolute ethanol under an atmosphere of nitrogen and the Schiff base thus obtained was reduced with sodium borohydride (1.5 g) to form compound (23). The experimental procedure used was

similar to one used in the synthesis of compound (2).

N-(4-hydroxy-3-methoxyphenethyl)-6-bromo-3-hydroxy-4-methoxybenzylamine (24) was prepared similarly by the condensation of 6-bromo-isovanillin and 4-hydroxy-3-methoxy-phenethylamine.

Photolytic coupling of compound (24) on the solid phase resin.

The compound (24) was anchored to modified succinoyl resin (2 g) and was suspended in a mixture of water and para-dioxane (ratio 1:1) (300 ml) containing sodium hydroxide (800 mg). The mixture was irradiated for 45 hours at room temperature under the atmosphere of nitrogen. We used Hanovia 73A36 mercury lamp with a pyrex filter for irradiation. The resin was filtered, washed with water, ethanol and acetone respectively and dried under vacuum. The infrared spectrum of the resin indicated the decrease in the intensities of the bands at 1730 (ester) and 1650 cm^{-1} (amide) which indicated some deanchoring of the substrate during photolysis.

The resin (after photolysis) was deanchored via transesterification with methanol and potassium carbonate. The product mixture was separated over silica gel preparative TLC plate using ethyl acetate as a developer. The visualization of the components was done with 3% ceric sulphate in 3M sulphuric acid. The products were obtained via soxhlet extraction. The more polar fraction (2.7 mg)

had the following spectral characteristics.

IR: ν max (CHCl_3) 1725 (ester), 1665 (amide), 1565 and 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 210 ($\log \epsilon = 4.5115$), 238 ($\log \epsilon = 4.1506$) and 285 nm ($\log \epsilon = 1.8165$).

The mass spectrum indicated the absence of the fragmentation peaks at $m/e = 215$, 217 and $m/e = 137$.

The less polar fraction (11 mg) from the TLC plate had spectral properties similar to unreacted substrate (24) as its methyl ester of the succinoyl amide derivative.

Benzynes reaction.

The compound (23) anchored on the modified succinoyl resin (5 g) was suspended in liquid ammonia (200 ml).

About ten fold mole excess of sodium metal (1.5 g) was added slowly to the mixture. When all the sodium was dissolved in ammonia, ferric nitrate nonahydrate (25 mg) was added slowly to the deep blue reaction mixture, which turned into light grey in colour. The sodium amide-liquid ammonia treatment of the resin was continued for the next 18 hours. The sodium amide was neutralized with ammonium chloride (3 g) and the liquid ammonia was allowed to evaporate. The residue was suspended in water (200 ml) and the resin was filtered, washed with water, ethanol and acetone respectively and finally dried under vacuum.

The infrared spectrum of the resin revealed the absence of deanchoring during the reaction as the intensities of the 1730 (ester) and 1655 cm^{-1} (amide) bands were intact. The resin was transesterified with methanol and potassium carbonate by refluxing it for 18 hours. The solvent was removed under reduced pressure and the residue was acidified with 3M hydrochloric acid to pH 5 and rebasified with ammonium hydroxide to pH 8-9. The aqueous solution was extracted with ethyl acetate, the latter was dried over anhydrous magnesium sulphate and then evaporated to dryness. The oily product mixture was dissolved in a minimum amount of methanol and an ethereal solution of diazomethane was added to it until a distinct yellow colour persisted in the solution. This solution was kept in the freezer for 18 hours and then the excess diazomethane was destroyed with the addition of a few drops of acetic acid. The solvent was removed under reduced pressure and the methylated product was dissolved in anhydrous ether and the solution was filtered to remove insoluble dicyclohexyl urea. The solvent was removed and oily residue was separated over silica gel preparative TLC plate which was first developed in chloroform, dried and redeveloped in a mixture of chloroform and ethyl acetate (ratio 1:1). The visualization of the components was done with iodoplatinic acid reagent and the soxhlet extraction yielded the various fractions.

The most polar fraction (compound 26) (35 mg) was found to be the methyl ester of the succinoyl amide of completely methylated compound (23). The spectral properties of this compound were,

IR: ν max (CHCl_3) 1730 (ester), 1665 (amide), 1610, 1515 cm^{-1} .

