SYNTHETIC AND MECHANISTIC STUDIES

IN

ALKALOID CHEMISTRY

A thesis submitted by

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TO

MY MOTHER AND FATHER

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PREFACE

SUMMARY

The opening section of this thesis describes the first reported preparation of potentially biologically-interesting alkoxy 1-benzyl-3(2H)-isoquinolone derivatives incorporating dissimilarly-substituted aryl rings.

Treatment of alkyl 2-arylacetylarylacetates ("keto-esters") with strongly basic amines gave only 2-aryl-3-hydroxy-1,4-naphthaquinones. Reaction with hydrazine hydrate however afforded colourless labile intermediates which were readily converted into N-amino-1-benzyl-3(2H)-isoquinolones. Similarly reaction with hydroxylamine hydrochloride in pyridine gave derivatives of N-hydroxy-1-benzyl-3(2H)-isoquinolone.

Members of the series which could not be obtained from the keto-ester by these methods were available following selective reduction of the ketone function, conversion to the corresponding hydroxy-dimethylamide and re-oxidation to the keto-amide. Treatment of the latter with amines or amine acetates in hot acetic acid gave good yields of 3(2H)-isoquinolone derivatives.

A somewhat unstable N-methyl 3(2H)-isoquinolone prepared in this way was also available *via* an alternative method, namely reaction of the keto-amide with methylamine hydrochloride in pyridine.

The chemical and spectroscopic properties of the 1-benzyl derivatives appear closely to parallel those of 1-H analogues. In particular the *o*- quinonoid lactam tautomer appears to predominate over hypothetical stilbenoid-lactam, lactim and acyl-imine tautomers (where appropriate).

An application of an earlier synthesis of alkoxy 1-H 3(2H)-isoquinolones to the preparation of the tetrahydroprotoberberine alkaloid (±) -norcoralydine has been completed in the present work.

The second major part of the thesis constitutes an investigation into the influence of variously-oriented hydroxyl and methoxyl groupings in the Hof-

mann degradation of the tetrahydrobenzylisoquinoline alkaloids, following reports that certain combinations of these substituents appeared to facilitate the elimination process.

Examination of the relative rates of stilbene formation from quaternary hydroxides derived from a series of 1-N,N-dimethylamino-1,2-diarylethanes suggested that methoxyl substituents in the 1-aryl ring did not appear to have a significant effect (at least under the conditions used). This was in sharp contrast to the effect of hydroxyl groups in positions 2 or 4 of the 1-aryl ring, decomposition of even the quaternary methiodides proceeding rapidly to stilbenes.

Evidence is presented that 3-hydroxy substituents in the 1-aryl ring of 1-N,N-dimethylamino-1,2-diarylethanes and 5- or 7-hydroxy substituents in tetrahydrobenzylisoquinoline derivatives retard Hofmann elimination in the derived quaternary hydroxides by removal of hydroxide ion with formation of relatively stable phenolate zwitterions (hydroxide ion being normally responsible for initiating the decomposition of quaternised non-phenolic amines *via* removal of a methylene proton β to the amino moiety). In contrast, quaternised phenolic amines with hydroxyl groups in the 2 or 4 positions (aminodiarylethanes) and 6 or 8 positions (benzylisoquinolines) are themselves capable of facile decomposition, presumably *via* uncharged "quinone-methide" intermediates.

The structure of an orange-red crystalline by-product formed in the course of the above work during the preparation of 1-(3,4-dimethoxy)-1-keto-2-phenylethane from veratrole and phenylacetyl chloride is shown by spectroscopic and other evidence to be 1-benzylidene-5,6-dimethoxy-2-phenyl-3-veratryl indene.

The final section of the thesis deals with synthetic approaches to the pentacyclic antineoplastic alkaloid camptothecin, a constituent of the Chinese tree *Camptotheca acuminata*.

A study of the reduction of quinoline-2,3-dicarboxylic acid derivatives as a source of potential synthetic intermediates gave mixtures of hydroxy-amides and lactones in which the heterocyclic ring was partly or wholly reduced. No 2H-pyrrolo (3,4-b) quinoline was detected and the low yields of individual products obtained made this approach less attractive than recently published syntheses.

ABBREVIATIONS

ANAL	elemental analysis
aq	aqueous
b	broad (NMR)
b.p.	boiling point
CAN	ceric ammonium nitrate
conc.	concentrated
d	doublet (NMR)
decomp.	decomposes (m.p.)
dil.	dilute
DNP	2,4-dinitrophenylhydrazine
hr	hour(s)
infl.	inflexion (UV)
IR	infrared
irr	irradiation (NMR)
J	coupling constant (NMR)
m	multiplet (NMR)
max	maximum (a) (IR, UV)
min	minute(s)
m.p.	melting point
MS	mass spectroscopy, spectrum
NMR	nuclear magnetic resonance
PLC	preparative thin layer chromatography
q	quartet (NMR)
r.o.d.	relative optical density (UV)
R.T.	room temperature
s	singlet (NMR)
s.g.	specific gravity

t	triplet (NMR)
TLC	thin layer chromatography
UV	ultraviolet
XS	excess

TECHNIQUES

For reactions requiring prolonged periods at elevated temperatures baths containing liquid paraffin (< 200°) or Wood's metal (>75°) heated by electrical hot plates were generally preferred to electrical heating mantles, affording closer control of temperature and (in the former case) allowing the use of magnetic stirrers. Reaction temperatures quoted are those of the heating bath unless otherwise stated.

Nitrogen for reactions requiring an inert atmosphere was dried by passage through concentrated sulphuric acid. Blue silicagel was generally employed as a drying agent in dessicators and in drying tubes attached to the outlet of reaction flasks.

Organic extracts from aqueous media were dried by washing several times with saturated aqueous sodium chloride solution followed by standing over anhydrous magnesium sulphate. Evaporation of solvents was achieved by means of a rotary film evaporator employing a water or liquid paraffin bath for heating the distillation flask and ice-salt or acetone-solid carbon dioxide for cooling the receiving flask as necessary.

Solutions were decolourised by addition of animal charcoal prior to crystallisation. Compounds which did not crystallise readily were purified for microanalysis by sublimation in narrow-bore glass tubes (~1cm diameter) under high vacuum. All analytical samples (solid or liquid) were evacuated for several hours (normally at 30-100°) over potassium hydroxide pellets to remove traces of solvent and water vapour. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Temperatures are given in degrees Celsius.

Thin layer chromatography was carried out on 0.25mm layers of Merck Kieselgel G, H or HF 254. In preparative TLC layers of up to 1.00mm thickness were used on 20x20 or 20x100 cm plates. Spots were most commonly detected

by charring with ceric ammonium nitrate-sulphuric acid reagent although iodine vapour, ferric chloride reagent and dinitrophenylhydrazine reagent were also used where appropriate. Colours shown in parentheses immediately following the Rf values of compounds described in the various experimental sections are those produced by the former method. Woelm neutral alumina was used for column chromatography.

Ultraviolet spectra were measured on a Unicam SP800 automatic recording instrument (with provision for repeat scanning) employing 95% aqueous ethanol ("EtOH") as solvent unless otherwise stated. Routine infrared spectra (Nujol mulls and liquid films) were obtained on Unicam SP 200 or SP 1000 spectrometers, while spectra of higher resolution (K Br discs and solutions) were measured on Perkin Elmer PE 225 or Unicam SP 100 instruments. Mass spectra were recorded on AEI MS 9 or MS 12 machines. Nuclear magnetic resonance spectra at 60MHz were measured on a Perkin Elmer R10 or on a Varian T60 instrument, while spectra at 100 MHz were obtained on a Varian HA 100 spectrometer (using tetramethylsilane as internal standard).

The term "light petroleum" refers to the fraction of boiling point 40-60° unless otherwise stated. Reaction yields are normally quoted to the nearest 5% (erring on the low side).

ACKNOWLEDGEMENTS

In expressing my thanks to Dr. N. J. McCorkindale for his supervision of the research work described herein, I should like particularly to mention the interest shown by him and the guidance and encouragement given during the preparation of this thesis.

I gratefully acknowledge the award of a three-year Research Studentship from the Science Research Council (1967-1970), and wish to thank Professor R. A. Raphael for granting me the opportunity to undertake research at the University of Glasgow.

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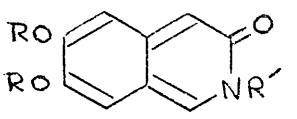
Thanks are due to the following members of Glasgow University Chemistry Department, the efforts of whom were much appreciated : the late Mr. G. Milmine and staff (preparation of intermediates); Dr. J. S. Roberts and staff (mass spectra); Mr. J. Gall and staff (nuclear magnetic resonance spectra); Mrs. F. Lawrie and staff (infrared spectra); Mr. J. M. L. Cameron and staff (elemental analyses); and also to the librarians, laboratory maintenance engineers, glassblowers, storemen, laboratory attendants and cleaners for their cooperation and assistance at all times.

Finally I should like to thank Mrs. A. Masterton for the trouble she has taken in the typing of this thesis, and also my fiancée, Jean, for her constant encouragement during its preparation.

April 1973

PART I (1)

Synthesis of 1- Benzyl- 3(2H)-isoquinolones



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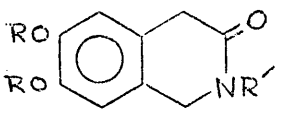

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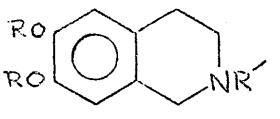

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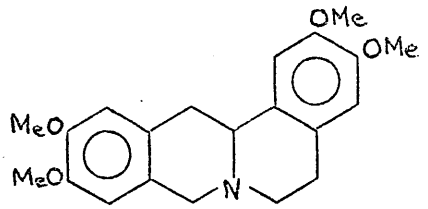

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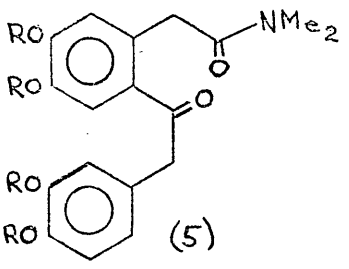

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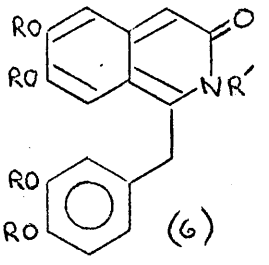

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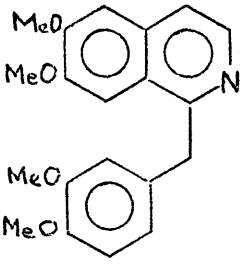

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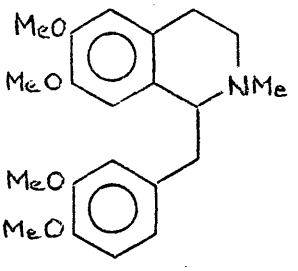

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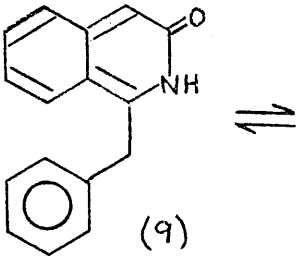

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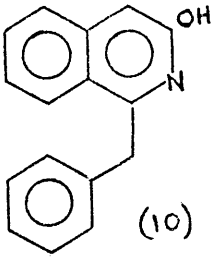

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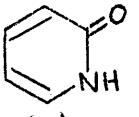

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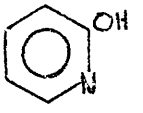

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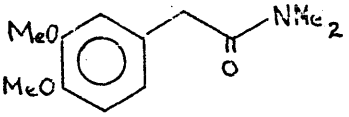

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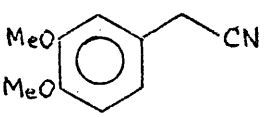

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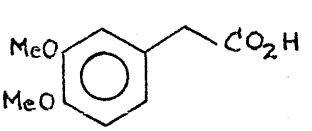

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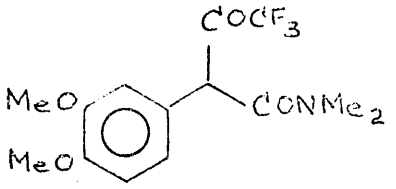

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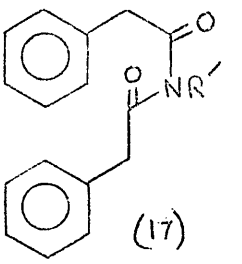

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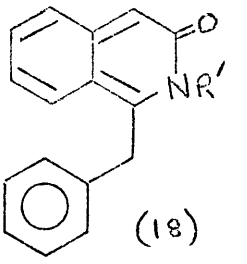

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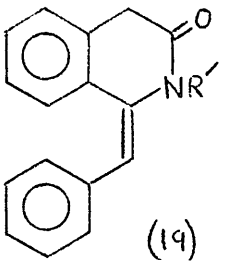

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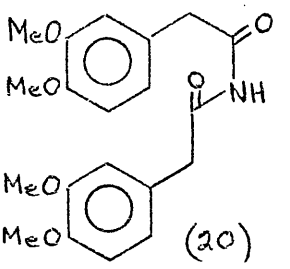

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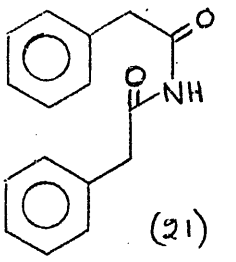

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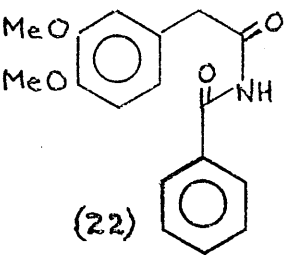

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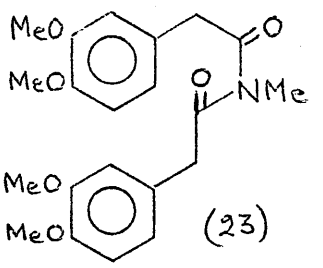

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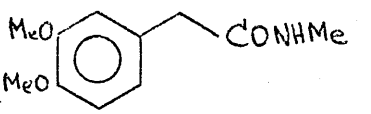

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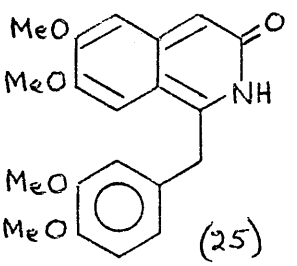

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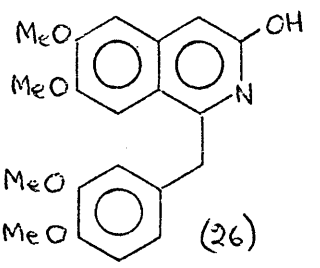

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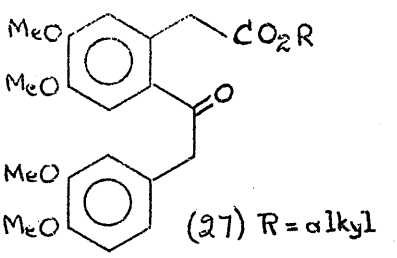

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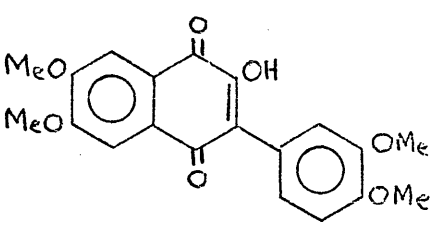

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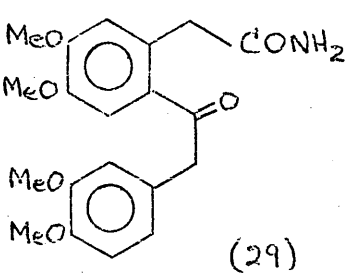

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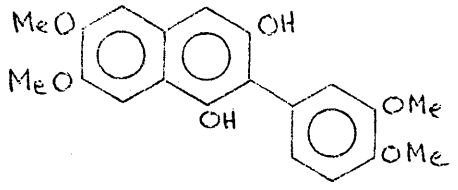

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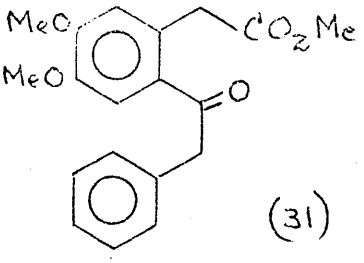

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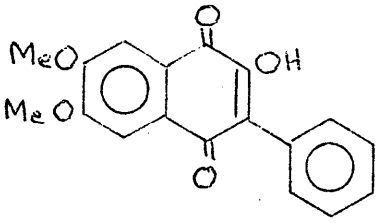

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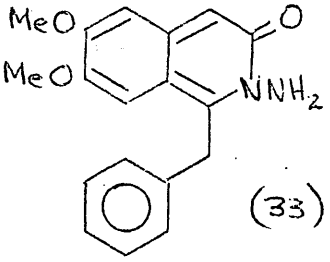

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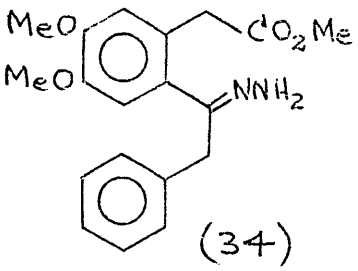

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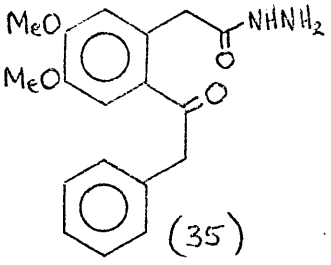

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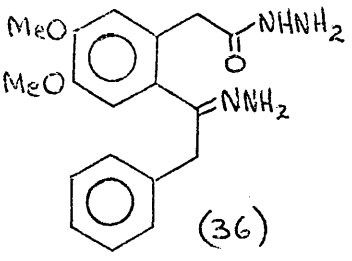

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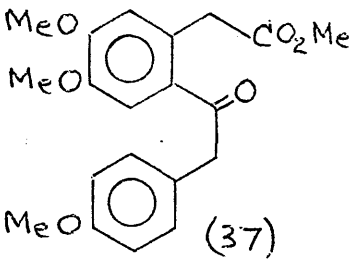

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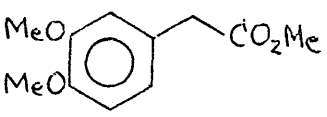

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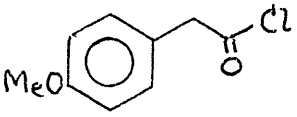

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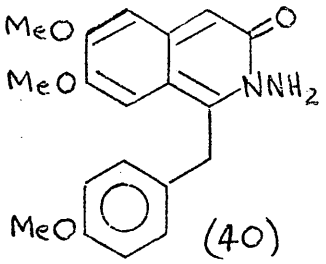

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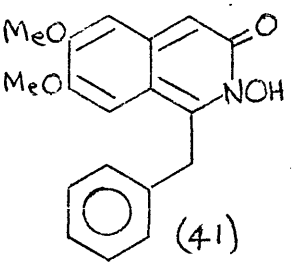

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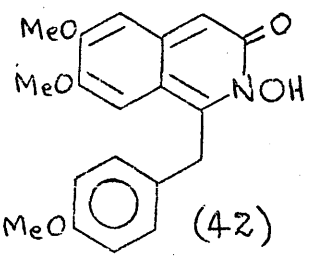

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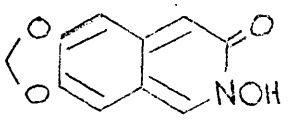

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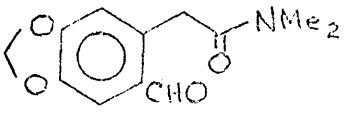

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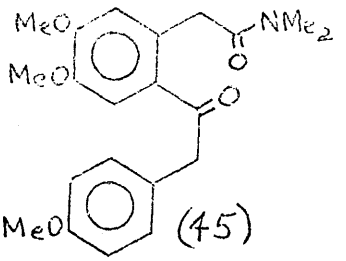

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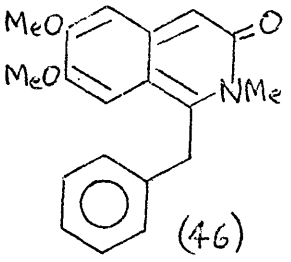

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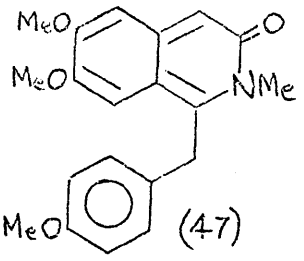

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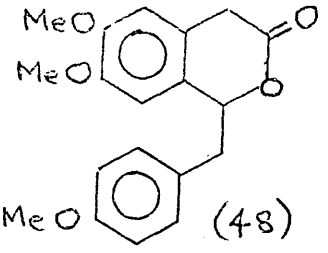

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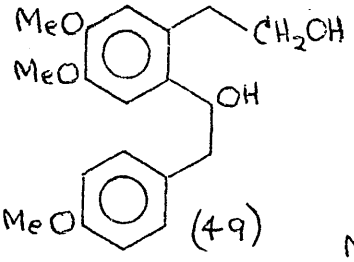

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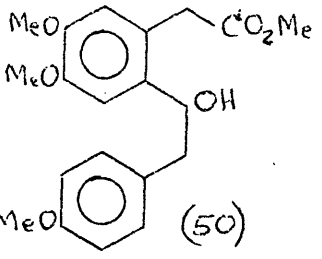

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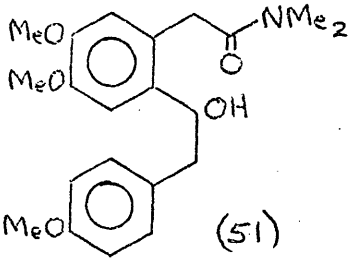

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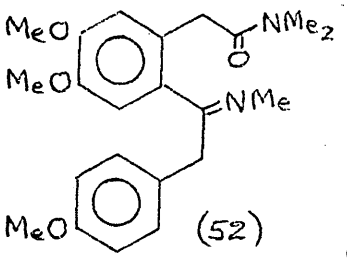

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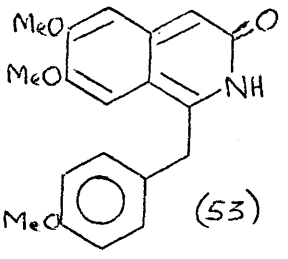

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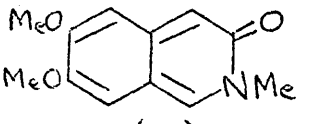

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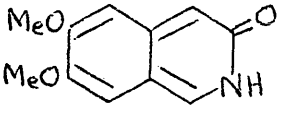

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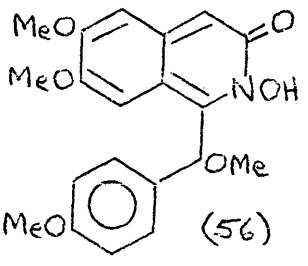

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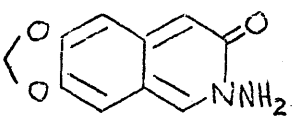

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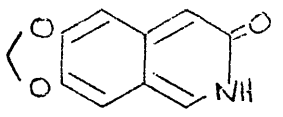

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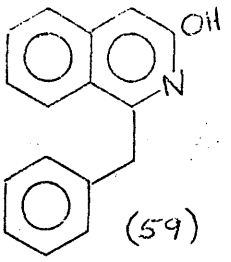

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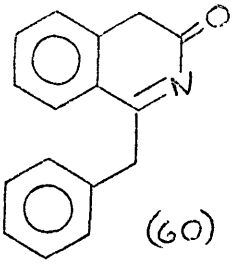

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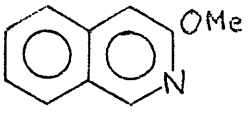

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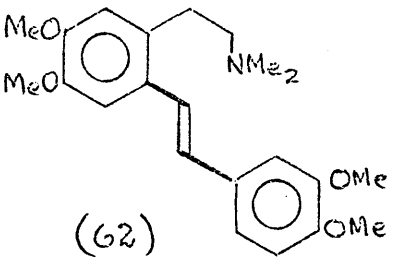

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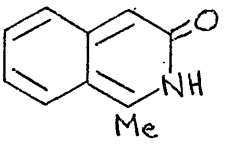

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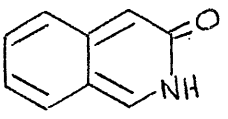

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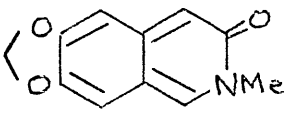

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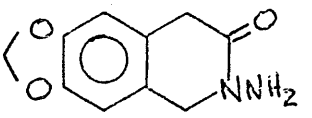

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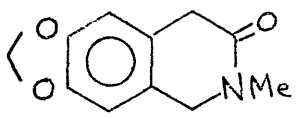

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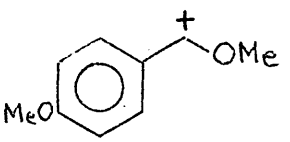

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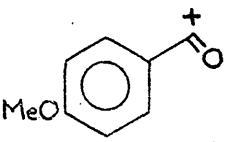

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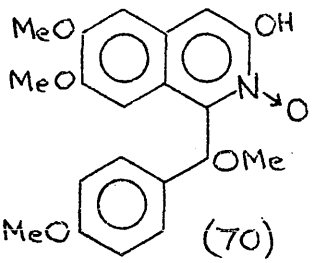

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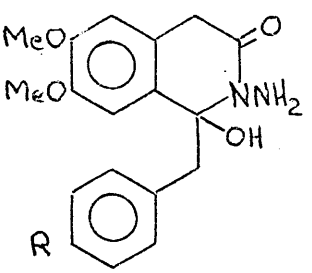

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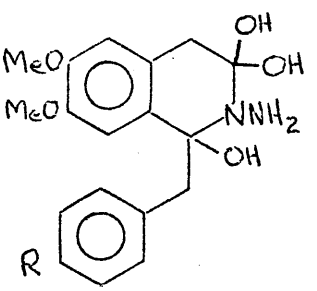
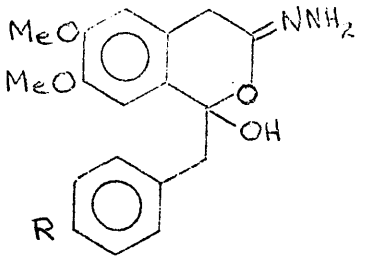
(73) R = MeO



(72) R = H

(74) R = MeO



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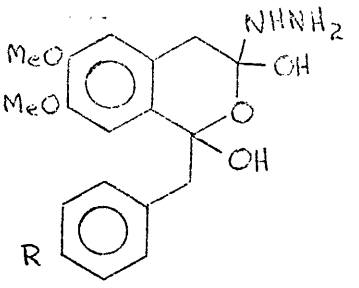
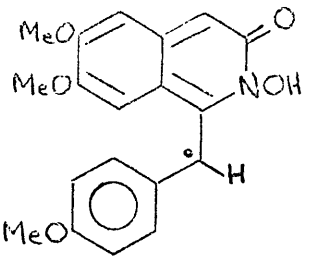
(77) R=MeO



(76) R=H
(78) R=MeO



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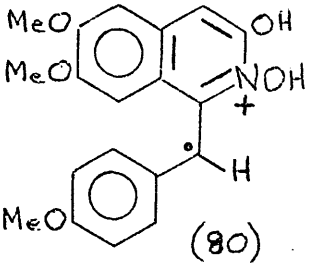

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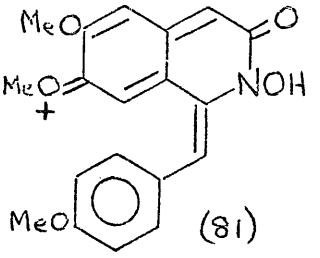

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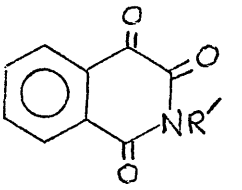

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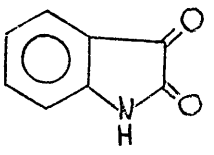

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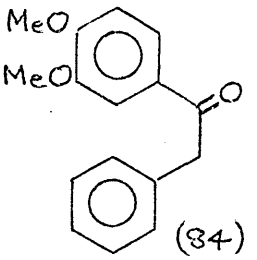

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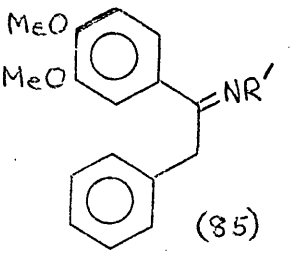

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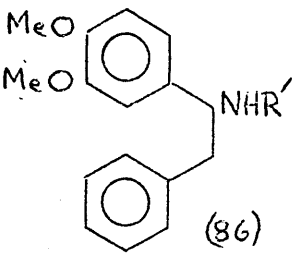

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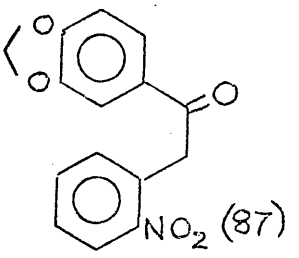

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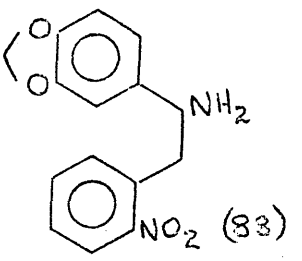

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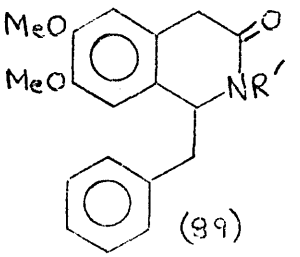

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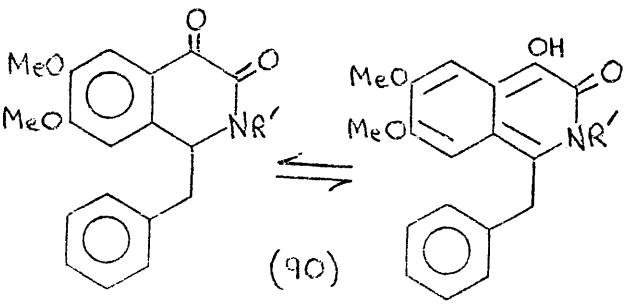

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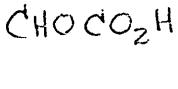

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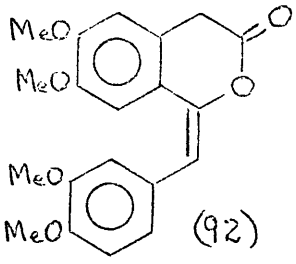

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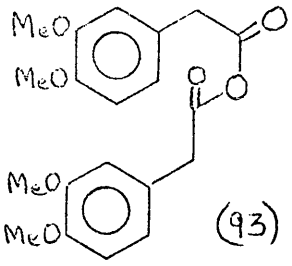

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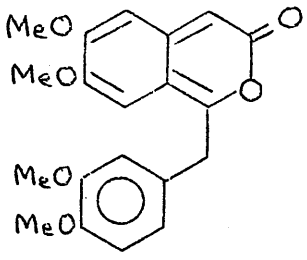

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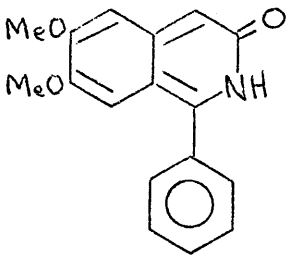

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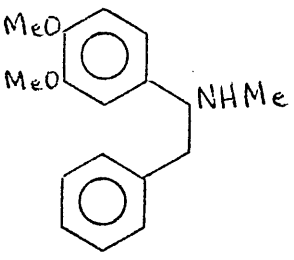

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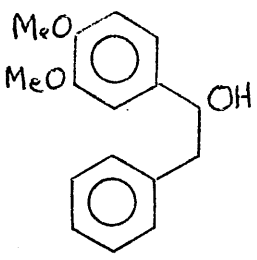

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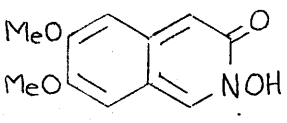


(98)

FIGURE 1.1–01 *

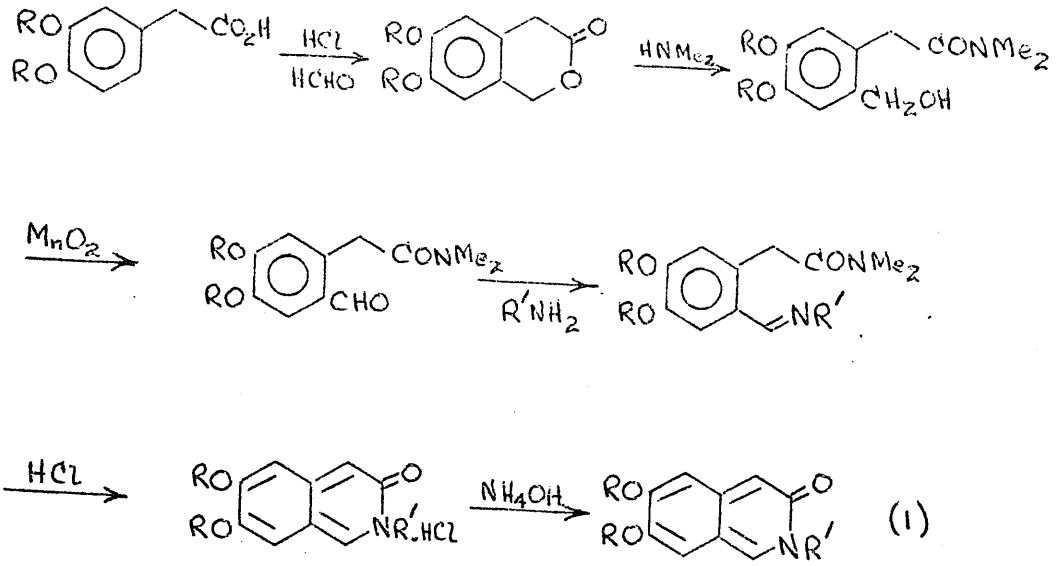
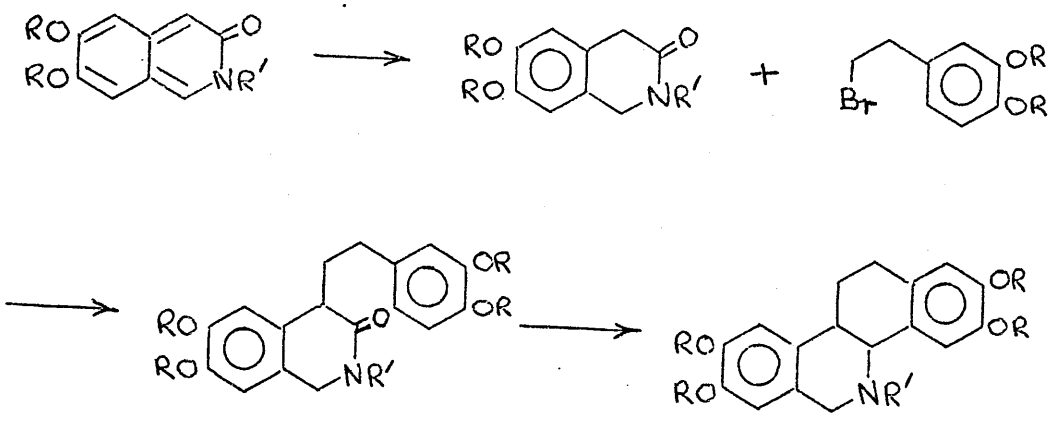


FIGURE 1.1–02 *



(* R = Me or C_2H_5 ; R' = Me, H, OH, NH_2, etc.)

Chapter 1.1 Introduction

The 3(2H)-isoquinolone system has received little attention in the past, probably because of its relative inaccesibility.[1] A recent upsurge of interest in compounds of this type has taken place however, mainly centred around the problem of the correct tautomeric forms existing under varying conditions of solvent, pH, etc.[1-4]

One of these studies followed the development of a new synthesis of alkoxy-3(2H)-isoquinolones (1) from 2-hydroxymethylarylacetic acid lactones via 2-formimino-N, N-dimethyl arylacetamides (Figure 1.1-01).[1] The route is claimed by McCorkindale and McCulloch to be fairly general. The key step, involving acid-catalysed cyclisation of an intermediate imino-amide, is reported to be dependent on the basicity of the primary amine ($R'NH_2$) used for initial imine formation, the time required for reaction varying from 1min (e.g. for R' = Me) to 20-30 min (e.g. for R' =NH_2).

This efficient synthesis seemed capable of extension to other more complex structures containing the 3(2H)-isoquinolone system, and was obviously of great potential value in the field of benzylisoquinoline-derived alkaloids.[5] Of special interest in this connection was the reduction of the 3(2H)-isoquinolones, catalytic hydrogenation or sodium borohydride treatment yielding 1,4-dihydro derivatives (2) which could be further reduced by lithium aluminium hydride to tetrahydro derivatives (3).[1]

Thus, McCulloch outlined several hypothetical routes leading to various alkaloidal systems in which the 3(2H)-isoquinolone fragment prepared by the method already described (Figure 1.1-01) was to be further reduced either before or after addition of other substituent groups.[5] A foundation was thereby established for the construction of the elusive benzophenanthridine skeleton (Figure 1.1-02),[5] and a synthesis of the tetrahydroberberine alkaloid norcoralydine (4) initiated[5] (which has been completed in the present work : see Chapter 2).

Of more direct relevance to the major part of the

FIGURE 1.1–03

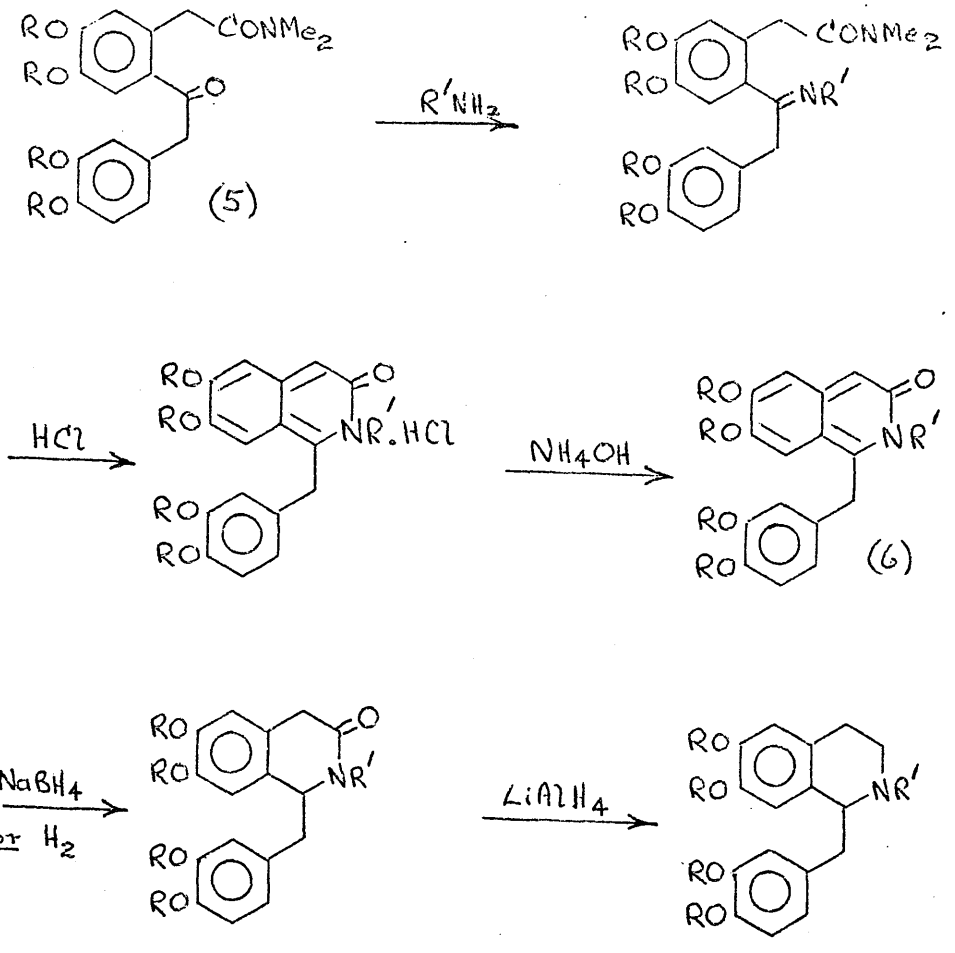
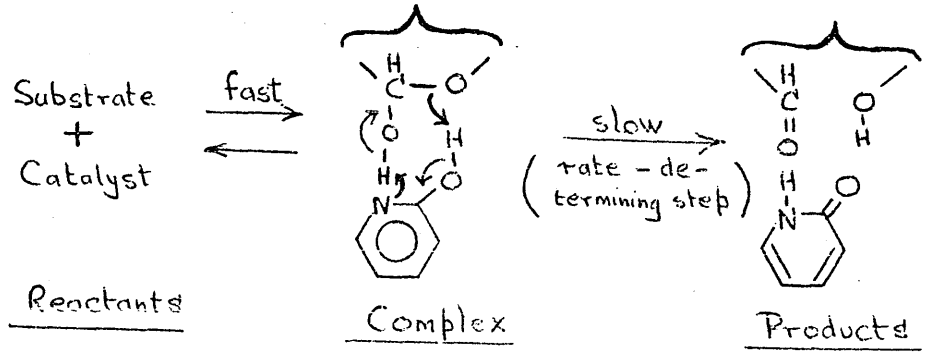


FIGURE 1.1–04



present work however is McCulloch's proposed synthesis of the simple tetrahydrobenzylisoquinoline system illustrated in Figure 1.1-03.[5] For this route to be successful several assumptions would have to be made : (a) that it would be possible to prepare keto-amides of type (5); (b) that these would readily form imines with primary amines; and (c) that the required cyclisation would take place (e.g. with acid). No difficulty was envisaged during the final reduction, although it was considered that the 1-benzyl-3(2H)-isoquinolones (6) would prove to be of sufficient interest to merit their preparation alone.

It was hoped for example that these 3(2H)-isoquinolones might possess some degree of biological activity on account of their close similarity in structure to the benzylisoquinoline alkaloids, e.g. papaverine (7) (antispasmodic, anaesthetic)[6] and laudanosine (8) (convulsive, paralytic).[7] In addition the previously mentioned tautomeric equilibria could possibly create or enhance such activity: e.g. the production of spontaneous cell mutations has been attributed to the presence in DNA of nucleotide bases in abnormal tautomeric forms at the time of replication.[8]

More specifically, the N-H species (9,10) should be a potential bifunctional catalyst by analogy with 2-pyridone (11, 12).[5] The latter was shown to effect first-order catalysis of the mutarotation of tetramethyl glucose in benzene solution, the rate of reaction being considerably greater than when mixtures of phenol and pyridine were employed and in which third-order kinetics prevailed.[9]

It has been suggested that polyfunctional catalysis of this type in which nucleophilic and electrophilic groups are present in the same molecule may be the basis of enzyme action.[9] Like the enzymic systems, 2-pyridone functions more efficiently in near neutral conditions, at low temperature and in high dilution, and high catalyst-substrate specificity is demonstrated. Catalyst-substrate complexes are also formed prior to reaction in both cases, the probable mode of action of 2-pyridone in the example cited above being as shown in Figure 1.1-04.[9]

The properties of 1-benzyl-3(2H)-isoquinolones incorporating potential bifunctional catalytic activity into a benzylisoquinoline framework should therefore be of considerable interest.

The following chapter describes the preparation of a number of such compounds by various synthetic routes, after which a discussion of spectral and other properties of 1-benzyl-3(2H)-isoquinolones is given.

FIGURE 1.2-01

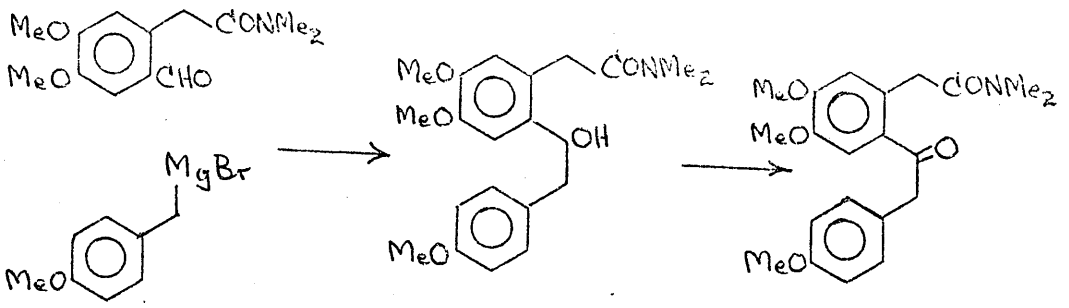


FIGURE 1.2-02

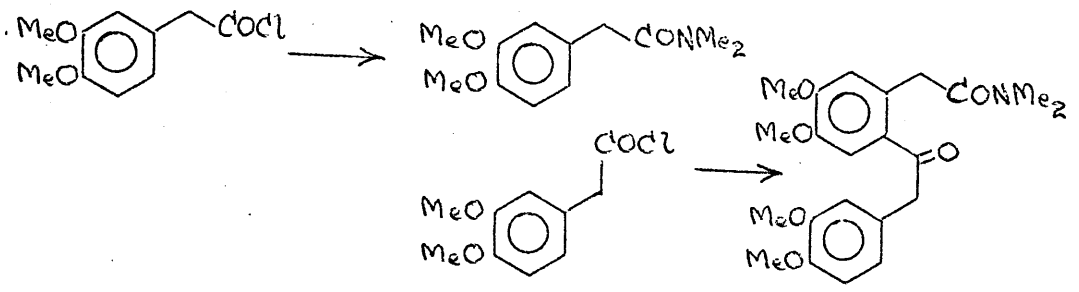


FIGURE 1.2-03

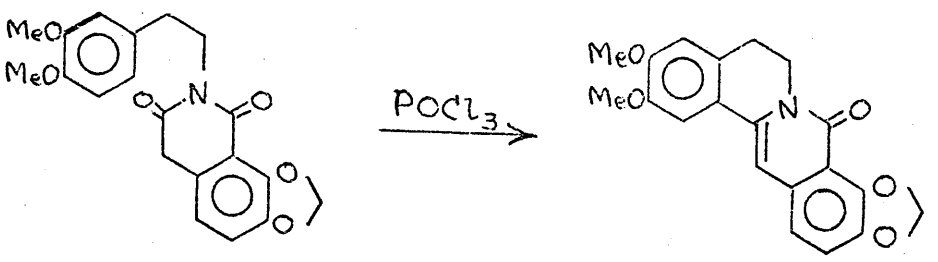
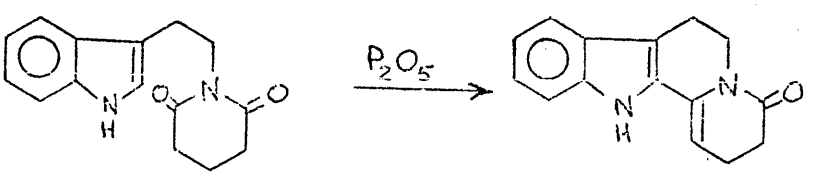


FIGURE 1.2-04



Chapter 1.2 Preparation of 3(2H)-isoquinolones

With a view to developing the route devised by McCorkindale and McCulloch for the synthesis of alkoxy-3(2H)-isoquinolones along the lines shown in Figure 1.1-03, Flood made some preliminary attempts to prepare keto amides of type (5) by two routes (Figures1.2-01 and 1.2-02).[10] Little progress was made however, and it was concluded[10] that the dimethylamido group was in some way responsible for the failure of the essential Grignard[cf.11] and acylation reactions (Figures 1.2-01 and 1.2-02 respectively).

In the present work the dimethylamide (13) was again prepared, and fully characterised. Acylation was attempted using (a) 3,4-dimethoxyphenylacetonitrile (14) with stannic chloride or aluminium chloride and (b) 3,4-dimethoxyphenylacetic acid (15) with trifluoroacetic anhydride. In the first reaction mixtures of products much more polar than the initial amide resulted (probably phenols arising from demethylation) whereas in the second a quantity of the trifluoroacetyl derivative (16) was obtained. In no case however was there evidence that the required reaction had occurred and no further attempts were made to acylate dimethylamides.

Reports of "Bischler-Napieralski" cyclisation of imides (*cf.* *e.g.* Figures 1.2-03 and 1.2-04)[12,13] suggested that a rather different approach might be more profitable. Thus it was hoped that treatment of an imide such as (17) with phosphorus oxychloride or phosphorus pentoxide would result either in direct formation of the isoquinolone (18) or, by direct analogy with Figures 1.2-03 and 1.2-04 afford the stilbenoid structure (19) which it was thought might be capable of transformation into (18) (if the latter was not in fact the preferred tautomeric form).

To obtain the N-H imide (20) recourse was made to a reported method for the preparation of "bisphenylacetimide" (21) from 2 moles of phenylacetyl chloride and 1 mole of benzamide, the latter acting merely as a nitrogen donor.[14] However, microanalysis of the product

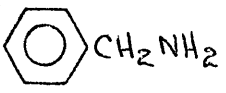
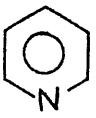
obtained using 3,4-dimethoxyphenylacetyl chloride in place of phenylacetyl chloride showed that 1mole of benzamide had condensed with 1 mole of the acid chloride to form the imide (22), $C_{17}H_{17}NO_4$, instead of the desired product (20), $C_{20}H_{23}NO_6$.

In view of the availability of this imide (22) it was decided to test its possible cyclisation to a 3(2H)-isoquinolone in spite of the lack of a methylene group adjacent to the carbonyl group potentially involved in cyclisation. However, although phosphorus oxychloride treatment appeared to give rise to a single product less polar than starting material (possibly a chloro compound), no evidence could be obtained for 3(2H)-isoquinolone f ormation.

It seemed that a closer analogy to the imide cyclisations previously cited (Figures 1.2-03 and 1.2-04) would be cyclisation of the N-Me imide (23). Treatment of 3,4-dimethoxyphenylacetyl chloride with methylamine in ethanol-benzene or ether yielded the monomethyl amide (24). Although reaction of this with 3,4-dimethoxyphenylacetic acid and trifluoroacetic anhydride afforded a complex mixture of products, a reasonable yield of the tetramethoxy-N-methyl imide (23) was obtained on treatment of (24) with excess 3,4-dimethoxyphenylacetyl chloride. However in view of the success achieved in the alternative approaches to 3(2H)-isoquinolones described later cyclisation of this imide was not in fact studied, although it is considered that this reaction holds considerable promise.

In 1952, Bentley, Dawson and Spring sought a new synthesis of papaverine (7) <u>via</u> the benzylisoquinolone derivative (25) which, incidentally, they believed would exist as the 3-hydroxyisoquinoline tautomer (26).[15] They were unsuccessful in their attempts to prepare this inter - mediate as keto esters of type (27) were found to afford bright red naphthaquinones (28) on treatment with for example aqueous ammonia, rather than the intermediate keto amide (29) or indeed the 3(2H)-isoquinolone ("3-hydrxyisoquinoline") which had been hoped for. The mechanism of naphthaquinone formation was

FIGURE 1.2-05

Amine	pK_b
$MeNH_2$	3·38
	4·64
NH_2NH_2	5·93
	8·80

proved to involve initial condensation to give a 1,3-dihydroxynaphthalene (30) which was readily oxidised in alkaline solution to the final highly coloured product on exposure to air, and aqueous sodium hydroxide was also found to effect this transformation in good yield. The project was apparently abandoned at this stage, although "3-hydroxyisoquinolines" were obtained (for only the second time, according to the chemical literature) cf.[16] by ammonia treatment of esters of 2-acetyl- and 2-benzoyl-4,5-dimethoxyphenylacetic acids, phenolic character being supposedly indicated by solubility in sodium hydroxide and a violet colour test with ferric chloride.

From these results, then, it seemed that keto esters of type (27) would yield naphthaquinones on treatment with any base strong enough to cause carbanion formation by removal of a proton α to the ketone. In order to study this situation in greater detail the preparation of keto ester (31) was undertaken, and its properties examined with a view to obtaining imino or amide derivatives which might act as intermediates in 3(2H)-isoquinolone formation.

Conversion to the naphthaquinone (32) was found to occur not only with ammonia but also with sodium hydrogen carbonate and even to a small degree with sodium acetate. On testing the keto ester (31) with a series of amines in ethanol solution (taking as evidence of naphthaquinone formation the development of colour, the anion appearing deep red in dilute alkaline solution), the following results were obtained: methylamine caused rapid colour formation on shaking in air at room temperature, benzylamine reacted more slowly to give a red solution, and hydrazine hydrate and pyridine produced no colouration at all. (Incidentally these results are in keeping with the order of basicities, values of pK_b for these amines being shown in Figure 1.2-05).[17]

Since hydrazine did not appear sufficiently basic to cause rapid self-condensation of the keto ester, it was hoped that a reaction under carefully controlled conditions might produce either the N-amino-3(2H)-isoquinolone (33) or at least an intermediate suitable for

further conversion : e.g. hydrazone (34), hydrazide (35), or even hydrazonehydrazide (36). Accordingly a methanolic solution of keto ester (31) was treated with aqueous hydrazine hydrate in the dark at room temperature under nitrogen atmosphere. PLC of a chloroform extract of the yellow reaction mixture afforded a very small yield of a yellow crystalline solid, m.p. 183-185°, and a somewhat greater quantity of a colourless crystalline solid of indefinite melting point. The latter was found to be completely converted to the former on heating or on treatment with mineral acid followed by basification. (Even gentle warming in solution prior to recrystallisation caused slight conversion to the yellow product).

A study of spectral data and comparison with spectra of authentic 3(2H)-isoquinolones [1,5] (see Chapter 1.3) indicated that the yellow compound indeed appeared to be the required 1-benzyl-6,7-dimethoxy-N-amino-3(2H)-isoquinolone (33), $C_{18}H_{18}N_2O_3$. It thus seemed that the colourless compound was an intermediate, readily convertible to the 3(2H)-isoquinolone (for discussion of its structure see Chapter 1.4). Evidence from parallel experiments suggests that this colourless material is indeed the first product formed when extremely mild conditions are used, the 3(2H)-isoquinolone only being produced during work-up (possibly due to catalysis by a trace of hydrochloric acid present in the chloroform used for extraction and/or by the chromatographic media employed for final separation - see Chapter 1.4).

To test the generality of this reaction and also to approach more closely towards an "authentic alkaloidal structure"(in particular with regard to the substitution pattern of aromatic methoxyl groups) , the trimethoxy keto ester (37) was prepared, Friedel-Crafts reaction of methyl homoveratrate (38) with homoanisoyl chloride (39) in the presence of aluminium chloride in carbon disulphide affording a good yield of the required product, m.p. 118-121°. Treatment with hydrazine hydrate under conditions analogous to those

described above followed by chloroform extraction furnished a correspondingly labile colourless compound as main product. This was smoothly converted to the bright yellow 1-p-methoxybenzyl-6,7-dimethoxy -N-amino-3(2H)-isoquinolone (40) on heating or acid-base treatment, thus suggesting that keto esters (31) and (37) do indeed undergo the same type of reaction with hydrazine hydrate (see Chapter 1.4).

The weakly basic nature of hydroxylamine (pK_b 8.04)[17] suggested that this species would react analogously to hydrazine with the keto esters (31) and (37), yielding the corresponding N-hydroxy-3(2H)-isoquinolones (41) and (42). However the lability of this reagent is well known as is the difficulty incurred in its preparation,[18] and McCulloch had by-passed this problem in a synthesis of the N-hydroxy-3(2H)-isoquinolone (43) by use of hydroxylamine hydrochloride, the initial product being the 3(2H)-isoquinolone hydrochloride.[1]

In the hope of achieving a similar result a methanolic solution of keto ester (37) was treated initially with hydroxylamine hydrochloride and then, as very little reaction appeared to be taking place, refluxed with the addition of a small quantity of pyridine. PLC of the reaction mixture (following a work-up involving the addition of acid prior to basifying and extracting with chloroform) afforded a small yield of a yellow fluorescent compound with ultraviolet absorption spectral data in accord with that expected for a 3(2H)-isoquinolone,[1] and it thus seemed likely that this product was at least a derivative of 1-(p-methoxybenzyl)-6,7-dimethoxy-N-hydroxy-3(2H)-isoquinolone (42). A fuller discussion of its spectral properties is given in the next chapter, where it is shown that its structure is likely to be (56).

Although the amide aldehyde (44) had failed to react with ethylamine hydrochloride (in contrast to hydroxylamine hydrochloride),[5] the keto ester (37) was treated at room temperature with methylamine hydrochloride (a) in methanol, (b) in methanol containing sodium acetate

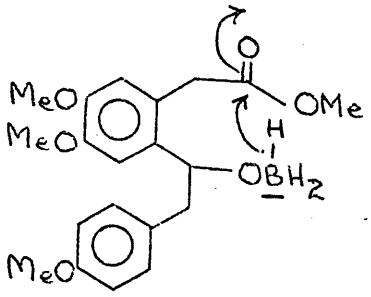
and (c) in methanol containing pyridine (all TLC scale). In no case did a reaction occur, but in the light of later experiments conducted with keto amide (45) and methylamine hydrochloride (see page 24), reactions of type (b) and (c) would appear to be worthy of further study with a view to achieving a preparation of the N-methyl 3(2H)-isoquinolones (46) and (47).

In order to arrive at a more general 1-benzyl-3(2H)-isoquinolone synthesis from 2-arylacetylaryl-acetates it now seemed necessary in view of the above results either: (a) to deactivate the arylacetyl methylene group (potentially capable of carbanion formation); (b) to activate the ketone towards imine formation; or (c) to deactivate the ester towards condensation reactions. It was thought that the latter approach would lend itself most readily to implementation since replacement of the ester function by either a carboxylate salt or an amide grouping should prevent naphthaquinone formation in the presence of even strongly basic amines.

However, although N,N-dimethyl-o-formyl arylacetamides have been smoothly converted to 3(2H)-isoquinolones (Figure 1.1-01)[1] it was evident from the foregoing that direct formation of a dimethylamide from keto esters (31) or (37) by the action of dimethylamine would be unlikely. To overcome this problem it was considered that an indirect preparation of the desired keto amide (45) could be achieved from (37) by selective reduction[19] of the ketone function to the corresponding alcohol followed by amide formation and reoxidation.

With sodium borohydride in methanol solution the keto ester was found to give a mixture of the lactone (48) cf.[20] and diol (49), cf.[21] the relative proportions varying considerably with scale, concentration of reactants and reaction time. The lactone presumably arose from base-catalysed elimination of methanol from the initially formed hydroxy ester (50).[19] Cases in which borchydride has reduced esters to alcohols are

FIGURE 1.2-06



certainly not unknown, [19] especially where the possibility exists of internal reduction by an intermediate substituted borohydride of the type postulated in Figure 1.2-06. It was extremely difficult (but not impossible) to obtain a reasonable yield of the lactone at the expense of the diol from this reaction.

With diborane in tetrahydrofuran solution the main product was the expected hydroxy ester (50) along with minor quantities of lactone (48) and diol (49). cf.[19] The hydroxy ester was found to be rapidly converted to the lactone on attempted crystallisation or sublimation, and more slowly on standing at room temperature.

Hydrogenation of the keto ester (37) under a variety of conditions of solvent, catalyst and reaction time [22] failed to give isolable yields of lactone or hydroxy ester, mixtures of products generally being obtained where indeed reaction took place at all (see Chapter 1.6).

Treatment of either the hydroxy ester or lactone with dimethylamine in ethanol solution afforded the required hydroxy amide (51) in almost quantitative yield. (Whether or not the hydr oxy ester was first converted to the lactone under these conditions was not established: a complicating factor in a study of this reaction would be the fact that the hydroxy amide seemed capable of losing dimethylamine with regeneration of the lactone on prolonged heating in solution or extended contact with chromatographic media).

Manganese dioxide treatment of the hydroxy amide (51) for several days gave a very small yield of impure material the infrared spectrum of which (ν_{max} at 1645 and 1680cm^{-1}) suggested that it may contain the keto amide (45), but the latter was more readily prepared in good yield by oxidation of (51) with ruthenium tetroxide in carbon tetrachloride solution. [23] As this was apparently a very clean reaction, it might have been possible to achieve an even better yield (cf. Chapter 1.6) but for the low solubility of the hydroxy amide (51) in carbontetrachloride. (Although chloroform has been used in such oxidations, it was found to be unsuitable in the present case).

Treatment of the keto amide (45) with methylamine in refluxing ethanol failed to yield the imine (52), the intermediate required for the synthesis of the 3(2H)-isoquinolone (47) as proposed by McCorkindale and McCulloch.[1] Due to the known difficulty in forming imines from aromatic ketones[24] this result was not altogether unexpected, and thus reaction of the keto amide with ammonia or other less nucleophilic amines was not attempted.

As proton and Lewis acids have been used successfully to catalyse the formation of imines from aromatic ketones,[25] and since it was believed that imines of type (52) once formed would be smoothly converted to 3(2H)-isoquinolones on acid treatment,[1] the keto amide (45) was now heated in acetic acid solution containing ethanolic methylamine. Ultraviolet absorption spectral data of the yellow fluorescent product suggested that the desired N-methyl-3(2H)-isoquinolone (47) had indeed been formed in good yield (TLC), but the product proved difficult to isolate in a pure condition, which was partly due to its apparent susceptibility to aerial oxidation. cf.[1] This compound was also produced on treatment of the keto amide with methylamine hydrochloride in pyridine, but again attempted isolation of a pure product was unsuccessful, as were attempts to prepare a crystalline hydrochloride.

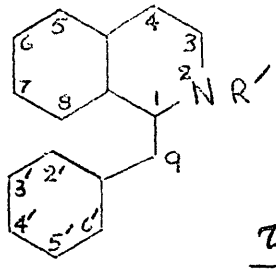
The N-H-3(2H)-isoquinolone (53) was satisfactorily prepared in a high state of purity from the keto amide (45) by means of ammonium acetate in acetic acid. cf.[2] This compound was practically unaffected by overnight exposure to the atmosphere : cf. the great susceptibility to oxidation exhibited by 6,7-dimethoxy-N-methyl-3(2H)-isoquinolone (54) with the comparative stability of 6,7-dimethoxy-N-H-3(2H)-isoquinolone (55).[1]

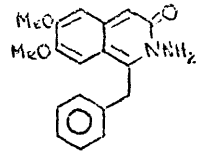
The N-amino-3(2H)-isoquinolone (40) was formed in good yield on treatment of the keto amide (45) with aqueous hydrazine hydrate in acetic acid. (Reaction of (45) with methanolic hydrazine hydrate in the absence of acetic acid (cf. reactions with keto esters (31) and (37))was not attempted.) Both the N-H and the N-amino derivatives on treatment with dilute hydro-

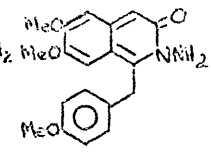
chloric acid readily formed colourless hydrochlorides, from which the 3(2H)-isoquinolones were recoverable by treatment with ammonia and extraction with chloroform. On heating, both hydrochlorides became yellow, perhaps suggesting facile loss of hydrogen chloride. cf.[5]

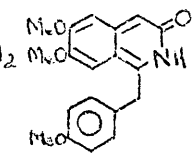
Spectral properties of all 3(2H)-isoquinolones prepared are discussed in the following chapter.

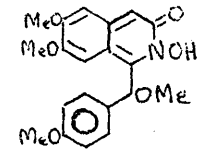
FIGURE 1.3-01











τ :-

Position	Proton (qty.)	(33)	(40)	(53)	(56)
2	NH_2 (0.1?)	<0?	<0?	—	—
	NH_2 (1.2?)	4.33 (s)	4.2-5.2 (b.m)	—	—
2	NH (1)	—	—	?	—
2	NOH (1)	—	—	—	<0?
(4)	(1)	3.40 (s)	3.41 (s)	3.41 (s)	3.41 (s)
(5)	ArH (1)	3.36 (s)	3.34 (s)	3.41 (s)	3.36 (s)
(8)	(1)	3.13 (s)	3.14 (s)	3.10 (s)	3.10 (s)
9	CH_2 (2)	5.34 (s)	5.41 (s)	5.63 (s)	—
9	CH (1)	—	—	—	4.34 (bs)
9	OCH_3 (3)	—	—	—	6.54 (s)
2', 6'	ArH (2)	2.73 (s)	2.92 (d, 9Hz)	2.77 (d, 9Hz)	2.77 (d, 9Hz)
3', 5'	ArH (2)	2.73 (s)	3.17 (d, 9Hz)	3.23 (d, 9Hz)	3.22 (d, 9Hz)
4'	ArH (1)	2.73 (s)	—	—	—
(6)	OCH_3 (3)	6.04 (s)	6.08 (s)	6.13 (s)	6.10 (s)
(7)	OCH_3 (3)	6.15 (s)	6.19 (s)	6.26 (s)	6.25 (s)
4'	OCH_3 (3)	—	6.30 (s)	6.36 (s)	6.25 (s)

FIGURE 1.3-02

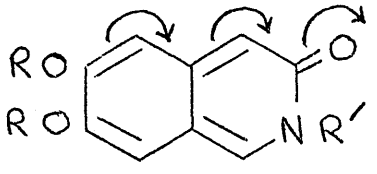


FIGURE 1.3-03

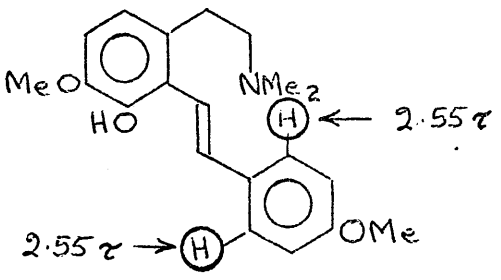
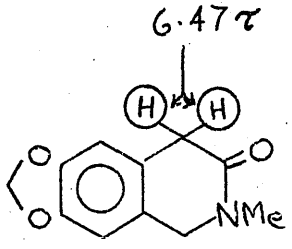
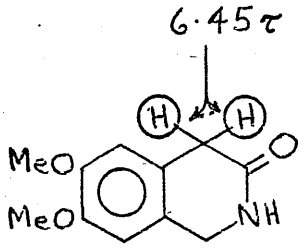


FIGURE 1.3-04





Chapter 1.3 Spectral Properties

Nuclear magnetic resonance spectra

Details of NMR spectra of four of the 3(2H)-isoquinolones synthesised are listed in Figure 1.3-01. The tentative assignments indicated for protons H_4, H_5 and H_8 and methoxyl groups at C_6 and C_7 are based on consideration of the relative electron densities at the various positions, taking into account the probable direction of electron flow and the somewhat greater overall "aromaticity" of the non-heterocyclic ring system (Figure 1.3-02). [5]

In both of the N-NH_2 derivatives (33) and (40) integration suggests that only one of the two NH_2 protons resonates at positive τ (between 4 and 5 τ), the other presumably occurring at very low field due to strong hydrogen bonding, possibly intermolecular (cf. values of 2.9 and -3.8 τ exhibited by the two amino protons in N-amino-6,7-methylenedioxy-3(2H)-isoquinolone (57)). [5] As with 6,7-methylenedioxy-3(2H)- isoquinolone (58) or 6,7-dimethoxy-3(2H)-isoquinolone (55) [1] a resonance was not observed corresponding to N-H in (53). However, although it has been reported that the N-OH proton in N-hydroxy-6,7-methylenedioxy-3(2H)-isoquinolone (43) appears at 4.16 τ, [1] no similar resonance could be detected corresponding to the hydroxyl proton in (56). (It now seems possible that this proton actually occurs at very low field).

The NMR spectra of the benzylisoquinolones suggested predominance of the "3(2H)-isoquinolone" tautomeric form (18) over stilbenoid (19) and other proposed tautomers (such as the lactim (59) and acylimine (60) for N-H derivatives). [1-4, 26] While it is known that a carbon-carbon double bond connected to an aromatic nucleus deshields the ortho protons (cf. e.g. values of 2.55 τ for the corresponding protons in petaline methine, Figure 1.3-03), [27] in the four compounds under discussion the protons $H_{2'}$ and $H_{6'}$ resonate between about 2.7 to 2.9 τ, values close to those found in many alkylated

FIGURE 1.3-05

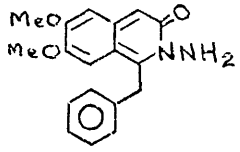
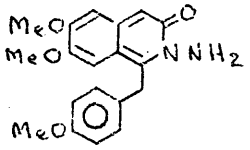
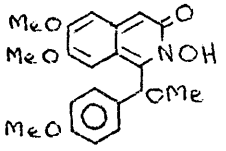
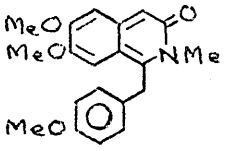
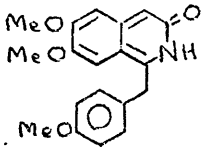
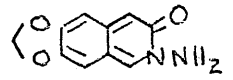
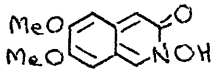
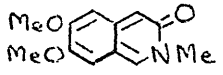
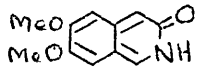
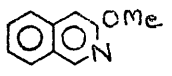
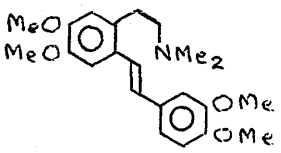
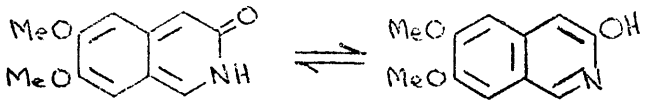
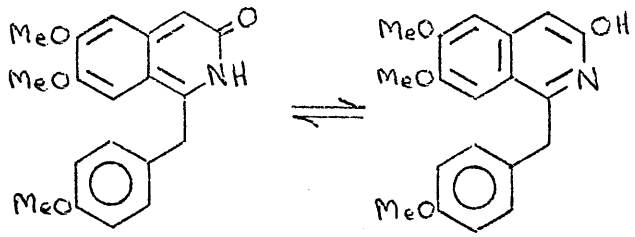
Compound	Ref.	Max or infl., nm (log ε)	* (r.o.d.)
	(33)	233 257 288 306 318 — 395 (4.00) (4.43) (3.30) (3.34) (3.35) — (3.39)	
	(40)	229 257 282 305 317 — 398 (4.13) (4.53) (3.49) (3.42) (3.42) — (3.47)	
	(56)*	228 257 — 305 317 355 402 (1.00) (1.70) — (0.18) (0.17) (0.11) (0.19)	
	(47)*	225 257 282 302 316 — 403 (1.00) (1.94) (0.32) (0.16) (0.15) — (0.17)	
	(53)	227 256 282 302 313 355 399 (4.26) (4.61) (3.55) (3.31) (3.29) (3.24) (3.55)	
	(57)	250 293 307 319 — 400 (4.81) (3.50) (3.71) (3.73) — (3.71)	
	(98)	251 — 305 314 — 390 (4.64) — (3.69) (3.69) — (3.48)	
	(54)	248 290 306 316 — 399 (4.76) (3.43) (3.51) (3.55) — (3.63)	
	(55)	247 288 301 313 354 396 (4.70) (3.55) (3.53) (3.57) (3.35) (3.54)	
	(61)	339 (3.56)	
	(62)	296 309 330 (4.15) (4.17) (4.23)	

FIGURE 1.3-06

(55) 

$\frac{\varepsilon_{396}}{\varepsilon_{354}} = 1.55$

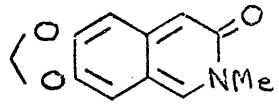
λ_{max} ($\log \varepsilon$), nm: 396 (3.54) 354 (3.35)

(53) 

$\frac{\varepsilon_{399}}{\varepsilon_{355}} = 2.24$

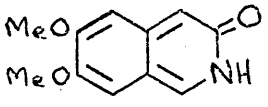
λ_{max} ($\log \varepsilon$), nm: 399 (3.55) 355 (3.20)

FIGURE 1.3-07



(65)

ν_{max} (Nujol), cm^{-1}: 1662, 1648, 1618



(55)

ν_{max} (KCl), cm^{-1}: 1656, 1638, 1614

benzene derivatives.[28] Moreover, with the exception of the solitary methine proton of (56) which appears at somewhat lower field, the methylene protons all resonate between 5 and 6 τ, rather lower than would be expected for H_4 methylene protons in hypothetical stilbenoid – lactam structures (19) by analogy with the value (usually about 6.5 τ) found for the corresponding protons in 1,4-dihydro-3(2H)-isoquinolones (see e.g. Figure 1.3-04).[1]

Ultraviolet spectra

Figure 1.3-05 illustrates ultraviolet spectra of all 3(2H)-isoquinolones prepared in the present work along with 1-H analogues,[1] 3-methoxyisoquinoline (61)[3] and an example of a polymethoxy stilbene (62)[5] for comparison purposes. It is evident that spectra of all compounds believed to be 3(2H)-isoquinolones show striking similarities, and it would appear that the possible stilbenoid tautomeric form[2] is not present to any noticeable extent under these solvent conditions (95% aqueous ethanol). Slight changes occurred on addition of acid or base which in general paralleled those observed for the 1-H derivatives, and tended to confirm protonation on oxygen under acid conditions[1] (again with no evidence for tautomerisation to stilbenoid forms).

In the case of N-H 3(2H)-isoquinolones the intensities of absorption at around 350nm and 400nm have been quoted as being indicative of the relative proportions of lactim and lactam tautomer, respectively.[1,3] Comparison of the ratio of these intensities for (55) and (53) suggests that there is less of the lactim tautomer present in the 1-anisyl derivative than in the 1-H analogue (Figure 1.3-06), and this is in keeping with the finding that 1-methyl-3(2H)-isoquinolone (63) favours the lactam tautomer even more than (64).[3]

Other spectral properties

In the infrared spectra the 1-benzyl and 1-anisyl 3(2H)-isoquinolone derivatives all exhibited solid-state absorption in the 1610-1615, 1630-1635 and 1645-1660cm^{-1} regions, values roughly comparable to corresponding data for e.g. (65) and (55) (Figure 1.3-07).[1]

FIGURE 1.3-08

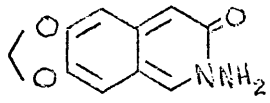
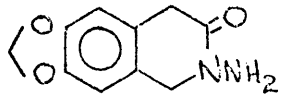
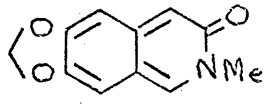
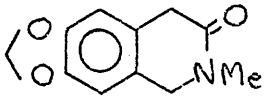
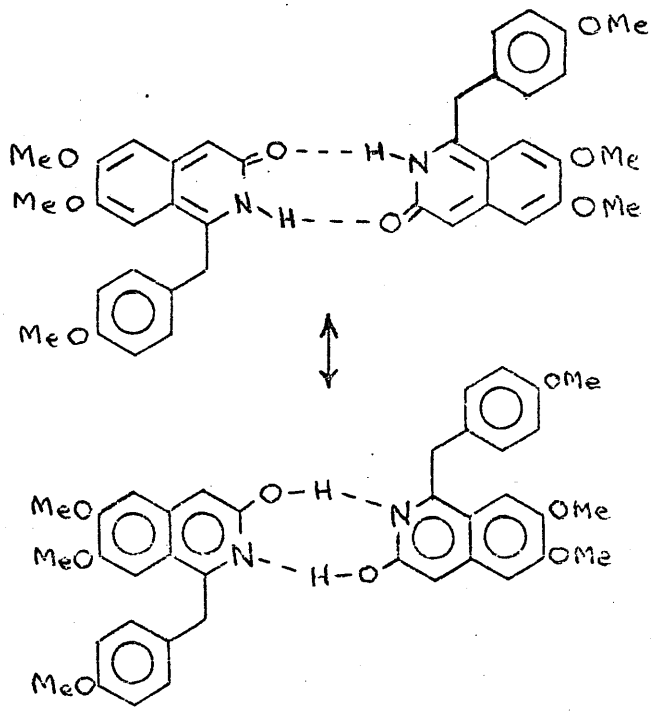
		ν_{max} , cm^{-1}	
	(57)	1659	(KCl)
	(66)	1644	(KCl)
	(65)	1662	(Nujol)
	(67)	1650	(KCl)

FIGURE 1.3-09



At least in the case of the N-NH_2 3(2H)-isoquinolones, the carbonyl absorption tends to confirm predominance of "isoquinolone" over possible stilbenoid forms in the solid phase, since in the stilbenoid tautomer amide C=O absorption might be expected to appear at lower wavelength than in its α,β- unsaturated analogues.[29,30] (A rough illustration of this effect is provided by comparison of carbonyl absorption of 3(2H)-isoquinolones (57) and (65) with their 1,4-dihydro derivatives (66) and (67) (Figure 1.3-08) ; however, N-H 3(2H)-isoquinolone derivatives do not appear to follow this trend).[1]

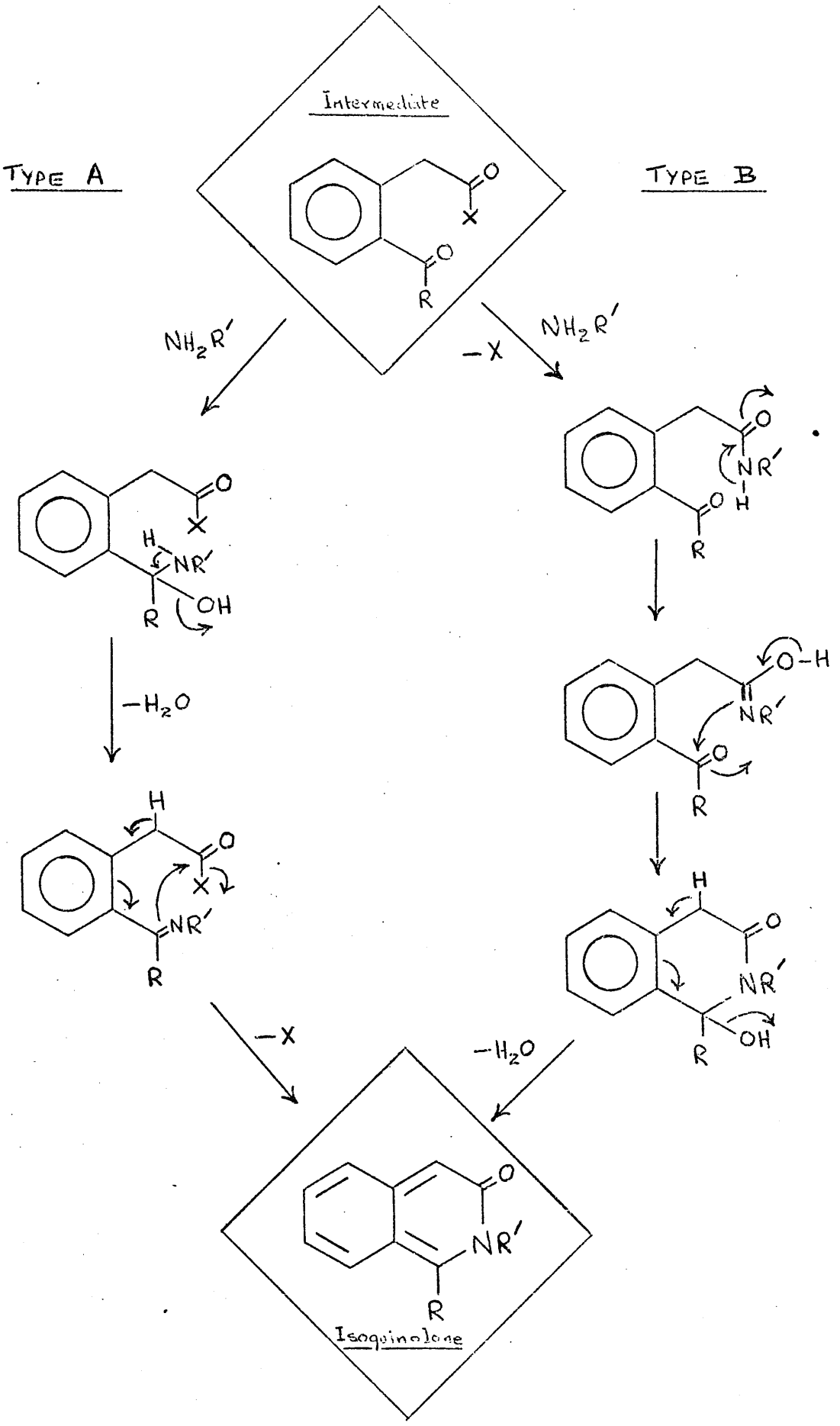
In the N-H derivative (53) a broad band at 2600-2700cm^{-1} is present, and this has been taken as evidence of the presence of a strongly hydrogen-bonded resonance-stabilised dimer (Figure 1.3-09).[1,31] This seems to preclude the existence of the hypothetical acyl-imine form of type (60)[2,26] and also lends support to the belief that the stilbenoid tautomer[2] (in which resonance-stabilised dimerisation of this type - though possibly not simple intermolecular hydrogen-bonding - is impossible) does not make an important contribution to the structure.

The greatest value of mass spectroscopy in the present work has been in the structural elucidation of the N-hydroxy derivative, believed to have structure (56) (NMR spectroscopy having shown that not three but four methoxyl groups were probably present in the molecule- see Figure 1.3-01). The mass spectrum showed a base peak at m/e 151 with an abundant ion at m/e 135. This is most readily explained in terms of the species (68) and (69), arising from breakdown of a parent molecule with structure (56).

No parent ion was evident in the spe ctrum, the ion of highest mass occurring at m/e 355 (50%) suggesting a loss of 16 mass units. This can be accounted for as a loss of oxygen from the N-oxide tautomer (70)[32] (a loss characteristic of such N-oxides).[33] It is interesting to note that the breakdown pattern of the analogous compound (43) is reported to be virtually identical to that of (58) under normal conditions, the parent ion being observed only if a direct insertion probe is used

in the mass spectrometer.[1,5] (Perhaps worthy of mention here is the appearance in the ultraviolet spectrum of (56) of fairly weak absorption at 355nm, which may be due to the presence of a small percentage of the N-oxide form in ethanolic solution).

FIGURE 1.4-01


Intermediate
TYPE A
TYPE B
NH2R'
-X
NH2R'
-H2O
-X
-H2O
Isoquinolone

Chapter 1.4 Modes of Formation

Two distinct mechanisms have been postulated to explain the cyclisation of o-acyl arylacetic acid derivatives with amines or amine salts to 3(2H)-isoquinolones (see Figure 1.4-01).[1] Factors which may influence the course of the reaction (i.e. whether it corresponds to Type A or Type B) include the nature of R (H or alkyl), R′ (H, alkyl, NH_2, OH, etc.) and COX (acid, ester, or amide), and possibly also other variables such as solvent, pH and reaction temperature.

In the present work it would seem that reaction of keto amide (45) with (a) amine acetates in acetic acid or (b) amine hydrochlorides in pyridine or methanolic sodium acetate would be more likely to take a Type A course (i.e. initial imine formation rather than transamidation) from consideration of relative reactivities of ketones and amides to nucleophilic attack (even under acid-base catalysis).

In cases where keto esters (31) or (37) were treated with hydrazine hydrate a type B mechanism would appear to be more probable because of the greater reactivity to nucleophilic attack of esters over aromatic ketones. In support of this theory is the evidence to be drawn from a study of the colourless products isolated in each case along with the bright yellow 3(2H)-isoquinolones (33) and (40). These were convertible into the latter slowly on treatment with base and rapidly on heating or on acid-base treatment (and also on mass spectral fragmentation); and this considerable sensitivity made purification and recording of satisfactory spectra difficult.

However, on one occasion analytical figures were obtained for the "N-NH_2-1-benzyl" intermediate which suggested a molecular formula of $C_{18}H_{22}N_2O_5$, corresponding to the formula of the eventual 3(2H)-isoquinolone (33), $C_{18}H_{18}N_2O_3$, plus 2 molecules of water. The fact that the only evidence of absorption in the infrared spectrum over the range 1600-1800cm^{-1} was a fairly strong band at 1610cm^{-1} seemed to point to the loss

of the ester and ketone groupings from the original keto ester (31), but suggested that if a carbonyl function was in fact present (perhaps a hydrazide) cf.[34] it must be very strongly hydrogen-bonded.[29] The ultraviolet spectrum (λ_{max} at 214, 259, 282 and 287 nm) ruled out any possibility of a stilbenoid structure,[35] and the presence of two methylene groups with magnetically non-equivalent protons was suggested by 1H doublets in the NMR spectrum at 5.63 and 6.62 τ (J= 13Hz) and at 6.63 and 7.55 τ (J= 21Hz).[28]

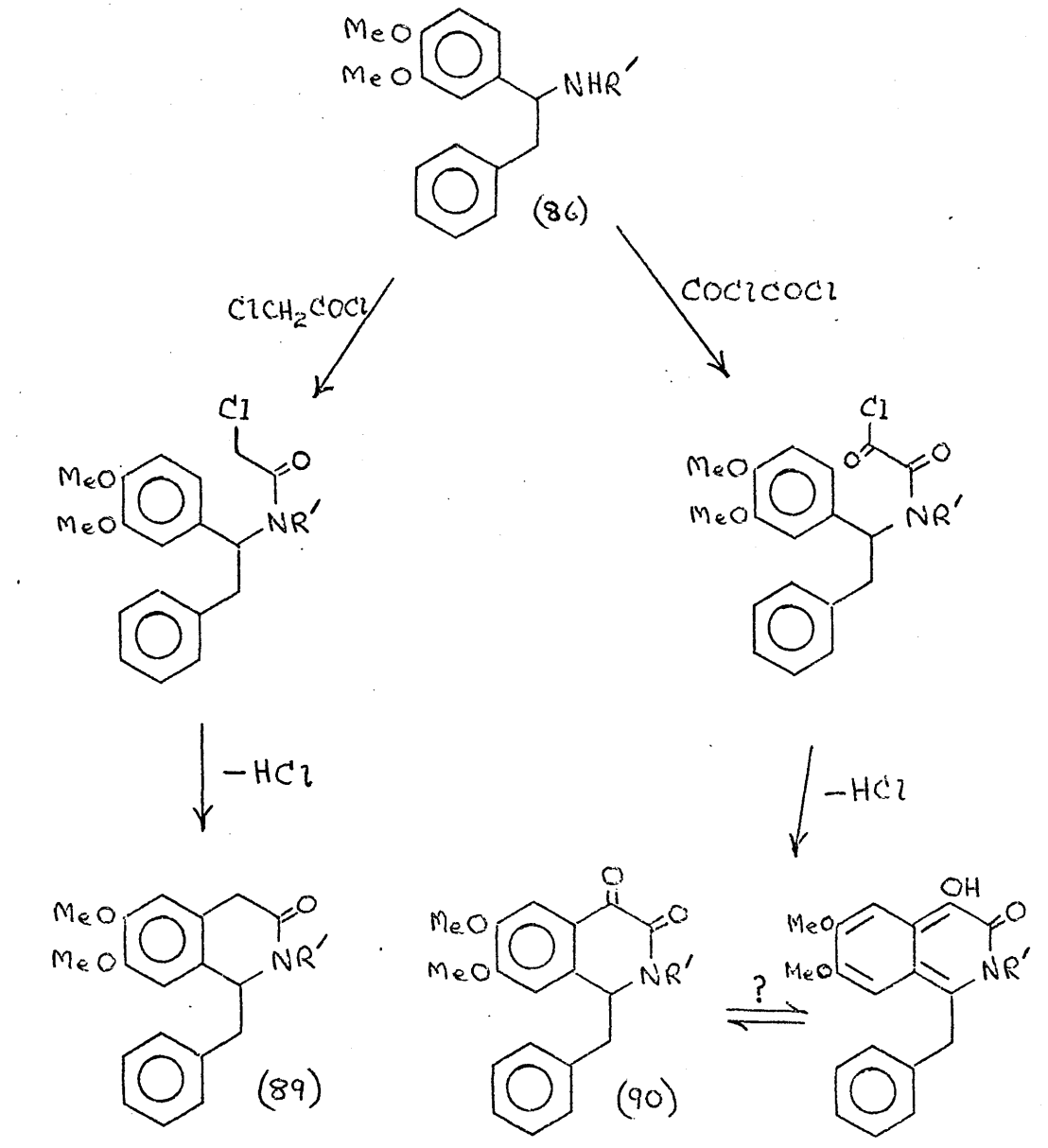
Consideration of structures for this intermediate in the light of the above data led eventually to (71) which it was believed might crystallise with one molecule of water, perhaps in a hydrated form such as (72). It is assumed here that the keto hydrazide (35) is first formed, and that this forms its ring tautomer under mild conditions. The extreme lability of such a species (71) to heat or acid-base treatment then becomes readily apparent, 1,4-elimination of water immediately forming the 3(2H)-isoquinolone (33).

The "N-NH_2-1-anisyl" intermediate exhibited spectral properties which followed very closely those of the 1-benzyl derivative described above, and would thus appear to exist as (73) or (74). (However it must be stated that the alternative though perhaps less likely structures (75), (76) and (77), (78) cannot be ruled out for these compounds on the above evidence).

The mode of formation of the tetramethoxy-N-hydroxy-3(2H)-isoquinolone (56) is more obscure, but it seems most likely that this would follow a Type B mechanism at least as far as the initial step is concerned in which hydroxamic acid formation probably predominates over oxime formation. Introduction of the fourth methoxyl group may follow oxidation (presumably aerial)[36] at the anisyl methylene position : e.g. it is envisaged that methanol could perhaps react with the radical species (79) or (80) cf.[27] or a hypothetical "quinone methide" derivative such as (81).cf.[37] A colourless product was also isolated from this reaction but not

in a sufficiently pure state for meaningful spectral data to be recorded (see Chapter 1.6) and no attempt was made to discover whether it was convertible to the yellow 3(2H)-isoquinolone (56). However, repetition of the reaction under more carefully controlled conditions would be of interest.

FIGURE 1.5 – 01



Reduced isoquinolone

Oxidised isoquinolone

Chapter 1.5 Further studies

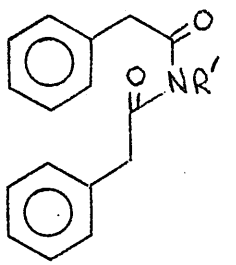
Controlled oxidation of 1-benzyl-3(2H)-isoquinolones is of interest as their structure does not permit the formation of products directly analogous to the phthalonimides (82) previously obtained on oxidation of 1-H-3(2H)-isoquinolones.[1, cf. 38] Although neither oxidation nor reduction were studied in detail in the present work, some attention was paid to a synthetic route which would offer independent syntheses of possible oxidation or reduction products (e.g. for comparison purposes) and which (it was originally hoped) might be capable of modification in such a way as to yield an alternative synthesis of 1-benzyl-3(2H)-isoquinolones.