MS: $m/e = 495$, 493 (2.5%) (M^+), 464, 462 (5%) ($\text{M}^+ - \text{OCH}_3$), 414 (88.8%) ($\text{M}^+ - \text{Br}$), 361, 359 (28%) ($\text{M}^+ - 134$), 231, 229 (base peak), 151 (44%).

The second most polar fraction, compound (27) (45 mg) was the debromination product of compound (26) and was same as the methyl ester of the succinoyl amide of methylated compound (2). Its spectral properties were,

IR: ν max (CHCl_3) 1730 (ester), 1665 (amide), 1615 and 1515 cm^{-1} .

MS: $m/e = 415$ (13.3%) (M^+), 281 (16.7%) ($\text{M}^+ - 164$) and 151 (base peak).

The least polar fraction, compound (28) (12 mg) had the following spectral properties.

IR: ν max (CHCl_3) 1730 (ester), 1668 (amide), 1615, 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 203 ($\log \epsilon = 4.6101$), 223 ($\log \epsilon = 4.0692$), 278-282 nm ($\log \epsilon = 1.0012$).

NMR (CDCl_3) δ : 3.69 (6H, s, $-\text{OCH}_3$), 3.86 (6H, s, $-\text{OCH}_3$), 4.5 (2H, d, $\text{Ar}-\text{CH}_2-\text{N}$), 6.65 (m, aromatic protons).

MS: $m/e = 413$ (base peak) (M^+), 298 (9.75%) ($M^+ - 115$),
256 (75.6%) ($298 - CH_2CO$), 213 (31.70%) ($298 - CH_3CO$).

The compound (28) was thus the biphenyl derivative.

The yields of this compound were in the range of 12 to 15%.

Similarly when the compound (24) anchored on the modified succinoyl resin was treated with sodium amide in liquid ammonia for 12 hours, the compounds (29), (30) and (31) were formed in 28, 67 and 4.5 percent respectively. The compound (31) was biphenyl derivative similar to compound (28) and its spectral characteristics were as follows.

IR: ν_{max} ($CHCl_3$) 1725 (ester), 1670 (amide), 1600,
1520 cm^{-1} .

UV: λ_{max} (C_2H_5OH) 211 ($\log \epsilon = 4.5219$), 231 ($\log \epsilon = 3.9261$), 282 nm ($\log \epsilon = 0.9815$).

MS: $m/e = 443$ (base peak) (M^+), 412 (21%) ($443 - OCH_3$),
328 (78%) ($443 - 115$), 313 (26%) ($328 - CH_3$), 285 (14%)
($313 - CO$) and 270 (16%) ($285 - CH_3$).

Vanadium oxytrichloride oxidation of the compound (7)
on the solid phase resin.

The compound (2) anchored to the modified succinoyl resin (or resin 14) (5-g) was suspended in dry methylene chloride (40 ml) in a three necked flask under the atmosphere of dry nitrogen. The flask was immersed in a Dewar flask filled with acetone which was cooled down to $-55^\circ C$ with Cryo Cool. The flask was also fitted with a mercury

sealed mechanical stirrer. When all the air was flushed out with nitrogen, a ten mole excess of vanadium oxytrichloride (2.4 ml) was added quickly in the flask and the reaction mixture was stirred for the next 48 hours at -55°C . After this period, the resin was filtered, washed with methylene chloride, water, 6M sulphuric acid, water, ethanol and acetone respectively and finally dried in vacuum.

The infrared spectrum of the resin revealed the absence of any deanchoring process during the oxidation. The resin was transesterified with methanol and potassium carbonate and the product mixture thus obtained was methylated with diazomethane. The methylated product mixture was dissolved in dry ether to remove insoluble dicyclohexyl urea and the oily residue thus obtained was separated over silica gel preparative TLC plate which was developed first in chloroform, dried and redeveloped in a mixture of ethyl acetate and chloroform (ratio 1:1). The visualization of the components was done with 3% ceric sulphate in 3M sulphuric acid and the soxhlet extraction in chloroform gave the products.

The least polar fraction (47 mg) on standing in concentrated ethereal solution produced globular crystals (m.p. $132-134^{\circ}\text{C}$) which had the following spectral characteristics.