The scheme constitutes a development of Stollé's synthesis of substituted isatins (83)[39] and appears capable of considerable generality (see Figure 1.5-01). Due to the ready availability of the dimethoxy ketone (84) (previously required for work described in Part II of this thesis) some preliminary attempts were made to form imines of type (85) for subsequent reduction to (86), but perhaps not surprisingly little progress was made.[25] However, a recent publication describes the conversion of an analogous ketone (87) to a primary amine (88) via the oxime and oxime acetate,[24] and this route could perhaps be adapted towards a general synthesis of substituted amines of type (86).

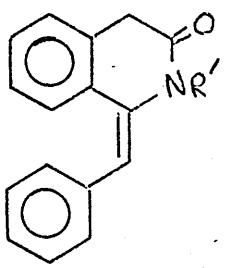
Besides yielding 1,4-dihydro derivatives (89) by two-stage treatment with e.g. chloroacetyl chloride,[cf. 40] it seems likely that the amine (86) could readily be converted on reaction with oxalyl chloride to the perhaps more interesting structure (90), the tautomeric properties of which should be worthy of study. To apply the route to a direct synthesis of 3(2H)-isoquinolones would however require the use of a two-carbon unit of the same oxidation level as glyoxylic acid (91) in a suitably protected and/or activated form, and this might prove rather more troublesome.

As stated in Chapter 1.2 it is believed that dehydrative cyclisation of imides of the type shown in

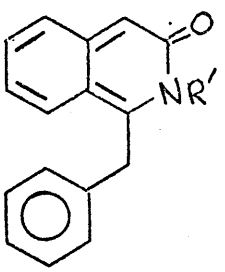
FIGURE 1.5 - 02



(17)



(19)



(18)

Figure 1.5-02 under the proper conditions may afford a useful route to 1-benzyl-3(2H)-isoquinolones, the reaction perhaps proceeding *via* a stilbenoid-lactam intermediate of the type described by Elliott.[2] By analogy, and in view of the latter's successful conversion of the benzylidene-3-isochromanone derivative (92) to the corresponding N-methyl 3(2H)-isoquinolone,[2] it would be of some interest to attempt an alternative preparation of species such as (92) by means of a carefully controlled dehydrative cyclisation of the anhydride (93).

(Added note: in a publication appearing after completion of this section of the present thesis, Elliott revises his original stilbenoid-lactam and acyl-imine structural assignments for 1-benzyl-3(2H)-isoquinolone derivatives in favour of the *o*-quinonoid tautomers; however the benzylidene-3-isochromanone (or "stilbenoid-lactone") form is still preferred for the analogous oxygen derivative (92) rather than the *o*-quinonoid form (94)).[41]

(Further note: in an even later publication, it is stated that pharmacological investigation of certain 1-benzyl-3(2H)-isoquinolone derivatives reveals peripheral vasodilator activity in the dog).[45]

Chapter 1.6 Experimental

N, N-Dimethyl-3,4-dimethoxyphenylacetamide (13) and its attempted acylation

A chilled solution of dimethylamine (170ml) in benzene (80ml) was added dropwise with stirring to a solution in benzene (10ml) of 3,4-dimethoxyphenylacetyl chloride, prepared from 3,4-dimethoxyphenylacetic acid (15) (10g) and oxalyl chloride (2g) in benzene (20ml). After refluxing for 3 hr the solution was cooled, decanted from dimethylamine hydrochloride and washed with dilute aqueous sodium hydrogen carbonate. Addition of ether broke up the resultant emulsion, and separation of the organic layer followed by removal of solvents afforded the amide (13) as a reddish-brown oil (6.5g, 55%). The product was purified by passage through a column of neutral alumina (Grade 1, 30 : 1, elution with benzene) followed by sublimation at 100°-0.02 mm, yielding a colourless oil crystallising in large prisms on cooling in ice but remelting on attaining room temperature.

TLC Rf (6% MeOH-$CHCl_3$) : 0.6 (brown).

IR ν_{max} (liquid film), cm^{-1} : 2950, 1640, 1590, 1510.

ANAL Found, % : C, 64.51; H, 7.69; N,6.14; M^+ at m/e 223.

$C_{12}H_{17}NO_3$ requires C, 64.55; H,7.67; N, 6.27; MW223.

Attempted acylation of the amide (13) with 3,4-dimethoxyphenylacetic acid in trifluoroacetic acid anhydride-benzene-ether for 14 days at room temperature gave a small yield of N, N-dimethyl-3,4-dimethoxyphenyltrifluoroacetylacetamide (16), purified by repeated chromatography on silicagel. This crystallised from ether-light petroleum in small plaques of colourless needles, m.p. 95-100°.

TLC Rf (2% MeOH-$CHCl_3$) : 0.6 (brown).

IR ν_{max} (K Br), cm^{-1} : 1620, 1511, 1370, 1340.

UV λ_{max} (EtOH), nm (log ε) : 236 (3.91), 279 (3.47),

UV (contd.) 284 (3.42, infl.).

NMR 100MHz ($CDCl_3$), τ: 3.1 (3H, m, ArH), 5.84 (1H, s, CH), 6.13 (6H, s, OCH_3), 6.98 (3H, s, NCH_3), 7.02 (3H, s, NCH_3).

MS Found, m/e : M^+ at 319.1019.

$C_{14}H_{16}NO_4F_3$ requires MW 319.1031.

Attempted acylation of (13) with 3,4-dimethoxyphenylacetonitrile (14) in methylene chloride with stannous chloride or aluminium chloride as catalyst afforded mainly unchanged amide along with hydrolysis products from the aqueous work-up. An attempted self-acylation of 3,4-dimethoxyphenylacetonitrile (14) with phosphorus oxychloride similarly yielded starting material and hydrolysis products.

N-methyl-3,4-dimethoxyphenylacetamide (24)

Prepared from the acid chloride and methylamine-ethanol-benzene or (better) methylamine-ether, the monomethylamide (24) was obtained using a similar work-up to that for the dimethylamide (13) and crystallised from benzene-petroleum ether (b.p. 60-80°) in small colourless needles, m.p. 91-95°.

TLC Rf (6% MeOH-$CHCl_3$) : 0.5 (brown).

IR ν_{max} (Nujol), cm^{-1} : 3300, 1640, 1520, 1235, 1030.

ANAL Found, % : C,63.39; H,7.17; N, 6.60; M^+ at m/e 209.

$C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.23; N, 6.69; MW 209.

N-methyl-di-(3,4-dimethoxyphenylacetyl) imide (23)

3,4-Dimethoxyphenylacetyl chloride (440 mg) and N-methyl-3,4-dimethoxyphenylacetamide (24) (209mg) were mixed together and heated at 100-120° for 72hr. Water and excess sodium hydrogen carbonate were added after allowing to cool slightly, and the mixture thoroughly extracted with chloroform. Evaporation yielded a reddish-brown oil (433mg) which was purified by chromatography on silicagel to give a slightly yellowish oil

believed to consist of the imide (23) (350mg, 75%). Although pure according to TLC, this failed to crystallise and decomposed on attempted sublimation at 150° - 0.05mm yielding a nitrogen-free sublimate. cf.[42] (An attempted preparation of (23) via acylation of the amide (24) with 3,4-dimethoxyphenylacetic acid (15) and trifluoroacetic acid anhydride resulted in a complex mixture of products).

TLC Rf (1% MeOH-$CHCl_3$) : 0.8 (brownish-black).

IR ν_{max} (liquid film), cm^{-1} : 3 000, 1740, 1695, 1520, 1260, 1235, 1030.

(Cf. IR spectrum of the imide (22), below).

Insufficient sample was available for an NMR spectrum.

N-Benzoyl-3,4-dimethoxyphenylacetamide (22) and its attempted cyclisation

Benzamide (0.25g) was stirred with 3,4-dimethoxyphenylacetyl chloride (prepared from the corresponding acid (1g) and oxalyl chloride (2g) in benzene (20ml)) and heated at 80-95° for 24hr. cf.[14] After cooling, water and sodium hydrogen carbonate were added and chloroform extraction carried out to yield on evaporation a yellowish partly crystalline oily solid (1.32g). In order to remove coloured oily impurities the product was allowed to stand for 3 weeks in contact with a large volume of ether at 0° . Decantation and further washing with ice-cold ether afforded fairly pure imide (22) (0.41g, 65%), crystallising from chloroform-ether or (better) from benzene-light petroleum in small colourless plates, m.p. 129-131°.

TLC Rf (2%MeOH-$CHCl_3$) : 0.7 (brownish-black).

IR ν_{max} (KBr), cm^{-1} : 3260, 1735, 1690, 1510, 1265, 1145, 1025, 720.

NMR 100MHz ($CDCl_3$), τ : 1.20 (1H, s, D_2O-exchangeable, NH), 2.2 (2H, m, ArH o to C=O), 2.5 (3H, m, ArH), 3.18 (3H, bs, ArH), 5.80 (2H, s, CH_2), 6.19 (6H, s, OCH_3).

AN AL Found, % : C,68.25; H, 5.65; N,4.75; M^+ at m/e 299.

$C_{17}H_{17}NO_4$ requires C, 68.22; H, 5.72; N, 4.68; MW 299.

Treatment of the imide with phosphorus oxychloride at 115° for 24 hr yielded one main product shown by TLC to be less polar than the imide (22), but having spectral properties different from those expected for the desired 3(2H)-isoquinolone (95).[1]

TLC Rf (2%MeOH-$CHCl_3$) : 0.8 (brown).

IR ν_{max} (liquid film), cm^{-1} : 3400, 1700, 1510, 1250, 1075.

UV λ_{max} (EtOH), nm (absorbance) :208 (1.6), 231 (1.4), 250 (0.6, infl.), 280 (0.4), 286 (0.35,infl.), 310 (0.15).

This compound was not studied further.

Attempted preparation of 1-N-methylamino-1-(3,4-dimethoxyphenyl)-2-phenylethane (96)

Hydrogenation of 1- (3,4-dimethoxyphenyl)-1-keto-2-phenylethane (84) in ethanolic methylamine solution over palladium on charcoal, or hydrogenation after previously refluxing the ketone with ethanolic methylamine for 24hr, yielded a mixture of products from which quantities of starting material and 1-(3,4-dimethoxyphenyl)-1-hydroxy-2-phenylethane (97) were isolated. This crystallised from ether in rosettes of colourless needles, m.p. 58-60°.

TLC Rf ($CHCl_3$) : 0.5 (reddish-brown).

IR ν_{max} (liquid film), cm^{-1} : 3500, 1255, 1225, 1130, 1030.

NMR 60 MHz($CDCl_3$), τ: 2.77 (5H, bs, ArH), 3.16 (3H, s, ArH), 5.18 (1H, t, J= 7Hz, CH), 6.14 (3H, s, OCH_3), 6.16 (3H, s, OCH_3), 7.04 (2H, d, J= 7Hz, CH_2), 7.90 (1H, s, D_2O-exchangeable, OH).

MS M^+ at m/e 258; $C_{16}H_{18}O_3$, MW258.

Methyl 2-phenylacetylhomoveratrate (31) and its basic condensation - oxidation product (32) [15]

Prepared by the method of Bentley, Dawson and Spring, the keto ester (31) was purified by crystallisation from ethanol to give slightly reddish needles m.p. 89-98° (cf. lit. m.p. 94° for material obtained as colourless needles from chloroform-light petroleum (b.p. 60-80°)).[15] Crystallisation from chloroform-light petroleum or benzene-light petroleum afforded material nearly always contaminated by a yellow oil or red solid.

TLC Rf ($CHCl_3$) : 0.3 (black).

IR ν_{max} (Nujol), cm^{-1} : 1735 (ester), 1665 (aryl ketone).

NMR 60MHz ($CDCl_3$), τ : 2.64 (1H, s, ArH o to C=O), 2.72 (5H, s, ArH), 3.29 (1H, s, ArH), 5.80 (2H, s, CH_2 α to C = O), 6.10 (6H, s, OCH_3), 6.17 (2H, s, CH_2 α to CO_2Me), 6.34 (3H, s, CO_2 CH_3).

A sample of the keto ester (31) was shaken for 48 hr with concentrated aqueous ammonia (s.g. 0.88). Acidification, filtration and drying of the resultant precipitate, and crystallisation from methanol-chloroform and methanol-ether afforded 2-hydroxy-3-phenyl-6,7-dimethoxy-1,3-naphthaquinone (32) as red needles, m.p. 249-250° (cf. lit. m.p. 255° for material obtained as long red needles from methanol-chloroform).[15]

TLC Rf (5% MeOH-$CHCl_3$) : 0.7 (brown).

IR ν_{max} (Nujol), cm^{-1} : 3375 (phenolic hydroxyl group), 1650 (quinone).

Using the development of colour (slightly pink to deep red) as evidence that a basic condensation -oxidation reaction was taking place, the following reagents were shown to be capable of initiating naphthaquinone (32) formation (all reactions freely exposed to the atmosphere) :

(a) aqueous sodium hydroxide, aqueous sodium carbonate, aqueous sodium hydrogen carbonate, aqueous ammonia, methanolic methylamine - almost immediate development of deep redness on shaking;

(b) methanolic benzylamine - redness developed more slowly (15 - 20 min) but did not appear to reach the same intensity as in (a) ;

(c) methanolic sodium acetate - slightly pink after 12 hr, no further change after 12 days.

Neither methanolic pyridine nor methanolic hydrazine hydrate caused naphthaquinone formation.

(In the reaction of (31) with benzylamine (above) it was interesting to note that the colour changed to yellow on standing for 1 week, a transformation identical to that produced on acidifying a basic solution of the naphthaquinone (32). Although this phenomenon was not studied further it would appear that consumption of benzylamine was taking place, either by aerial oxidation to benzoic acid or by absorption of atmospheric carbon dioxide (forming benzylamine carbonate ?), thereby causing protonation of the naphthaquinone anion. A colourless solid which crystallised from the reaction mixture during the week was found to be almost insoluble in methanol or ethanol but was not examined further.)

1-Benzyl-6,7-dimethoxy-N-amino-3(2H)-isoquinolone (33)

Aqueous hydrazine hydrate (85%, 5ml) was added dropwise with stiriing over 15 min to a solution of keto ester (31) (1.00g) in methanol (anhydrous, 50ml) under nitrogen atmosphere. The solution was allowed to stand in the dark at room temperature for 20hr after which most of the methanol was evaporated at low temperature ($\leqslant 40^{\circ}$). Ice-water was added and the slightly yellow mixture thoroughly extracted with chloroform. Evaporation yielded a yellow-brown oil (513mg) mainly consisting of one colourless product more polar than (31) (TLC).

PLC of the mixture in 5% methanol-chloroform afforded a red band corresponding to the main component, and a slightly less polar yellow band. Elution of the red band with warm ethyl acetate furnished a yellow-brown oil (199mg) which partly solidified on standing. By

dissolving in cold ethyl acetate and adding ether the isoquinolone intermediate (71) or (72) precipitated in slightly yellowish needles (70mg) becoming colourless on further washing with ice-cold ethyl acetate-ether. The compound crystallised from methyl acetate-light petroleum or methanol-ether-light petroleum (1:2:2) in long fine colourless needles, m.p. 85-110° to 145-150° depending on rate of heating (turning yellow).

TLC Rf (5%MeOH-$CHCl_3$) : 0.5 (olive-brown).

IR ν_{max} (KBr or Nujol), cm^{-1} : 3410, 2920, 1612, 1511, 1259, 1120, 758, 700.

UV (i) λ_{max}(EtOH), nm(logε) : 214 (3.94), 259 (2.88,infl.), 282 (3.47), 287 (3.42, infl.).

(ii) λ_{max}(EtOH+HClaq), nm(absorbance) : 206(0.92), ~250 (>2), 290 (0.22), 307 (0.42), 316 (0.46), 370 (0.31), 395 (0.25, infl.); turns yellow instantaneously.

(iii) λ_{max} (EtOH+HClaq+XS NaOHaq), nm (absorbance): ~250 (>2), 291 (0.76), 305 (0.80), 316 (0.79), 388 (0.66), 395 (0.65, infl.).

(iv) λ_{max}(EtOH+NaOHaq) : as (iii) above (yellowness also develops, but more slowly than in (ii)).

NMR 100MHz (Pyridine-D_5),τ: 2.30 (1H, s), 2.7-2.9 (4-5H, m), 3.52 (1H, s), 4.83 (6-8H, bs, D_2O-exchangeable), 5.63 (1H, d, J=13HZ), 6.14(3H, s, C_6-OCH_3), 6.32 (3H, s, C_7-OCH_3), 6.62 (1H, d, J= 13Hz), 6.63 (1H, d, J= 21Hz), 7.55 (1H, d, J=21Hz).

MS M^+ at m/e 310 : corresponds to the 3(2H)-isoquinolone (33), $C_{18}H_{18}N_2O_3$, MW 310.

ANAL Found, % : C, 62.52; H, 6.20; N, 7.30 (7.75 in separate analysis).

$C_{18}H_{22}N_2O_5$ requires C, 62.42; H, 6.40; N, 8.09; MW 346.

Careful elution of the yellow band gave 1-benzyl-6,7-dimethoxy-N-amino-3(2H)-isoquinolone (33) (24mg, 2%) as a yellow oil, crystallising on trituration with ether in small yellow needles, m.p. 183-185° (softening from

173°). This compound was also produced (in almost quantitative yield) on heating the colourless material described above at 75° overnight under vacuum or on treating it with dilute mineral acid followed by basification (cf. above ultraviolet spectra).

TLC Rf (5%MeOH-$CHCl_3$) : 0.6 (red-brown).

IR ν_{max} (Nujol), cm^{-1} : 3350, 3240, 1660, 1645, 1635, 1610, 1510, 1500, 1280, 1230, 870.

UV (i) λ_{max} (EtOH), nm (log ε): 205 (4.00), 233 (4.00, infl.), 257 (4.43), 288 (3.30), 306 (3.34), 318 (3.35), 395 (3.39).

(ii) λ_{max} (EtOH+HClaq), nm (absorbance): 204 (0.60), 254 (> 2), 311 (0.31,infl.), 318 (0.33), 363 (0.20).

(iii) λ_{max} (EtOH+HClaq+XSNaOHaq), nm (absorbance) : 210 (1.52), ~ 255 (> 2), 288 (0.51), 318 (0.50), 390 (0.43).

NMR See Chapter 1.3.(100MHz, $CDCl_3$).

MS Found, m/e : M^+ at 310.1295.
$C_{18}H_{18}N_2O_3$ requires MW 310.1317.

Methyl 2-homoanisoylhomoveratrate (37)

A mixture of homoanisic acid (30g) and oxalyl chloride (45ml) in benzene (100ml) was stirred overnight at room temperature and refluxed for 1hr. Following removal of solvent and excess reagent the product distilled at 143° -12mm (lit. b.p. 143° -10mm) [43] yielding homoanisoyl chloride (39) as a slightly yellowish oil (18.3g, 60%).

IR ν_{max} (liquid film), cm^{-1} : 1790(C=O).

Aluminium chloride (14g) was well stirred for 10min at 30-40° with carbon disulphide (redistilled, 175ml), and to this was added dropwise over 5min a solution of homoanisoyl chloride (39) (18.3g) and methyl homoveratrate (38) (redistilled at 170°- 12mm, 19.3g) in carbon disulphide (redistilled, 25ml). The resultant dark complex was broken up (spatula) and the mixture refluxed for 1hr 30min. During this period consider-

able evolution of hydrogen chloride took place. The mixture was now stirred for 3hr at room temperature and kept at 0° for 12hr.

Following removal of carbon disulphide by decantation the dark gummy solid was washed with light petroleum and then triturated with ice-water. Extraction with chloroform and washing with sodium hydrogen carbonate afforded upon evaporation a reddish-brown oil (22.8g), about 20% of which was shown by TLC to consist of unreacted methyl homoveratrate (38). Treatment of the oil with ice-cold methanol (anhydrous, 20ml) and further cooling at 0° afforded solid keto ester (37) (7.52g, 30%), crystallising with increasing purity from ether-light petroleum, ethyl acetate-light petroleum and finally from methanol in colourless needles, m.p. 118-121°.

TLC Rf ($CHCl_3$) : 0.3 (reddish brown).

IR ν_{max} (Nujol), cm^{-1} : 1730, 1675, 1520, 1255, 1135.

NMR 60 MHz ($CDCl_3$), τ : 2.63 (1H, s, ArH o to C=O), 2.83 (2H, d, J=8Hz, collapsing to s upon irr at 3.18, ArH o to $CH_2C=O$), 3.18 (2H, d, J=8Hz, collapsing to s upon irr at 2.83, ArH o to single OMe), 3.29 (1H, s, ArH o to CH_2CO_2Me), 5.87 (2H, s, $CH_2C=O$), 6.09 (6H, s, OCH_3), 6.11 (2H, s, CH_2CO_2Me), 6.22 (3H, s, OCH_3), 6.32 (3H, s, CO_2CH_3).

ANAL Found,% : C, 67.23; H, 6.05; M^+ at m/e 358.
$C_{20}H_{22}O_6$ requires C, 67.03; H, 6.19; MW358.

1-(p-Methoxybenzyl)-6,7-dimethoxy-N-amino-3(2H)-isoquinolone (40)

To a solution of keto ester (37) (500mg) in methanol (50ml) under nitrogen atmosphere was added aqueous hydrazine hydrate (85%, 15ml) dropwise over 5 min with ice-cooling. Within 4hr all keto ester had reacted (TLC), affording a slightly yellow solution. Stirring was continued at room temperature for a further 14hr after which partial evaporation was followed by addition of ice-water and extraction of the resultant yellowish suspen sion with chloroform.

Evaporation of the extract yielded a yellow-brown oil (290mg) which was subjected to PLC in 8% methanol-chloroform following charcoal treatment. Elution of the main band with cold ethyl acetate followed by room temperature evaporation yielded the isoquinolone intermediate (73) or (74) (98mg) which crystallised from ether-ethylacetate in small plaques of colourless needles, m.p. 132-135° (turning yellow).

TLC Rf (5% MeOH-$CHCl_3$) : 0.3 (brown).

IR ν_{max} (K Br), cm^{-1}: 3400, 3330, 2930, 1610, 1510, 1250, 1130, 1030, 870, 760.

UV (i) λ_{max} (EtOH), nm (absorbance) : 237 (1.89), 281 (1.45, infl.), 284 (1.60), 290 (1.18, infl.).

(ii) λ_{max} (EtOH+HClaq), nm (absorbance) : 232(1.61), ~250 (>2), 310 (0.53), 318 (0.57), 376 (0.39), 396 (0.20, infl.).

(iii) λ_{max} (EtOH+HClaq+XSNaOHaq), nm (absorbance): ~250 (>2), 307 (0.75), 318 (0.74), 400 (0.71).

NMR 100MHz (Pyridine-D_5), τ: 2.30 (1H, s), 2.61(2H,s), 3.01(2H, d, J=10Hz, ArH o to CH_2), 3.22 (2H, d, J=10Hz, ArH o to single OMe), 3.48 (1H, s), 4.2-4.4(2-3H, bs, D_2 O-exchangeable), 5.0-5.3 (2H, bs, D_2O- exchangeable), 5.67 (1H, d, J=13Hz), 6.64 (1H, d, J=13Hz), 6.13 (3H, s, C_6-OCH_3),6.26 (3H, s, C_7-OCH_3?) 6.37 (3H, s, C_4-OCH_3?), 6.59(1H, d, J= 22Hz), 7.40 (1H, d, J=22Hz).

MS M^+ at m/e 340 : corresponds to the 3(2H)-isoquinolone (40), $C_{19}H_{20}N_2O_4$, MW340.

ANAL Found, % : C,61.33; H, 6.00; N, 7.45.
$C_{19}H_{24}N_2O_6$ requires C, 60.63; H, 6.43; N, 7.44; MW 376.

(Although still outwith the normally accepted limits of experimental error, etc.,the above set of figures was the closest to $C_{19}H_{24}N_2O_6$ obtained in any one analysis).

Complete conversion to the bright yellow 3(2H)-isoquinolone (40) took place on heating the above inter-

mediate at 55° for 6 hr under vacuum, the crude product obtained in this way melting at 210-220° (cf. pure sample prepared later (see page 64) : m.p. 218-219°). This material exhibited the strong blue-green fluorescence on exposure to ultraviolet light (350nm) known to be characteristic of the 3(2H)-isoquinolone system (in solution or after adsorption on chromatographic media).[5]

Apart from the conversion of the colourless intermediate to (40) upon addition of a trace of mineral acid to its ethanol solution at 20° (cf. above ultraviolet spectra), the 3(2H)-isoquinolone was also produced on addition of a trace of metallic sodium and deuterium oxide to a solution of the intermediate in deuterated pyridine-deuterated methyl cyanide at 35° (during observation of the NMR spectrum). In the latter case evaporation yielded a crude product of m.p. 203-215° with chromatographic behaviour identical to that of an authentic sample of (40) (see page 65, on which full spectral data are listed).

Treatment of keto ester (37) with hydroxylamine hydrochloride-pyridine : formation of a derivative (56) of 1-(p-methoxybenzyl) -6,7-dimethoxy-N-hydroxy-3(2H)-isoquinolone (42)

A solution (pH4-5) of the keto ester (37) (361mg) in methanol (anhydrous, 40ml) containing hydroxylamine hydrochloride (425mg) was refluxed under nitrogen atmosphere for 3hr. TLC of the light brown reaction mixture showed that most of the keto ester was unreacted and refluxing was continued for a further hour with the addition of pyridine (anhydrous, 2ml). The solution (pH7-8) was partially evaporated and dilute hydrochloric acid (6N, 5ml) added. After gentle warming for 15 min, basification with ammonium hydroxide was followed by extraction with chloroform to yield a light yellow-brown oil (403 mg).

PLC in 7% methanol-chloroform (twice) afforded 3 main components, the least polar of which was shown to

consist of unreacted keto ester (37) (IR absorption spectrum, Rf and staining characteristics similar to authentic sample; m.p. of crude product 95-115°, m.p. of pure keto ester 118-121°).

The second component isolated (of slightly greater polarity) consisted of a light brown gum (60mg), rendered colourless (38mg) on treatment with charcoal in ethyl acetate-chloroform solution. This compound was not obtained in crystalline condition and was not studied further (cf. page37).

TLC Rf (5%MeOH-$CHCl_3$) : 0.5 (brown).

IR ν_{max} (Nujol), cm^{-1} : 3500, 3300, 1735, 1715, 1700, 1640, 1610, 1580.

NMR 60MHz($CDCl_3$), τ : 2.93 (2H, d, J=9Hz, ArH m to single OMe), 3.16 (1H, s), 3.23 (2H, d, J=9Hz, ArH o to single OMe), 3.82 (1H, s), 6.13 (3H, s, OCH_3), 6.26 (3H, s, OCH_3), 6.35 (3H, s, OCH_3) 6.35 (2-3H, s), 6.0-6.6 (2-3H, m), 6.61 (2H, s).

MS m/e (abundance, %) : 373(10), 355 (15), 325 (20), 324 (15), 310 (10), 296 (20), 283 (15), 235 (15), 223 (25), 205 (20), 176 (30), 151 (35), 150 (30), 149 (100), 121 (35), 78 (85), 57 (55), 55 (50), 43 (55), 41 (60).

The most polar product isolated was a bright yellow oily semi-solid (26mg) exhibiting blue-green fluorescence on TLC under ultraviolet light (350nm), and staining blue-red on spraying with ferric chloride reagent (cf. action of ferric chloride on hydroxamic acids).[44] This compound is believed to have structure (56) (see Chapters 1.3 and 1.4).

TLC Rf (5%MeOH-$CHCl_3$) : 0.3 (dark reddish brown).

UV (i) λ_{max} (EtOH), nm (absorbance) : 208 (0.50), 228 (0.95), 257 (1.62), 305(0.17), 317 (0.16), 355 (0.10), 402 (0.18).

(ii) λ_{max} (EtOH+HClaq), nm (absorbance) :225-250(>2), 283 (0.51), 309 (0.83), 318 (0.86), 373 (0.63).

(iii) λ_{max} (EtOH+HClaq+XSNaOHaq), nm (absorbance) : 225-250 (> 2), 276 (1.36, infl.), 287 (1.06,infl.), 373 (0.76).

NMR See Chapter 1.3. (60MHz, $CDCl_3$).

MS m/e (abundance, %): 355 (50), 340 (25), 325 (50), 324 (20), 323 (15), 310 (15), 308 (25), 151 (100), 135 (30).

Doubly-charged ions : 177.5 (with 355), 162.5 (with 325), 161.5 (with 323), 75.5 (with 151).

Reduction of methyl 2-homoanisoylhomoveratrate (37) with sodium borohydride

In a typical experiment, sodium borohydride (6g) was added in portions over 75 min to a well-stirred suspension of keto ester (37) (4.00g) in methanol (250ml) kept at 5-10° by periodical cooling in ice. The reaction was followed throughout by TLC in chloroform and 2% methanol-chloroform and the amount of borohydride necessary to reduce all keto ester determined from these results. Acid alumina (Gradel, 15g) was added to the clear solution which was then evaporated to dryness. The resultant solid was extracted overnight with benzene in a Soxhlet apparatus. (A violet colouration appeared in the solution during the latter stages of the reaction and during transfer of the solution containing alumina to the rotary eveporator. It was observed that this could be temporarily dispersed by addition of small amounts of sodium borohydride).

Removal of solvent from the benzene extract afforded an oil (4.15g), shown by TLC to contain two main products, one more polar than keto ester (37), the other slightly less polar. PLC of the mixture (about 4g) on six 1metre x 1mm silicagel HF254 plates run in 4% methanol-chloroform afforded the lactone (48) (0.36g, 10%) and the more polar diol (49) (2.64g, 65%).

It was possible to obtain much better yields of the lactone at the expense of the diol in small-scale experiments studied by TLC, but these could not be reproduced when the reaction was scaled up.

The lactone (48) crystallised from ethyl acetate-

light petroleum in small colourless prisms, m.p. 135-137°.

TLC Rf ($CHCl_3$) : 0.4 (greyish brown).

IR ν_{max}(CCl_4), cm^{-1} : 2930, 1750, 1612, 1514, 1250.

NMR 60MHz ($CDCl_3$), τ : 3.2 (4H, m, mono-OMe ArH), 3.49 (2H, s, di-OMe ArH), 4.40 (1H, t, J= 4Hz, collapsing to s upon irr at 6.79, CH), 6.1-6.2 (9H, 3s, OCH_3), 6.79 (2H, d, J= 4Hz, collapsing to s upon irr at 4.40, p-OMe-Ph-CH_2), 6.6 and 7.2 (2H, 2d, J= 20Hz, $CH_2C{=}O$).

MS Found, m/e : M+ at 328.1322.
$C_{19}H_{20}O_5$ requires MW 328.1311.

The diol (49) crystallised from ethyl acetate-light petroleum in small colourless needles, m.p. 108-110°.

TLC Rf (5%MeOH-$CHCl_3$) : 0.4 (brownish-black with yellow halo).

IR ν_{max} (liquid film, pre-crystallisation), cm^{-1} : 3500, 3000, 1610, 1520, 1250, 1050.

NMR 60MHz ($CDCl_3$), τ : 2.8-3.4 (6H, m, ArH), 5.00 (1H, t, J= 6Hz, CH), 6.09 (6H, s, OCH_3), 6.20 (3H, s, OCH_3), 6.29 (2H, t, J= 7Hz, $\underline{CH_2}OH$), 6.98 (2H, d, J= 6Hz, p-OMe-Ph-CH_2), 7.20 (2H, bt, J= 7Hz, $\underline{CH_2}$-CH_2OH).

ANAL Found, % : C, 68.49; H, 7.30.
$C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28.

Reduction of methyl 2-homoanisoylhomoveratrate (37) with diborane-tetrahydrofuran and with zinc dust-acetic acid

To a stirred solution of the keto ester (37) (2.22g) in tetrahydrofuran (anhydrous, 100ml) at 0° under nitrogen atmosphere was added a solution of diborane in tetrahydrofuran (1M in BH_3, 11ml) in portions over 2hr (by injection through a rubber septum cap). The course of the reaction was followed throughout by TLC in chloroform and in 5%

methanol-chloroform, and the quantity of diborane and reaction time required decided accordingly. It was observed that a trace of diol (49) was beginning to form before all keto ester (37) had reacted.

The mixture was stirred for a further 20min (in ice) and excess diborane decomposed by addition of ethanol (anhydrous, 4ml). After a further 10min ice-cold water (50ml) was added, followed 10min later by extraction with chloroform. Evaporation of solvent from the organic extract at 40-50° afforded the hydroxy ester (50) as a red viscous oil (2.32g), shown by TLC to be at least 90-95% pure, and containing traces of keto ester (37) and diol (49). (Probable yield of (50) from (37) would be ~ 85-95%).

A small-scale reaction with diborane prepared *in situ* from sodium borohydride and acetic acid furnished a product with similar Rf to the hydroxy ester (50), but this was not pursued further. A small-scale reaction with zinc dust in acetic acid also yielded a product with similar Rf to (50), but in very low yield.

Attempted purification of the hydroxy ester (50) by sublimation or crystallisation invariably resulted in almost total conversion to the lactone. Similar decomposition took place in the mass spectrometer.

TLC Rf (5%MeOH-$CHCl_3$) : 0.7 (greyish-brown with lighter halo).

IR ν_{max} (liquid film), cm^{-1} : 3500 (hydroxyl), 3 000, 1730 (ester) , 1610, 1515, 1245, 770.

Hydrogenation of methyl 2-homoanisoylhomoveratrate (37) [22]

Several small-scale reactions were carried out at room temperature and atmospheric pressure, the products being examined by TLC and compared with keto ester (37), lactone (48), diol (49) and hydroxy ester (50). In no case was a promising reaction observed despite the variety of reaction conditions employed. The results are shown below (the third column referring to the quantity

of catalyst used, expressed as a percentage of the quantity of (37) used).

Reference	Catalyst	Quantity (%)	Solvent	Reaction Time (hr)
(i)	5%Pd-C	10-20	95%EtOH	7
(ii)	"	"	95%EtOH+HClaq	"
(iii)	"	100-150	95%EtOH	12
(iv)	"	"	95%EtOH+HClaq	"
(v)	"	50	EtAc	4
(vi)	"	"	"	18
(vii)	1%Pd-C	"	50%EtOH-EtAc	13
(viii)	"	100	"	"
(ix)	"	"	95%EtOH	16
(x)	10%Pd-C	"	EtAc	"
(xi)	PtO_2	50	AcOH	2
(xii)	"	"	95%EtOH+$FeSO_4$aq	"
(xiii)	"	"	"	16

Remarks No reaction appeared to take place in the case of (i), (ii), (v), (vii), (viii) and (ix), and very little reaction occurred in (vi). In (xi), (xii) and (xiii) complex mixtures were formed, (xi) containing at least 7 products, (xii) at least 4, and (xiii) was even more complex than (xi) with possibly a trace of lactone (48). Reaction (x) appeared to give a single product less polar than (48). In the case of (iii), 2 new products different from (37), (48), (49) and (50) were formed, one of which was also produced in reaction (iv) along with one further product. No attempt was made to isolate any of these new products.

N, N-Dimethylamino-2-anisylhydroxymethylhomoveratramide (51)

(i). From 2-anisylhydroxymethylhomoveratric acid lactone (48)

A solution of the lactone (330mg) in ethanolic dimethylamine (33%, 50ml) was heated for 12 hr under nitrogen atmosphere at 70°. The mixture was then stirred

for 30 min at room temperature with a further quantity of ethanolic dimethylamine (20ml) and solvent removed at $\leqslant 30^{\circ}$. The alcohol amide (51) was obtained as a very slightly yellowish oil (371mg, 95%) shown by TLC to be fairly pure.

(ii) From methyl 2-anisylhydroxymethylhomoveratrate (50)

A solution of the hydroxy ester (2.32g, from diborane reduction of (37) without further purification) in ethanolic dimethylamine (33%, 130ml) was refluxed for 12hr under nitrogen atmosphere. Evaporation as under (i) above yielded a reddish oil (2.41g). This was purified by PLC on five 1 metre x 1mm silicagel HF_{254} plates run in 5% methanol-chloroform and 1% methanol-chloroform (once each), eluting the bands with warm ethyl acetate (not boiling, in case elimination of dimethylamine resulted). The alcohol amide (51) was obtained as an almost colourless oil (2.35g, 90%), solidifying overnight at 0° and crystallising from chloroform-ethylacetate-ether (5: 25: 70) in long colourless needles, m.p. 105-106°.

TLC Rf (5%MeOH-$CHCl_3$) : 0.6 (brown with purple halo).

IR ν_{max} (liquid film, pre-crystallisation), cm^{-1} : 3500, 2950, 1630 (broad), 1580, 1520, 1250, 1040.

NMR 60MHz ($CDCl_3$), τ : 2.7-3.5 (6H, m, ArH), 5.20 (1H, t, J= 6Hz, collapsing to s upon irr at 7.0, CH), 6.1-6.2 (9H, 3s, OCH_3), 6.48 (2H, s, CH_2CONMe_2), 6.95 (3H, s, NCH_3), 7.0 (2H, bd, J= 6Hz, collapsing to s upon irr at 5.20, p-OMe-Ph-CH_2), 7.02 (3H, s, NCH_3), 7.1 (1H, bs, D_2O-exchangeable, OH).

MS m/e : 355 (corresponds to loss of H_2O) ; 328 (corresponds to loss of $HNMe_2$).

ANAL Found, % : C, 67.82; H, 7.21; N, 3.54. $C_{21}H_{27}NO_5$ requires C, 67 .54; H, 7.29; N, 3.75; MW 373.

Manganese dioxide oxidation of alcohol amide (51)

The alcohol amide (124mg) was shaken for 4 days with manganese dioxide (5g) in chloroform (20ml). TLC showed the product to consist of about 70% of the unreacted starting material (51) together with 3 compounds less polar than (51). One of these after isolation by PLC in 5% methanol-chloroform was a semi-solid (12mg, 10%) which crystallised on evaporation of its solution in chloroform-light petroleum. This compound was later shown to have similar infrared and TLC behaviour to the keto amide (45), which was prepared in much better yield by ruthenium tetroxide oxidation of (51) as described below.

Ruthenium tetroxide oxidation [23] of alcohol amide (51)

To a well-stirred suspension of the alcohol amide (1.96g) in carbon tetrachloride (200ml) under nitrogen atmosphere and with partial ice-cooling, was added portionwise over 2hr 45min a solution of ruthenium tetroxide in carbon tetrachloride (250ml) prepared by treatment of ruthenium dioxide (2g) in carbon tetrachloride (350ml total, including final washings) with sodium metaperiodate (16g) in water (250ml).

The reaction was kept at 0-10° and followed closely throughout by TLC in 2% methanol-chloroform, the amount of ruthenium tetroxide being regulated accordingly. On completion of the oxidation a few ml of methanol and ether were added to destroy excess reagent and the mixture filtered through glass paper, the black residue being thoroughly washed with chloroform. Treatment of the filtrate with charcoal and removal of solvents afforded semi-solid material (2.56g). This was triturated with a little ice-cold chloroform-carbon tetrachloride to yield the keto amide (45) which, after filtering and washing with ice-cold ether, was obtained as a yellow crystalline solid (884mg). A further quantity was isolated along with some alcohol amide (51) (218mg, 15%) by

PLC of the filtrate in 2% methanol-chloroform, affording a total yield of (45) of 1.05g, 50%. (It is probable that higher yields could have been obtained by further oxidation, as the unreacted alcohol amide in suspension in carbon tetrachloride together with ruthenium dioxide was not detected until work-up of the reaction). The product crystallised from methanol in colourless prisms, mp. 159-160°. Difficulty was experienced in preparing a pure sample for microanalysis as solutions of (45) appeared to decompose somewhat (turning yellow) shortly after heating to effect complete dissolution prior to crystallisation.

TLC Rf (3%MeOH-$CHCl_3$) : 0.6 (brownish-black).

IR ν_{max}(Nujol), cm^{-1}: 1680, 1650, 1245, 1130.

NMR 60MHz ($CDCl_3$), τ: 2.70-3.26 (6H, m, ArH), 5.85 (2H, s, $CH_2C{=}O$), 6.03 (2H, s, CH_2CONMe_2), 3.17-3.20 (9H, 3s, OCH_3), 6.94 (3H, s, NCH_3), 7.02 (3H, s, NCH_3).

MS Found, m/e : M^+ at 371.1733.
$C_{21}H_{25}NO_5$ requires MW 371.1733.

Attempted preparation of the trimethoxy dimethylamide imine (52)

The keto amide (45) (5mg) was treated with ethanolic methylamine (2ml, added in portions) in refluxing benzene (2ml) for 15hr under nitrogen atmosphere, employing a Dean-Stark apparatus for removal of water. Evaporation yielded a semi-crystalline solid with m.p. 125-155°, shown by TLC to consist of unreacted keto amide (45) (m.p. 157-159°).

Apparent preparation of 1-(p-methoxybenzyl)-6,7-dimethoxy-N-methyl-3(2H)-isoquinolone (47) from the keto amide (45)

(i) Using ethanolic methylamine in acetic acid

The keto amide (45) (5mg) was heated with ethanolic methylamine (0.5ml) in acetic acid (1ml) at 90° for 14 hr under nitrogen atmosphere. Following partial evap-

oration and addition of water, the reaction mixture was extracted with chloroform and the extract washed with dilute sodium hydrogen carbonate. Evaporation yielded a yellow gum, apparently pure (TLC under nitrogen atmosphere), exhibiting blue-green fluorescence under ultraviolet light (350 nm), and believed to be the N-methyl-3(2H)-isoquinolone (47).

TLC Rf (5%MeOH-$CHCl_3$) : 0.5 (brown).

UV (i) λ_{max}(EtOH), nm(absorbance) : 203(0.92), 225 (0.95), 257 (1.84), 282 (0.30, infl), 302 (0.15), 316 (0.14), 403 (0.16).

(ii) λ_{max}(EtOH+HClaq), nm (absorbance) : 203(0.99), 226 (0.99), 253 (1.81), 270 (0.38, infl.), 307 (0.30), 318 (0.31), 366 (0.20).

(iii) λ_{max}(EtOH+HClaq+XSNaOH) , nm (absorbance) : 200-225 (>2), 255 (>2), 280 (0.62, infl.), 302 (0.46), 316 (0.41), 401 (0.33).

The compound appeared to decompose rapidly on exposure to the atmosphere, and a sample stored under nitrogen for 2 weeks also exhibited some decomposition (TLC). cf.1,5

In a parallel experiment involving heating the keto amide (45) (100mg) at 105° for 11hr, attempted purification of t he crude product (133mg) by PLC in 4% methanol-chloroform resulted in further decomposition (TLC) despite efforts to keep all operations under nitrogen atmosphere as much as possible. Attempts to form a crystalline hydrochloride by treatment of partially purified material with hydrochloric acid also failed, even more complex mixtures apparently being formed (TLC).

(ii) Using methylamine hydrochloride in pyridine

A solution of th e keto amide (45) (5mg) in pyridine (anhydrous, 2ml) containing methylamine hydrochloride (30mg) was heated for 15hr at 110° under nitrogen atmosphere. Examination of the bright yellow reaction mixture by TLC indicated the presence of one main product, identical in Rf and staining characteristics to

the product formed in method (i) above, and exhibiting the same blue-green fluorescence under ultraviolet light (350nm).

(iii) Using methylamine hydrochloride and sodium acetate in methanol

Examination of the yellow reaction mixture produced on heating the keto amide (45) (7mg) with methylamine hydrochloride (3mg) and sodium acetate (anhydrous, 3mg) in methanol (anhydrous, 1ml) for 15min on the steam bath suggested that this method may also be suitable for preparation of the N-methyl-3(2H)-isoquinolone (47), although several other products were also apparent (TLC).

1-(p-Methoxybenzyl) -6,7-dimethoxy-N-H-3(2H)-isoquinolone (53)

A solution of the keto amide (45) (99mg) in acetic acid (2ml) containing ammonium acetate (185mg) was heated at 100-110° for 20hr under nitrogen atmosphere. On cooling the reaction mixture solidified and the 3(2H)-isoquinolone (53) was obtained as small feathery pale lemon-yellow needles (68mg, 80%) after washing with water, filtering and drying under vacuum.

A sample crystallised from methanol-chloroform in small needles (as above). On heating to 200-210° conversion to long fine needles took place, these turning brown at 232° and finally melting at 237-240°.

The 3(2H)-isoquinolone (53) exhibited intense blue-green fluorescence under ultraviolet light (350nm) in solution or when adsorbed on chromatographic media and, in contrast to the N-methyl analogue (47), appeared to be unaffected by overnight exposure to the atmosphere (m.p. and TLC behaviour unchanged).

TLC Rf (5%MeOH-$CHCl_3$) : 0.3 (brown).

IR ν_{max} (KBr), cm^{-1} : 3400 (broad), 2990, 2950, 2820, 2650 (broad), 1650, 1635, 1610, 1565, 1510, 1490, 1425, 1245, 1210, 1160, 1025, 830, 780, 770.

UV (i) λ_{max} (EtOH), nm (log ε) : 206 (4.02), 227 (4.26), 256 (4.61), 282 (3.55, infl.), 302 (3.31), 313 (3.29), 355 (3.24, infl.), 399 (3.55).