IR: ν max (CH_2Cl_2) 3420 (-OH), 1730 (ester), 1640 (amide),
1600, 1520 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 205 ($\log \epsilon = 4.1231$), 227 ($\log \epsilon =$
3.3240), 277.5 nm ($\log \epsilon = 1.0727$).

NMR (CDCl_3) δ : 3.715 (6H, m, - OCH_3), 3.93 (3H, d, - OCH_3),
4.76 (2H, d, Ar- CH_2 -N), 6.2-7.1 (5H, m, aromatic protons).

MS: $m/e = 399$ (base peak) (M^+), 368 (27.6%) ($\text{M}^+ - \text{OCH}_3$),
284 (44.8%) ($\text{M}^+ - 115$), 268 (32%) (284-16), 255 (31%)
(284- CHO), 241 (84.8%) (284- CH_3CO), 151 (24.1%),
115 (48.3%).

High resolution mass spectrum: M^+ ion at 399.1682
(the calculated mass based on the composition of $\text{C}_{22}\text{H}_{25}\text{O}_6\text{N} =$
399.1682).

Thus this compound (33) was the intramolecularly
coupled biphenyl derivative which contained a free phenolic
hydroxyl group.

The medium polar fraction (4 mg) had following spectral
characteristics.

IR: ν max (CH_2Cl_2) 1730 (ester), 1645 (amide), 1605,
1510 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 207 ($\log \epsilon = 3.3998$), 226 ($\log \epsilon =$
3.7013), 283 ($\log \epsilon = 1.2131$).

NMR (CDCl_3) δ : 3.66 (3H, s, - OCH_3), 3.9 (9H, t, - OCH_3),
5.25 and 3.1 (2H, dd, Ar- CH_2 -N), 6.7 to 7.4 (5H, m,
aromatic protons).

MS: m/e = 413 (base peak) (M^+), 382 (19.4%) ($M^+ - OCH_3$), 298 (25.4%) ($M^+ - 115$), 283 (22.4%) ($298 - CH_3$), 282 (26.9%) ($298 - 16$), 270 (49.25%) ($298 - CH_2N$), 269 (98.5%) ($298 - CHO$) or ($298 - CH_2NH$), 255 (71.64%) ($298 - CH_3CO$), 115 (28.35%).

The high resolution mass spectrum had M^+ ion at 413.1855 (the calculated mass based on the composition of $C_{23}H_{27}O_6N$ = 413.1838). Thus this compound was completely methylated cyclized biphenyl derivative (32).

The most polar fraction (42 mg) from the silica gel TLC plate was the methyl ester of the succinoyl amide of completely methylated substrate (2).

Similarly the vanadium oxytrichloride oxidation of the compound (7) on the solid phase resin (4.3 mg) gave the cyclized biphenyl derivative (34) (4.3 mg) which had the following spectral properties.

IR: ν max (CH_2Cl_2) 1725 (ester), 1635 (amide), 1600 and 1515 cm^{-1} .

UV: λ max (C_2H_5OH) 203 ($\log \epsilon$ = 4.0913), 225 ($\log \epsilon$ = 3.7640), 280 nm ($\log \epsilon$ = 1.0014).

MS: m/e = 443 (24%) (M^+), 412 (23%) ($M^+ - 31$), 368 (base peak) ($M^+ - CH_3 - H - COOCH_3$), 328 (61.5%) ($M^+ - 115$).

Methylation of compound (33) to compound (32).

Compound (33) (20 mg) was dissolved in methanol (10 ml) and mixed with methyl iodide (100 mg). Two drops of 10% potassium hydroxide solution in methanol was added to the reaction mixture which was heated with reflux for 4 hours under the atmosphere of nitrogen. The solvent was removed under reduced pressure. The residue was dissolved in minimum amount of water and extracted with chloroform. The chloroform solution was washed with 15% sodium thio-sulphate solution in water, water respectively and dried over anhydrous magnesium sulphate. The chloroform was removed under reduced pressure and the residual oil (16 mg) was separated over silica gel TLC plate which was developed in ethyl acetate. The middle fraction on soxhlet extraction in chloroform gave an oil (7.4 mg) which was identical with compound (32).

Vanadium oxytrichloride oxidation of N-nororientaline and N-norreticuline on solid phase resin.

The vanadium oxytrichloride oxidation of N-nororientaline (compound 16) and N-norreticuline (compound 17) was carried out on a smaller scale (2 grams of solid phase resin) utilizing an identical procedure as above. Both the compounds gave one product (35) (5 and 6.2 mg) respectively. The spectral properties

of these compounds were as follows.

Compound (35).

IR: ν max (CH₂Cl₂) 1730 (ester), 1670 (amide),
1605, 1515 cm⁻¹.

UV: λ max (C₂H₅OH) 210 (log ϵ = 4.5216), 274 nm
(log ϵ = 1.1214)

MS: m/e = 340 (33.33%), 306 (9.19%), 213 (47.61%),
182 (30.95%), 151 (10.34%), 115 (base peak).

Compound (38).

IR: ν max (CH₂Cl₂) 1725 (ester), 1665-1645 (amide),
1600, 1515 cm⁻¹.

UV: λ max (C₂H₅OH) 220 (log ϵ = 4.6934), 275 nm
(log ϵ = 0.9859)

MS: m/e = 340 (41.17%), 306 (85.88%), 226 (42.35%),
213 (7.26%), 192 (73.81%), 151 (11.76%), 115
(base peak).

The high resolution mass spectroscopy of the m/e = 340
ion in compound (35) indicated measured mass at 340.1042.
The calculated mass based on the composition of C₂₀H₂₂O₄N
is 340.1674, while the composition of C₁₆H₁₉O₅NCl leads
to mass 340.7865.

The minor component (36) (4.3 g) obtained from the vanadium oxytrichloride oxidation of compound (16) on the solid phase resin (5 g) had following spectral properties.

IR: ν max (CH_2Cl_2) 1730 (ester), 1665 (amide), 1600 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 214 ($\log \epsilon = 4.4138$), 280 nm ($\log \epsilon = 1.0076$).

MS: $m/e = 455$ (absent) (M^+) 340 (base peak) ($M^+ - 115$), 312 (70%) ($340 - \text{CH}_2\text{N}$), 310 (60%) ($340 - \text{CH}_2\text{O}$), 115 (93%).

Preparation of succinoyl derivative of the compound (2).

The compound (2) (2.75 g) was mixed with succinic anhydride (1.5 g) in dry pyridine (50 ml) and the solution was heated at 90°C overnight. The solvent was removed under reduced pressure and the oily residue was suspended in dry chloroform. The unreacted succinic anhydride settled down as a precipitate. The solution was filtered and passed through a silica gel column. Elution with 10% methanol-chloroform mixture gave an oil (2.2 g) which solidified on standing. Crystallization from chloroform-petroleum ether (b.p. 60°C) afforded needles. (m.p. 177°C).

IR. ν max (nujol) 3450, 2900, 1705 (carboxyl), 1625 (amide), 1515 cm^{-1} .

Above carboxylamide derivative (20 mg) was methylated with diazomethane to yield a tetramethyl derivative which

was identical with the compound (27).

Succinoyl derivatives of compounds (23), (16), and (17) were prepared using a similar procedure.

A large, bold, and heavily textured number '3'. The texture is grainy and stippled, giving it a three-dimensional, almost metallic appearance. The number is centered vertically and horizontally on a plain white background.

OF/DE

A large, bold, black number '3' with a halftone dot pattern, centered on a white background.

PART IIISyntheses of N-trifluoroacetyl methylated derivatives of norbelladine. (compounds 37, 38, 39 and 40).

The compound (2) (2 g) was dissolved in a minimum amount of methanol (50-75 ml) and this solution was cooled to 0° C. An ethereal solution of diazomethane (containing about 1.5 g of diazomethane) was added to it and the combined solution was kept in freezer overnight. The excess of diazomethane was destroyed by the dropwise addition of glacial acetic acid and the solvent was removed under reduced pressure. The oily residue was dissolved in ethyl acetate (100 ml) and washed with 0.6M sodium hydroxide solution, water respectively and dried over anhydrous magnesium sulphate. The ethyl acetate was removed under reduced pressure and the methylated product was crystallised from methylene chloride-ether mixture to form needles (1.65 g). M.P. 215° C. The spectral properties of this compound were

IR: ν max (CHCl_3): 2840 ($-\text{OCH}_3$), 1600, 1515 cm^{-1} .