UV Contd.

(ii) λ_{max}(EtOH+HClaq), nm (absorbance) : 203 (0.67), 227 (0.91), 252 (>2), 306 (0.32), 315 (0.33), 370 (0.26).

(iii) λ_{max}(EtOH+HClaq+XSNaOHaq), nm (absorbance) : 200-250 (>2), 276 (0.86, infl.), 284 (0.76, infl.), 366 (0.46), 398 (0.29, infl.).

NMR See Chapter 1.3. (100MHz, $CDCl_3$).

MS Found, m/e : M^+ at 325.1305.
$C_{19}H_{19}NO_4$ requires MW 325.1313.

Addition of dilute hydrochloric acid (6N) to the 3(2H)-isoquinolone (53) (either with or without a trace of methanol) resulted in crystallisation of the 3(2H)-isoquinolone hydrochloride in colourless needles. On heating to 138-145° these melted and turned yellow, recrystallising at 148-185° in a "flower-petal" pattern. At 185-210° the crystal structure changed again, forming plaques of fine needles which partially decomposed at 224° and melted at 238-246°.

The 3(2H)-isoquinolone was recoverable from the hydrochloride on treatment with ammonium hydroxide followed by extraction with chloroform.

1-(p-Methoxybenzyl)-6,7-dimethoxy-N-amino-3(2H)-isoquinolone (40)

(Cf. alternative preparation on page 51)

A solution (pH7-8) of keto amide (45) (100mg) in acetic acid (4ml) containing hydrazine hydrate (aqueous, 85%; 3ml, added in portions) was heated at 100-110° for 22hr. After cooling the reaction mixture was poured into ice-water and extracted with chloroform. Evaporation yielded a yellow gum (66mg) from which the 3(2H)-isoquinolone (40) was isolated by PLC in 4% methanol-chloroform, crystallising from ethyl acetate or ether-ethyl acetate in small yellow needles (46mg, 50%), m.p. 218-219°. The product exhibited blue-green fluorescence under ultraviolet light (350nm) both in solution

and when adsorbed on chromatographic media.

TLC Rf (5%MeOH-$CHCl_3$) : 0.8 (brown).

IR ν_{max}(KBr), cm^{-1} : 3400 (broad), 3270, 3150, 2990, 2950, 2920, 2820, 1650, 1630, 1615, 1550, 1510, 1490, 1270, 1245, 1225, 1175, 1030, 840, 820, 760.

UV (i)

λ_{max}(EtOH), nm (log ε) : 203 (3.81), 229 (4.13), 257 (4.53), 305 (3.42), 317 (3.42), 398 (3.47).

(ii)

λ_{max}(EtOH+HClaq), nm (absorbance) : 202 (0.65), 228 (0.90), 255 (1.93), 308 (0.28), 365 (0.18).

(iii)

λ_{max}(EtOH+HClaq+XSNaOHaq), nm (absorbance) : ~255 (>2), 303 (0.60), 317 (0.56) 387 (0.40).

NMR See Chapter 1.3. (100 MHz, $CDCl_3$).

MS Found, m/e : M^+ at 340.1415.

$C_{19}H_{20}N_2O_4$ requires MW 340.1416.

Conversion to the 3(2H)-isoquinolone hydrochloride was effected with dilute hydrochloric acid (cf. preparation of the hydrochloride of the N-H analogue), the product crystallising in long colourless needles. These melted on heating at 132-138° (the melt becoming yellow) and recrystallised at 148-175° in a solid flaky mass, finally melting at 207-214°.

The 3(2H)-isoquinolone (40) was regenerated from its hydrochloride on treatment with ammonium hydroxide and isolable by extraction with chloroform.

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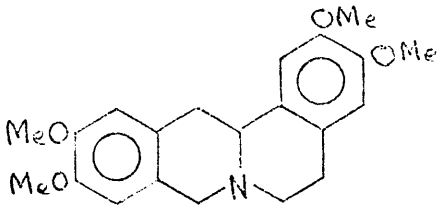
PART I (2)

Synthesis of (±) - Norcoralydine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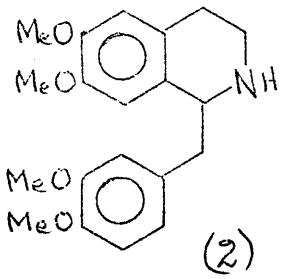
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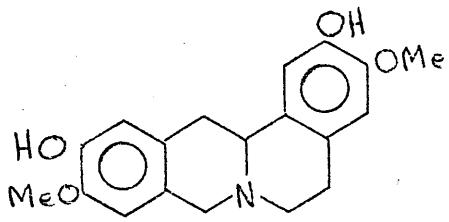
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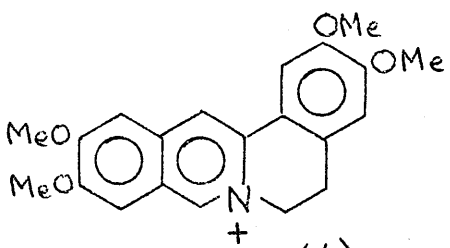
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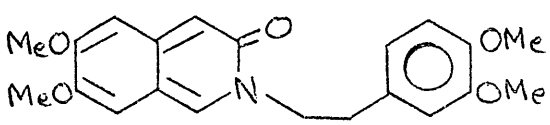
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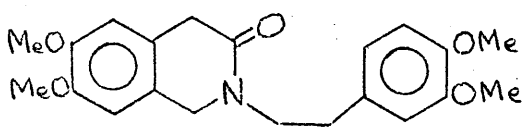
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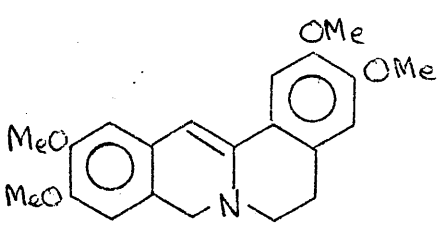
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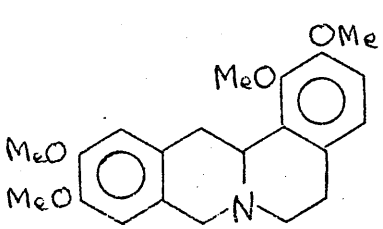
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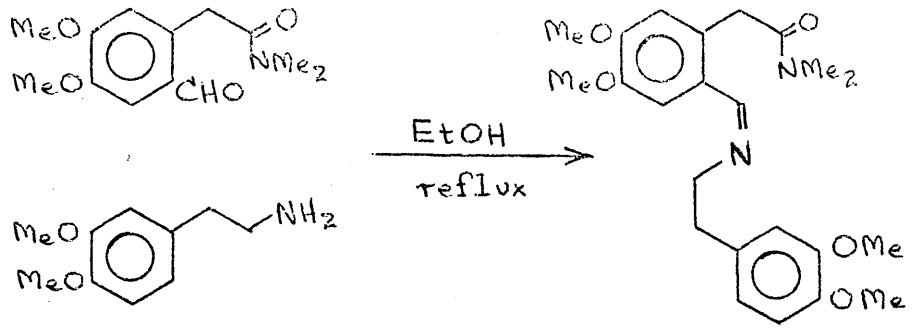
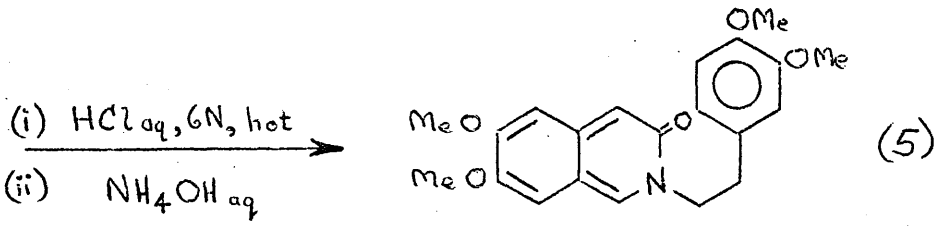
(8)

FIGURE 2.1-01





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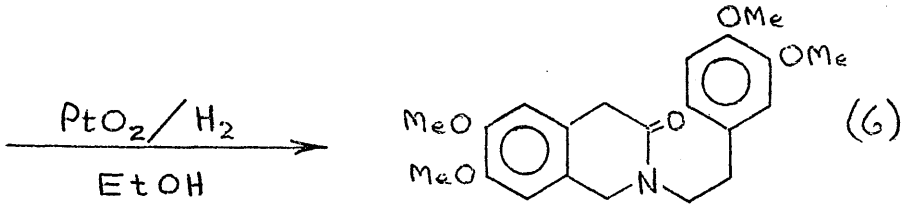

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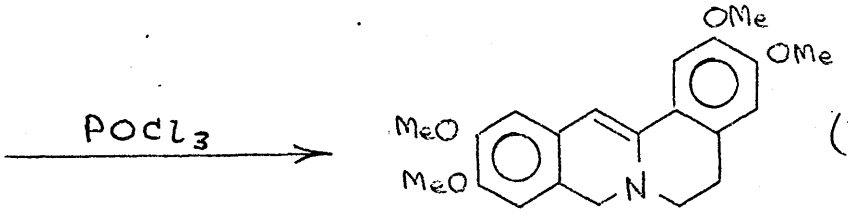

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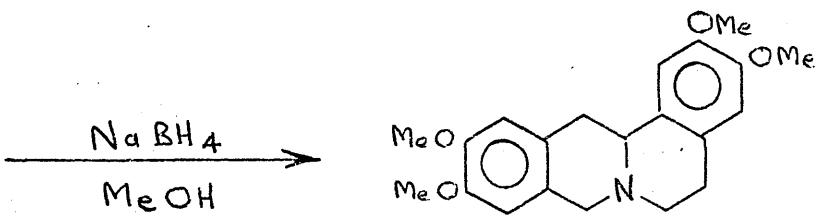

(1)

Chapter 2.1 Introduction and discussion

As mentioned previously, the 3 (2H) - isoquinolone system and its derivatives are potentially useful as intermediates in alkaloid synthesis. The example presented here illustrates such an application in a new route to the protoberberine alkaloid (±) - norcoralydine (1) m.p. 157°, [1] the laevorotatory form of which, (-) - xylopinine m.p. 182°, is found in Xylopia discreta Sprague and Hutchins (Anonaceae). [2,3] An early "biogenetically - orientated" synthesis of (±) - norcoralydine from tetrahydropapaverine (2) was achieved by formaldehyde-hydrochloric acid treatment, [1, 4] and the racemic material is also obtainable from (-) - coreximine (3) (ex Dicentra eximia) [5,6] on methylation, oxidation to a quaternary derivative (4) and reduction by (e.g.) zinc dust, [7] as well as by later independent syntheses. [8]

The greater part of the experimental work in this section was carried out by A. W. McCulloch, [9] and the reaction sequences employed are shown in Figure 2.1- 01. An important step is the imine cyclisation with hot dilute hydrochloric acid to form an N -homoveratryl -3 (2H)-isoquinolone hydrochloride, exploiting the 3(2H)- isoquinolone synthesis developed earlier. cf. [10] Treatment with ammonia liberated the 3(2H) - isoquinolone (5) in good overall yield. Cyclisation of the corresponding 1,4 - dihydro derivative (6) to the tetracyclic product (7) was satisfactorily achieved using phosphorus oxychloride, recovery of unreacted material having been made after prolonged refluxing with phosphorus pentoxide in benzene. Immediate reduction of (7) with methanolic sodium borohydride afforded a good yield of crude (±) -norcoralydine (1), purified by crystallisation from ether.

Elemental analysis and mass spectral examination were in keeping with the molecular formula $C_{21}H_{25}NO_4$, and convincing proof of structure (1) was afforded by four distinct singlet aryl-proton resonances in the NMR spectrum at 3.19, 3.26, 3.31 and 3.35τ. The possible alternative structure (8) for the product of cyclisation, in which spin-spin coupling of the ortho aryl protons would be expected (J usually 5-10 Hz), was thus ruled out.

The product readily formed a picrate of m.p. 136-139°, in keeping with the reported melting point of (±) - norcoralydine picrate, 139°.[1] The cyclisation product itself had m.p. 146-149°, and although this is rather lower than the most widely reported m.p. for (±) - norcoralydine of 157°, melting points of 151.5 - 152.5°[7] and 147-148°[4] have also been quoted for samples proved to be identical with (±) - norcoralydine on the basis of mixed m.p. and other evidence.

Chapter 2.2 Experimental

(±) - Norcoralydine (1) [9]

Treatment of the dihydro isoquinolone (6) (520mg), obtained from hydrogenation of 7,8- dimethoxy - N-homoveratryl-3 (2H) - isoquinolone (5), [cf.10] with refluxing phosphorus oxychloride (12ml) for 4hr followed by standing overnight under nitrogen at room temperature and pouring on to ice, yielded a yellow solid cyclisation product (503mg). A methanolic solution of this material (100 mg) was treated with sodium borohydride (200mg) for 15 min at room temperature followed by refluxing under nitrogen for 30 min. Addition of water and extraction with chloroform afforded a yellowish gummy solid shown by TLC to consist of one major product. Purification by PLC in 5% methanol- chloroform yielded (±) - norcoralydine (1) as a slightly yellow solid (97mg, 95%) which crystallised from ether in small colourless needles, m.p. 146- 149°(lit. m.p. 147, 151, 157°). [1,4,7]

TLC Rf (2% MeOH-$CHCl_3$) : 0.3 (greyish brown).

IR νmax (Nujol), cm^{-1}: 1610, 1520.

UV λmax (EtOH), nm (r.o.d.) : 226(1.00), 283 (0.53), 286 (0.53).

NMR 60MHz ($CDCl_3$), τ : 3.18 (1H,s), 3.27 (1H, s),3.31(1H,s), 3.35(1H, s), 6.12 (12H,s), 5.5-6.0 and 6. 1-7.4(9H,m).

MS m/e (abundance, %) : 355 (25), 190 (20), 165 (30), 164 (100), 149 (15), 121 (25), 91 (10).

ANAL Found, % : C, 70. 90 ; H, 7.23;N,3.90; M^+ at m/e355. Calc. for $C_{21}H_{25}NO_4$: C,70.96; H, 7.09; N, 3.94; MW 355.

Treatment with ethanolic picric acid solution gave the picrate, crystallising in clusters of yellow-orange needles, m.p. 136-139°(lit. m.p. 139°). [1]

MS As that of (1), plus m/e 229 (100%, picric acid) and m/e 199 (50%, P-30).

Chapter 2.3 References

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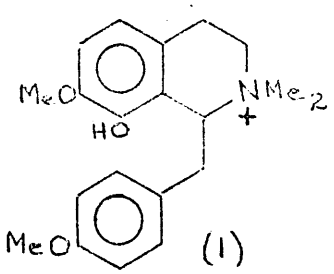
PART II (3)

Hofmann Degradation of Benzylisoquinoline Alkaloids



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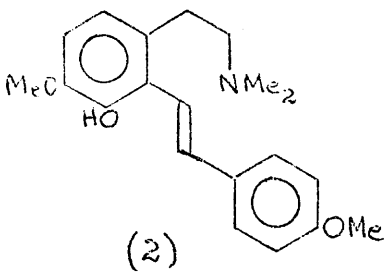

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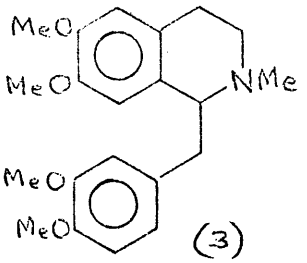

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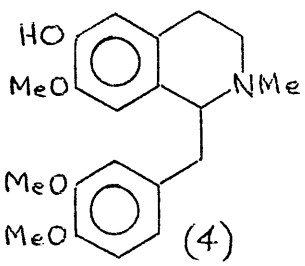

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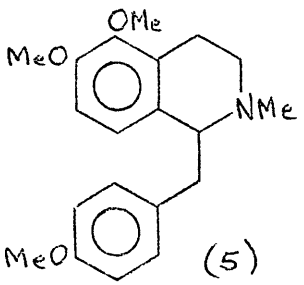

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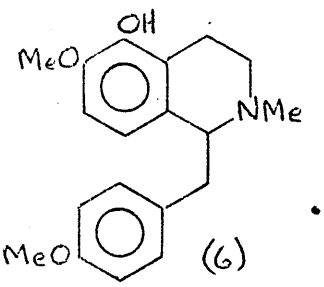

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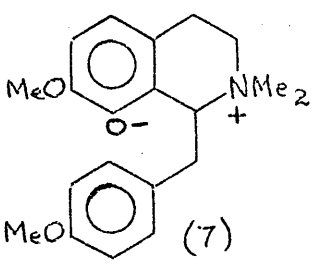

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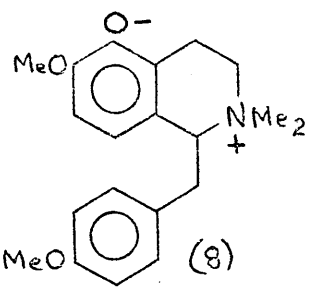

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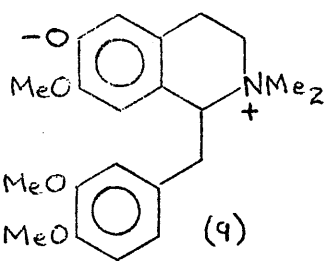

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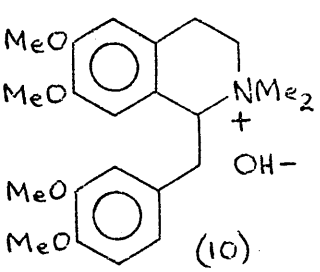

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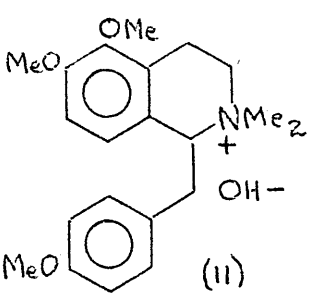

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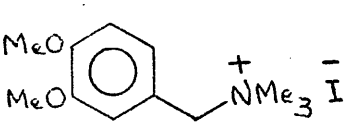

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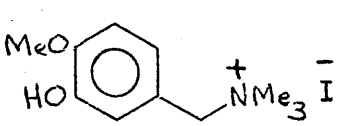

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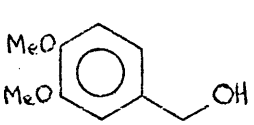

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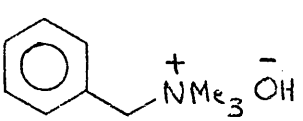

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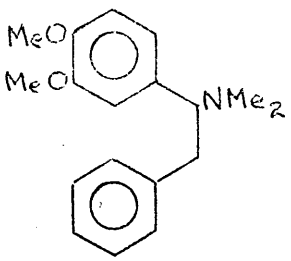

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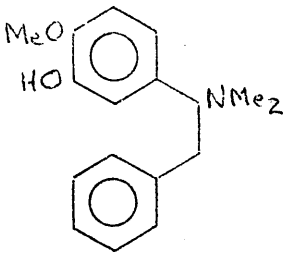

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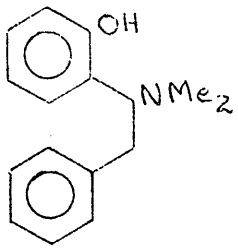

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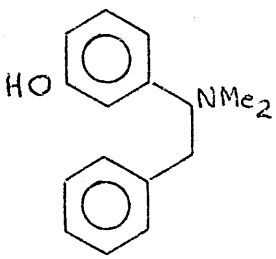

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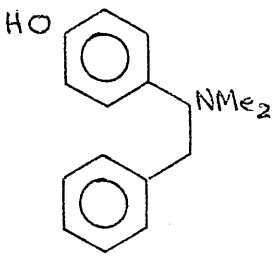

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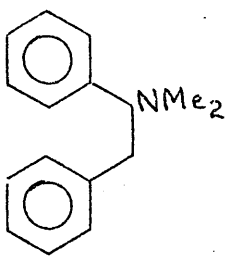

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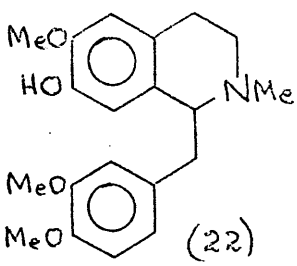

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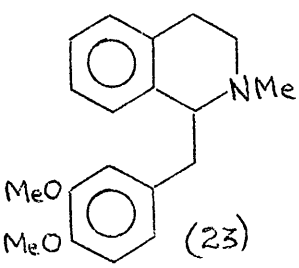

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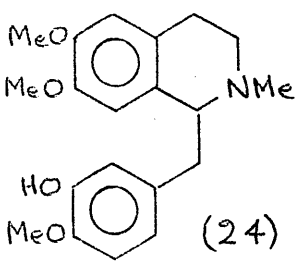

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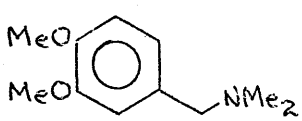

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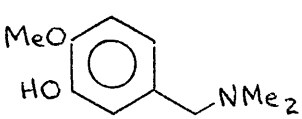

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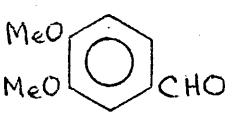

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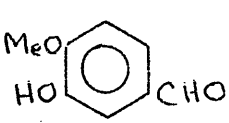

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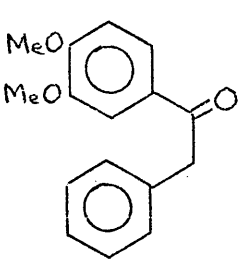

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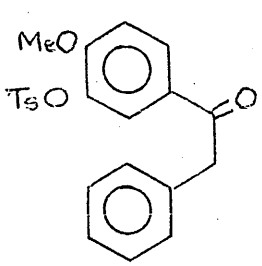

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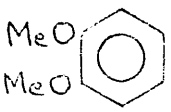

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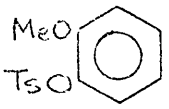

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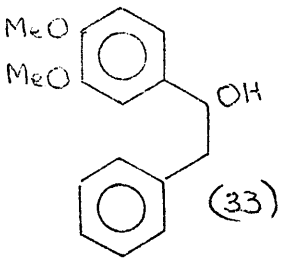

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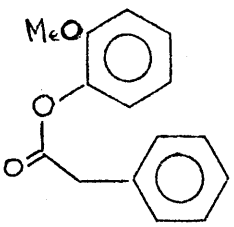

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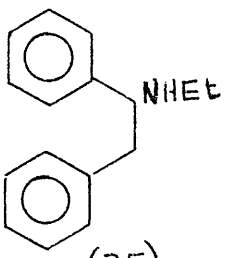

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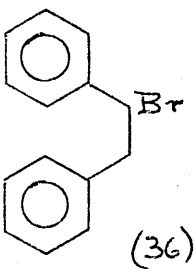

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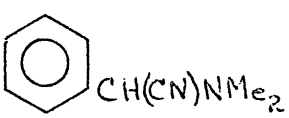

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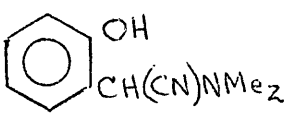

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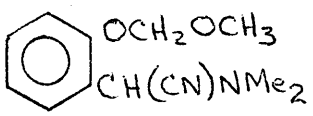

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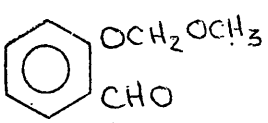

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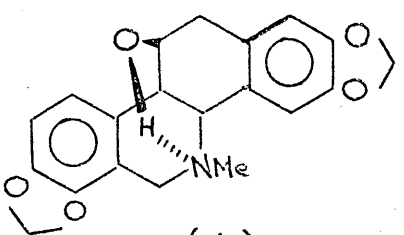

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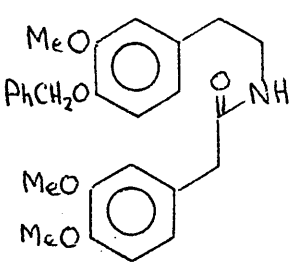

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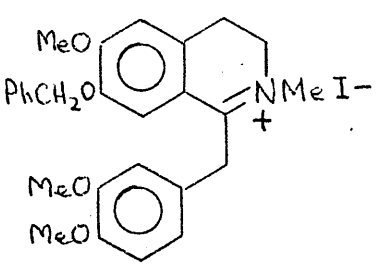

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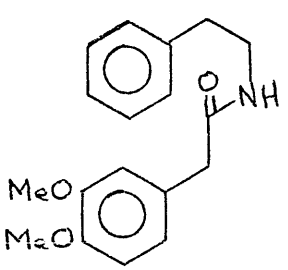

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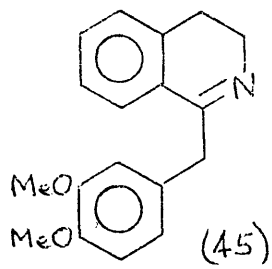

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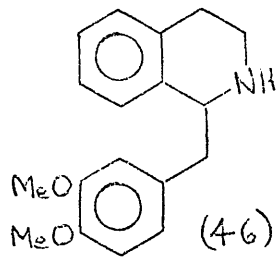

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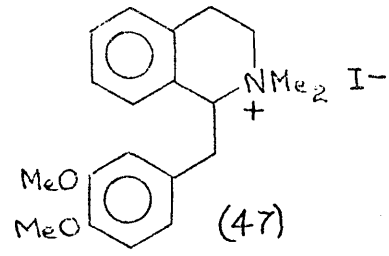

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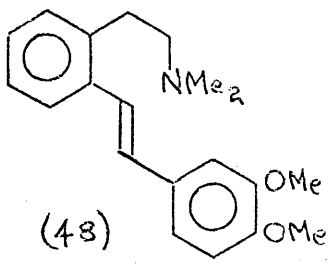

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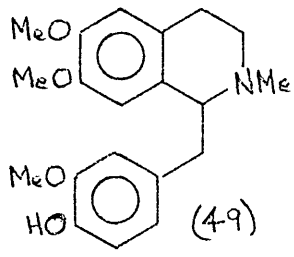

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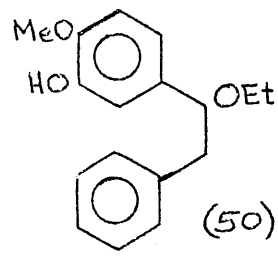

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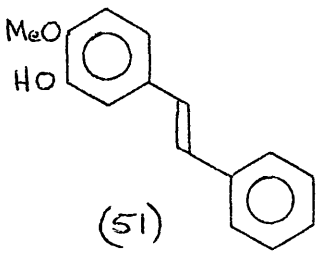

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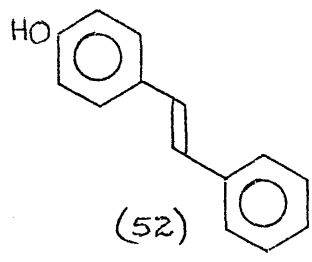

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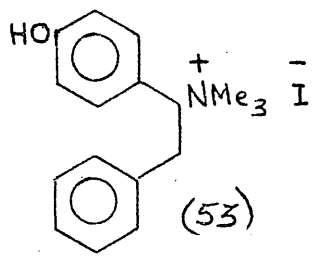

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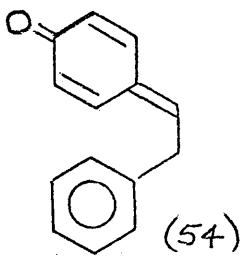

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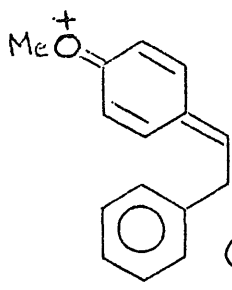

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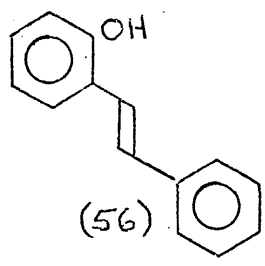

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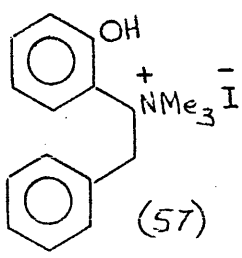

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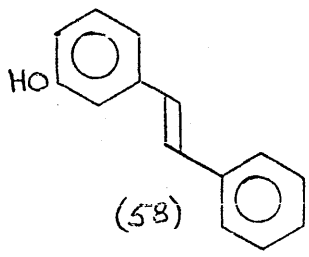

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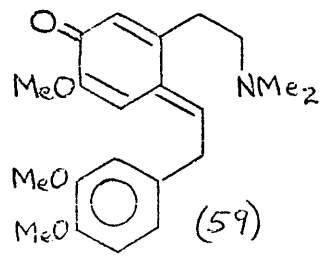

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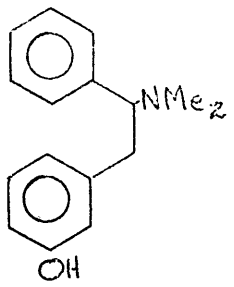

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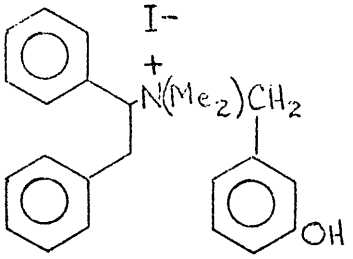

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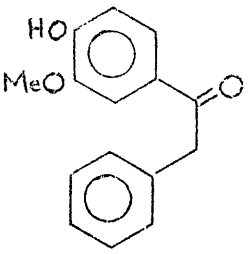

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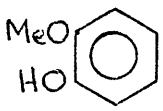

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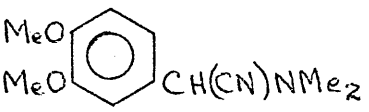

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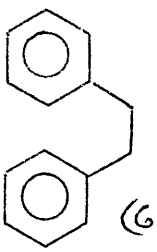

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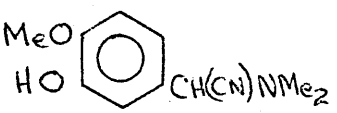

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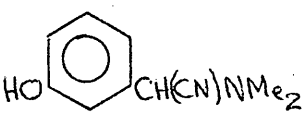

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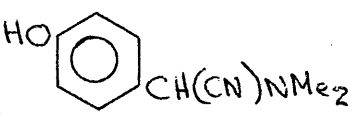

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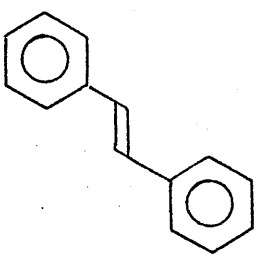

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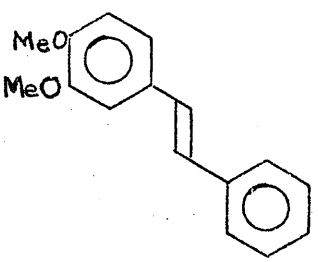

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Chapter 3.1 Introduction

Since there seemed a strong likelihood however that the phenolic quaternary salt would actually exist as the

Ifrom the allegedly antiepileptic Eastern Mediterranean plant Leontice leontopetalum Linn has revealed the pre-

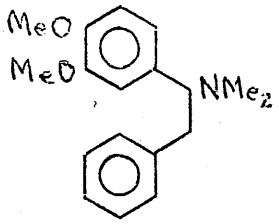
sfrom the allegedly antiepileptic Eastern Mediterraneaid pplant Leontice leontopetalum Linn has revealed the propty and producing tonic convulsions.[1] On passage of an ethanolic solution of the reineckate, chloride or iodide through Amberlite IRA 400 (OH) anion exchange resin (thereby producing the quaternary hydroxide) followed by evaporation to dryness under reduced pressure, petaline underwent Hofmann elimination yielding the methine (2). The latter was also isolated from L. leontopetalum and given the name "leonticine," but whether it is normally present in the plant or constitutes an artefact produced during extraction procedures does not seem to have been established.[2]

Since such facile Hofmann degradations are apparently not well known, McCulloch carried out a preliminary study of a number of quaternised benzylisoquinoline alkaloids under identical conditions, in an effort to discover the factors governing the elimination process and the mechanisms operating.[2] Thus the methiodides of laudanosine (3), ψ-laudanine (4) and O-methyl-ψ- petaline (5) were all found to furnish stilbenes in an analogous manner to petaline. Evaporation of the corresponding solution obtained following passage of ψ -petaline (6) methiodide through the resin yielded a stable quaternary hydroxide however, which was not converted to the methine even on fairly strong heating.

It appeared from this that facile decomposition of the quaternary hydroxide occurred where there was in the 6- or 8- position a hydroxyl group, or a methoxyl group which was not ortho to a hydroxyl group. It was suggested that electron release from a methoxyl group hydrogen bonded to an ortho group might be significantly less.[2]

Since there seemed a strong likelihood however that the phenolic quaternary salt would actually exist as the

FIGURE 3.1-01



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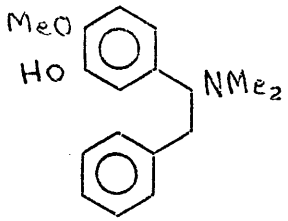

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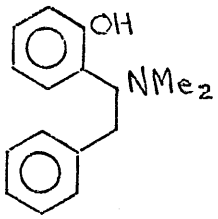

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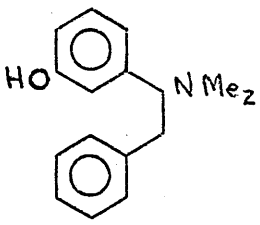

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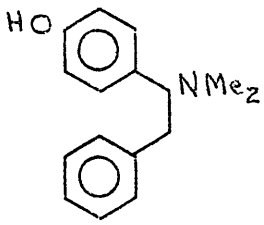

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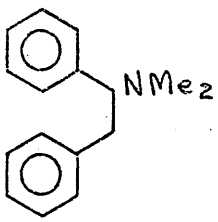


(21)

phenolate zwitterion (see later discussion) it was evident that further study of the factors governing the facility of elimination was required, involving more precise definition of conditions.

Re-examination of the ultraviolet spectra obtained by McCulloch from ethanolic solutions of petaline, ψ-petaline and ψ-laudanine methohydroxides confirmed the existence of phenolate zwitterions (7), (8) and (9) respectively, with λ_{max} 300-305 nm. Assuming the quaternary hydroxides (10) and (11) of laudanosine and O-methyl-ψ- petaline (respectively) to behave normally, McCulloch's results were thus seen to relate more precisely to the effect of evaporation to dryness under reduced pressure upon ethanolic solutions containing the species (7), (8), (9), (10) and (11), all but (8) affording the corresponding stilbenoid methine.

At first oxygenated benzylamines were considered as possible models which were readily accessible, since these included a number of the features of benzyltetrahydroisoquinolines which appeared to be involved in these eliminations. 3,4-Dimethoxy-(12) and 3-hydroxy-4-methoxybenzyltrimethylammonium iodide (13) were prepared and the behaviour of the corresponding quaternary hydroxides compared. It was hoped that the dimethoxy derivative might yield 3,4-dimethoxybenzyl alcohol (14) by displacement of the amino function by hydroxyl ion, [3] under conditions which would allow the corresponding phenolic compound to be recovered unchanged. However the dimethoxy quaternary hydroxide was found to be unaffected even by refluxing in aqueous solution, and on discovery that aqueous benzyltrimethylammonium hydroxide (15) requires a minimum temperature of 145° for decomposition, [4] this approach was discontinued.

As a closer analogy to the alkaloidal systems with the structural features necessary for potential stilbene formation, a series of 1,2-diaryl-1-dimethylaminoethanes was now prepared (Figure 3.1-01). Amines (16) and (17) were comparable to laudanosine (3) (m,p - OMe) and ψ-petaline (6) (m-OH, p-OMe) respectively, and amines (18), (19) and (20) were included to enable a thorough study to

be made of the effect of the phenolic group in isolation from other functional groups (i.e. OMe). Amine (21) was considered to be of vital importance as a standard against which to compare the observed reactivities of the others.

In order to obtain a more complete range of oxygenated benzyltetrahydroisoquinolines than had been available, (±)- codamine (22) and 1-(3,4-dimethoxybenzyl) - N - methyl - 1,2,3,4-tetrahydroisoquinoline (23) were also synthesised. However laudanine (24), an example of an alkaloid with a hydroxyl grouping in the aromatic ring apparently less directly involved in controlling the ease of Hofmann elimination, could not be obtained.

The behaviour of these various amines on attempted Hofmann degradation will be discussed in Chapter 3.3, following the description of their preparation in Chapter 3.2.

Chapter 3.2 Preparation of amines

The first two amines studied, N,N- dimethyl-3,4-dimethoxybenzylamine (25) and N,N-dimethyl-3-hydroxy-4-methoxybenzylamine (26), were prepared in good yield from the corresponding aldehydes (27) and (28) by hydrogenation over palladium on charcoal in ethanolic dimethylamine.[5] A method initially attempted for obtaining (25) involving sodium borohydride reduction of a veratraldehyde-dimethylammonium chloride-sodium acetate mixture in aqueous ethanol[6] gave 3,4-dimethoxybenzyl alcohol (14) as the main product. Other routes explored for (25), namely reduction of veratraldehyde N-methyl imine with sodium borohydride and formaldehyde or treatment of this imine with methyl iodide followed by sodium borohydride,[7] both led to complex mixtures of products.

It was hoped that it might be possible to effect a similar reductive amination of 1,2-diaryl-1-ketoethanes, although these could be expected to be less reactive than aldehydes.[8] Suitable ketones (29) and (30) were prepared by Friedel-Crafts acylation of veratrole (31) and O-tosyl guaiacol (32) respectively with phenylacetyl chloride, but when (29) was submitted to the reductive amination procedure described above the required amine (16) could not be detected, the main product being the corresponding alcohol (33). Since it was found that the desired amines could conveniently be prepared as described below, however, further work with this type of aryl benzyl ketone was discontinued. (Such ketones may also have been formed in a Fries rearrangement of guaiacol phenylacetate (34) (see Chapter 3.4),[9] but this was not further investigated).

An interesting discovery incidental to the above work was the production of an orange crystalline by-product during the preparation of the ketone (29). The structure of this compound and that of a colourless hydrogenation product will be discussed in Chapter 4.1.

Preparation of 1- dialkylamino-1,2-diarylethanes has previously been extensively studied by Goodson and

Christopher.[10] Treatment of appropriate primary and secondary amines with alkyl halides had afforded only limited success : for instance, N-ethyl-1,2-diphenylethylamine (35) gave a 70% yield of tertiary amine on treatment with ethyl bromide at 120-140°, whereas only a 10% yield of tertiary amine resulted from the reaction of piperidine and 1,2-diphenylethyl bromide (36), stilbene being the major product.[10] (This suggested that conversion of the alcohol (33) to a satisfactory yield of the corresponding amine (16) *via* a halide would have little chance of success).

An efficient synthesis was however developed using the reaction of Grignard reagents (RMgX) with α-amino nitriles of the type Ar CH (NR'_2) CN.[10] This was known to take one of three different pathways depending on the nature of the substituent groups : (a) replacement of the cyano group, yielding Ar CH(NR'_2) R; (b) addition to the cyano group to form Ar CH(NR'_2) COR; and (c) removal of cyano groups from 2 molecules of the amino nitrile, giving rise to the coupled product ArCH(NR'_2) CH(NR'_2) Ar. When α - (N,N-dimethylamino)-phenylacetonitrile (37) was treated with an ethereal solution of benzylmagnesium chloride it was found following an acid work-up that the hydrochloride of the required amine, N,N-dimethyl-1,2-diphenylethylamine (21) was formed in over 80% yield, and by this means Goodson and Christopher were able to prepare a series of 1,2-diphenylethylamines (*cf.* pathway (a) above).[10]

In the present work a similar procedure was applied to the synthesis of the amines (16) to (20) (as well as (21)) (Figure 3.1-01), variations in *e.g.* the period of heating being made where necessary. In three cases purification of the product was particularly simple since the hydrochloride crystallised out of the reaction mixture in a high state of purity.*cf.*[10] The preparation of amine (18), 1-(N,N-dimethylamino)-1-(2-hydroxyphenyl)-2-phenylethane, proved more troublesome however, since the appropriate amino nitrile (38) failed to react with benzylmagnesium chloride.

Attention was focused on the influence of the *ortho*

FIGURE 3.2-01

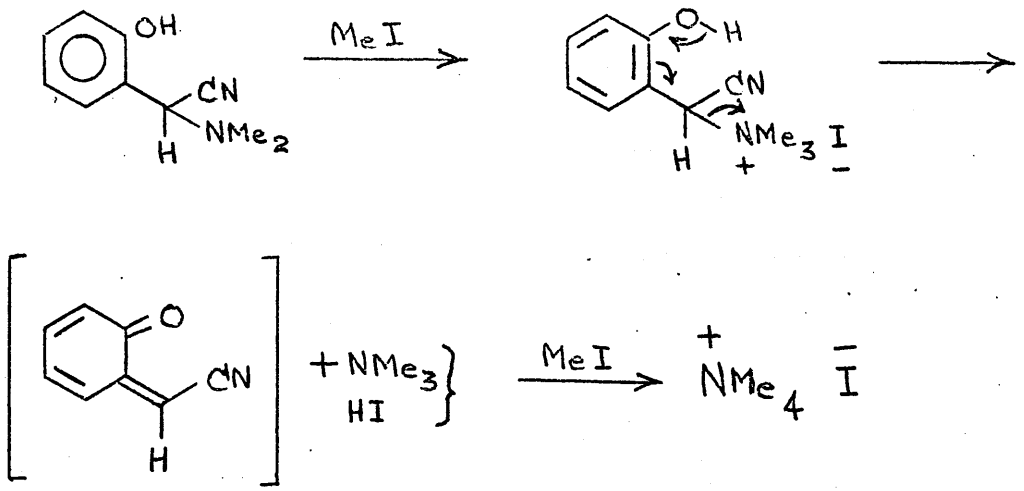


FIGURE 3.2-02

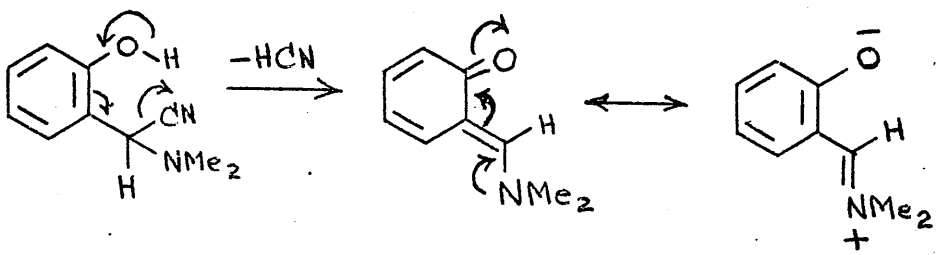
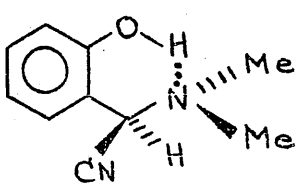


FIGURE 3.2-03



hydroxyl group in this compound (38) when it was noted that methyl iodide treatment of the extract expected to contain the required o-hydroxy diphenylethylamine (18) following normal Grignard work-up afforded a considerable yield of tetramethylammonium iodide, m.p. > 300°(correct analysis obtained for $C_4H_{12}NI$). In a later experiment the corresponding extract (before such methyl iodide treatment) was found to consist almost entirely of unchanged amino nitrile (38). It seems possible (although not further studied for confirmation purposes) that a reaction of the type shown in Figure 3.2-01 could have taken place, the hypothetical cyano-quinonoid species being the initial product formed on decomposition of the iodide salt.

The presence of the ortho hydroxyl group in (38) could also account for another remarkable property, namely the production of a deep red solution upon heating (38) in light petroleum on the steam bath. This could perhaps result from formation of the dimethylamino-quinonoid species shown in Figure 3.2-02 in which elimination of HCN rather than $HNMe_2$ is proposed (cf. above Grignard reactions). The solubility of the amino nitrile (38) in light petroleum showed the very high degree of hydrogen bonding in the molecule(cf. insolubility of corresponding m- and p-hydroxy compounds). This was corroborated by its Rf in chloroform of 0.4 (cf. m - and p - hydroxy analogues with Rf 0.1) and the resonance of the phenolic proton in its NMR spectrum at 0.80 τ [11](cf. m-hydroxyl at 3.59τ and p-hydroxyl at 3.08τ).

Since no difficulty had been experienced with the Grignard reaction in the case of the m - and p- hydroxyphenyldimethylaminoacetonitriles in which there is no possibility of intramolecular hydrogen bonding, the possible effects of the latter were considered in the light of the failure of the ortho isomer to react in the Grignard reaction.

A rigid structure containing the seemingly fairly strong O-H-N bond shown in Figure 3.2-03 would presumably preclude free rotation about the bond connecting the aromatic nucleus with the aminoacetonitrile substituent, thus effectively blocking any possibility of back-

side attack by the Grignard reagent at the methine position. However it is probable that the excess of Grignard reagent used would first of all react with the phenolic hydrogen atom despite hydrogen bonding, forming toluene and Ar OMg Cl.[12] The most likely explanation for failure thus seems to be that the neighbouring -OMg Cl moiety, if formed, simply provides sufficient steric interference to cancel any further approach made by a bulky benzyl group towards the methine position. (Any theory based on possible insolubility of the intermediate Ar OMg Cl species appears to be untenable, as there is no reason to suppose that the o -hydroxy analogue should behave any differently from the corresponding m- and p- intermediates in this respect).

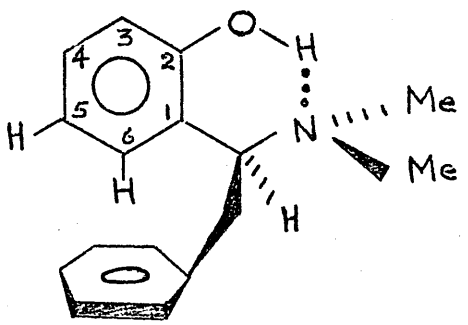
It was therefore decided to protect the phenolic group in question, and in such a way that the steric factor would be minimized. For this purpose the preparation of the methoxymethyl ether (39) was undertaken, this possessing the added advantages of stability to base and (hopefully) facile acid-catalysed removal during normal Grignard work-up.[13]

Accordingly the sodium salt of salicylaldehyde was treated with chloromethyl methyl ether to give the methoxymethylated aldehyde (40), showing 2 new singlets in the NMR spectrum at 4.68 τ (2H, methylene) and 6.47 τ (3H, methyl). Eventual conversion to the amino nitrile (39) was reflected by the disappearance in the infrared spectrum of the aldehydic stretching frequency at 1680cm $^{-1}$ and development of a weak band at 2250cm $^{-1}$ corresponding to nitrile absorption. In addition to the methoxymethylene proton resonances, the NMR spectrum now exhibited singlets at 4.92 τ (1H, methine) and 7.63 τ (6H, N-methyls), the previously apparent aldehydic proton at -0.53 τ having completely disappeared.

An attempt to convert a quantity of o-hydroxyphenyldimethylaminoacetonitrile (38) to this methoxymethyl derivative (39) resulted in hydrolysis of the cyano and amino groups, O-methoxymethyl salicylaldehyde (40) being obtained instead.

The Grignard reaction was now carried out on (39)

FIGURE 3.2-04



and examination of the mixture by TLC following normal acid work-up showed that a fairly complex mixture was present. Treatment of the crude product with gaseous hydrogen chloride in benzene failed to effect formation of a crystalline hydrochloride, but it is known that difficulty can sometimes be experienced in the formation of salts of amines which are strongly hydrogen-bonded to an adjacent hydroxyl group (as exemplified by the reluctance of chelidonine (41) to form a methiodide under normal conditions).[14]

Following neutralisation, TLC indicated that one main product was now present, and it was evident that the extra treatment with hydrogen chloride had probably been necessary to remove all of the methoxymethyl protecting group. Sublimation of the product yielded a colourless oil shown by TLC to be of high purity and analysing correctly for $C_{16}H_{19}NO$, the required amine (18). Conclusive evidence for this structure was provided by the NMR spectrum which exhibited sharp singlets at -0.15 τ (1H, hydrogen-bonded phenolic) [11] and 7.58 τ (6H, N-methyls), and a broad singlet at 2.99 τ (5H, benzyl group aromatics).

That the preferred conformation of the amine was probably as shown in Figure 3.2-04 was indicated by a broad multiplet at about 3.7 τ integrating for at least 1 proton and presumably brought about by shielding of the 1-aryl group's C_6 proton (and possibly also C_5 proton) by the phenyl ring of the benzyl group.[15]

Two of the desired three remaining amines of the tetrahydrobenzylisoquinoline type were now obtained by methods involving the Bischler-Napieralski synthesis. A sample of the first of these, (±) - codamine (22) (as the picrate), was available following phosphorus oxychloride-induced cyclisation of N-(3-methoxy-4-benzyloxyphenylethyl)-homoveratramide (42), conversion of the resultant imine hydrochloride to the methiodide (43), reduction of this with sodium borohydride, and acid-catalysed removal of the benzyl protecting group.[16]

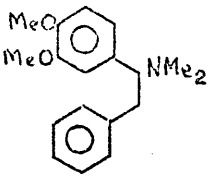
A similar route was attempted in the preparation of

the relatively less accessible N-methyl-1-veratryl-1, 2, 3, 4-tetrahydroisoquinoline (23). Since no activating group was present in the phenyl ring of the intermediate N-phenylethylhomoveratramide (44) to assist cyclisation, it was decided to employ phosphorus pentoxide rather than the milder phosphorus oxychloride for this step. The cyclisation product (45) was then immediately reduced with sodium borohydride sin ce it was known that 1-benzyl-3,4-dihydroisoquinolines readily oxidise in air to give 1-benzoyl derivatives.[17] Catalytic reduction of a mixture of the resultant secondary amine (46) (ν_{max} at 3500cm^{-1}, N-H-stretch) and formaldehyde followed by treatment with excess methyl iodide yielded a very crude sample of the required methiodide (47).cfl This exhibited an ion of m/e 311 in the mass spectrum , corresponding to the stilbene (48) which was lated isolated and characterised as the product of Hofmann degradation.

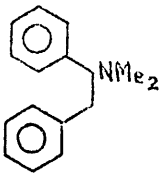
Two synthetic approaches were made towards obtaining laudanine (24), the last of the amines required. The first method examined was that of Schopf and Thierfelder in 1939, involving treatment of racemic laudanosine (3) with aluminium chloride in nitrobenzene.[18] A complex mixture of products was obtained, however, and no attempt was made at separation. An older method in which laudanosine was heated with concentrated hydrochloric acid in a sealed tube (Späth and Burger, 1926)[19] was now attempted, but the only compound to be isolated in pure condition from the reaction mixture appeared most likely to be ψ- codamine (49) with m.p. 129-131° (lit. m.p.of ψ— codamine, 129-130° ;[20] cf. lit m.p. of laudanine, 166-167°).[21] Due to the absence of a convenient route to 3-hydroxyphenylacetic acid derivatives, a total synthesis involving the Bischler-Napieralski method was not considered, and although laudanine was at one time available commercially (at prohibitive cost) this was no longer the case.

FIGURE 3.3-01

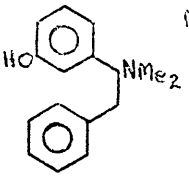
GROUP A



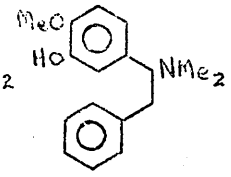
(16)



(21)

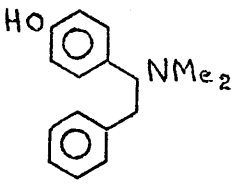


(19)

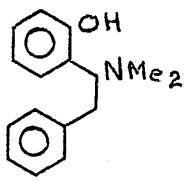


(17)

GROUP B

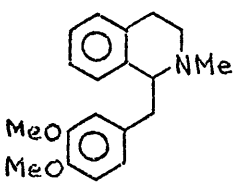


(20)

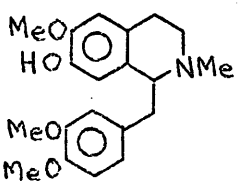


(18)

GROUP C

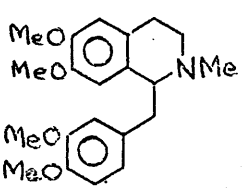


(23)

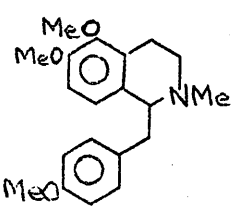


(22) Codamine

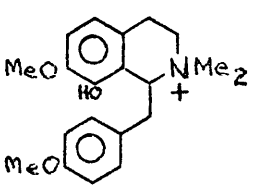
GROUP D



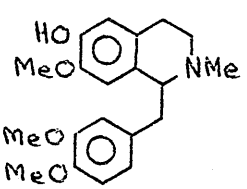
(3) Laudanosine



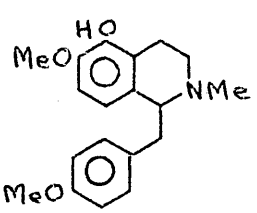
(5) O-Me-ψ-petaline



(1) Petaline



(4) ψ-Laudanine



(6) ψ-Petaline

Chapter 3.3 Degradative Results

For the purposes of the following discussion the amines studied are grouped as in Figure 33-01. Group A consists of those N, N-dimethylamino-1,2-diarylethanes which formed stable, readily isolable methiodides; Group B contains two phenolic amines which reacted rather differently with methyl iodide (see below); Group C comprises the two "alkaloidal" systems which were prepared in order to widen the scope of the preliminary survey undertaken by McCulloch; and, for completeness, the amines studied by the latter are listed in Group D.[2]

Conversion of all stable amine methiodides to quaternary hydroxides was achieved by passage of their ethanolic solutions over Amberlite IRA 400 (OH) ion exchange resin (see Chapter 3.5).[2] These solutions were evaporated under fairly uniform conditions and the products of reaction studied by ultraviolet spectroscopy. Stilbenes were isolated and identified where appropriate, and quaternary hydroxides found to be stable up to this point were then g enerally subjected to more drastic measures to discover conditions under which they also would yield stilbenes.

Since there are certain difficulties inherent in the control of temperature and concentration during evaporation of ethanolic solutions to dryness in a rotary evaporator however, it was felt that this method of monitoring the Hofmann elimination was not sufficiently discriminating to enable a proper comparison of reaction rates to be made. A method was therefore sought in which temperature and concentration could be kept reasonably constant for a range of quaternary hydroxides. As it was anticipated that there would probably be some difference in reactivity between comparably substituted "alkaloidal" and N, N-dimethylamino -1,2-diarylethane derivatives[22] it was decided to limit this approach (initially) to the 4 amines of Group A.

It was eventually found on observing the decomposition in n-butanol solution in a U V cell held at 74 ± 1°

FIGURE 3.3-02

λ_{max} or infl. (EtOH), nm (r.o.d); >230nm only:

Reference	(i) Methiodide	(ii) From column	(iii) Upon evaporation
(16)	237 (3·39) 280 (1·00) 285 (0·89)	241 (2·56) 282 (1·00) 285 (0·91)	231 (0·80) 238 (0·78) 293 (1·00) 302 (1·16) 323 (1·44)
(21)	253 (1·00) 258 (1·16) 264 (1·20) 270 (1·00)	As (i)	295 (1·00) 308 (0·97)
(19)	282 (1·00) [+NaOH: 247 (2·41) 305 (1·00)]	250 (1·94) 286 (1·00) 289 (1·06) 306 (0·85)	248 (1·96) 287 (1·00) 291 (1·08) 306 (1·14)
(17)	283 (1·00) 286 (0·96)	238 (1·69) 282 (1·00) 286 (0·93)	237 (1·74) 282 (1·00) 287 (0·95) 302 (0·40)

FIGURE 3.3-03

[QH = quaternary hydroxide; PZ = phenolate zwitterion; S = stilbene]

Reference	(ii) From column	(iii) Upon evaporation
(16)	QH	S
(21)	QH	S
(19)*	QH + PZ	QH + PZ
(17)	QH	QH + PZ

(* [PZ]/[QH] in (iii) > [PZ]/[QH] in (ii).)

FIGURE 3.3–04

λ_{max} or infl. (n-BuOH), nm (r.o.d); > 250 nm only:

Reference	(i) Methiodide	From Column (ii) Initial heating	From Column (iii) Prolonged heating
(16)	As 3.3-02(i)	282 (1·00) 286 (0·96) 323 (0·48)	293 (1·00) 304 (1·10) 325 (1·27)
(21)	As 3.3-02(i)	253 (0·88) 260 (1·00) 264 (1·13) 270 (1·00) 287 (0·88)	 291 (1·00) 296 (1·02) 308 (0·97) 321 (0·66)
(19)	As 3.3-02(i)	252 (2·38) 311 (1·00)	252 (2·38) 311 (1·00)
(17)	As 3.3-02(i)	275 (0·88) 283 (1·00) 288 (0·81) 311 (1·13)	 282 (1·00) 287 (0·93)

FIGURE 3.3–05

Reference	(ii) From col., initial heating	(iii) From col., prolonged heating
(16)	QH + trace of S	S
(21)	QH	S
(19)	PZ	PZ
(17)	QH + PZ	Amine (16)?

(see Chapter 3.5) that the quaternary hydroxide of the dimethoxy derivative (16) prepared from a 1×10^{-3} M solution of the methiodide was completely converted to the corresponding stilbene in less than 30 minutes, and these conditions were therefore employed for the reactions of the 3 remaining amines.

The results obtained both from experiments conducted in ethanol and in n-butanol solution will now be discussed group by group.

Group A

Ultraviolet absorptions (i) of the methiodides in ethanol solution, (ii) of the solutions obtained directly from the ion exchange column, and (iii) of the products obtained upon evaporation (in ethanol) are listed in Figure 3.3-02. An indication of the species present at stages (ii) and (iii) could be obtained from these values: see Figure 3.3-03.

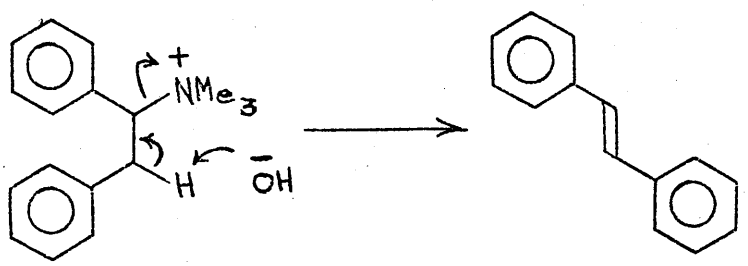
Corresponding data for the experiments conducted in n-butanol are listed in Figures 3.3-04 and 3.3-05. Column (ii) in Figure 3.3-04 refers to the first UV absorption spectrum obtained after placing the sample in the instrument cell-holder (i.e. after about 30 seconds at $74 \pm 1^{\circ}$), while column (iii) refers to the spectrum observed after completion of any reaction, the absorption pattern remaining constant for at least a further 30 minutes.

Amines (16) and (21)

Quaternary hydroxides of these amines were smoothly converted to the stilbenes both in ethanol and in n-butanol. There appeared to be no significant difference in rates of reaction in n-butanol, the time taken for stilbene absorption to reach half of its final value being approximately three minutes in both cases (see Chapter 3.5). This suggests that an electron-releasing group ortho or para to the potential amino leaving group is unnecessary for elimination to take place either under McCulloch's conditions (ethanol) or on heating in n- butanol.

Heating the methiodides themselves in n-butanol on

FIGURE 3.3-06



the steam bath before converting to the quaternary hydroxides did not result in formation of stilbenes. cf.[22] Hence it would appear that the hydroxyl anion is necessary for elimination to take place, presumably involving removal of a methylene proton (see Figure 3.3-06).[23] In this mechanism it does seem likely that electron releasing groups in the 2 or 4 positions would facilitate loss of trimethylamine thereby speeding up the overall reaction rate,[22] and it is possible that this effect could be observed by using even more tightly controlled conditions: e.g. lower temperatures and/or more dilute solutions (with consequently somewhat longer reaction times).

Amine (19)

In ethanol, partial conversion to the phenolate zwitterion took place on passage through the column, the ratio of phenolate to phenolic quaternary hydroxide appearing to increase on evaporation. Since an effort was made to ensure that ultraviolet spectra were obtained from solutions of approximately equal concentration both before and after evaporation, this appeared to suggest that attainment of an equilibrium slightly in favour of the phenolate was being hastened by the effect of heating and concentrating during evaporation to dryness.

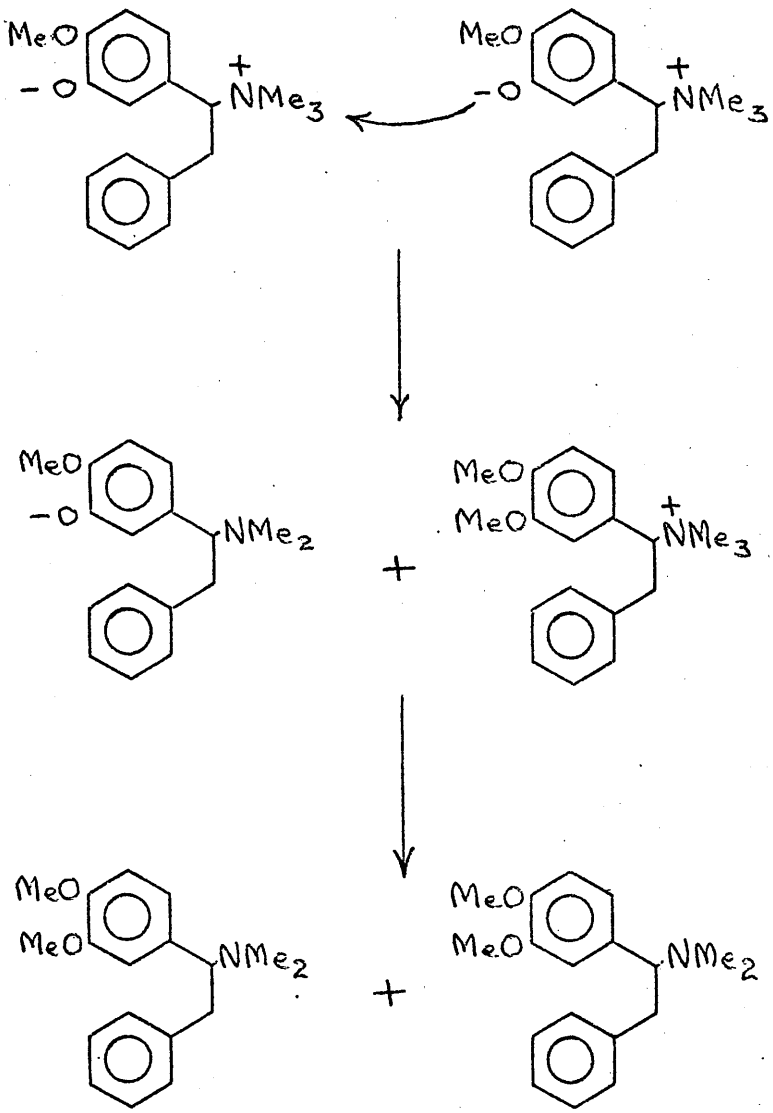
In n- butanol, however, no absorption due to the normal phenolic quaternary hydroxide was observed, suggesting that in this solvent at least the equilibrium is strongly in favour of the phenolate (which, incidentally, appeared to be unchanged even after 45 min at 70-75°).

In neither case was conversion to the stilbene detected, although evaporation of the ethanolic quaternary hydroxide at atmospheric pressure followed by strong heating for an hour on the steam bath did result in some stilbene formation.

Amine (17)

There was very little evidence of phenolate in the ethanolic solution obtained directly from the column, but a proportion became apparent after evaporation (cf. previous phenolic amine discussed). In the case of the

FIGURE 3.3-07


MeO
−O
+
NMe3
MeO
−O
+
NMe3
MeO
−O
NMe2
+
MeO
MeO
+
NMe3
MeO
MeO
NMe2
+
MeO
MeO
NMe2

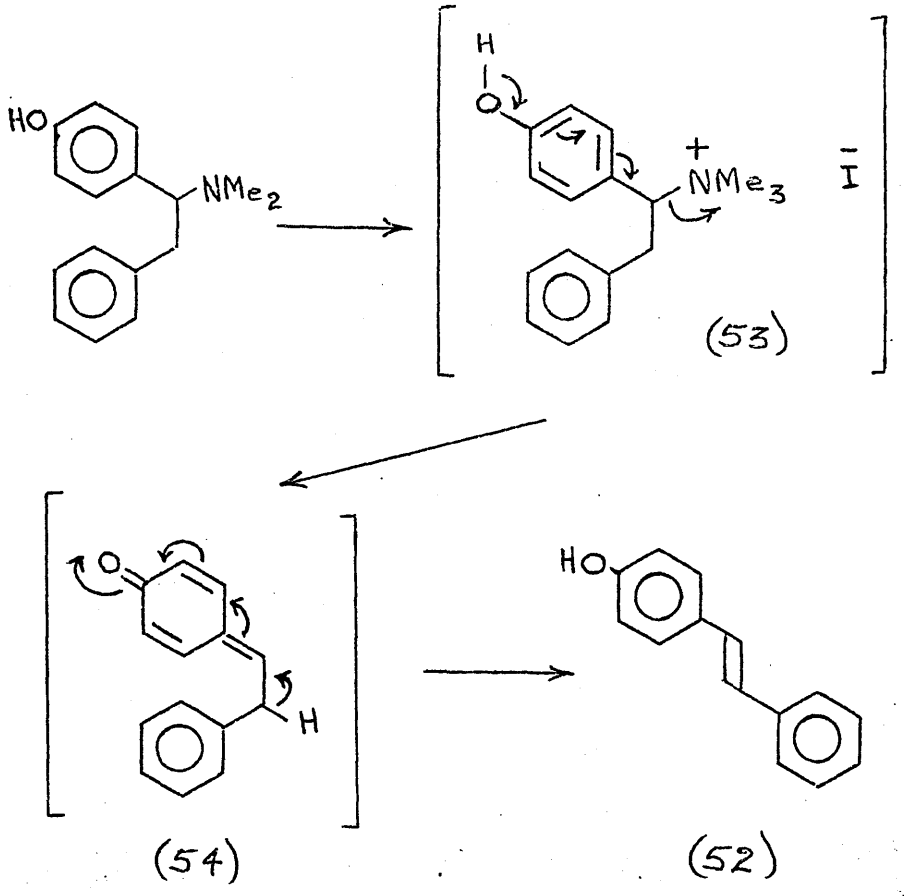
n-butanol solution the first scan after placing the sample in the UV cell suggested that the quantity of phenolate zwitterion present probably exceeded that of the phenolic quaternary hydroxide. By the time the second scan was run however (2 minutes later) a hypsochromic shift (25-30nm) of the main absorption band (previously due to phenolate) had taken place, and this absorption pattern remained constant during the next 30 minutes of the experiment. After this period of time a drop of aqueous hydrochloric acid was added, producing no change in the observed spectrum.

Since it seems unlikely for the phenolate zwitterion to have reverted to the normal phenolic quaternary hydroxide (cf. above experiments), it is possible that intermolecular methylation may have taken place as illustrated in Figure 3.3-07 (although no further evidence for this was sought). Analogies for this type of behaviour are well known, e.g. [24, 25] as is also the fact that phenolate anions preferentially attack carbon atoms rather than hydrogen atoms;[26] consequently, where these have been used as bases in "destructive" Hofmann degradations (i.e. usually employing strong heating) they tend to give less olefin than does hydroxide ion.[26]

That in no case was conversion to the stilbene observed lends support to the suggestion put forward earlier that hydroxide ion is required to initiate the elimination process.

(The question arises as to why, if the intermolecular methylation theory is correct, this does not occur on heating the quaternary hydroxide of the meta-hydroxy amine (19) in n-butanol. A plausible explanation is that the presence of an ortho electron-releasing methoxyl group as in amine (17) will increase the nucleophilicity of the derived phenolate anion, thus presumably facilitating reactions such as O-methylation. That this type of reaction was not observed with (17) in ethanol solution nor (apparently) by McCulloch in the case of ψ-petaline(6) may in part be due to the lower temperatures used for the ethanolic degradations, and also perhaps in the latter case because of the greater rigidity of

FIGURE 3.3-08



the alkaloidal system).

Treatment of the quaternary hyd roxide of (17) with sodium ethoxide in refluxing ethanol yielded a mixture consisting mainly of the ethyl ether (50) together with some stilbene (51). Formation of products of the former type (50) is also well-known in Hofmann degradation reactions,[26] arising from direct replacement of the amino group by ethoxide ion.

Group B

In the case of the two amines of this group it appeared that mere treatment with methyl iodide in acetone solution was sufficient to cause some degree of stilbene formation. This suggested a level of reactivity quite different from that of the amines of Group A.

Amine (20)

During attempted methiodide formation at 0°, a crystalline solid was isolated, consisting mainly of tetramethylammonium iodide. The ultraviolet spectrum of the residue obtained on evaporation at low temperature of the decanted solution indicated the presence of the stilbene (52) (λ_{max} at 284, 304 and 318 nm), which was later extracted and characterised. At no stage was the presumed methiodide intermediate (53) detected, suggesting that this species is immediately converted to the stilbene on its formation.

To explain this behaviour the effect of the para hydroxyl group must be taken into account, and a plausible mechanism is outlined in Figure 3.3-08. This is very much related to McCulloch's original theory about electron-releasing groups,[2] but the point now made is that a hydroxyl group in a position para (or ortho, see below) to the amino moiety would seem to be much more effective as an "electron-releaser" than a similarly positioned methoxyl group.[29] Although quaternised amines containing methoxyl groups could possibly give rise to species such as (55),[22] these would presumably be less stable than the uncharged quinone methide (54) postulated in Figure 3.3-08. cf.[27]

It would be expected that some trimethylamine hydriodide would form if the suggested mechanism is correct,[22] but probably in much smaller quantities than tetramethylammonium iodide due to the large excess of methyl iodide employed. Although no absorption between 2,200-1,800 cm^{-1} (NH^+) was detected in the infrared spectrum, the presence of a trace of this hydriodide in the isolated crystalline solid cannot be discounted.

An apparent anomaly associated with this particular amine is the comparative stability of its hydrochloride. It seems remarkable that it should be possible to recrystallise this unchanged when only decomposition products of the alleged methiodide can be detected from reactions conducted at 0°. One factor involved may be the greater release of steric crowding arising from loss of a nitrogen atom substituted with three methyl groups (as in the methiodide) compared to that substituted with only two methyl groups and one hydrogen atom (as in the hydrochloride).

Amine (18)

Although this amine reacted much more slowly with methyl iodide (TLC) than did the *para*-hydroxy derivative (presumably due to fairly strong intramolecular hydrogen bonding; *cf.* chelidonine (41)),[14] tetramethylammonium iodide was again the first product crystallising from a reaction conducted at 0°. The corresponding stilbene (56) was detected in the decanted solution by TLC comparison with an authentic sample isolated later (characteristic green stain after spraying with ceric ammonium nitrate solution following iodine treatment).

However, on treatment of this residual solution with a further quantity of methyl iodide a second batch of crystalline solid was obtained. Analysis figures on this material (without further purification) were reasonably close to those expected for the required amine methiodide (57), and a positive Beilstein flame test for the presence of halogen lent support to this structural assignment.

In the mass spectrum the ion of highest mass was

FIGURE 3.3-09

λ_{max} or infl. (EtOH), nm (r.o.d.); >230 nm only:

Reference	(i) Methiodide	(ii) From column	(iii) Upon evaporation
(23)	282 (1·00) 284 (1·00)	279 (1·00)	282 (1·00) 287 (1·00) 303 (0·95) 317 (0·97)
(22)	282 (1·00) 285 (0·98)	230 (2·27) 282 (1·00) 285 (0·95)	253 (0·84) 282 (1·00) 285 (0·99) 306 (0·50)

FIGURE 3.3-10

Reference	(ii) From column	(iii) Upon evaporation
(23)	QH	QH(?) + S
(22)	QH	QH + PZ

FIGURE 3.3-11

Reference	(i) Methiodide	(ii) From col., initial heating	(iii) Prolonged heating
(22) (n-BuOH solution)	As 3.3-09(i)	260 (1·64) 278 (1·00) 287 (0·93) 312 (1·00)	As (ii)

at m/e 196 being that required for the ortho-hydroxy stilbene (56), and the latter was also identified among the several products to which the above material appeared to decompose on dissolving in methanol at room temperature and subjecting to examination by TLC in 5% methanol-chloroform.

The stilbene itself (56) was later isolated by extraction and crystallisation, and the main ultraviolet absorption band exhibited a reversible bathochromic base shift similar to that shown by the corresponding meta-hydroxy and para-hydroxy stilbenes (58) and (52) respectively.

The apparent greater stability of the ortho-hydroxy amine methiodide (57) to that of the hypothetical para-hydroxy analogue (53) may be related to the possibility in the former case of electrostatic stabilisation of the positively-charged nitrogen atom by the lone pair of electrons belonging to the oxygen atom of the ortho hydroxyl group.[28] Nevertheless, decomposition of this methiodide would presumably occur eventually by a mechanism analogous to that proposed for the para-hydroxy compound (as shown in Figure 3.3-08).

Group C

Details of ultraviolet spectra and species present at the various stages of react ion in ethanol are listed in Figures 3.3-09 and 3.3-10.

Amine (23)

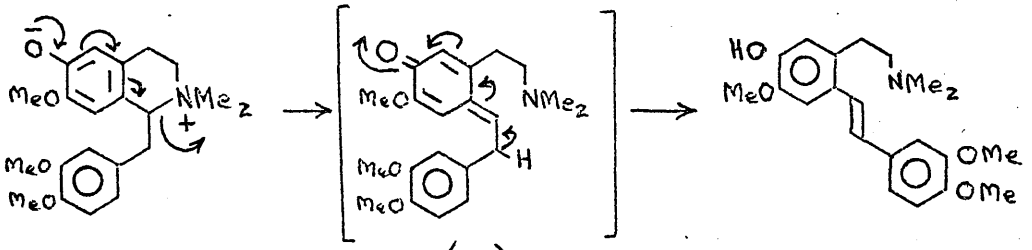
Examination of the residue obtained after evaporation of the ethanolic quaternary hydroxide revealed ultraviolet absorption due to the stilbene (48), which was later isolated and identified. This result agrees with the corresponding findings from Group A, indicating that even in the "alkaloidal" system the presence of an electron-releasing substituent in a position ortho or para to the potential amino leaving group appears unnecessary for smooth Hofmann elimination under the conditions specified.

FIGURE 3.3 – 12

λ_{max} or infl. (EtOH), nm (r.o.d) :

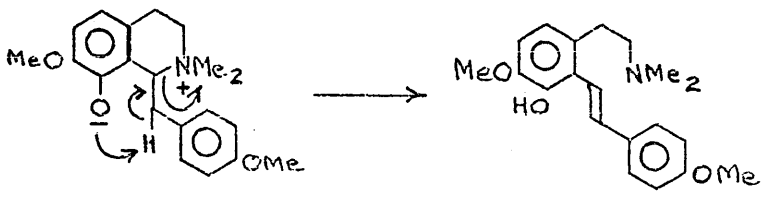
Reference	From column	Species present
(3) (Laudanosine)	214 (2.35) 235 (2.50) 282 (1.00)	QH
(5) (O-Me-ψ-petaline)	235 (1.68) 278 (1.00) 284 (1.00)	QH
(1) (Petaline)	230(2.27) 285(1.00) 260 (1.14) 300 (0.83) 278 (1.00)	QH + PZ
(4) (ψ – Laudanine)	226(2.29) 305(0.49) 260 (1.04) 282 (1.00)	QH + PZ
(6) (ψ- Petaline)	231 (2.35) 284(1.00) 259 (0.96) 300(0.83) 278 (0.95)	QH + PZ

FIGURE 3.3 – 13



(59)

FIGURE 3.3 – 14



Codamine (22)

Evaporation of the ethanolic solution from the column resulted in a mixture of phenolic quaternary hydroxide and phenolate zwitterion, but no stilbene. The experiment was also conducted in n- butanol (Figure 3.3-11) and in this case a somewhat greater proportion of phenolate zwitterion was suggested, but still no indication of either stilbene formation or of the hypothetical intermolecular O-methylation discussed in connection with the corresponding amine (17) of group A (even after 2 hours at 74 ± 1°).

Group D

Ultraviolet absorption data obtained by McCulloch[2] for solutions directly from the column, including tentative assignments for species present at this stage, are shown in Figure 3.3-12.

Laudanosine (3) and O-methyl-ψ- petaline(5)

The suggested mechanism for Hofmann elimination in these cases is analogous to that proposed for the two comparably substituted amines of Group A, inv olving initial removal of a methylene proton by hydroxide ion (cf. Figure 3.3-06).

ψ- Laudanine (4)

A plausible mode of decomposition of the phenolate zwitterion is shown in Figure 3.3-13. Excess base is unnecessary here, due to the powerful electron-releasing effect of the phenolate function which induces loss of trimethylamine and eventual stilbene formation via the hypothetical "quinone methide" intermediate (59).[27]

Petaline (1)

Two different mechanisms are possible in this instance: the first is analogous to that proposed above for ψ-laudan ine, and the second (Figure 3.3-14) cf.[30] allows for removal of a methylene proton by the phenolate anion (the proximity of these groupings being considered vital for a reaction of this type). In view

of the behaviour of ψ-laudanine, the former mode may be more likely, but this cannot be stated with any certainty.

ψ- Petaline (6)

Since this phenolate zwitterion cannot decompose by any of the mechanisms described above, it seems reasonable that evaporation of its ethanolic solution should not result in Hofmann elimination.

Conclusion

The mechanistic pathways proposed above underline the importance in Hofmann elimination reactions of the presence and location of phenolic groupings. By comparison, methoxyl substituents in the aromatic ring closest to the amino function appear to have a minimal effect under the conditions uused. The hypothesis put forward to account for the inability of meta-hydroxyl quaternary hydroxides to undergo elimination under conditions in which other quaternary hydroxides readily decompose is that only in the former case does no suitable mechanism exist for reaction to occur.

In view of these results the following experiments should be of interest (using amines of the same basic structural type as in the preceeding work) :

(i) addition of base to t he solution of a meta-hydroxy phenolate zwitterion;

(ii) addition of a phenol (e.g. guiacol) to the solution of a non-ph enolic quaternary hydroxide;

(iii) utilisation of amines incorporating a hydroxyl substituent in an aromatic ring not directly involved in the potential elimination (for example the amine (60), the alkaloid laudanine (24), or perhaps even non-phenolic amines quaternised with m-hydroxybenzyl iodide, e.g. (61)).

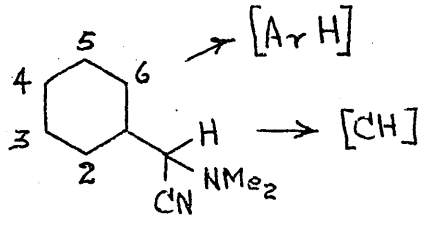
If the proposed hypothesis is correct it might be predicted that Hofmann elimination would take place in the case of (i) but not in cases (ii) and (iii).

A study of the Hofmann degradation of polyphenolic

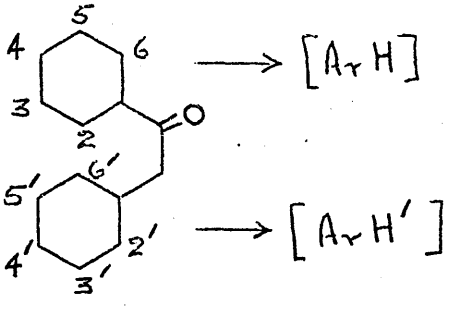
and bisbenzylisoquinoline alkaloids under controlled conditions should also be worthwhile.

FIGURE 3.4 – 01

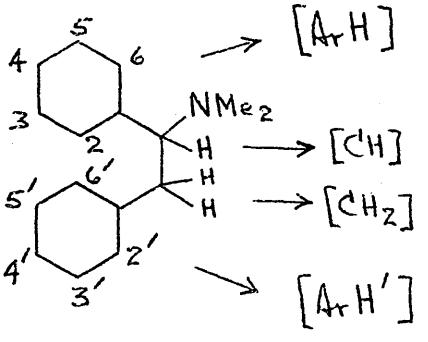
Cyano dimethylamino methyl benzenes



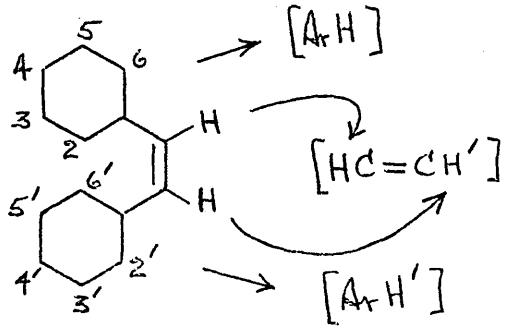
Aryl benzyl ketones



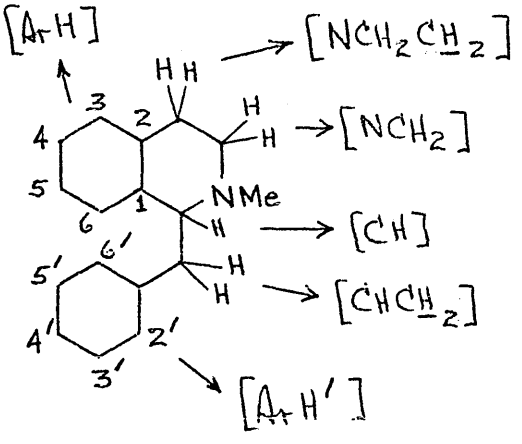
Dimethylamino diarylethanes



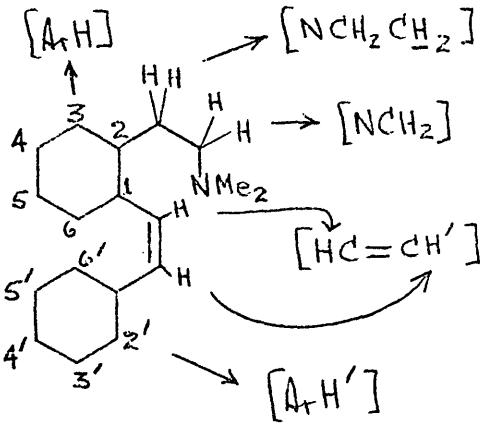
Stilbenes



Tetrahydrobenzylisoquinolines



Dimethyl amino ethyl stilbenes



Chapter 3.4 Experimental (with 3.2)

(Note: to simplify the description of many of the N M R spectra recorded in this and the following chapter the reference systems illustrated in Figure 3.4-01 have been employed)

3,4-Dimethoxybenzyltrimethylammonium iodide (12)

Veratraldehyde (27) (10g) was hydrogenated over palladium on charcoal (10%, 2g) in ethanolic solution containing dimethylamine (33%, 10ml) for 22 hr at room temperature and atmospheric pressure. Filtration through glass paper and removal of solvents gave an oil which was dissolved in ether and extracted with dilute aqueous hydrochloric acid (2N). Basification, ether extraction and evaporation yielded N,N-dimethyl-3,4-dimethoxybenzylamine (25) as a yellowish oil (7.3g, 60%).

TLC Rf (10% MeOH-$CHCl_3$) : 0.5 (brownish-blue).

IR ν_{max}(liquid film), cm^{-1} : 2800, 1590, 1515, 1260, 1230, 1030.

NMR 60MHz ($CDCl_3$), τ : 3.13(1H, bs, ArH), 3.21(2H,bs,ArH), 6.12(3H,s,OCH_3), 6.13(3H,s,OCH_3), 6.65(2H,s,CH_2), 7.79 (6H,s,NCH_3).

(Alternative preparations of the benzylamine which were attempted included (i) sodium borohydride reduction of a veratraldehyde-dimethylammonium chloride-sodium-acetate mixture in aqueous ethanol, affording mainly 3,4-dimethoxybenzyl alcohol(14); (ii) methyl iodide treatment of veratraldehyde N-methyl imine followed by sodium borohydride reduction in pyridine or ethanol, leading to a complex mixture of products; and (iii) treatment of veratraldehyde N-methyl imine with sodium borohydride and formaldehyde in aqueous ethanol followed by extraction with hydrochloric acid, giving a mixture of amines which decomposed during attempted column separation on silicagel).

The methiodide (12) formed readily on treatment of

the amine with excess methyl iodide at room temperature with or without added solvent (acetone or methanol), and crystallised from methanol-ether in very small colourless prisms, m.p. 180-182°.

ANAL Found, % : C, 42.71; H, 6.00; N, 4.06.
$C_{12}H_{20}NO_2$ I requires C, 42.74; H, 5.99; N, 4.16.

3-Hydroxy-4-methoxybenzyltrimethylammonium iodide (13)

Isovanillin (28) (10g) was hydrogenated over palladium on charcoal (10%, 2g) in ethanolic solution containing dimethylamine (33%, 150ml) for 20hr at room temperature and atmospheric pressure. Filtration through glass paper and evaporation gave fairly pure N, N-dimethyl-3-hydroxy-4-methoxybenzylamine (26) as a brownish oil (11.3g, 95%).

TLC Rf (5%MeOH-$CHCl_3$) : 0.1 (brown).

IR ν_{max}(liquid film), cm^{-1} : 3350, 1590, 1515, 1440, 1280, 1040, 810.

NMR 60MHz ($CDCl_3$), τ : 3.15 (1H, bs, ArH), 3.21(2H,bs,ArH), 4.09(1H, s, OH), 6.19 (3H, s, OCH_3) 6.62(2H, s, CH_2),7.79(6H, s, NCH_3).

The methiodide (13), prepared as for 3,4-dimethoxybenzyltrimethylammonium iodide, crystallised from ethanol-ether in long colourless needles, m.p. 196-198°.

ANAL Found, % : C, 41.02; H, 5.55; N, 4.36.
$C_{11}H_{18}NO_2I$ requires C, 40.87; H, 5.62; N, 4.33.

1-(3,4-Dimethoxyphenyl)-1-keto-2-phenylethane (29)

Prepared by the Friedel-Crafts reaction of veratrole (31) (13.8g) with phenylacetyl chloride (15.5g) and aluminium chloride (20.0g) in ether solution, the ketone (29) (3.5-4.0g, ~15%) crystallised from ether-light petroleum in long colourless needles, m.p. 84-86° (lit. m.p. 87-88°).[31]

(For full experimental details see Chapter 4.2).

TLC Rf ($CHCl_3$) : 0.6 (brown).

IR ν_{max} (Nujol), cm^{-1} : 1665, 1595, 1585, 1260, 1155, 1030, 725.

NMR 60MHz ($CDCl_3$), τ : 2.36 (1H, d, J= 8Hz, ArH_6), 2.42 (1H, s, ArH_2), 2.73 (5H, s, ArH'), 3.15 (1H, d, J= 8Hz, ArH_5), 5.80 (2H, s, CH_2), 6.12 (6H, s, OCH_3).

Hydrogenation of the ketone (2.0g) over palladium on charcoal (10%, 0.50g) in ethanolic solution containing dimethylamine (33%, 100ml) for 42 hr at room temperature and atmospheric pressure yielded a mixture shown by PLC to consist mainly of starting material together with some 1-(3,4-dimethoxyphenyl)-1-hydroxy-2-phenylethane (33). This crystallised from ether in rosettes of colourless needles, m.p. 58-60 °. (Spectroscopic properties are described in Chapter 1.6).

Guiacol phenylacetate (34)

Guiacol (12.4g) and phenylacetyl chloride (15.5g) were heated in benzene (50ml) containing pyridine (20ml) for 3 hr at 70° and stirred for 2 days at room temperature. Addition of water and extraction of organic material with ether followed by washing with aq. sodium hydroxide (2.5N) and hydrochloric acid (2N) gave upon evaporation guiacol phenylacetate (34) as a yellowish oil (22.8g, 95%) which crystallised on standing in long needles, m.p. 30-35° (lit.m.p. 32°).[32]

TLC Rf ($CHCl_3$) : 0.8 (brown).

IR ν_{max} (liquid film), cm^{-1} : 3030, 2950, 1750, 1600, 1500, 1250, 1120, 755.

NMR 60MHz ($CDCl_3$), τ : 2.70 (5H, s, ArH'), 2.7 -3.2 (4H, m, ArH), 6.23 (2H, s, CH_2), 6.45 (3H, s, OCH_3).

Fries rearrangement with aluminium chloride in nitrobenzene solution resulted in a mixture of products, three of which gave a positive test with dinitrophenylhydrazine reagent. No attempt was made to isolate 1-(4-hydroxy-3-methoxyphenyl)-1-keto-2-benzylethane (62).

Guiacol tosylate (32)

Guiacol (63) (12.4g) and p-toluenesulphonyl chloride (38.2g) were allowed to stand in pyridine (75ml) for 24hr

at 0°. After adding the mixture to ice-water (250ml), filtering, and drying under vacuum over calcium chloride for 12hr, guiacol tosylate (32) was obtained as a white solid (27.04g, 95%) crystallising from light petroleum in long colourless needles, m.p. 78-80°.

TLC Rf ($CHCl_3$) : 0.8 (slightly pink).
ANAL Found, % : C, 60.00; H, 5.00; M^+ at m/e 278.
$C_{14}H_{14}SO_4$ requires C, 60.43; H, 5.07; MW278.

1-(4-methoxy-3-p-toluenesulphonyloxyphenyl)-1-keto-2-phenylethane (30)

Guiacol tosylate (32) (0.6g) was added with stirring to a mixture of phenylacetyl chloride (0.6g) and carbon disulphide (10ml), and the reaction allowed to proceed in a stoppered flask for 12 hr at room temperature. (Starting material was recovered from preliminary experiments using ether or nitrobenzene as solvent). The resultant brown oil was added to dilute hydrochloric acid and the mixture extracted with ether-benzene. Evaporation of solvent furnished a light brown semi-crystalline solid (1.68g), further purified by washing with ether to give the ketone (30) (0.67g, 80%), crystallising from chloroform-light petroleum or benzene-light petroleum in colourless prisms, m.p. 145-148°.