NMR (CDCl_3) δ : 3.83 (9H,s,-O-CH₃), 4.53 (2H,s, Ar-CH₂-N-), 6.6 (7H,m,ArH).

This methylated derivative (1 g) was dissolved in a

mixture of ethyl acetate and chloroform (ratio 1:1) (50 ml) and trifluoroacetic anhydride (2.25 g) was added to it. The reaction solution was refluxed with stirring for 1 hour. The solution was cooled in ice-water and the excess of trifluoroacetic anhydride was decomposed with ice. The organic solution was washed with a saturated aqueous solution of sodium bicarbonate, and water respectively and dried with anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the oily product (37) was purified through a silica gel column using ethyl acetate as an eluant (0.7 g).

IR: ν max (CHCl_3) 1675 (amide), 1600, 1515 cm^{-1} .

The compound (38) was prepared similarly to the compound (7).

In the synthesis of the compound (39), an equimolecular mixture of 4-benzyloxy-3-methoxy-phenethylamine (2.57 g) and 3,4,5-trimethoxybenzylamine (3.5 g) was used via an identical experimental procedure as in the synthesis of compound (2). The above compound was dissolved in ethanol (75 ml) and glacial acetic acid (5 ml) was added to it. This acidic solution was hydrogenolysed using palladium on charcoal (10%) (0.4 g) overnight. The solution was filtered, the charcoal was washed with hot methanol and the combined solution was evaporated under reduced pressure. The oily residue was purified through a silica gel column using a 1% methanol-chloroform

mixture as an eluant. The NMR spectrum indicated complete debenzylation. The phenolic oily compound was dissolved in methanol and treated with diazomethane in ether. The methylated derivative was N-trifluoroacetylated using the experimental procedure as mentioned in the synthesis of compound (37). The compound (39) thus obtained was repurified via a passage through a silica gel column using ethyl acetate as an eluant to produce an oil (1.83 g). The spectral properties of this compound corroborated the assigned structure.

The compound (40) was prepared from 3,4,5-trimethoxyphenethylamine and 3,4,5-trimethoxybenzaldehyde utilizing an identical experimental procedure to the synthesis of compound (37).

General Electrolysis Procedure:

Preparative anodic oxidations were performed in a three compartment cell as shown in the figure 74. This cell separated anode, cathode and the silver-silver nitrate reference electrode solutions by ceramic frits in conjugation with an "Electronischer Potentiostat nach Wenking" 115V, 60 CPS and "Tacussel Electronique" type GSTP 3-pulse generator. The anode and cathode were platinum discs in diameter 6 cm and 4.8 cm respectively. The anode compartment had an approximate 850 ml volume in which the solutions were agitated by means of a mechanical stirrer. The reference electrode was connected to the anode via a Luggin capillary to measure the electrode potential accurately. A 0.1M silver nitrate solution in acetonitrile in contact with a silver disc served as the reference and all the potentials were given as compared to this reference. The entire cell was maintained at room temperature or immersed in an ice bath. The oxidations were carried out under dry nitrogen atmosphere.

All the preparative experiments were conducted in very dry acetonitrile (distilled twice over phosphorous pentoxide) and tetramethyl ammonium tetrafluoroborate was used as a background electrolyte. Sufficient

electrolyte was added to the anode and cathode compartments to have an approximately 0.1M solution in electrolyte. Some solid sodium carbonate was added to the anode compartment prior to electrolysis to prevent the increase in the acidity of the anolyte during oxidation, which might reduce the yields of coupled products.

A general description of the preparative oxidation was as follows. The anodic compartment was filled with the electrolyte solution, some of which percolated in the cathode compartment through the ceramic frit and covered the cathode. The silver nitrate solution was added to the reference electrode and all the air bubbles trapped in the Luggin capillary were removed by tilting the cell. The cell was flushed with dry nitrogen and maintained at room temperature or in an ice bath. Approximately 1.26×10^{-3} mol of substrate dissolved in dry acetonitrile along with anhydrous sodium carbonate (5 g) was added to the anodic compartment. The potential was pulsed from +1.5V (5 sec) to +0.5V (1 sec) between the electrodes. The initial current was in the range of 80 to 90 mA, which dropped slowly to about 40 mA in about 3 to 5 hours. The anolyte was then removed, stripped under vacuum to dryness, then taken up in water and extracted with chloroform. The combined organic layers were dried with anhydrous