TLC Rf ($CHCl_3$) : 0.4(brown).
IR ν_{max} (Nujol), cm^{-1} : 1680 (aryl ketone), 1600, 1360 (sulphonate S=O), 900.
NMR 60MHz ($CDCl_3$), τ : 2.16 (1H, dd, J_o = 8Hz, J_m = 2Hz, ArH_6), 2.25 (1H, d, J= 2Hz, ArH_2), 2.29 (2H, d, J= 8Hz, Tosyl ArH o to SO_2), 2.73 (2H, d, J= 8Hz, Tosyl ArH o to Me), 2.74 (5H, s, ArH'), 3.16 (1H, d, J= 8Hz, ArH_5), 5.90 (2H, s, CH_2), 6.40 (3H, s, OCH_3), 7.61 (3H, s, CH_3).
ANAL Found, % : C, 66.14; H, 5.10; M^+ at m/e 396.
$C_{22}H_{20}SO_5$ requires C, 66.66; H, 5.09; MW 396.

1-(3,4-Dimethoxyphenyl)-1-N,N-dimethylamino-2-phenylethane (16) methiodide

To a stirred suspension of veratraldehyde (27) (8.3g) and dimethylammonium chloride (4.08g) in water (7.5ml) at room temperature was added a solution of potassium cyanide (3.6g) in water (15ml) dropwise over 15 min. The mixture was heated on a water bath at 90-100° for 2hr 30min and cooled in ice. The yellowish upper oily layer crystallised, and the solid was filtered and washed with water. After drying, fairly pure cyano-3,4-dimethoxyphen yl-N, N-dimethylaminomethane (64) (10.8g, 75%) was obtained, crystallising from ether-light petroleum in large colourless needles, m.p. 86-88°.

TLC Rf ($CHCl_3$) : 0.4 (brown).

IR ν_{max}(Nujol), cm^{-1} : 2250 (cyano), 1585, 1515, 1250, 1140, 1030, 865, 790.

NMR 60MHz ($CDCl_3$), τ : 2.91 (1H, dd, J_o= 8Hz, J_m= 2Hz, ArH_6),
3.02 (1H, d, J=2Hz, ArH_2),
3.16 (1H, d, J=8Hz, ArH_5),
5.21 (1H, s, CH), 6.09 (6H, s, OCH_3),
7.68 (6H, s, NCH_3).

The amino nitrile (64) (9.7g) in benzene (50ml) was added in portions with stirring over 15 min to a cooled solution of benzylmagnesium chloride prepared from benzyl chloride (11.51g) and magnesium turnings (2.21g) in ether (50ml) under nitrogen atmosphere. The mixture became yellowish white and very thick, with the production of heat and evolution of gas. A gentle reflux was maintained for 3 hr during which the contents of the flask became almost completely solid. The mixture was transferred to a large beaker containing concentrated hydrochloric acid (20ml) and ice and, after stirring for 30 min the organic layer was separated and extracted once with dilute hydrochloric acid. This organic layer was found to contain 1,2-diphenyl ethane (65) (2.35g), crystallising in long colourless needles, m.p. 40-50°(lit. m.p. 52°).[33]

TLC Rf ($CHCl_3$) : 0.8 (brown).
IR ν_{max} (Nujol), cm^{-1} : 1600, 1595, 760, 705.
NMR 60MHz ($CDCl_3$), τ : 2.80 (10H, s, ArH),
7.12 (4H, s, CH_2CH_2).

(This compound, arising from combination of two molecules of Grignard reagent, was also identified together with quantities of toluene in some of the other reactions in this series).

The acid extracts were adjusted to pH7-8 with dilute aqueous sodium hydroxide and extracted thoroughly with ether. Evaporation afforded 1-(3,4-dimethoxyphenyl)-1-N, N-dimethylamino-2-phenyl ethane (16) as a yellowish oil (10.34g, 70%), becoming clear and colourless after sublimation at 100-120° - 0.04mm.

TLC Rf (2% MeOH-$CHCl_3$) : 0.2 (blue).
IR ν_{max} (liquid film), cm^{-1} : 2950, 1600, 1590, 1515, 1460, 1255, 1140, 1035, 705.
NMR 60MHz ($CDCl_3$), τ : 2.95 (5H, bm, ArH'), 3.31 (3H, s, ArH), 6.15 (3H, s, OCH_3), 6.17 (3H, s, OCH_3), 6.1-7.2 (3H, m, $CHCH_2$), 7.72 (6H, s, NCH_3).
ANAL Found, % : C, 75.82; H, 8.06; N, 4.71; M^+ at m/e 285.
$C_{18}H_{23}NO_2$ requires C, 75.76; H, 8.12; N, 4.91;
M W 285.

A solution of the amine (16) (2.49g) in acetone (20ml) was treated with methyl iodide (25ml). On standing for 20 hr at room temperature, heavy precipitation took place. The contents of the flask were filtered and washed with ice-cold acetone and ether, affording the methiodide as a white solid (1.86g, 50%), crystallising from methanol-ether in colourless needles, m.p. 198-255°.
UV λ_{max} (EtOH), nm (log ε): 237(3.99,infl.), 280(3.46), 285 (3.41, infl.).
ANAL Found, % : C, 53.61; H, 6.19; N, 3.09.
$C_{19}H_{26}NO_2I$ requires C, 53.40; H, 6.15; N, 3.28.

1-(4-Methoxy-3-hydroxyphenyl)-1-N,N-dimethylamino-2-phenylethane (17) methiodide

To a stirred suspension of isovanillin (28) (7.7g) and dimethylammonium chloride (4.1g) in water (3ml) at room temperat ure, was added an aqueous solution of potassium cyanide (3.6g in 10ml) dropwise over 10 min. Water bath heating (60-95°) was carried out for 2 hr and the resultant brownish oil extracted with chloroform. Evaporation gave cyano-(4-methoxy-3-hydroxyphenyl)- N,N-dimethylaminomethane (66) as a brownish gum (12.4g, 95%) which failed to crystallise. Two similar experiments afforded a total of 24g almost pure material.

TLC Rf ($CHCl_3$) : 0.3 (brown).

IR ν_{max}(liquid film), cm^{-1} : 3450, 2220, 1590, 1510, 1280, 1025, 765.

NMR 60MHz ($CDCl_3$), τ : 2.9-3.2 (3H, m, ArH), 5 .25 (1H, s, CH), 5.26 (1H, bs, OH), 6.10 (3H, s, OCH_3), 7.70 (6H, s, NCH_3).

The amino nitrile (66) (23.6g) in ether (100ml) was added in portions with stirring over 15 min to a cooled solution of benzylmagnesium chloride prepared from benzyl chloride (43.52g) and magnesium turnings (8.37g) in ether (170ml) under nitrogen atmosphere. Following a 3 hr reflux, the contents of the flask were added to concentrated hydrochloric acid (70ml) and ice and stirred thoroughly for 30 min. The acid extract was adjusted to pH 7-8 with dilute aqueous sodium hydroxide and extracted thoroughly with ether. Evaporation yielded 1-(3-hydroxy-4-methoxyphenyl)-1-N, N-dimethylamino-2-phenylethane (17) as a yellowish-brown oil (15.24g, 50%), crystallising on standing (m.p. 100-101°) and subliming at 100-120° -0.04mm as a colourless oil.

TLC Rf (5% MeOH-$CHCl_3$) : 0.2 (brown).

IR ν_{max}(Nujol), cm^{-1} : 1580, 1510, 1375, 1265, 1220.

NMR 60MHz ($CDCl_3$), τ : 2.91 (5H, m, ArH'), 3.2-3.3(3H, m, ArH), 4.22 (1H, bs, D_2O-exchangeable, OH),

NMR (contd.)
6.18 (3H, s, OCH_3), 6.4-7.1 (3H, m, $CHCH_2$),
7.76 (6H, s, NCH_3).

ANAL Found, % : C, 75.01; H, 7.73; N, 5.15; M^+ at m/e 271.
$C_{17}H_{21}NO_2$ requires C, 75.25; H, 7.80; N, 5.16; MW 271.

A solution of the amine (17) (3.5g) in acetone (75ml) was treated with methyl iodide (30ml). Heating on the steam bath for 5 min was followed by standing at room temperature for 12 hr. The slightly yellowish crystals were filtered and dried to give the methiodide (4.01g, 85%), purified by crystallisation from methanol-ether in small colourless needles, m.p. 187-224°.

UV (i) λ_{max}(EtOH), nm (log ε) : 283 (3.76), 286 (3.74,infl.).
(ii) λ_{max} (EtOH+NaOHaq), nm : 301.
(iii) λ_{max} (EtOH+NaOHaq + XSHClaq) : as (i).

ANAL Found, % : C, 52.48; H, 5.82; N, 3.22.
$C_{18}H_{24}NO_2I$ requires C, 52.30; H, 5.86; N, 3.39.

1-N,N-Dimethylamino-1,2-diphenylethane (21) methiodide

A solution of potassium cyanide (7.26g) in water (10ml) was added with stirring to an emulsion of benzaldehyde (10.60g) and dimethylammonium chloride (8.23g) in water (5ml) at room temperature. Heating at water bath temperature 60-90° was carried out for 2 hr, after which the mixture was cooled and thoroughly extracted with ether. Cyano-N, N-dimethyl aminophenylmethane (37) was obtained as a mobile yellowish oil (15.57g, 80%) upon evaporation.

TLC Rf ($CHCl_3$) : 0.7 (brown).

IR ν_{max} (liquid film), cm^{-1} : 3000, 2900, 2800, 2230, 1600, 1495, 1455, 1025, 745, 700.

NMR 60MHz ($CDCl_3$), τ : 2.55 (5H, m, ArH), 5.17 (1H, s, CH), 7.65 (6H, s, NCH_3).

The amino nitrile (37) (15.00g) in ether (100ml) was added in portions to an ice-cold solution of benzylmagnesium chloride prepared from benzyl chloride (23.00g) and magnesium (4.42g) in ether (90ml) under nitrogen atmosphere. Following a 2 hr reflux the mixture, now containing white solid, was allowed to stand overnight at room temperature. On pouring on to concentrated hydrochloric acid (40ml) and ice, 1- N,N-dimethylamino-1,2-diphenylmethane (21) hydrochloride was obtained as an off-white crystalline solid. After filtering, washing with dilute hydrochloric acid and ether, and overnight drying under vacuum over calcium chloride, fairly pure material (22.5g, 80%) was obtained, crystallising from ethanol-ether in colourless prisms, m.p. 185-190° (softening from 150°) with resolidification (long needles) on further heating and remelting at 205-208° (lit. m.p. 187-188° , resolidifying and remelting at 210-211°).[10,54]

ANAL Found, % : C, 73.19; H, 7.71; N, 5.22. Calc. for $C_{16}H_{19}N.HCl$: C, 73.41; H, 7.72; N, 5.35.

From the hydrochloride (294mg), the free amine (21) was prepared by adding a little warm water, adjusting to p H 10-11 with ammonium hydroxide and extracting with ether. Evaporation gave a colourless oil (246mg, 90%) which was purified by sublimation at 60°- 0.04mm.

TLC Rf ($CHCl_3$) : 0.2 (greyish-brown).

IR ν_{max} (liquid film), cm^{-1} : 3000, 2800, 1600, 1495, 1455, 1040, 745, 705.

NMR 60MHz ($CDCl_3$), τ : 2.81 (5H, bs, ArH'), 2.8-3.0 (5H, bm, ArH), 6.4-7.3 (3H, m, $CHCH_2$), 7.73 (6H, s, NCH_3).

ANAL Found, % : C, 85.34; H, 8.37; N, 6.10. Calc. for $C_{16}H_{19}N$: C, 85.29; H, 8.50; N, 6.22.

To t he amine (21) prepared as above from the hydrochloride (4.48g) was added acetone (25ml) and methyl

iodide (20ml). The solution was warmed 5 min on the steam bath and then allowed to stand overnight at room temperature. Evaporation afforded the methiodide as a slightly yellowish gum (7.33g, 100%) crystallising from methanol-ether in long colourless needles, m.p. 95-105°.

UV λ_{max} (EtOH), nm (log ε) : 253 (2.78), 258 (2.85), 264 (2.87), 270 (2.78).

ANAL Found, % : C, 55.78; H, 6.19; N, 3.64.
$C_{17}H_{22}NI$ requires C, 55.58; H, 6.04; N, 3.81.

1-N,N-Dimethylamino-1-(3-hydroxyphenyl)-2-phenylethane(19) methiodide

A solution of potassium cyanide (7.23g) in water (10ml) was added dropwise to a well-stirred suspension of m-hydroxybenzaldehyde (12.21g) and dimethylammonium chloride (8.23g) in water (5ml). Addition lasted 10min, and heating was carried out at 80-90° for 2 hr. The resultant brown emulsion was extracted with chloroform, evaporation yielding cyano-N, N-dimethylamino-3-hydroxyphenylmethane (67) as a slightly reddish-brown oil (19.7g, 95%).

TLC Rf ($CHCl_3$) : 0.2 (black).

IR ν_{max} (liquid film), cm^{-1} : 3500, 3000, 2800, 2250, 1590, 1475, 1285, 890, 780, 700.

NMR 60MHz ($CDCl_3$), τ: 2.85-3.25 (4H, m, ArH), 3.59 (1H, s, D_2O-exchangeable, OH), 5.18 (1H, s, CH), 7.64 (6H, s, NCH_3).

The amino nitrile (67) (19g) in ether (100ml) was added dropwise to a solut ion of benzylmagnesium chloride prepared from benzyl chloride (40.9g) and magnesium (7.9g) in ether (100ml) under nitrogen atmosphere. After a 3 hr reflux the mixture of liquid and white solid was added to concentrated hydrochloric acid (70ml) and ice, and stirred for 30min. On filtering the resultant yellowish crystalline solid, washing with dilute hydro-

chloric acid and ether, and drying overnight under vacuum over calcium chloride, fairly pure 1-N,N-dimethylamino-1-(3-hydroxyphenyl)-2-phenylethane (19) hydrochloride (21.0g, 65%) was obtained. This crystallised from methanol-ether in small colourless prisms, m.p.210-220°(softening from 194°).

ANAL Found, % : C, 69.02; H, 7.17; N, 4.89.
$C_{16}H_{19}NO.HCl$ requires C, 69.16; H, 7.27; N, 5.04.

The hydrochloride (3.80g) was added to warm water (5ml) and the solution adjusted to pH 10-11 with ammonium hydroxide. Extraction with ether-chloroform gave the free amine (19) as a slightly yellowish solid (3.07g, 90%) following removal of solvents. The amine crystallised from methanol-ether in long colourless needles, m.p. 144-146°.

TLC Rf (7% MeOH -$CHCl_3$) : 0.2 brown.
IR ν_{max} (Nujol), cm^{-1} : 2880, 2600, 1585, 1285, 740, 705.
NMR 60MHz ($CDCl_3$), τ : 2.85-3.40 (9H, m, ArH and ArH′),
4.10 (1H, bs, D_2O-exchangeable, OH),
6.4-7.1 (3H, m, $CHCH_2$), 7.73 (6H, s,NCH_3).
ANAL Found, % : C, 79.55; H, 7.82; N, 5.91.
$C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80.

Treatment of the amine (19) (3.00g) with acetone (25ml) and methyl iodide (15ml) at 0° for 12 hr, followed by exaporation of solvent s, yielded an oil which solidified on trituration with methanol. The methiodide (3.52g, 95%) crystallised from methanol-ether in small colourless needles, m.p. 110-120°.

UV (i) λ_{max} (EtOH), nm (log ε) : 282 (3.13).
(ii)λ_{max} (EtOH+NaOHaq), nm (r.o.d.) : 247 (2.41),
305 (1.00).
(iii)λ_{max} (EtOH+NaOHaq+XSHClaq) : as (i).
ANAL Found, % : C,53.03; H, 5.96; N, 3.45.
$C_{17}H_{22}NOI$ requires C, 53.27; H, 5.80; N, 3.66.

1-N,N-Dimethylamino-1-(4-hydroxyphenyl)-2-phenylethane(20)

A solution of potassium cyanide (7.2g) in water (12ml) was added dropwise to a suspension of p-hydroxybenzaldehyde (12.2g) and dimethylammonium chloride (8.2g) in water (5ml) at room temperature. Heating was carried out for 2hr at water bath temperature 70-90°, following which the reddish brown oil was extracted with chloroform after cooling. Solvent removal yielded cyano-N,N-dimethylamino-4-hydroxyphenylmethane (68) as a reddish oil (19.0g, 95%).

TLC Rf ($CHCl_3$) : 0.2 (brown).
IR ν_{max} (liquid film), cm^{-1} : 3450, 3000, 2800, 2250, 1610, 1590, 1515, 1270, 1170, 765.
NMR 60MHz($CDCl_3$), τ : 2.75-3.25 (4H, m, ArH), 3.08 (1H, s, D_2O-exchangeable, OH), 5.21 (1H,s,CH), 7.68 (6H, s, NCH_3).

The amino nitrile (68) (19.0g) was dissolved in ether (100ml) by refluxing for 10min. The solution was filtered while hot from some undissolved orange solid and black tar, and cooled to give a slightly colloidal solution. This was added dropwise to a solution of benzylmagnesium chloride prepared from benzyl chloride (40·95g) and magnesium (7.91g) in ether(200ml) under nitrogen atmosphere. Following this addition, lasting 15min, the reaction mixture was refluxed gently for 3hr, during which stirring became very difficult. The thick paste was added to concentrated hydrochloric acid (70ml) and ice, and after thorough stirring to break up solid particles, the mixture was allowed to stand overnight.

The yellow solid which separated was filtered, washed with dilute hydrochloric acid and ether, and dried overnight under vacuum over calcium chloride. 1-N,N-Dimethylamino-1- (4-hydroxyphenyl)-2-phenylethane (20) hydrochloride was thus obtained as a powdery light yellow-brown solid (18.6g, 50%), crystallising from methanol in

small colourless prisms, m.p. 180-196° (decomp).
ANAL Found, % : C, 69.20; H, 7.41; N, 5.02.
$C_{16}H_{19}N$ O.HCl requires C, 69.16; H, 7.27; N, 5.04.

The hydrochloride (90mg) was suspended in warm water (5ml) and the pH adjusted to 10-11 with ammonium hydroxide. After shaking to effect solution, extraction with chloroform yielded the free amine (20) as a yellowish solid (60mg, 85%) upon removal of solvent. The material crystallised from ethyl acetate-light petroleum in small colourless prisms, m.p. 190° (softening from 110°).

TLC Rf (10% MeOH-$CHCl_3$) : 0.2 (grey).
IR ν_{max} (Nujol), c m^{-1} : 2700, 1610, 1590, 1515, 1280, 1260, 1240, 765.
NMR 60MHz ($CDCl_3$), τ : 2.8-3.4 (9H, m, ArH and ArH′), 5.25 (1H, bs, D_2O-exchangeable, OH), 6.4-7.1 (3H, m, $CHCH_2$), 7.66 (6H, s, NCH_3).
MS Ion of highest mass at m/e 196 ($M^+ - HNMe_2$), corresponding to p-OH-stilbene (52).
ANAL Found, % : C, 79.35; H, 8.06; N, 5.82.
$C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80.

Cyano-N,N-dimethylamino-2-hydroxyphenylmethane (38)

Salicylaldehyde (12.2g, purified by means of its bisulphite addition compound) and dimethylammonium chloride (8.2g) were stirred with water (5ml) to give a mobile emulsion. This was cooled in ice and a solution of potassium cyanide (7.2g) in water (50ml) added dropwise over 5min. A yellowish oil gradually separated over the next 5min and partially solidified on standing in ice. The liquors were removed by decantation, and the solid washed with water, powdered in a mortar and dried over potassium hydroxide under vacuum overnight. The amino nitrile (38) was thus obtained as a light brownish-orange solid (15.8g, 90%) crystallising from light petroleum (charcoal) in long colourless needles, m.p. 70-71°.

TLC Rf ($CHCl_3$) : 0.4 (yellowish brown).

IR ν_{max}(Nujol), cm^{-1} : 2250, 1615, 1585, 1490, 1240, 1020, 760.

NMR 60MHz($CDCl_3$), τ : 0.80 (1H, bs, D_2O-exchangeable, OH), 2.6-3.2 (4H, m, ArH), 4.93 (1H, s, CH), 7.55 (6H, s, NCH_3).

ANAL Found, % : C, 68.13; H, 6.83; N, 15.93; M^+ at m/e 176.

$C_{10}H_{12}N_2O$ requires C, 68.16; H, 6.86; N, 15.90; MW 176.

(When heated in light petroleum open to the atmosphere on the steam bath for 1hr, decomposition took place with an associated change in colour of the solution from colourless to yellow to orange to deep red. A piece of filter paper closing the mouth of a glass tube containing a small (colourless) sample of the compound for analysis turned yellow overnight under vacuum at room temperature).

Reaction of o-hydroxy amino nitrile (38) with benzyl-magnesium chloride

The amino nitrile (38) (3.21g) prepared above was dissolved in ether (25ml) using mininum heating, and the solution added dropwise over 3-4 min to the Grignard solution newly prepared from benzyl chloride (6.93g) and magnesium (1.33g) in ether (30ml) under nitrogen atmosphere. The resultant very thick mixture was broken up with a spatula and gently refluxed for 3hr under nitrogen. The slightly yellowish solution and almost white solid were poured into concentrated hydrochloride acid (12ml) and ice, and stirred for 20min.

After separating the acid layer and washing thoroughly with more ether, sodium hydrogen carbonate was added to it to give pH 7-8. Some sodium chloride was added and constant ether extraction carried out for 24hr. Evaporation of solvent from the extract afforded a red mobile oil (1.45g) which crystallised on standing in long needles, consisting mainly of unreacted o- hydroxy amino nitrile (38) as indicated by IR, NMR, m.p. and TLC data.

Before this was realised, a sample of the crude oil

(200mg) had been treated with methyl iodide (5ml) in acetone (10ml). After standing overnight at 0° the solvents were removed and the oily residue taken up in acetone-ether containing some methyl iodide. On standing at 0° for 3hr a deposit of slightly yellowish crystalline solid formed. Removal of liquors by decantation followed by washing with acetone and ether afforded tetramethylammonium iodide (57mg), crystallising from methanol in colourless prisms, m.p. > 300° .

TLC Rf (10% MeOH-$CHCl_3$) : 0.0 (brown).

IR ν_{max} (Nujol), cm^{-1} : 1480, 1405, 960.

ANAL Found, % : C, 24.03; H, 6.01; N, 6.70.

$C_4H_{12}NI$ requires C, 23.89; H, 6.03; N, 6.97.

1-(N,N-Dimethylamino)-1-(2-hydroxyphenyl)-2-phenylethane (18)

Salicylaldehyde (11.73g) in toluene (20ml) was added dropwise to a stirred suspension of sodium hydride (4.69g of a 50% mineral oil dispersion) in toluene (75ml) at 40°. Following the addition, taking 15min, the reaction mixture was gently refluxed for 2 hr with stirring, producing a thick yellowish-green suspension of salicylaldehyde sodium salt,

Chloromethyl methyl ether (9.00g, dried and freed from hydrochloric acid by standing over Grade 1 basic alumina for 3 days at room temperature) in toluene (10ml) was now added and stirring continued at room temperature for 20hr. The solution was decanted from the suspended greyish-white solid which was then washed with ether and the combined organic extract washed with aqueous sodium hydroxide (1N). Removal of solvent yielded O-methoxymethyl salicylaldehyde (40) as a yellowish oil (2.51g, 15%).

TLC Rf ($CHCl_3$) : 0.7 (reddish brown).

IR ν_{max} (liquid film), cm^{-1} : 2950, 1680, 1595, 1475, 1145, 990, 765.

NMR 60MHz ($CDCl_3$), τ : -0.53 (1H, s, O=CH), 2.1-2.9 (4H, m, ArH), 4.68 (2H, s, CH_2), 6.47 (3H, s, OCH_3).

The methoxymethylated aldehyde (40) (2.16g) and dimethylammonium chloride (1·06g) were stirred for 5min in water (5ml) at 0°. Potassium cyanide (0.89g) in water (3ml) was added dropwise over 3min at 0°, and the mixture now stirred for 7hr at room temperature. Extraction with benzene afforded fairly pure cyano-N,N-dimethylamino-2-methoxymethoxyphenylmethane (39) as a mobile slightly yellowish oil (2.47g, 80%). TLC showed that traces of salicylaldehyde, O-methoxymethyl salicylaldehyde (40) and cyano-N,N-dimethylamino-2-hydroxyphenylmethane (38) were present in the product. (From an earlier attempt to prepare this compound via the sodium salt of cyano-N,N-dimethylamino-2-hydroxyphenylmethane (38), the only compound to be isolated from the resulting mixture of products was O-methoxymethyl salicylaldehyde (40)).

TLC Rf ($CHCl_3$) : 0.4 (brown).
IR ν_{max} (liquid film), cm^{-1} : 2950, 1600, 1500, 1155, 1005, 770.
NMR 60MHz($CDCl_3$), τ : 2.55-3.15 (4H, m, ArH), 4.81 (2H, s, CH_2), 4.92 (1H, s, CH), 6.54 (3H, s, OCH_3), 7.63 (6H, s, NCH_3).

The crude amino nitrile (39) (2.05g) in ether (15ml) was added dropwise over 10min with stirring at room temperature to a solution of benzylmagnesium chloride prepared from benzyl chloride (2.53g) and magnesium (0.49g) in ether (20ml) under nitrogen. Vigorous evolution of gas took place and a greenish-white solid separated. After breaking the latter up with a spatula the reaction mixture was refluxed gently with stirring for 3hr, added to concentrated hydrochloric acid (5ml) and ice, and finally allowed to warm to room temperature with occasional stirring during 30min. The acid layer was separated, washed thoroughly with ether, and adjusted to pH 7-8 with the addition of solid sodium hydrogen carbonate.

Chloroform extraction yielded a brown oil (1.31g), which dissolved only partly upon the addition of benzene (50ml). The solution was decanted from the remaining insoluble brown gum, and treated at 0° with dry hydrogen

chloride for 10min (in order to ensure complete removal of the methoxymethyl protecting group, and also in the hope that the amine (18) hydrochloride would crystallise out of the reaction mixture).

The solution was allowed to stand at 0° for 3 days during which time a dark reddish-brown oil separated. Water (10ml) and concentrated hydrochloric acid (2ml) were added, and after thorough shaking the aqueous layer was adjusted to pH 7-8 with aq. sodium hydrogen carbonate. Ethyl acetate extraction yielded 1-N,N-dimethylamino-1-(2-hydroxyphenyl)-2-phenylethane (18) as a brown oil (174mg, 10%), further purified by sublimation at 115° - 0.01mm when almost colourless material was obtained.

TLC Rf ($CHCl_3$) : 0.2 (grey with red halo).
IR ν_{max} (liquid film), cm^{-1} : 3100, 2800, 1605, 1590, 1495, 1255, 760.
NMR 60MHz($CDCl_3$), τ : -0.15 (1H, bs, D_2O-exchangeable, OH), 2.8-3.7 (9H, m, ArH and ArH′), 6.3-7.2 (3H, m, $CHCH_2$), 7.58 (6H, s, NCH_3).
ANAL Found, % : C, 79.77; H, 7.90; N, 5.84.
$C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.80.

(The o-hydroxy stilbene (56) was identified as one of the products in the dark reddish-brown oily residue from sublimation, by TLC comparison with an authentic sample obtained at a later stage).

(±) - Codamine (22) methiodide

A sample of (±)-codamine picrate (m.p. 188-192°; cf. lit.m.p. 187°)[16] prepared by the method of Shamma and Slusarchyk[16] was shaken with aqueous ammonium hydroxide and the solution extracted with chloroform. Removal of solvent afforded crude semi-crystalline (±) codamine (22), m.p. 40-55° (lit. m.p. 106-108°).[35] Despite this low melting point the product was fairly pure according to TLC.

TLC Rf (10% MeOH-$CHCl_3$) : 0.5 (brown).

IR ν_{max} (liquid film), cm^{-1} : 3500(hydroxyl), 3000, 1605, 1590, 1520, 1270, 780.

NMR 60MHz ($CDCl_3$), τ : 3.2-3.5 (5H, m, Ar^H and $Ar^{H'}$), 6.20 (6H, s, OCH_3), 6.23 (3H, s, OCH_3), 6.7-7.4 (7H, m, CH and CH_2), 7.53 (3H, s, NCH_3).

A sample of codamine (22) (230mg) in dry benzene (2-3ml) containing excess methyl iodide (1ml) was allowed to stand for 5hr at 0-10°. The benzene was removed and the residue gently warmed in acetone-methyl iodide solution until TLC showed absence of starting material (about 5-10min). Solvent was again removed and the semi-crystalline mass washed thoroughly by suspending in a little refluxing acetone. Cooling by means of an ice-salt bath afforded the almost colourless methiodide, crystallising from acetone in small needles (196mg), m.p. 222-227°(lit. m.p. 217.5-218.5°).[35]

UV λ_{max} (EtOH), nm (r.o.d.) : 282 (1.00), 285 (0.99).

N-Homoveratroyl-β- phenylethylamine (44)

Stirring an ethereal solution of β-phenylethylamine and homoveratroyl chloride with aqueous sodium hydroxide (0.5N) for 1hr at room temperature afforded a poor yield of brown gummy solid. This was triturated successively with aqueous sodium hydroxide (0.1N), water, aqueous hydrochloric acid (0.1N), and water again. After drying at room temperature, the amide (44) crystallised from ethyl acetate-ether in small colourless prisms, m.p. 106-111° (lit. m.p. 110-112°).[36]

TLC Rf (10%MeOH-$CHCl_3$) : 0.7 (brown).

IR ν_{max} (Nujol), cm^{-1} : 3340(N-H), 1650 (C=O).

NMR 60MHz ($CDCl_3$), τ : 2.80 (5H, m, ArH), 3.30 (3H,m,ArH'), 4.61 (1H, s, D_2O-exchangeable, NH), 6.18(3H, s, OCH_3), 6.20 (3H, s, OCH_3), 6.55 (2H, s, CH_2 CONH), 6.55 (2H, t, J=7Hz, collapsing to s upon irr at 7.27, $CONHCH_2$), 7.27 (2H, t, J=7Hz, collapsing to s upon irr at 6.55, $CONHCH_2CH_2$).

N, N-dimethyl-1-veratryl-1,2,3,4-tetrahydroisoquinolinium iodide (47)

The above amide (44) (260mg) was treated with phosphorus pentoxide (3-4g) in refluxing xylene (40ml) for 2hr 30min. After cooling and decanting the xylene under nitrogen the yellowish cyclisation product (45) was thoroughly washed with light petroleum. The residue was immediately dissolved in aqueous methanol (25% H_2O) and treated with sodium borohydride (500mg) with ice-cooling. The resultant bright yellow solution was now basified with dilute aqueous sodium hydroxide and a further portion of sodium borohydride (500mg) added. After 10 min most of the methanol from the now almost colourless solution was removed and the residue extracted with chloroform. Evaporation of solvent afforded crude 1-veratryl-1, 2, 3, 4-tetrahydroisoquinoline (46) as a slightly yellowish oily solid (140mg).

TLC Rf (10% MeOH-$CHCl_3$) : 0.5 (greenish black, main spot).

IR ν_{max}(Nujol), cm^{-1} : 3500 (N-H).

An ethanolic solution (15ml) of the amine (46) (140mg) containing aqueous formaldehyde (33%, 5ml) and palladium on charcoal (10%, 100mg) was hydrogenated at room temperature and atmospheric pressure for 24hr. The solution was filtered free of catalyst using a little methanol for washing purposes, reduced to a volume of 10ml, and dilute hydrochloric acid added (10ml). After extracting with ether the aqueous residue was adjusted to pH 7-8 with aqueous ammonium hydroxide and chloroform extraction carried out. Removal of solvent yielded very crude N-methyl-1-veratryl-1,2,3,4-tetrahydroisoquinoline (23) as a slightly yellowish oil (73mg).

TLC Rf (10% MeOH-$CHCl_3$) : 0.6 (main spot).

Without further purification, this was dissolved

in dry ethanol (10ml) containing excess methyl iodide (5ml), and left at room temperature for 24hr and at 0-10° for 3 days. Removal of solvent afforded crude N,N-dimethyl-1-veratryl-1,2,3,4-tetrahydroisoquinolinium iodide (47) as a hard brownish gum (63mg).

TLC Rf (10% MeOH-$CHCl_3$) : 0.1 (main spot; spot at Rf 0.6 completely absent).

UV λ_{max} (EtOH), nm (r.o.d.) : 282 (1.00), 284 (1.00).

Attempted preparation of laudanine (24) from laudanosine (3)

The methods of Späth and Burger[19] and Schopf and Thierfelder [18] were followed as closely as possible (several attempts), but in neither case was there evidence for the formation of laudanine (24) (cf. Chapter 3.2).

Chapter 3.5 Experimental (with 3.3)

Hofmann degradations in ethanol solution and isolation of products

For 300mg methiodide the following procedure was adopted (quantities being adjusted proportionately for lesser amounts) : Amberlite IRA 400(OH) ion exchange resin (6g) was shaken with a solution of sodium hydroxide (Analar, 10g) in distilled water (90ml) for 15min. This slurry was added to a short glass column (½" x 5" approx.) and the resin washed with distilled water (500ml, to give washings neutral to pH paper) and, immediately before use, ethanol (95%, 250ml). The column volume was adjusted to roughly 10ml so that some indication of quaternary hydroxide concentration could be obtained where necessary.

A solution of the methiodide (300mg) in ethanol (95%, 10ml) was allowed to pass fairly slowly through the column and the eluate (10ml) recycled at least 6 times, an attempt being made to cause each methiodide to remain in contact with the resin for the same total length of time (generally about 15min). After the last pass the eluate (10ml) was collected in a weighed flask, along with a further quantity of solution obtained by washing the column through with fresh ethanol (20ml). This solution was evaporated to dryness at 40-50° under reduced pressure, employing a cooled receiving flask (acetone-solid carbon dioxide).

At each stage the course of the reaction was monitored by TLC, pH measurement using BDH Universal Indicator Paper (quaternary hydroxides being strongly basic) and observation of the ultraviolet spectrum (qualitative, in ethanol solution). Where decomposition products of the quaternary hydroxides were formed, these were isolated by extraction and chromatography, and their spectral properties determined. Where the quaternary hydroxides were stable to these conditions, more drastic measures (such as stronger heating and/or addition of base) were employed in an attempt to effect

decomposition to the stilbene.

1-Dimethylamino - 1,2-diphenylethane (21)

Evaporation of the ethanolic quaternary hydroxide yielded trans-stilbene (69), crystallising from ethanol in colourless prisms, m.p. 120-123° (lit.m.p. 125°).[37]

TLC Rf ($CHCl_3$) : 0.9 (grey).
UV λ_{max} (EtOH), nm (logε) : 229 (4.13), 235 (3.96,infl.) 295 (4.36), 308 (4.35), 319 (4.14, infl.).
NMR 60MHz ($CDCl_3$), τ : 2.40-2.75 (10H, m, ArH and ArH′), 2.88 (2H, s, HC=CH′).

1-Dimethylamino-1-(3,4-dimethoxyphenyl)-2-phenylethane(16)

Evaporation of the ethanolic quaternary hydroxide yielded the stilbene (70), crystallising from methanol in long feathery colourless needles, m.p. 105-106°.

TLC Rf ($CHCl_3$) : 0.7 (greyish brown).
IR ν_{max} (Nujol), cm^{-1} : 1590, 1515, 1265, 1155, 1135, 1030, 965, 820.
UV λ_{max}(EtOH), nm (logε) : 232 (4.23), 293 (4.34, infl.), 302 (4.40), 323 (4.49).
NMR 60MHz ($CDCl_3$), τ : 2.5-3.2 (10H, m, ArH, ArH′ and HC=CH′), 6.07 (3H, s, OCH_3), 6.12 (3H, s, OCH_3).
ANAL Found, % : C, 80.14; H, 6.74.
$C_{16}H_{16}O_2$ requires C, 79.97; H, 6.71.

1-Dimethylamino-1-(3-hydroxy-4-methoxyphenyl)-2-phenylethane (17)

The quaternary hydroxide appeared largely unchanged (TLC) after evaporation of its ethanolic solution. Complete decomposition was achieved by refluxing with ethanolic

sodium ethoxide, sublimation of the product at 100°-0.05mm yielding a colourless oil consisting mainly of the ether (50) together with some stilbene (51) (TLC and UV).

TLC Rf ($CHCl_3$) : 0.6-0.7 (2 overlapping brown spots).
IR ν_{max} (liquid film), cm^{-1} : 3540, 2950, 1595, 1515, 1500, 1440, 1270, 1130, 1035, 820, 765, 705.
UV (i) λ_{max} (EtOH), nm(r.o.d.) : 282 (1.00), 285 (0.80, infl.), 322 (0.32).
(ii) λ_{max} (EtOH+NaOHaq), nm (r.o.d.) : 246 (1.34), 295 (1.00), 346 (0.22).
(iii) λ_{max} (EtOH+NaOHaq+XSHClaq) : as (i).
NMR 60MHz ($CDCl_3$), τ : 2.6-3.3 (m, ArH, ArH′ and HC=CH′), 4.40 (bs, D_2O-exchangeable, OH), 5.70 (m, CH), 6.14 (s, OCH_3), 6.5-6.8 (m, $CHCH_2$), 7.00 (q, J= 7Hz, OCH_2), 8.88 (t, J=7Hz, OCH_2CH_3).
ANAL Found, % : C, 74.97; H, 7.60; M^+ at m/e 272.
$C_{17}H_{20}O_3$ (50) requires C, 74.97; H, 7.40; MW272.

1-Dimethylamino-1-(3-hydroxyphenyl)-2-phenylethane(19)

The quaternary hydroxide was apparently unchanged (TLC) after evaporation of its ethanolic solution under normal conditions(pH remaining at 8-9). Heating a concentrated solution for 1hr on the steam bath and then evaporation to dryness at atmospheric pressure did however cause some decomposition, and extraction with benzene followed by sublimation at 105°- 0.025mm afforded a small yield of the stilbene (58) as small colourless prisms, m.p. 119-121°.

TLC Rf (10% MeOH-$CHCl_3$) : 0.7 (brown).
UV (i) λ_{max} (EtOH), nm (r.o.d.) : 295 (1.00), 305 (0.93, infl.), 325 (0.54, infl.).
(ii) λ_{max} (EtOH+NaOHaq), nm (r.o.d.) : 267 (0.86), 300 (1.00), 337 (0.41).
(iii) λ_{max} (EtOH+NaOHaq+XS HClaq) : as (i).
NMR 60MHz ($CDCl_3$), τ : 2.5-3.3 (11H, m, ArH, ArH′ and

HC=CH′), 5.00 (1H, bs, D_2O-exchangeable, OH).
ANAL Found, % : C, 85.28; H, 6.31.
$C_{14}H_{12}O$ requires C, 85.68; H, 6.16.

1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (23)

Evaporation of the crude quaternary hydroxide solution yielded a complex mixture of products (λ_{max} at 225, 282, 287, 303 and 317 nm), the main constituent of which on isolation by PLC in 10% methanol-chloroform was identified as the stilbene (48), which failed to crystallise.

TLC Rf (10% MeOH-$CHCl_3$) : 0.5 (grey).
IR ν_{max} (liquid film), cm^{-1} : 2970, 1600, 1525, 1480, 1270, 1150, 1035, 815, 760.
NMR cf.[38] 100MHz ($CDCl_3$), τ : 2.3-3.3 (9H, m, ArH, ArH′ and HC = CH′), 6.11 (3H, s, OCH_3), 6.15 (3H, s, OCH_3) 6.8 -7.5 (4H, m, CH_2CH_2), 7.66 (6H, s, NCH_3).
MS M^+ at m/e 311; $C_{20}H_{25}NO_2$ requires MW 311.

Codamine (22)

The quaternary hydroxide was unchanged after evaporation of its ethanolic solution. No attempt was made to effect decomposition under more drastic conditions.

Action of methyl iodide on 1-dimethylamino-1-(4-hydroxyphenyl)-2-phenylethane (20)

Treatment of the amine (20) (250mg) with methyl iodide (30ml) in acetone (30ml) at 0° afforded a quantity of colourless prisms (33mg), decomposing above 300° and apparently identical with tetramethylammonium iodide.

TLC Rf (10% MeOH-$CHCl_3$) : 0.0 (brown, main spot).
IR ν_{max} (Nujol), cm^{-1} : 1480, 1405, 960.

UV λ_{max} (EtOH) : no strong absorption > 230nm.

Following removal of this crystalline material, evaporation of the filtrate under reduced pressure with gentle heating (< 30°) afforded a yellowish oil which partly crystallised :

UV (i) λ_{max} (EtOH), nm (r.o.d.) : 284 (1.00), 304 (1.08), 318 (1.05).

(ii) λ_{max} (EtOH+NaOHaq), nm (r.o.d.) : 300 (1.00), 345 (1.08).

(iii) λ_{max} (EtOH+NaOHaq+XSHClaq) : as (i).

After partitioning between chloroform and water, evaporation of the organic layer yielded a yellowish white semi-solid (135mg). Trituration with ether (charcoal) furnished the stilbene (52) (115mg) which crystallised from benzene-light petroleum-ether (5:45:50) in colourless prisms, m.p. 187-189° (lit.m.p. 189°).[39]

TLC Rf (10%MeOH-$CHCl_3$) : 0.8 (grey).

IR ν_{max} (Nujol), cm^{-1} : 3440, 1595, 1580, 1505, 1245, 960, 820.

NMR 60MHz ($CDCl_3$), τ : 2.5-3.3 (11H, m, ArH, ArH′ and HC=CH′), 5.21 (1H, bs, D_2O-exchangeable, OH).

ANAL Found, % : C, 85.75; H, 6.17.

Calc. for $C_{14}H_{12}O$: C, 85.68; H, 6.17.

Action of methyl iodide on 1-dimethylamino-1-(2-hydroxyphenyl)-2-phenylethane (18)

A solution of the amine (18) (66mg) in acetone (2ml) at 0° was treated dropwise with methyl iodide (2ml). Crystallisation occurred within 30min and increased on standing overnight at 0°. TLC examination of the solution (only) in 5% methanol-chloroform indicated the presence of three main components :

Rf	Percentage	Staining with I_2-CAN (cold)	Constitution (see later)
0.00	30	Brown	Methiodide(57)
0.60	40	Orange-brown	Unreacted amine (18)
0.65	30	Green	Stilbene (56)

Following evaporation of the mixture under reduced pressure with no external heating, the residue was triturated with further methyl iodide-acetone at 0° and allowed to stand for 1hr at room temperature. The solution was decanted and the residual solid (11mg) washed with ice-cold acetone and ether. The resultant colourless prisms did not melt below 300°, and identity with tetramethylammonium iodide (m.p. > 300°) was indicated by comparison of the infrared spectrum with that of an authentic sample.

TLC Rf (10% MeOH-$CHCl_3$) : 0.0 (brown).
IR ν_{max} (Nujol), cm^{-1} : 1480, 1405, 960.

Due to the presence of unreacted amine in the decanted solution even at this stage (TLC), a further quantity of methyl iodide was added (plus a little ether to aid crystallisation of any salt formed) and the mixture allowed to stand overnight at room temperature. By this means, a second crop of crystalline product was obtained following decantation and washing with acetone and ether. The resultant colourless prisms (25mg), believed to be the o-hydroxy amine methiodide (57), partially melted at 132-140° with further melting to about 200° (resolidification taking place on cooling, with remelting on heating to 205-220°).
TLC Rf (5% MeOH-$CHCl_3$) : 0.0 (brown).
(Spots corresponding to at least 3 decomposition products including that of the stilbene (56) were also evident).
IR ν_{max} (Nujol), cm^{-1} : 3200, 1605, 1275, 1205, 1065, 1020, 980, 895, 875, 850, 845, 780, 760, 730, 710.

(Cf. IR spectrum of the corresponding m-hydroxy amine (19) methiodide →

ν_{max} (Nujol), cm^{-1} : 3500, 1605, 1590, 1280, 1255, 1175, 1020, 980, 905, 880, 845, 820, 780, 770, 755, 710).

MS Decomposition resulted under mass spectral conditions to give the stilbene (56) :

M^+ at m/e 196; $C_{14}H_{12}O$ (56) requires MW 196.

ANAL The following figures were obtained from the initially formed product without further crystallisation (which it was believed would probably have caused decomposition) :

Found, % : C, 57.37; H, 6.36; N, 3.62.

$C_{17}H_{22}NOI$ requires C, 53.27; H, 5.80; N, 3.66.

TLC examination of the decanted solution revealed that the three components originally observed (Rf 0.00, 0.60, 0.65) were now present in approximately equal quantities. Evaporation to low bulk yielded a third crop of crystalline solid (5mg) : TLC however, showed that this was a complex mixture and it was not studied further.

Examination of the liquors and washings now indicated that the least polar spot previously observed (Rf 0.65) might in fact represent two components running very close together : on developing the plate with I_2-CAN, the upper part of the spot appeared yellowish-green while the lower part was greyish-black.

This solution was refluxed for 1hr with the addition of further methyl iodide in benzene (to achieve a higher reflux temperature), and then evaporated almost to dryness on the steam bath. Following partitioning of the residue between water and benzene-chloroform (1:3), evaporation of the organic layer afforded an oily semi-solid (26mg), trituration of which with chloroform yielded an impure, partly crystalline sample of the o-hydroxy stilbene (56), m.p. 120-136° (cf. lit. m.p. 147° as crystallised from ethanol).[39]

TLC Rf (4% MeOH-$CHCl_3$) : 0.6 (green before baking, black after baking).

UV (i) λ_{max} (EtOH), nm (r.o.d.) : 286 (1.00), 297 (0.86), 323 (0.95), 326 (0.95).
(ii) λ_{max} (EtOH+NaOHaq), nm (r.o.d.) : 245 (1.21), 291 (1.00), 370 (0.98).
(iii) λ_{max} (EtOH+NaOHaq+XSHClaq) : as (i).

NMR 60MHz ($CDCl_3$), τ : 2.4-3.3 (11H, m, ArH, ArH′ and HC=CH′), 5.52 (1H, bs, D_2O-exchangeable, OH).

MS M^+ at m/e 196; $C_{14}H_{12}O$ requires MW 196.

Hofmann degradations in n-butanol solution under controlled conditions

From preliminary experiments conducted with ethanolic solutions of the dimethoxy derivative (16), it appeared that stilbene formation was very slow when highly dilute solutions of the quaternary hydroxide were employed at temperatures up to 40°. On heating to 60-70° in an attempt to speed up the rate of reaction, losses of solvent by evaporation were a problem, and ethanol (b.p. 78°) was replaced by n-butanol (b.p. 118°) for further trials. This had the disadvantage that the methiodides were rather less soluble, and to obtain roughly 1×10^{-3} M solutions, it was necessary to grind them to a fine powder and dissolve by heating on the steam bath (no decomposition apparently taking place (TLC) during this procedure).

At 74 ± 1° all reactions were found to be complete within 30 min, no change in the ultraviolet spectrum being observed during the next 30min (apart from some concentration fluctuation due to slight evaporation losses). The following procedure was developed for use in these degradations.

The column was prepared from resin (2g) previously stirred for 10-15min with aqueous sodium hydroxide prepared as above, and washed successively with distilled water (750ml, to give washings neutral to pH paper), ethanol (95%, 250ml), n-butanol (commercial, 100ml) and

finally n-butanol (Analar, 50ml). The methiodide (25mg) in n-butanol (Analar, 50ml) was now recycled 6 times through the column as described above and a sample transferred to a 1mm UV cell. This was placed in the cell-holder of an ultraviolet spectrophotometer heated by a recirculating hot water bath thermostatically controlled to give a constant cell temperature of 74 ± 1°, and the solution scanned at regular intervals taking careful note of the time of initial insertion in the cell-holder and of each scan.

Where a stilbenoid spectrum appeared, the time taken for the absorbance of the strongest band to reach half of its final (constant) value was noted, this being a rough indication of the relative rate of reaction. All ultraviolet spectral data obtained are described fully in Chapter 3.3.

Chapter 3.6

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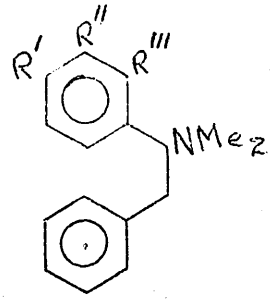
PART II (4)

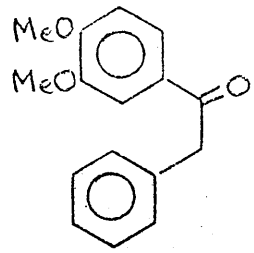
Synthesis of

1-Benzylidene - 5,6-dimethoxy-2-phenyl-3-veratryl indene



(1)

$R', R'', R''' = H, OH,$ or OMe



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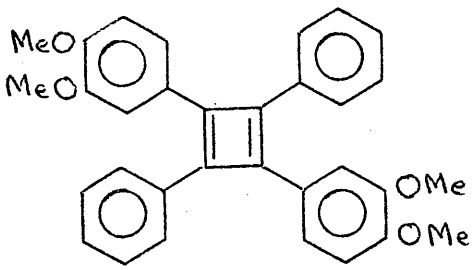

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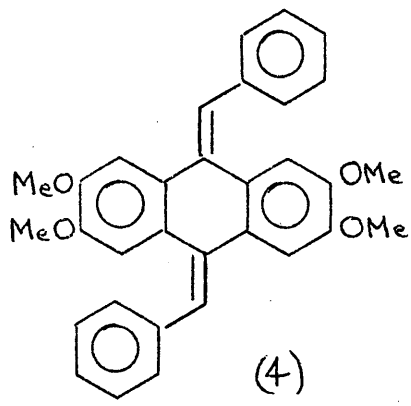

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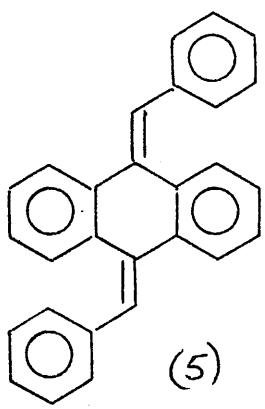

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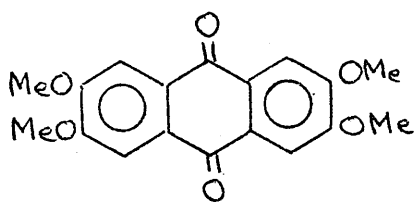

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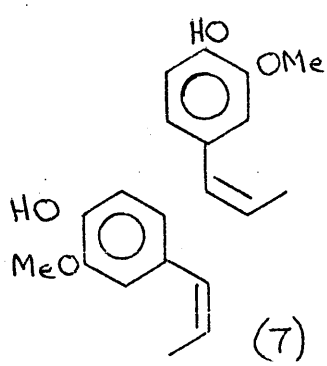

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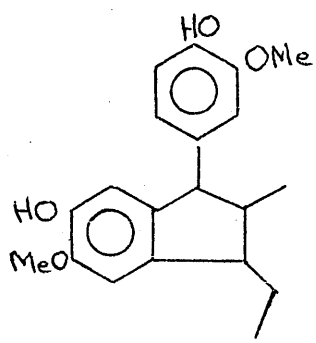

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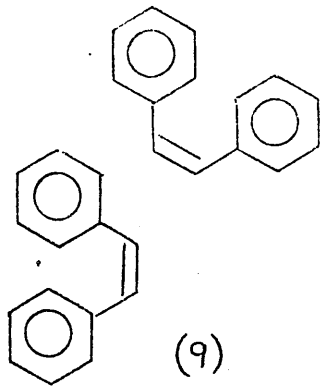

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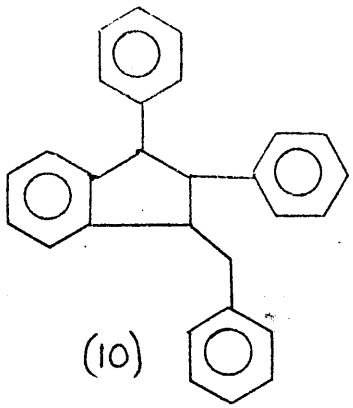

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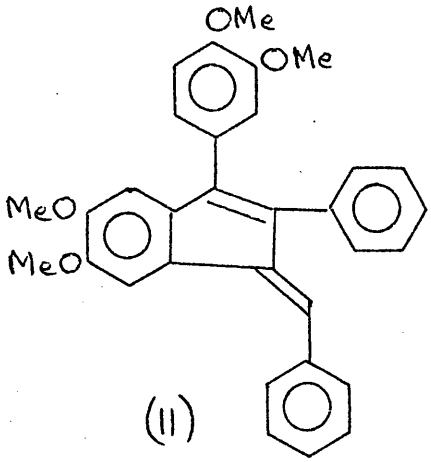

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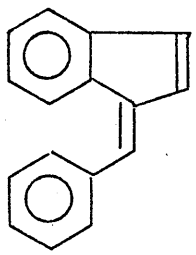

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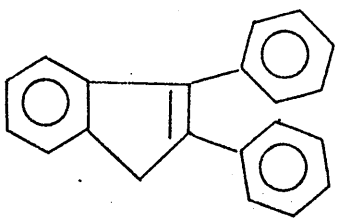

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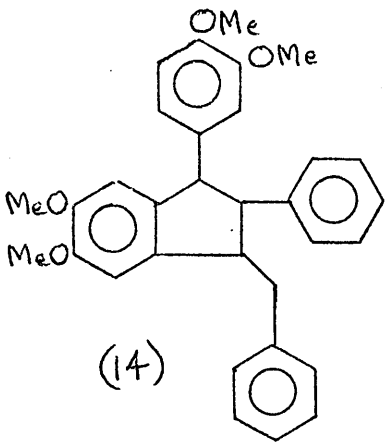

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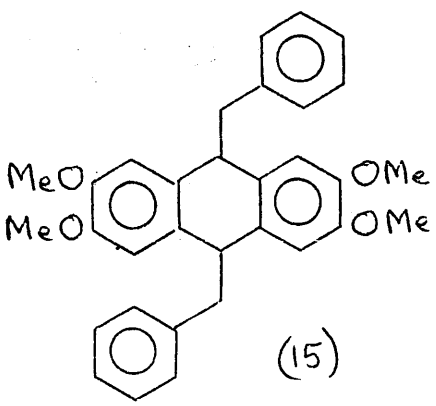

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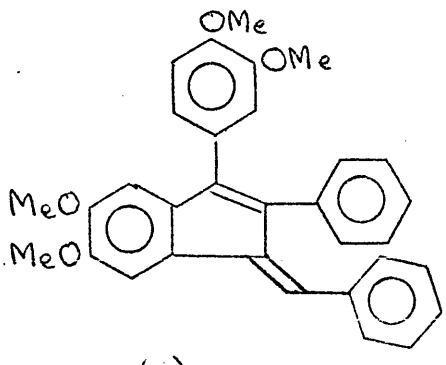

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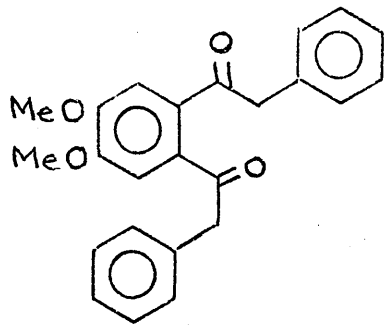

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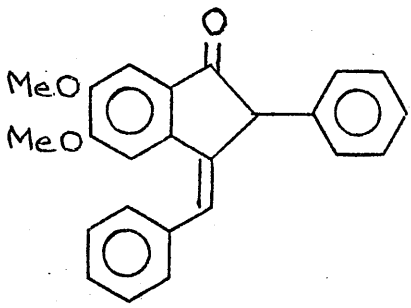


(18)

Chapter 4.1 Introduction and discussion

References to the use of various solvents in the Friedel-Crafts reaction abound in the literature, but very little attention appears to have been directed towards the use of diethyl ether. [1] This solvent has the advantage of dissolving aluminium chloride while being non-toxic (contrast carbon disulphide) and having low boiling point (contrast nitrobenzene), and it has been shown to be particularly effective in the preparation of acetophenone derivatives. [1]

In connection with studies on 1-(N,N- dimethylamino) - 1,2 - diarylethanes (1)(see Chapter 3.2) a quantity of 1- (3,4 -dimethoxyphenyl) -1-keto-2-phenylethane (2) was required, and it was decided to attempt the preparation of this compound by a Friedel-Crafts reaction using ether as solvent. Room temperature reaction of phenylacetyl chloride with veratrole using aluminium chloride in ether indeed afforded the expected ketone (2), but in addition gave isolable quantities of a slightly more polar crystalline solid, initially dark red, but becoming light orange in colour on repeated crystallisation from benzene. The structural elucidation of this product will now be discussed.

The mass spectrum revealed a strong parent ion at m/e 476 and was in agreement with elemental analysis in suggesting a molecular formula of $C_{32}H_{28}O_4$ and molecular weight 476. That the compound was olefinic was suggested by the fact that an ethyl acetate solution rapidly absorbed ozone at -70°, becoming colourless. (Two colourless products which were formed following a reductive work-up interestingly turned bright blue on acid treatment, but the nature of these has not as yet been determined).

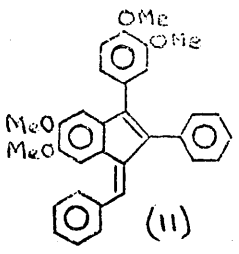
Hydrogenation of the orange compound over palladium on charcoal yielded a colourless crystalline product with Rf (chloroform) identical to that of the starting material: this stained deep pink, however, on spraying

with ceric ammonium nitrate reagent after iodine vapour treatment, whereas the starting material stained green under these conditions . Elemental analysis and mass spectrum of this compound indicated that four hydrogen atoms per molecule had been incorporated, pointing to the molecular formula $C_{32}H_{32}O_4$ and molecular weight 480.

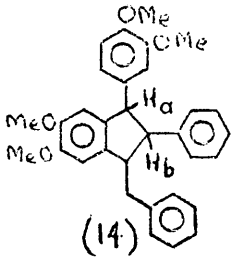
This evidence suggested that two molecules each of veratrole and phenylacetyl chloride were involved in formation of the orange compound, this probably possessing two olefinic C=C bonds. The four oxygen atoms were thus satisfactorily accounted for as the methoxyl groups from two veratrole molecules (there being little absorption in the infrared spectrum above 1600cm $^{-1}$). At this stage structures (3) and (4) were eliminated on the basis of the ultraviolet spectrum (λ max at 264, 290 and 346nm) which bore no resemblance to that expected for (3)[2] or to that of the hydrocarbon (5) (λmax at 220, 250 and 380nm).[3] It was also considered improbable that a species such as (3) should be so readily synthesised under the conditions used, and (4) seemed unlikely since ozonolysis would be expected to lead smoothly to the coloured tetramethoxy anthraquinone (6).

In view of the well-known acid-catalysed dimerisation of propenylphenol ethers such as isoeugenol (7) to diisoeugenol (8)[5] and also the more recently reported stannic chloride-catalysed photochemical dimerisation of cis - or trans - stilbene (9) to (10),[6] structure (11) was now considered. Comparison of the orange compound's ultraviolet spectrum with those of 1- benzylidene indene (12) (λmax at 238, 280 and 340nm)[7] and 2, 3- diphenyl indene (13) (λmax at 237 and 310nm)[8] lent support to this structural assignment, and further evidence was supplied by the nuclear magnetic resonance spectra of both the orange compound and its colourless hydrogenation product, which now seemed likely to possess structure (14).

FIGURE 4.1–01



(11)



(14)

τ (acetone), 100Mz :

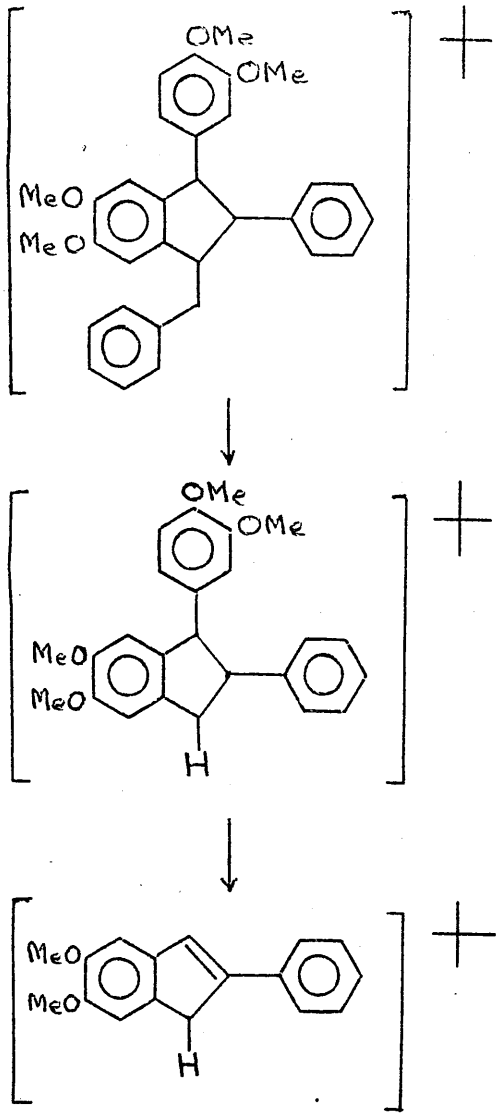
	(11)	(14)
Methoxyl	6·49 (3H, s) 6·45 (3H, s) 6·24 (6H, s)	6·64 (3H, s) 6·38 (3H, s) 6·35 (3H, s) 6·21 (3H, s)
Methine, methylene	——	6·2–7.3 (4H, m) 5·35 (H_a, d, J = 6Hz)
Aryl, olefinic	3·18 (1H, s) 3·05 (1H, s) 2·96 (1H, s) 2·93 (1H, s) 2·84 (1H, s) 2·4–2·7 (11H, m)	3·73 (1H, s) 2·6–3·5 (14H, m)

FIGURE 4.1–02

(11)

Solvent	τ (60 or 100 MHz)		
Dimethylsulphoxide	6·25 (3H, s)	6·53 (3H, s)	6·70 (6H, s)
Acetone	6·24 (6H, s)	6·45 (3H, s)	6·49 (3H, s)
Chloroform	6·13 (3H, s)	6·16 (3H, s)	6·42 (6H, s)
Carbon disulphide	6·28 (3H, s)	6·30 (3H, s)	6·57 (6H, s)
Benzene	6·53 (3H, s)	6·61 (6H, s)	6·66 (3H, s)

FIGURE 4.1–03



m/e 480 (30%)

−91 | m* 315.2

m/e 389 (100%)

−138 | m* 161.9

m/e 251 (30%)

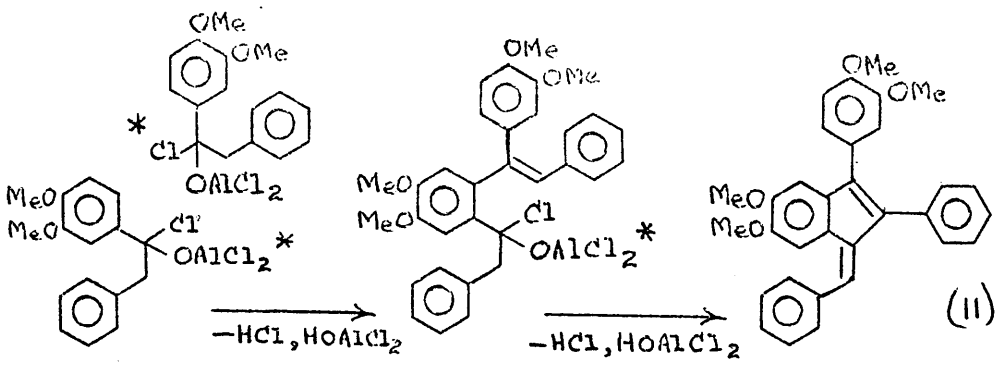
NMR signals for both species (11) and (14) are shown in Figure 4.1-01 (acetone solutions). While it has not been possible to assign these values to specific protons with any degree of confidence due to the complex pattern of possible shielding and deshielding effects obtaining, the data are in good general agreement with the proposed structures and at variance with the symmetrical alternatives (4) and (15).

Although the configuration of the benzylidene moiety in the orange compound is not altogether clear, the isomer as drawn (11) would perhaps be favoured as the alternative (16) would involve two phenyl rings in very close proximity. A feature of interest in the spectrum of (11) was the great variation in the position of the methoxyl resonances (in particular) which occurred in different solvents, probably partially due to conformational isomerism [9] (see Figure 4.1-02).

Removal of the olefinic double bonds on reduction of (11) was clearly illustrated by the general drift to higher field observed in the aryl protons signals of (14). (This, along with the stronger shielding effects of adjacent aromatic nuclei now becoming evident, caused upfield shifts of as much as 0.5 τ). cf. [10] The doubly benzylic proton H_a was identified as a broadened doublet ($J = 6Hz$) at the rather low value of 5.35 τ (acetone) or 5.41 τ (chloroform). Irradiation at 6.41τ (chloroform) caused collapse to a singlet (again slightly broadened, perhaps by benzylic coupling) and irradiation at 5.41 τ caused a simplification of the spectrum in the vicinity of 6.4 τ (H_b). (Chloroform solution revealed the 6 - 7 τ area more clearly than acetone).

Whereas no major mass spectral breakdown pattern was discernable for the orange compound (apart from early losses of methyl and methoxyl groups), it appeared that the main fragmentation of the reduced product (14) was that proposed in Figure 4.1 -03 (the ions illustrated being the only ones in the spectrum with abundance greater than 20%). An interesting feature of the mass spectra of both products was the presence of a considerable number of doubly-charged ions, mainly in the range m/e

FIGURE 4.1-04



(* Salt-like form may be predominant : $\geq \overset{+}{O}AlCl_2\ \bar{C}l$)

FIGURE 4.1-05

(R = Cl or $OAlCl_2$)

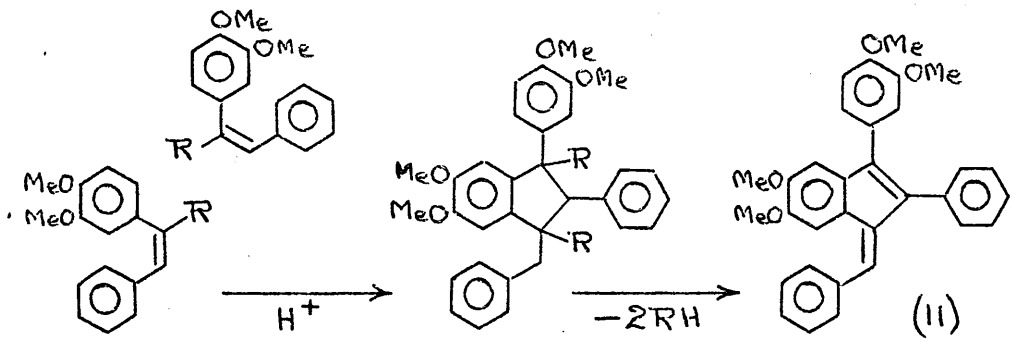
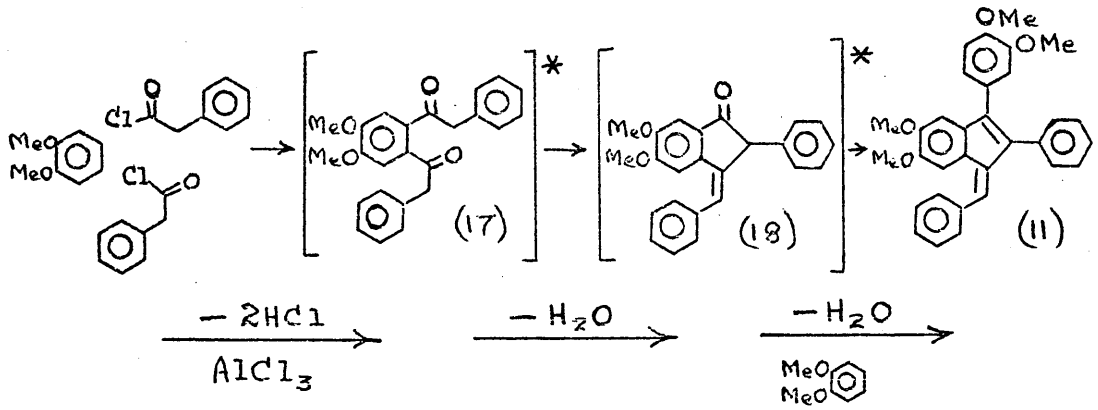


FIGURE 4.1-06



(* As $AlCl_3$ — complex)

120 - 240 for (11) and m/e 100 - 200 for (14).

Some attention was now paid to the mechanism of formation of the orange product, assuming structure (11). Since almost complete recovery of unreacted ketone (2) was made following treatment with aluminium chloride in ether or with hydrochloric acid, pathways involving dimerisation of ketone-aluminium chloride complexes (cf. e.g. Figure 4.1-04) or hypothetical "enol" derivatives (cf. e.g. Figure 4.1 - 05) seemed unlikely. (It is difficult to envisage a "dimerisable ketone-intermediate" arising from the action of phenylacetyl chloride on veratrole in the presence of aluminium chloride which could not also be produced by the action of aluminium chloride on pre-formed ketone (2)).

A mechanism not involving such a ketone (2)- intermediate, complex or derivative is outlined in Figure 4.1-06. Diacylation of veratole (perhaps only possible in ether due to special complexing effects?) is followed by cyclisation, further reaction withveratrole and elimination of HO $AlCl_2$, eventually yielding (11). It would be of interest to attempt isolation and further treatment of the hypothetical intermediates (17) and (18) with a view to testing the plausibility of this theory.

A study of the degree of generality of this reaction and of the influence (if any) of diethyl ether as solvent would seem to be worthwhile. The chemistry of the oxidation products of (11) is also of interest, in view of the marked colour changes associated with the presence of acid. cf11

Chapter 4.2 Experimental

Reaction of veratrole with phenylacetyl chloride and aluminium chloride in ether

Slow addition of aluminium chloride (20.00g) to ether (100ml) afforded a clear very slightly brownish solution. To this was added a solution of veratrole (13.80g) in ether (25ml) with stirring , followed by phenylacetyl chloride (15.50g) in ether (25ml) dropwise over 30 min. The solution gradually darkened through yellowish-brown to reddish-brown and eventually to a very dark greenish-brown. Stirring was continued for a further 20 hr at room temperature after which hydrochloric acid (conc. aq HCl, 1 part:water, 1.5 parts; 50ml) was added dropwise with ice-cooling of the reaction mixture. Evolution of gas took place and the solution became reddish-orange, containing suspended white gelatinous solid and a dark brown oil. After allowing to stand for 15 min the mixture, now containing a suspension of fine yellowish-red needles, was extracted with benzene and the extract washed thoroughly with water. Removal of solvents from the organic layer afforded a red oil (30.05g).

A portion of the oil (about 25g) was dissolved in hot benzene and light petroleum added to the warm solution until a cloudiness was evident. On cooling to 0- 10° a precipitate of red needles appeared (about 600mg) , becoming lighter in colour on further crystallisation from benzene- light petroleum to give a first crop of orange needles (500 mg) and a second crop of dark red needles (75 mg).

On evaporating the original liquors to low bulk, further crystallisation took place furnishing 1- (3,4- dimethoxy phenyl) - 1 - keto - 2 - phenylethane (2) as colourless needles (3.52g), m.p. 83 - 87°, followed by a second crop of slightly pink needles (0.61g), m.p. 82 - 84°(lit m.p. 88°).[12]

The remaining liquors were evaporated to dryness yielding a very dark red viscous oil, shown by TLC to be a complex mixture of products and including one component with similar Rf and staining behaviour to the previously isolated orange needles.

Both the orange and the dark red needles melted between 190 and 200° and had similar Rf (0.8 in chloroform) and staining behaviour on TLC: a very bright green spot was obtained on spraying the plate with ceric ammonium nitrate reagent after removal from iodine tank. (Dilute mineral acid alone did not produce this effect). A sample of 1 - benzylidene - 5,6 - dimethoxy - 2 -phenyl - 3 - veratryl indene (11) crystallised from benzene-light petroleum in long orange needles, m.p. 198 - 202°.

TLC	Rf ($CHCl_3$)	: 0.8 (green).
IR	ν max (Nujol), cm^{-1}	: 1600, 1575, 1515, 1255, 1140, 705.
UV	λ max (EtOH), nm (log ε)	: 264 (4.32), 290 (4.24), 346 (4.06).
NMR	See Chapter 4.1.	
MS	476 (100%), 461 (30%), 445 (10%), 429 (40%), 387 (20%), 371 (10%), 355 (10%), 339 (10%), 326 (10%), 315 (10%), 302 (10%), 295 (10%), 238 (20%), 238.5 (5%), 199 (40%), 199.5 (15%), 191.5 (10%), 177.5 (15%), 163 (35%), 156.5 (30%), 151 (30%), 150 (25%), 144.5 (15%),138 (15%), 78 (40%).	
ANAL	Found, % : C, 81.12; H, 5.92; M^+ at m/e 476. $C_{32}H_{28}O_4$ requires C, 80.65 ; H, 5.92; MW 476.	

Ozonolysis of the orange compound(11)

Ozone was passed into a solution of the orange needles (100mg) in ethyl acetate (50ml) cooled in acetone-solid carbon dioxide mixture for 10min. The solution became colourless then blue due to excess ozone, which was subsequently removed by passing dry nitrogen through the solution while allowing to warm to 0°. Following addition of palladium on charcoal (10%, 50mg), the mixture was shaken under an atmosphere of hydrogen for 90min, filtered, and evaporated to yield a slightly yellowish oil. This was dissolved in glacial acetic acid-water (50%, 5ml) and gently warmed and shaken with zinc dust (large excess) for 30min.

Chloroform extraction after filtration yielded a yellowish-green solution, TLC examination of which showed the presence of two main products (Rf's 0.2 and 0.3 in chloroform) staining a characteristic orange-brown with ceric ammonium nitrate reagent on baking, and many other products one of which stained bright red under these conditions. Spraying with any reagent containing dilute mineral acid caused the two major products to appear bright blue in the cold, the colour fading on heating or standing at room temperature. This reaction was not studied further.

Hydrogenation of the orange compound (11)

The orange needles (100mg) in a solution of dry ethanol (3ml) and ethyl acetate (15ml) containing palladium on charcoal (10%, 100mg) were hydrogenated at room temperature and atmospheric pressure for 24hr. The now colourless solution was filtered through glass paper and evaporated to yield the hydrogenation product (14) as a colourless oil (120mg, 100%) which partially crystallised on cooling at 0°. TLC showed one compound of identical Rf to the starting material but staining reddish-pink on spraying with ceric ammonium nitrate reagent after treatment with iodine vapour (cf. starting material: green under these conditions). A sample crystallised from benzene-

light petroleum in small colourless needles, m.p. 168-170°.

TLC Rf ($CHCl_3$) : 0.8 (red).
NMR See Chapter 4.1.
MS 480 (30%), 465 (10%), 449 (10%), 403 (15%), 389 (10%), 374 (10%), 358 (20%), 343 (15%), 311 (15%), 298 (15%), 283 (15%), 251 (30%), 151 (20%), 91 (20%).
ANAL Found, % : C, 80.01; H, 6.75; M^+ at m/e 480.
$C_{32}H_{32}O_4$ requires C, 79.97; H, 6.71; MW 480.

It was noticed that on heating a solution of the compound (e.g. in benzene) or allowing a solution to stand for some time exposed to the atmosphere, a yellowness was produced. TLC showed that the new compound responsible for the colour was more polar than its precursor and stained a characteristic orange-brown on heating after iodine and ceric ammonium nitrate treatment. It was not studied further.

Treatment of the ketone (2) with aluminium chloride

Various small-scale experiments were carried out in which 1-(3,4-dimethoxyphenyl)-1-keto-2-phenylethane (2) was allowed to stand at or below room temperature in ether solution containing different quantities of aluminium chloride for different lengths of time. In a typical experiment where a mixture of ketone (5mg) and aluminium chloride (20mg) in ether (2ml) stood for 4-5 days, the resultant red solution (due to aluminium chloride-ketone complex) was poured into concentrated hydrochloric acid-water (1:1.5) with ice-cooling, and extracted with chloroform. TLC showed no trace of the orange compound, the main product being the unchanged ketone plus a very slight trace of a new more polar colourless compound and some baseline material. The ketone was also largely unaffected by treatment with dilute or concentrated hydrochloric acid at room temperature or on gentle warming, no coloured products being formed.

Chapter 4.3 References

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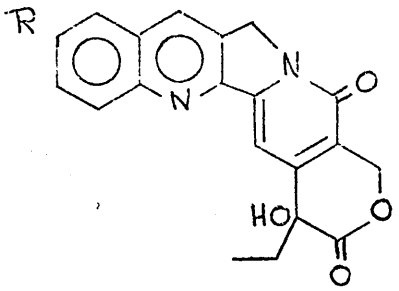
PART III (5)

Synthetic Approaches to Camptothecin



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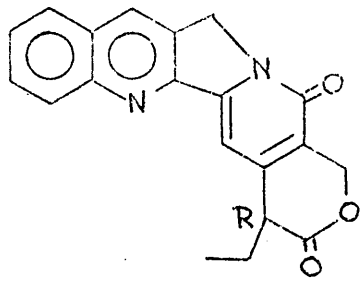
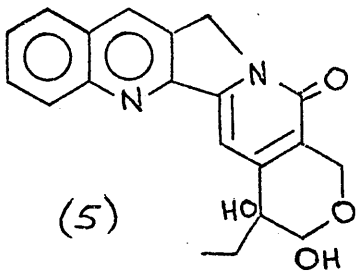


(4) R = $OCOCH_2I$
(6) R = OCOMe
(7) R = Cl
(8) R = H



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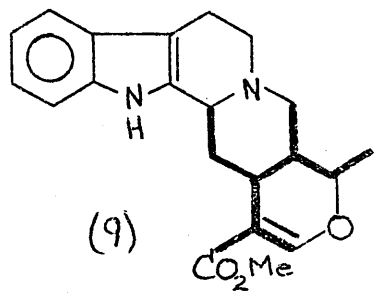

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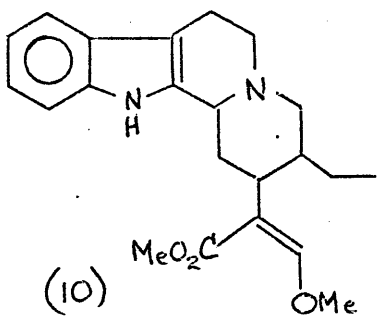

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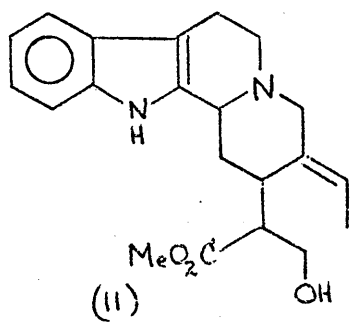

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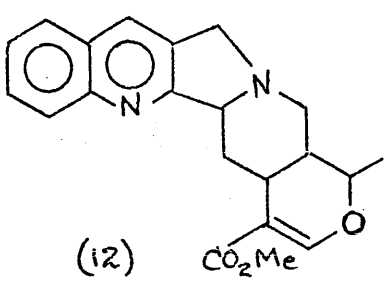

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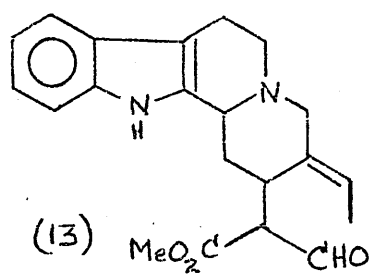

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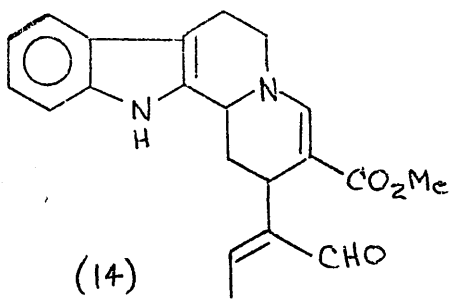

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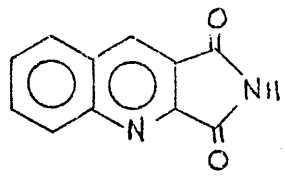

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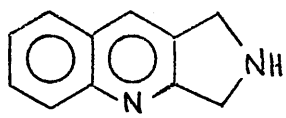

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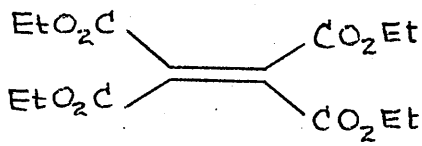

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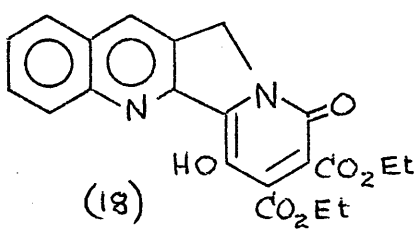

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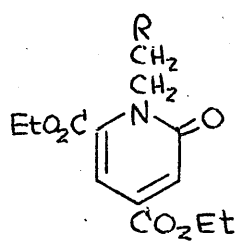

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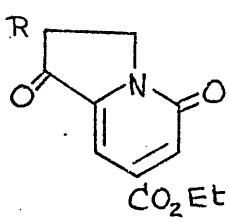

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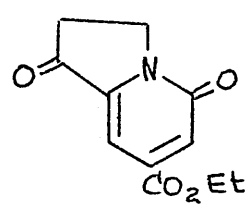
(22) R = CO_2Et



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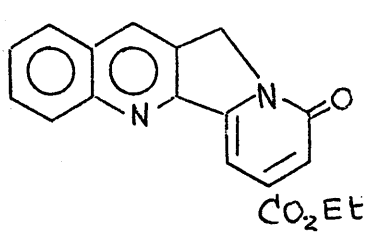

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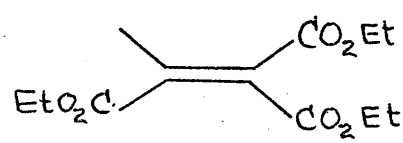

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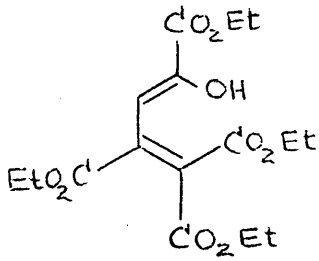

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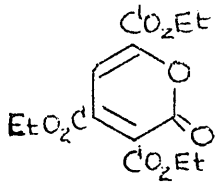

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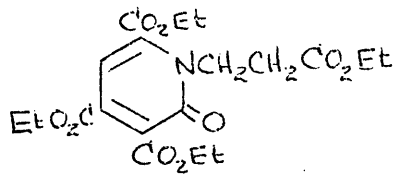

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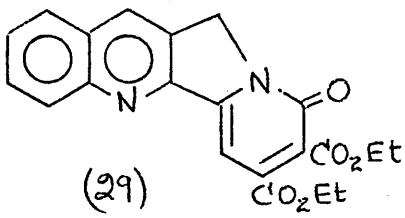

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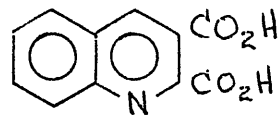

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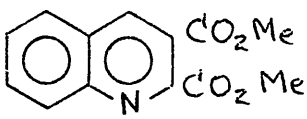

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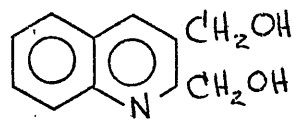

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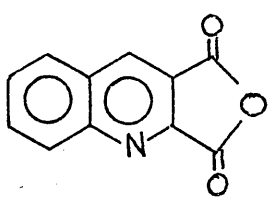

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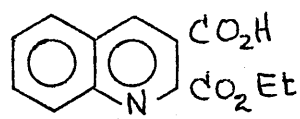

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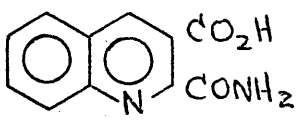

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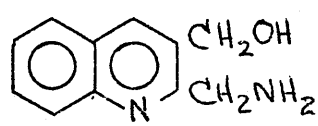

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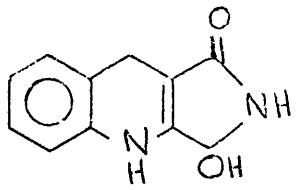

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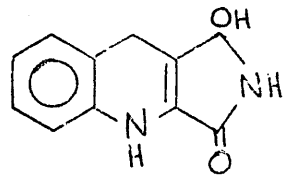

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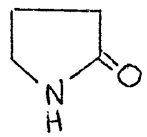

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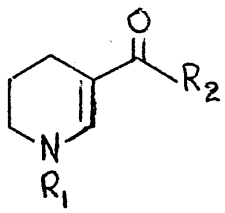

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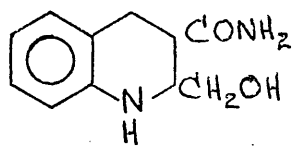
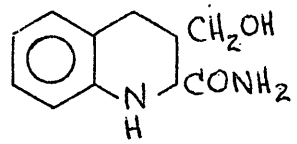


(41) trans
(46) cis



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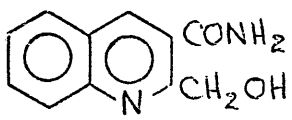

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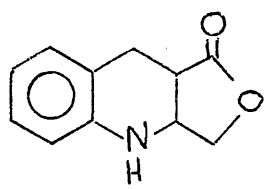

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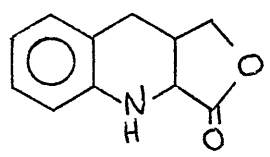
(47) trans



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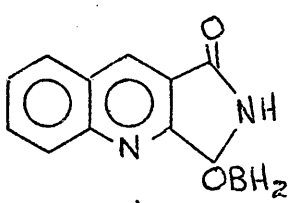

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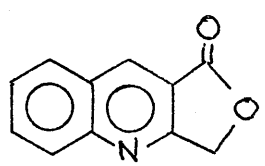

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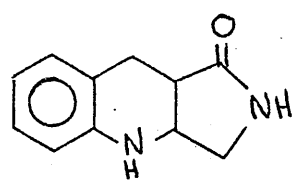

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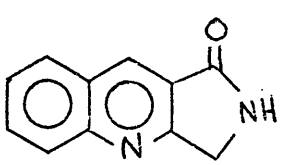

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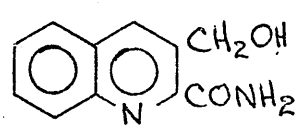

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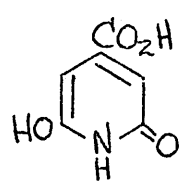

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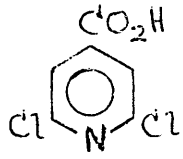

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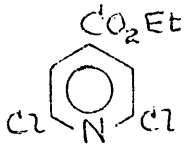

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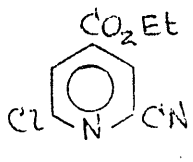

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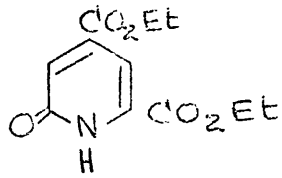

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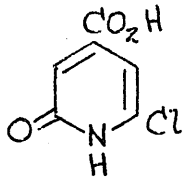

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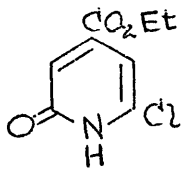

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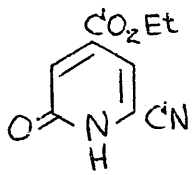

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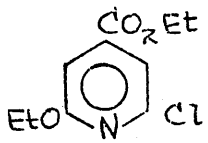

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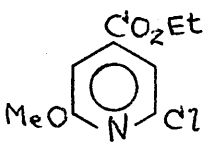

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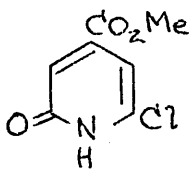

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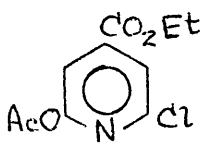

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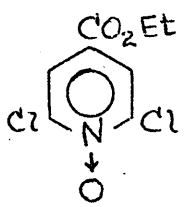

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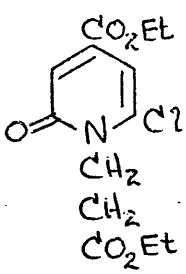

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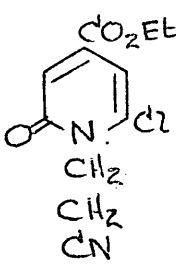

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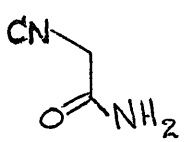

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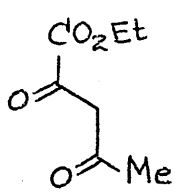

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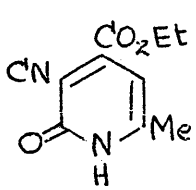

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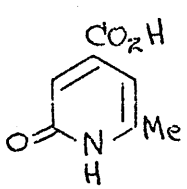

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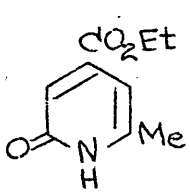

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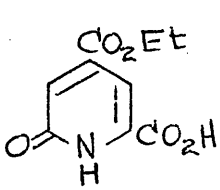

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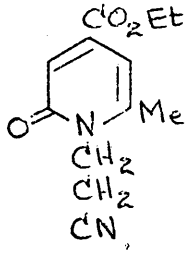

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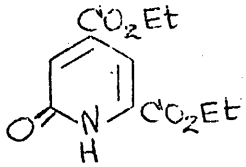

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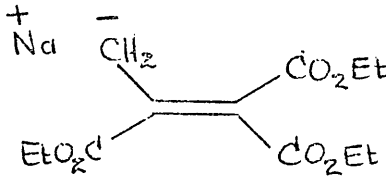

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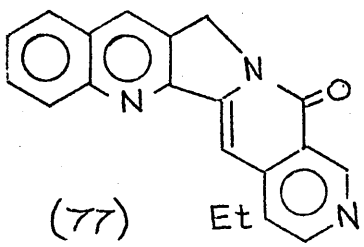

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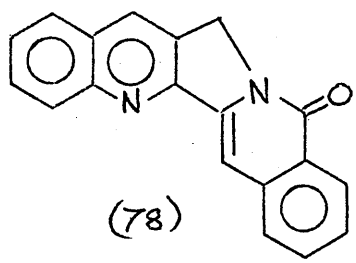

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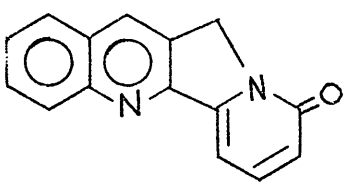

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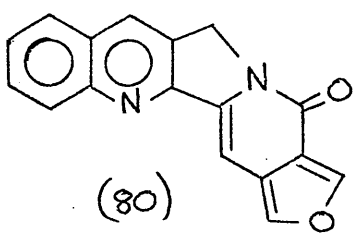