magnesium sulphate and evaporated to dryness. The oily residue thus obtained was mixed with potassium carbonate (1 g) and methanol (25 ml) and was heated with reflux for 6 hours. The solvent was evaporated under reduced pressure and the residue was suspended into water and brought to pH of 6. The aqueous solution was extracted with ethyl acetate and the latter was dried over anhydrous magnesium sulphate. Evaporation of the solvent gave an oily product which was separated on a preparative TLC plate. The plate was first developed with ethyl acetate, dried and then redeveloped with 3:2 benzene-methyl alcohol. Visualization of the nitrogenous compounds was done with iodoplatinic acid reagent and the silica gel fractions were extracted in a soxhlet to yield various components.

The anodic oxidation of the compound (37) did not lead to either intramolecular or intermolecular condensations, instead most of the substrate was recovered unchanged. We extended the electrolysis period up to 6 or 8 hours but were unsuccessful in achieving an oxidative coupling. Under these conditions the solvent acetonitrile was considerably polymerized and some decomposition of the substrate was also observed. The addition of palladium (II) chloride (200 mg) in the anodic solution did not influence the course of the reaction. We attempted to oxidize the N-trifluoroacetyl derivative of the substrate (2) and we did not observe

any indication of cross-coupling. The phenolic substrate was found to be unstable under these strong oxidative conditions and some coating of the anodic surface was observed.

The compound (38) (1.1 g) on anodic oxidation between the potential range +0.5 to +1.5V gave a dimer in low yields (52.3 mg, about 5%), while rest of the unreacted substrate was recovered unchanged.

The spectral properties of the dimer were as follows.

IR: ν max (CHCl_3) 3400 (amine), 2825 (methyl ether) 1600, 1515 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 214 ($\log \epsilon = 3.8294$), 225 ($\log \epsilon = 4.0924$), 277 ($\log \epsilon = 1.0197$), 283 nm ($\log \epsilon = 0.9811$).

NMR (CDCl_3) δ : 3.8 (m, Ar-O-CH₃), 4.5 (m, Ar-CH₂-N-), 7.1 (m, aromatic protons).

MS: m/e = 433 (1.4%), 419 (1.7%), 389 (1.82%), 346 (1.2%), 330 (1.4%), 314 (2.8%), 300 (5.7%), 299 (4.5%), (314-CH₃), 285 (5.1%) (314-CH₃), 181 (6.25%) (151 + NH = CH₂), 151 (base peak).

The compound (39) and (40) were oxidized under identical electrolytic conditions to produce a dimer, unreacted monomer and some oxidatively degraded derivatives arising from the substrate. The dimer obtained from the compound (40) was formed in the range of 5 to 8% ; and had following spectral characteristics.

IR: ν max (CH_2Cl_2) 3420 (amine), 2830 (methyl ether),
1600, 1520 cm^{-1} .

UV: λ max ($\text{C}_2\text{H}_5\text{OH}$) 219 ($\log \epsilon = 4.0138$), 226 ($\log \epsilon = 3.9265$), 285 nm ($\log \epsilon = 1.0012$).

NMR (CDCl_3) δ : 3.72 (m, Ar-O- CH_3), 4.67 (m, Ar- CH_2 -N),
6-7.3 (m, aromatic protons).

MS: m/e = 551 (22.4%), 537 (11.2%), 523 (14%), 313 (26.6%),
299 (9.4%), 285 (12.5%), 181 (53.1%), 137 (base peak)
(181-O CH_2 - CH_2).

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Appendix -1

Flow Chart:

(I)

(II)

Appendix -2:

(A) Fragmentation Routes in the Mass Spectra of
Norbelladine Derivatives.

Compound (27):

The major mass peaks arising from the fragmentation of trimethyl derivative of the substrate molecule are as follows.

These major fragments further lose the subunits such as CH_3^+ , CH_2O^+ , CH_2CO^+ , CH_3CO^+ , CH_3O^+ etc.

Compound (33).

Major fragmentation processes are as shown below.

The mass peak $m/e = 284$ loses the elements of methane to produce the $m/e = 268$ ion. This process is very rare.

Further fragmentation modes are the loss of radicals $\text{CHO}^\cdot$, $\text{CH}_3^\cdot$ and neutral CO unit.

Compound (32).

The mass peaks 382 ($M^+ - OCH_3$) and 298 ($M^+ - 115$) are formed via identical fragmentation process as shown for the compound (33). The severe crowding present in the molecule due to the arrangement of three adjacent methoxyl groups is relieved by the loss of a methyl radical or neutral methane.

The loss of methane probably might follow the pathway as shown below, although the occurrence of a similar process in various aromatic ethers is very rare.

Another mode to relieve the strain in the molecule due to the crowding of three methoxyl groups is via the loss of $\text{CH}_2 = \text{NH}$ radical.

The mass peak $m/e = 298$ also loses the elements of CH_3 radical and carbon monoxide to produce the ion $m/e = 255$. This fragmentation mode should be similar as indicated for the compound (33).

Compound (28).

This compound is isomeric to compound (32) and has a different substitution pattern of the three methyl ether groups of the aromatic rings. There is much less steric crowding of the functional groups and thus the fragmentation mode is quite simple.

In the mass spectrum of this compound, the mass peak at $m/e = 382 (M^+ - OCH_3)$ is absent and the peak at $m/e = 298 (M^+ - 115)$ has very low intensity. The other fragmentation peaks which are present, are $m/e = 256 (298 - CH_2CO)$, and $212 (256 - CH_3CO)$. The formation of these ions occurs as described in the fragmentation schemes for the compound (32). Another noticeable feature is the absence of the peaks at $m/e = 282, 283$ and 269 which were present in the mass spectrum of compound (32) indicative of the steric strain present in the former molecule.

(B) Fragmentation Routes in the Mass Spectra of
1-Benzyl tetrahydro isoquinoline Derivatives.

Fragmentation routes of aporphines and related alkaloids are described in detail by Djerassi ⁶⁵.

The substrate (16) or (17) in general follow the pathway as shown below.

$R = H \text{ or } Cl$

The compound (35) with $R = Cl$ also follows the above fragmentation route. These major mass peaks also lose subunits of Cl^+ , CH_3^+ , CH_2O , CH_3CO^+ , etc.

The compound (36) which is an aporphine derivative gives rise to following fragments.

Appendix 3:Nuclear Magnetic Resonance Spectra of Norbelladine
Derivatives.

The proton NMR spectrum of the triacetate of compound (2) has the resonances of aromatic protons situated in the range of δ 6.8 to 7.23 ppm.

The spin-spin splitting patterns are $A_2 X_2 - ABX$ type. These patterns overlap each other and are difficult to analyse. Gatti ⁶⁶ has analysed the chemical shifts of individual protons using Eu (DPM)_3 to expand the proton spectrum.

δ : 6.85 (1-H), 6.95 (9-H and 13-H), 7.05 (10-H and 12-H),
7.0 (4-H) and 7.1 (5-H) ppm.

The aromatic protons of the compound (28) have AX-ABX type spin-spin splitting patterns. The chemical shifts and the coupling constants are roughly estimated from its proton NMR.

δ : 6.8 (dd, 1, $J = 3, 5$ Hz, 13-H), 6.83 (s, 1, 1-H), 7.0 (d, 1, $J = 3$ Hz, 9-H), 7.04 (d, 1, $J = 5$ Hz, 12-H), 7.08 (s, 1, 4-H) ppm.

The compound (32) has its aromatic protons arranged in AB-ABX type spin spin splitting pattern. The chemical shift and the coupling constant of each proton are as follows.

δ : 6.8 (d, 1, $J = 8\text{Hz}$, 12-H), 6.85 (s, 1, 1-H),
6.95 (m, 1, $J = 3\text{Hz}$, 9-H), 7.15 (dd, 1, $J = 3$,
8Hz, 13-H), 7.4 (s, 1, 2-H) ppm.

Appendix -4:Known Lycorine type Alkaloids:

All these alkaloids have pyrrolophenanthridine skeleton in common and are present in various daffodil (Twink, Texas, Deanna Durbin, King Alfred) and with Nerine bowdenii plants.

Norpluviine

Caranine

Lycorine

Lycorenine

Narcissidine

(Secolycorine)

END

10 03 77

FIN