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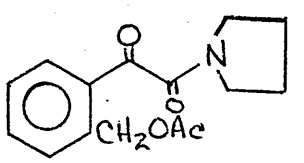

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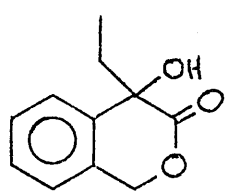

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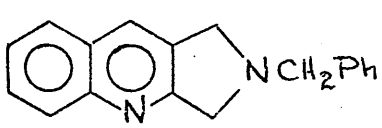

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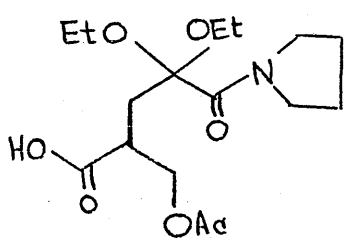

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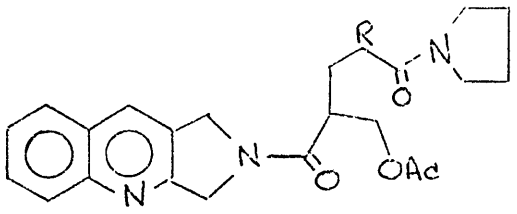
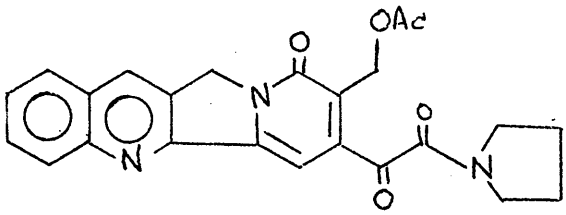


(85) R = $(OEt)_2$

(86) R = =O



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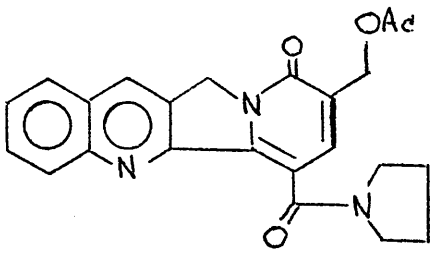

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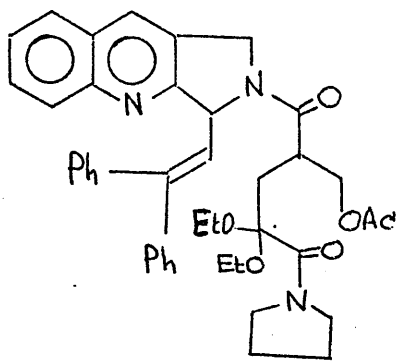

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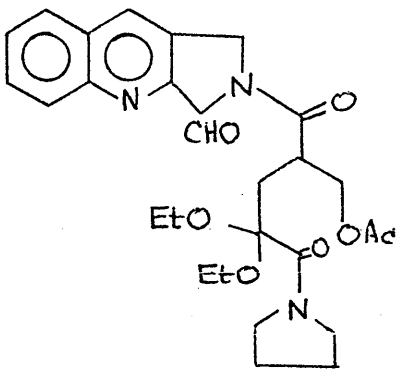

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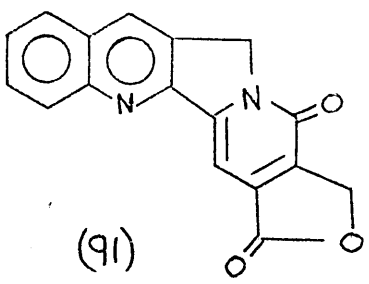

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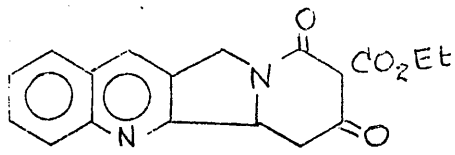

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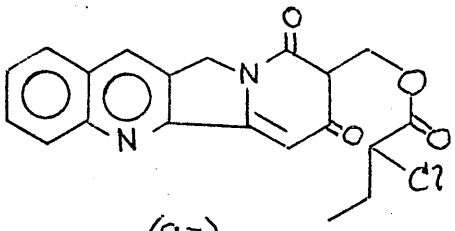

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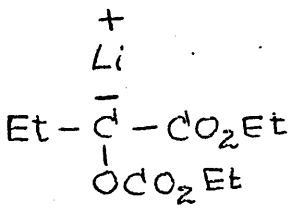

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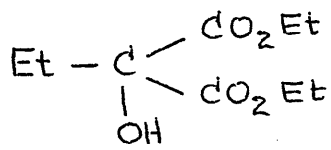

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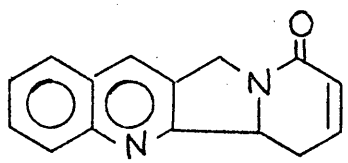

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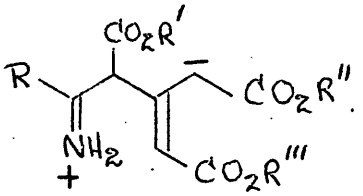

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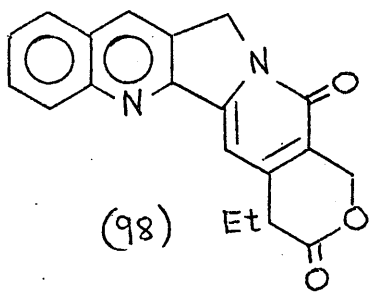

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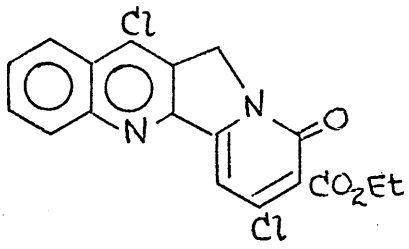

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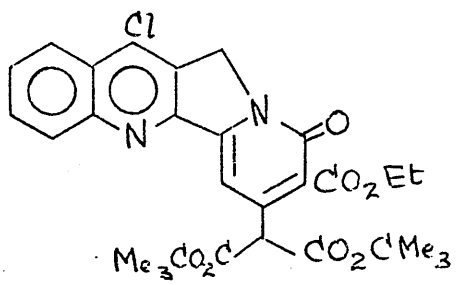

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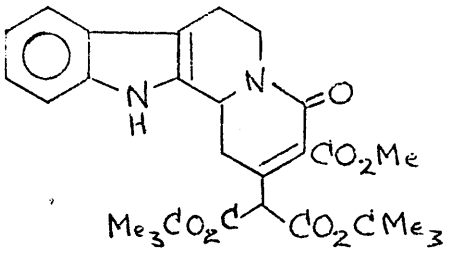

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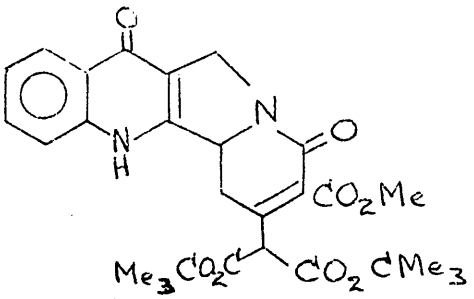

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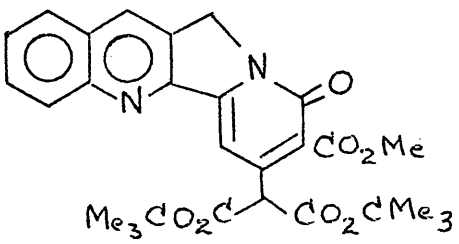

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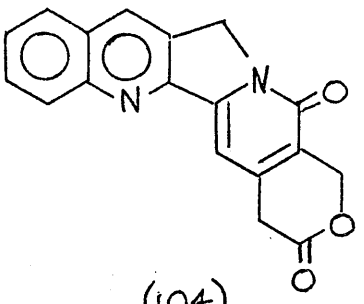

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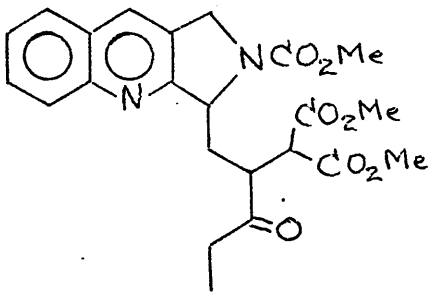

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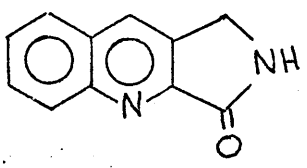
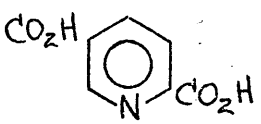


(106)



(107)

Chapter 5.1 Introduction

The search for a satisfactory cure for cancer presents mankind with a challenging and complex problem. The main difficulty associated with this work is that so little is known at a molecular level about the factors causing normal cells to alter their metabolism in such a way as to become malignant. A certain amount of progress albeit so far mostly empirical has however been made, [1] and certain biological, physical and chemical agents have been demonstrated to have a definite effect in this respect: [2,3] the theory that viruses may initiate cancerous growth is supported by cases such as the Rous fowl sarcoma [4,5] where the disease can be transmitted by inoculation with cell-free filtrates; some types of radiation such as X-rays, γ-rays and ultraviolet light exhibit cancer-inducing properties; [2] and the large number of chemical carcinogens is well-known.

Of this latter group may be mentioned particularly polycyclic aromatic hydrocarbons, [6] azo compounds and aromatic amines, [7] which have been known to give rise to cancer among workers using them in industry and elsewhere. Correlations have been made which relate carcinogenic activity to the electronic structure of many of these molecules, "K" and "L" regions being recognised as the active sites. [8] This demonstrates how even the methods of quantum chemistry have been brought to bear on the cancer problem and, incidentally, illustrates the possibility of using the molecular orbital method as a means of understanding the mode of action of biologically-active compounds in general.

Present prophylactic measures include the avoidance of contact with known carcinogenic agents (cigarette-smoking, for example, where certain groups of people appear to be more susceptible than others), while methods of treatment involve surgery, irradiation or chemotherapy. [9] An interesting example of an ancient

custom with a possible scientific basis is that of circumcision: cervical cancer is almost unknown among Jewish women and it has been suggested that among races which do not practise circumcision the cause of cancer in this part of the female body may be related to a constituent of penile smegma, the secretion found beneath the foreskin of the uncircumcised male. [10]

Chemotherapy is now widely regarded as offering most hope for the future as surgery and radiation bombardment cannot be used too often on a patient and are thus of limited application. [9] This method of treatment is complicated, however, by the many different causes and types of effect produced. [11] It is thus more difficult in principle than the treatment of diseases such as tuberculosis, diphtheria and poliomyelitis where the causative factor has been uniquely defined, and the cure depends upon the use of an agent selectively toxic to the invading organism whether it be bacterial or viral in nature, and where immunological methods can be used to supplement or take the place of drugs.

The aim of chemotherapy in cancer is at best the total eradication of malignant cells and at least the control and suppression of their growth. [12] Although complete cures have not yet been achieved, striking instances of tumour regression and control of the disease for periods of up to a few years have been observed with certain agents in some forms of cancer.

Four major classes of chemical compound are known to have activity against cancer: [12] sex hormones, adrenocortical hormones and pituitary hormones; cytotoxic alkylating agents, sometimes called "radiomimetic" due to the similarity of their action to that of X-rays (these can also have carcinogenic properties); [2] anti-metabolites which interfere with metabolic pathways to substances vital to cell growth; and lastly, a group of empirically tested antibiotics showing a wide diversity of chemical structure and often

producing undesirable side-effects. In addition to the more "traditional" sources of this latter group such as fungi and plants, [13] insect and marine specimens are now being studied for the presence of biologically-active compounds, and a number of species from Taiwan including a "horrendous rhinoceros beetle" has been shown to contain substances active against cancer, although none has yet reached clinical trials.[9]

Of the many biologically-active alkaloids which have been isolated from plant sources, one of the most interesting has proved to be camptothecin (1), a stem-wood constituent of the rare tree Camptotheca acuminata (Nyssaceae), native to mainland China. [14] Studied in 1950 for the presence of the steroid hormone cortisone and found to be inactive, [9] an extract of the tree on later examination was shown to possess activity against the tumour Carcinoma 755. [15, 16] This was the basis for further testing and in 1966 isolation and structure-determination of the active principle were reported, in which camptothecin was described as "a novel alkaloidal leukaemia and tumour inhibitor." [17] Recently, two further alkaloids, hydroxy- (2) and methoxycamptothecin (3) have been isolated from the same source and these too have considerable anti-leukaemic activity. [18]

At the time of isolation of camptothecin in 1966 potent activity against lymphoid leukaemia L - 1210 in mice and against the growth of Walker 256 carcinosarcoma (tumour of connective tissue) in rats was demonstrated. [14] In 1970 preliminary clinical trials showed that the drug was responsible for a 60% regression among patients suffering from cancer of the colon, and it was hoped that it might prove of great value in the treatment of cancer of the rectum and intestine. [9] Studies of its mode of action at a molecular level have also made good progress: for example, it has been found that camptothecin inhibits macromolecular synthesis in mammalian cells but not in isolated mitochondria. [19]

FIGURE 5.1–01

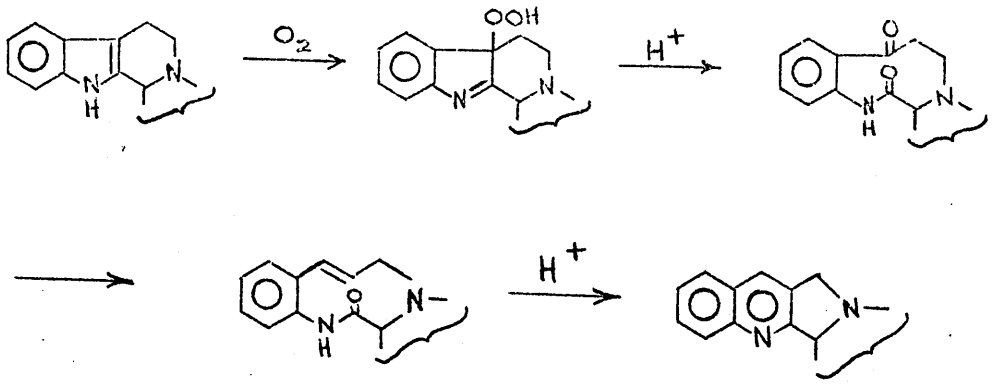
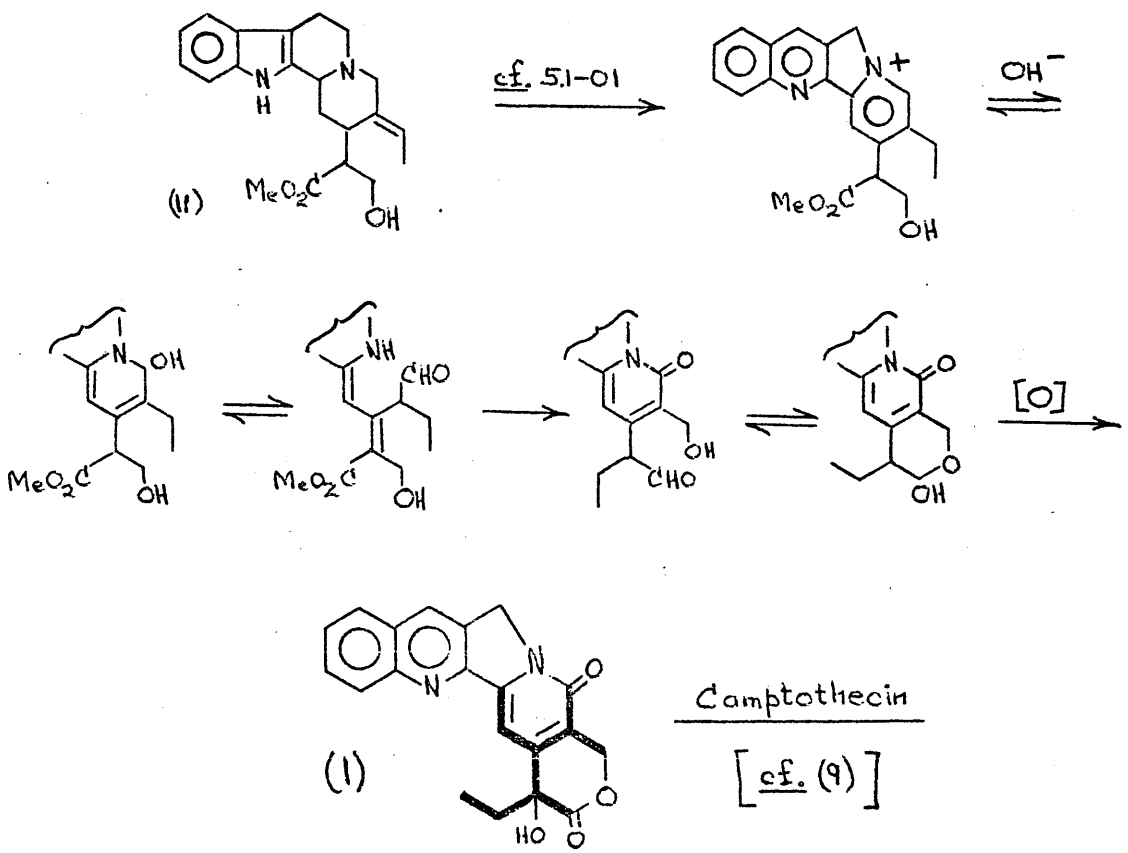


FIGURE 5.1–02



Isolated by silicagel chromatography of methanol-insoluble material from the organic fraction obtained after successive extraction of the stem wood with hot hexane-heptane mixture and hot 95% ethanol followed by partitioning between chloroform and water, camptothecin crystallises from methanol-acetonitrile as pale yellow needles, m.p. 264 - 267° (dec.) [17] Structure determination utilised infrared, ultraviolet and nuclear magnetic resonance spectroscopy, mass spectrometry, and X-ray analysis of the iodo-acetate (4). [17,22] An interesting property of the molecule is the intense blue fluorescence exhibited in ethanol solution (max at 434 nm) under ultraviolet light of wavelength 370nm, [20] and this in fact can be used as a sensitive method for detection of the drug in plasma and urine. [21]

The considerable reactivity of the lactone ring in (1) as shown by immediate sodium salt formation with bases and rapid reduction with sodium borohydride at room temperature to give (5) is believed due to the effect of intramolecular hydrogen bonding on the ring conformation (ν_{max} 3440 cm^{-1}, hydroxyl; and 1760 - 1745 cm^{-1}, lactone), and is closely connected with camptothecin's biological activity. [17, 23, 25] The acetate (6) does not form a sodium salt under the same conditions and in common with the readily prepared (5), (7) and (8) [23] has virtually none of the anti-leukaemic activity of (1) or its sodium salt, [17, 23] also active but highly toxic if administered in large doses. [26]

Camptothecin appears to be of tryptophane-terpene origin, [27, 28] containing (supposedly) the same ten-carbon moiety shown to be of terpenoidal origin in the indole alkaloids such as ajmalicine (9) . [18, 29] Figures 5.1 - 01 and 5.1 - 02 have been proposed for the probable main features of camptothecin's biogenesis. [27] The molecule is here regarded as being a masked indole alkaloid of the corynantheidine (10) type with isositsirikine (11) as a possible precursor. With reference to Figure 5.1-01, an interesting conversion of ajmalicine (9) to a pyrroloquinoline (12) <u>in vitro</u> has been carried out using a high

FIGURE 5.1-03

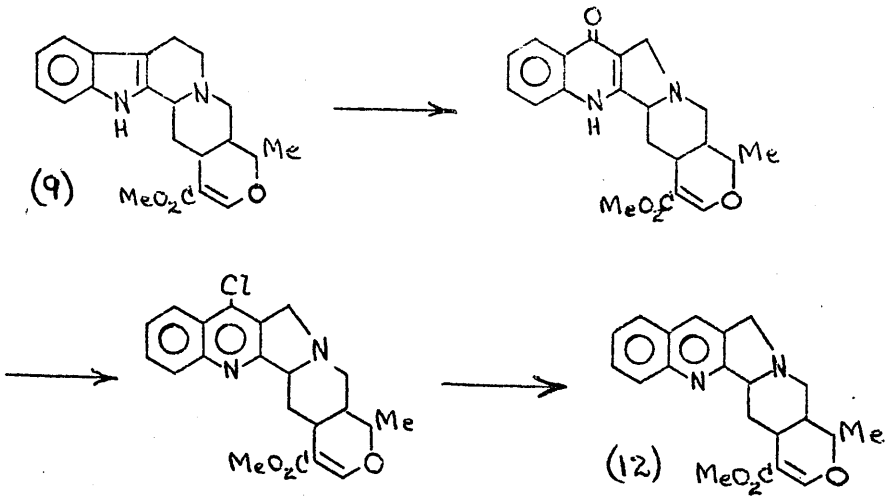


FIGURE 5.1-04

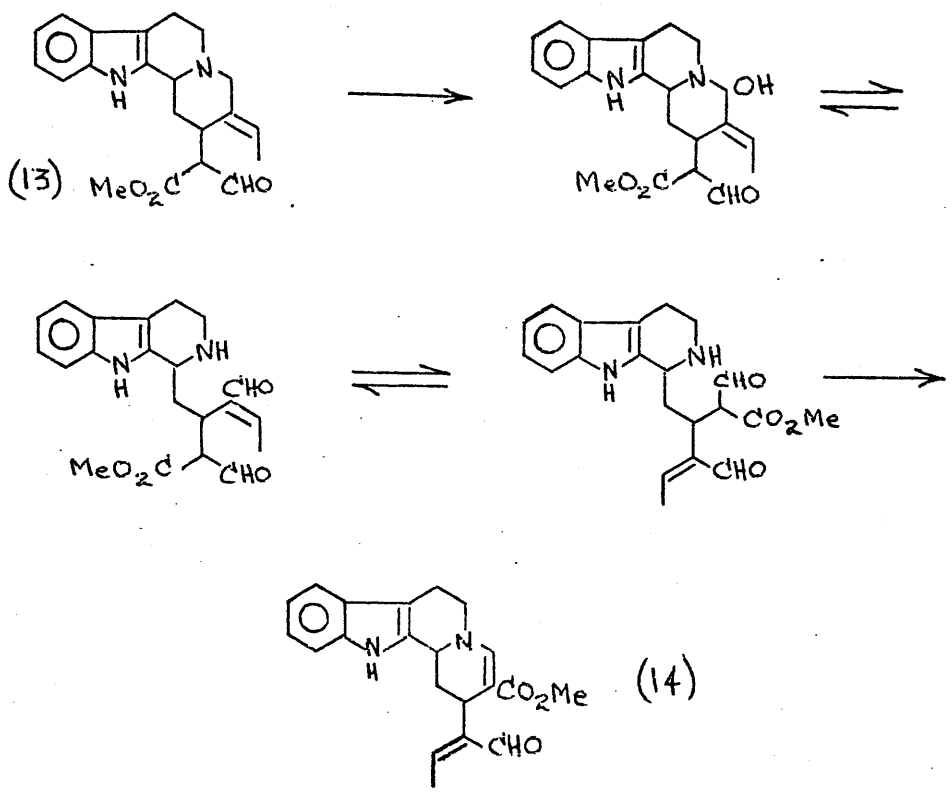
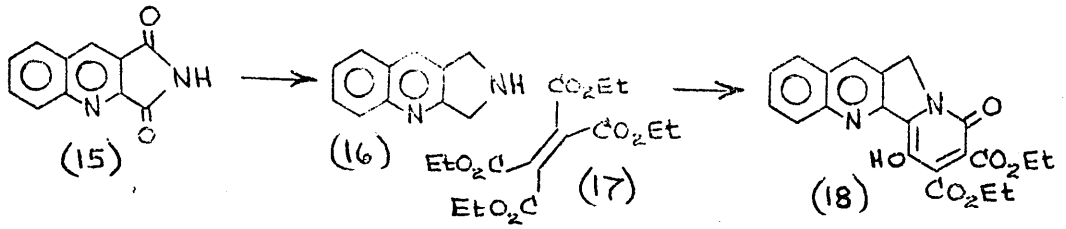


FIGURE 5.1-05



[* OAB = o-amino benzaldehyde in figures below ($C_6H_4(CHO)(NH_2)$)]

FIGURE 5.1-06

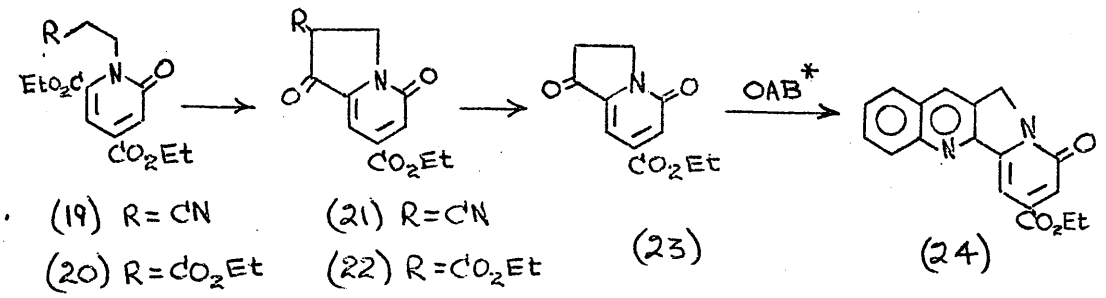
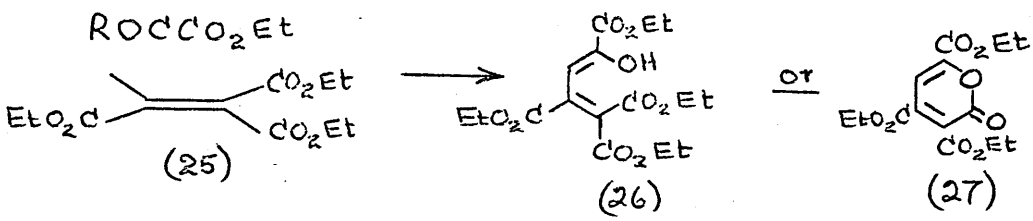
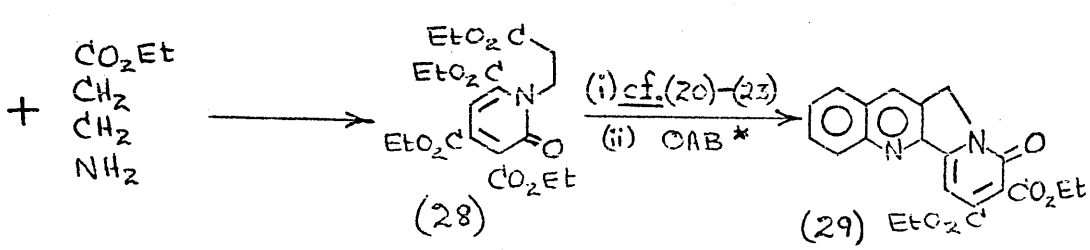


FIGURE 5.1-07



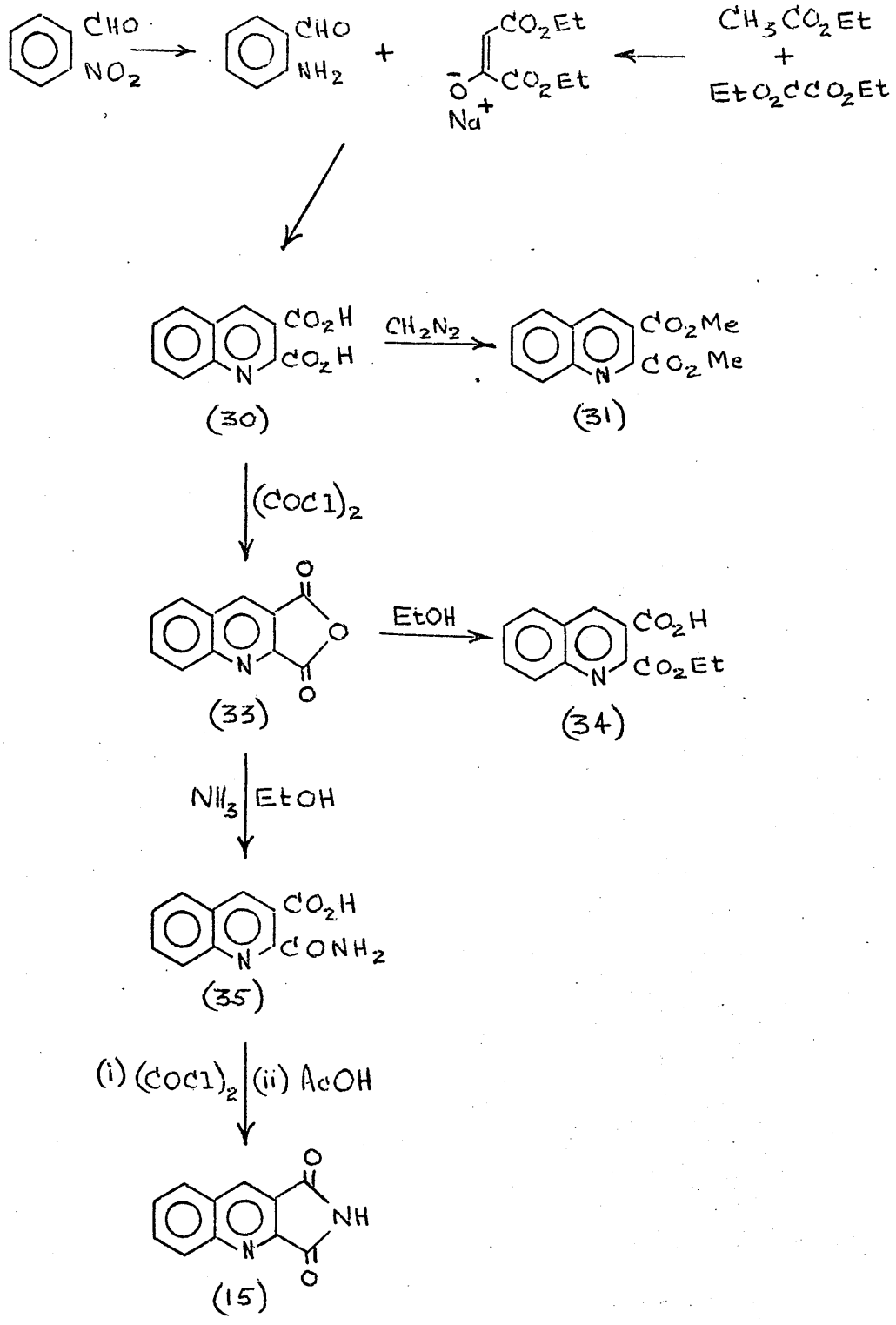


yield (over 90%) autoxidation reaction in the presence of potassium tert-butoxide in dimethylformamide for the first step.[30] Phosphorus oxychloride treatment followed by hydrogenolysis over platinum oxide-acetic acid completed the sequence, shown in Figure 5.1 - 03. (Further development of this approach later led Winterfeldt to a total synthesis of camptothecin : see Chapter 6.2, page 218). A similar type of transformation to that depicted in Figure 5.1- 02 has been proposed for the biogenesis of vallesia-chotamine (14) from a precursor of the geissoschizine (13) type, shown in Figure 5.1 - 04.[31]

The scarcity of Camptotheca acuminata (only a few trees being known outside China - in Taiwan, Hawaii and California) coupled with the lengthy isolation procedure necessary to obtain the active principle (3000 pounds of ground tree affording 10 ounces of camptothecin after a 12 -stage, 6-monthlong extraction process) make a synthesis of the drug all the more desirable, although a vigorous tree-planting campaign is currently being carried out at the U. S. Plant Introduction Centre in California where the tree grows to a height of 12 feet in 2 years.[9,14]

In the present work Figures 5.1-05, 5.1-06 and 5.1-07 denote pathways which were studied with a view to synthesizing compounds (18), (24) and (29), potentially capable of further elaboration towards the camptothecin structure. Although the pyrroloquinoline (16)[24] (Figure 5.1-05) was not obtained cf.[32] the results of the reduction of acridinic acid imide (15) and similar compounds with sodium borohydride and other reducing agents along with some of the chemistry of the products formed will be described. Various routes to compounds(19) and (20) (Figure 5.1-06) were explored and some of these are included here together with a brief account of preliminary approaches to compounds (26) and (27) (Figure 5.1-07). Although these synthetic studies did not lead to the camptothecin skeleton, their relevance in the light of work of other groups will be made clear.

FIGURE 5.2-01


CHO
NO2
CHO
NH2
+
CO2Et
CO2Et
O
Na+
CH3CO2Et
+
EtO2CCO2Et
CO2H
CO2H
N
(30)
CH2N2
CO2Me
CO2Me
N
(31)
(COCl)2
O
O
O
N
O
(33)
EtOH
CO2H
CO2Et
N
(34)
NH3
EtOH
CO2H
CONH2
N
(35)
(i) (COCl)2
(ii) AcOH
O
NH
O
N
O
(15)

Chapter 5.2

Routes involving quinoline carboxylic acid derivatives

The first approach towards a total synthesis of camptothecin (cf. Figure 5.1-05, page 176) required the preparation of the tricyclic amine (16) followed by reaction with tetracarbethoxyethylene (17). It was believed that the secondary amino group would condense with one ester substituent while the active methylene group condensed with a second (cf. reactions of picoline derivatives) [33] forming the tetracyclic species (18).

Attempts were made to provide a synthesis of amine (16) by reduction of the imide (15) of acridinic acid (30). The latter was prepared as shown in Figure 5.2-01, the route being substantially that employed by Hozer and von Niementowski [34] except for the introduction of oxalyl chloride which was found to be more convenient for obtaining good yields of anhydride (33) and imide (15) than the reported methods.

Treatment of the imide with lithium aluminium hydride or diborane resulted in the formation of complex mixtures of products (as was also the case when similar reductions were attempted on the anhydride (33), acid amide (35) or more soluble dimethyl ester (31)). However from reactions involving sodium borohydride, four new colourless crystalline imide reduction products were isolated, employing "constant extraction" procedures followed by careful fractional crystallisation. These compounds will be referred to in the first instance as A, B, C and D, this being the order in which they were obtained.

Compound A (Rf 0.2 in 10% methanol-chloroform) proved to be rather unstable, affording variable analytical results on repeated crystallisation from ethanol. However, the presence of an abundant molecular ion at m/e 202 indicated that this was a tetrahydro derivative, $C_{11}H_{10}N_2O_2$, of acridinimide. Reduction of one of the imide carbonyl groups was indicated by infrared absorption at 3340cm^{-1} (believed to be O-H stretch) cf. [35] and the existence of the remaining amide grouping was confirmed by absorption at 3220cm^{-1} (N-H stretch) and bands at 1660 and 1625cm^{-1}. [36]

Two structures (37) and (38) were suggested by the presence in the NMR spectrum of a sharp 2- proton singlet at 6.40 τ attributable to a benzylic methylene group lacking vicinal protons. A 1- proton doublet at 4.65 τ (J= 10Hz) was assigned to the only methine proton since on addition of D_2O this collapsed to a sharp singlet. The hydroxyl proton resonated at 3.80 τ (d, J= 10Hz) and the amide proton at 2.54 τ (cf. 2- pyrrolidone (39), N-H at 2.33 τ).[37] Slight coupling of the latter to the methine proton might be inferred by slight broadening of the appropriate signals. The resonance of the amino proton appeared as a sharp singlet at 0.75 τ, also disappearing on addition of D_2O. This low value possibly favours structure (37) in which the N-H is part of a vinylogous amide system.[38] Homoallylic coupling of the benzylic methylene group could not be detected but no conclusion could be drawn from this.

However (37) is indeed considered to be the most likely structure because of the probable mode of reduction of acridinic acid imide (15) : while it is known that an enamine grouping conjugated to a carbonyl group as in structure (40) may be fairly resistant to further reduction,[32, 39] it would seem probable that a structure such as (38) would be susceptible to further attack by borohydride. The apparent reduction of the 2- carbonyl group in preference to the 3- carbonyl group is in keeping with their probable reactivities to nucleophilic attack: the 2- position is under the influence of the strongly electron - withdrawing "imino" function in the quinoline ring and is therefore more susceptible to borohydride attack (cf. formation of (34) and (35) from (33), Figure 5.2 -01).

Compound B, which co-crystallised initially with compound C, was of similar polarity to compound A (Rf 0.2 in 10% methanol - chloroform). Elemental analysis and mass spectroscopy indicated that this was an octahydro derivative, $C_{11}H_{14}N_2O_2$, of acridinimide. In accord with the presence of an amide function strong absorption appeared at 1665 cm^{-1} and several peaks between 3170

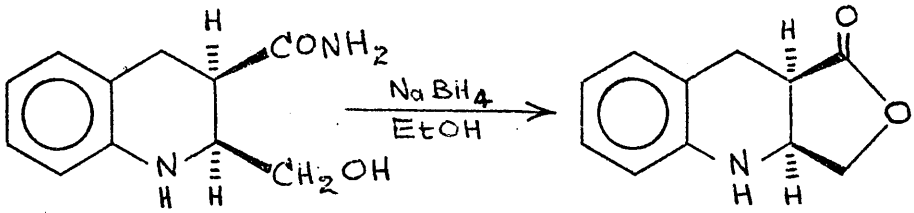
and 3530 cm^{-1} confirmed the existence of NH and OH groupings, the multiplicity suggesting that some hydrogen bonding was present.

Of the two structures (41) and (42) suggested by this evidence, the latter could be dismissed on the basis of the NMR spectrum which showed between 5 and 6 τ only a broad singlet which was exchangeable with D_2O and was attributed to OH. An α - amino acid amide methine proton such as that present in structure (42) would have been expected to appear as a doublet in the 5-6 τ region in the deuterated spectrum. cf.[40] The NMR data (as shown in Figure 5.2-03, page 184) can indeed all be appropriately assigned on the basis of structure (41).

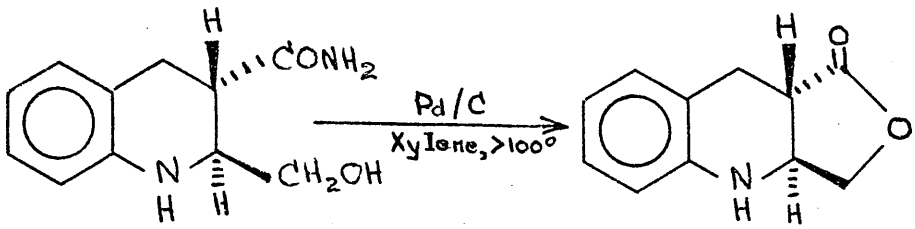
Compound C, only separable from compound B after several fractional crystallisations (Rf 0.6 in 10% methanol-chloroform) proved from analysis and mass spectroscopy to be a second tetrahydro derivative of acridinimide. The ultraviolet spectrum (λ_{max} at 211, 236, 287 and 319nm) suggested that the quinoline ring system was probably intact [41] (contrast UV of compound A : λ_{max} at 227, 231, 240 and 335 nm), a conclusion supported by the presence in the NMR of a sharp non- exchangeable 1- proton singlet at 1.33 τ, ascribed to H_4 of the quinoline ring. The very low value of this resonance also suggested that the carbonyl grouping in the 3- position had survived the reduction (cf. H_4 resonance in quinoline itself at about 2 τ [42] and in acridinic acid dimethyl ester (31) at 0.94 τ), the presence of an aromatic amide grouping being corroborated by infrared absorption at 1630 and 1690 cm^{-1}. This data alone pointed to structure (43) for compound C. Supporting evidence of the hydroxyl and amide groupings was provided by infrared absorption at 3440, 3250 and 3170 cm^{-1}, and by exchangeable protons at 1.6 - 1.8 τ (2H, amide) and 4.54 τ (1H, hydroxyl group) in the NMR.

The fourth product to be isolated, compound D (Rf 0.8 in 10% methanol - chloroform) had molecular weight 189 (with corresponding parent ion in mass spectrum) and molecular formula $C_{11}H_{11}NO_2$ (satisfactory elemental analysis). The fact that this formula corresponds to that of the octahydro compound B less one nitrogen atom and 3 hydrogen atoms and the presence of infrared absorption at

FIGURE 5.2-02



B' (46) D (44)



B (41) E (47)

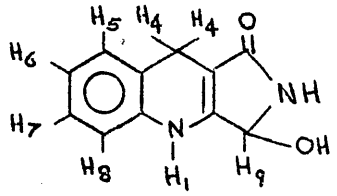
1750 cm $^{-1}$ suggested that lactonisation of an alcohol amide had probably occurred. The NMR spectrum was in accord with this finding, only one exchangeable proton being evident, and suggested structure (44). An alternative structure (45) was rejected on the basis that the 1- proton resonance centred at 5.62 τ, attributed to the proton vicinal to NH, appeared as a multiplet rather than a doublet even after deuteration. The low value of this resonance, assuming structure (44), is partially due to the deshielding effects normal at the β-position of a γ-lactone. [37]

In view of the above assignment, possible interrelation with compound B (41) by elimination of ammonia from the latter was of some interest, and lactonisation was achieved inadvertantly during attempted dehydrogenation of B using palladium charcoal in boiling xylene. This however afforded lactone E (ν_{max} 1740 cm $^{-1}$), m.p. 180 - 190°, isomeric with and slightly more polar than lactone D, m.p. 155 - 157°.

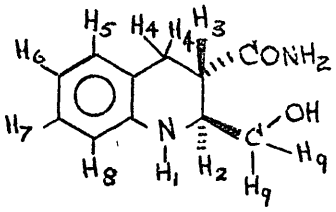
If the structural assignments for hydroxyamide B (41) and lactone D (44) are correct then the lactone E must be a stereoisomer rather than a structural isomer of D. It is tempting to assign the cis configuration to lactone D since this is obtained directly from the borohydride reduction of acridinimide (15) presumably by in situ facile cyclisation of the cis- hydroxyamide B′ (46). B would thus be the trans isomer, which would be stable under the mildly basic reduction conditions, but might lose ammonia in boiling xylene to form the more strained trans-lactone E (47) (cf. Figure 5.2- 02).

The fact that the tetrahydro derivatives A (37) and C (43) are both obtained suggests that primary attack by borohydride is at the imide carbonyl group α to the quinoline C = N moiety, probably giving a "dihydro" intermediate such as (48) which can undergo further reduction to give A or C. The orientation (assigned on spectroscopic evidence) of the residual carbonyl group in the more highly reduced hydroxyamide B (41) and lactone D (44) is also in keeping with initial reduction of the above type. However, careful monitoring of the borohydride reduction

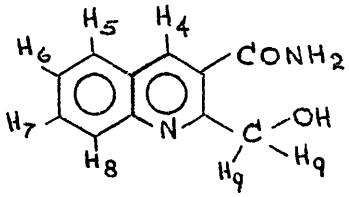
FIGURE 5.2-03



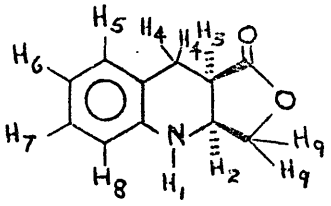
A (37)



B (41)



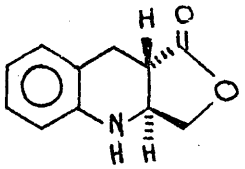
C (43)



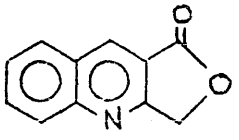
D (44)

τ (100 MHz, DMSO-D_6):

Proton	Compound A	B	C	D
NH	0·75	4·59	—	4·16
H_2	—	6·4-6·7	—	5·62
H_3	—	7·4-7·7	—	6·7-6·9
H_4	6·40	7·1-7·3	1·33	7·12
H_5	2·8-3·2	3·0-3·2	1·7-2·4	2·9-3·2
H_6	2·8-3·2	3·3-3·6	1·7-2·4	3·4-3·6
H_7	2·8-3·2	3·0-3·2	1·7-2·4	2·9-3·2
H_8	2·8-3·2	3·3-3·6	1·7-2·4	3·4-3·6
H_9	4·65	6·4-6·7	4·98	5·85
CONH	2·54	2·55 / 3·0-3·2	1·6-1·8	—
OH	3·80	5·2-5·3	4·54	—



E (47)



F (49)

and further treatment of isolated products, etc., would be required to give a more definite picture of the ease and order of reduction at the different sites in acridinic acid imide (15). Borohydride reduction of simple imides has previously been observed to give lactamols, hydroxy-amides and lactones, [35,43] and the reported behaviour of phthalimide under these conditions [44] was confirmed in the present work as a preliminary study.

Since the yields of the different compounds A, B, C and D obtainable from the borohydride reduction were all less than 10% (e.g. roughly 3% in the case of C), this appeared to offer little encouragement towards the intended route to camptothecin. If however the mixture instead of being submitted to a lengthy separation procedure could all be converted by dehydrogenation to e.g. the same lactone F (49) then workable amounts of intermediate might be obtained. Indeed dehydrogenation of lactone D afforded the aromatic lactone F in good yield on refluxing with palladium charcoal in diphenyl ether. When the unpurified product from one borohydride reduction mixture was treated similarly, crude product was obtained which appeared instead to contain the lactam (51) (molecular ion at m/e 184 and ν_{max} at 1695cm^{-1}), cf.[32,45] but as the yield again was considerably less than 10% this route was not investigated further.

For reference purposes, structures of compounds A to F and NMR spectra of A to D are illustrated opposite (Figure 5.2-03).

FIGURE 5.3-01

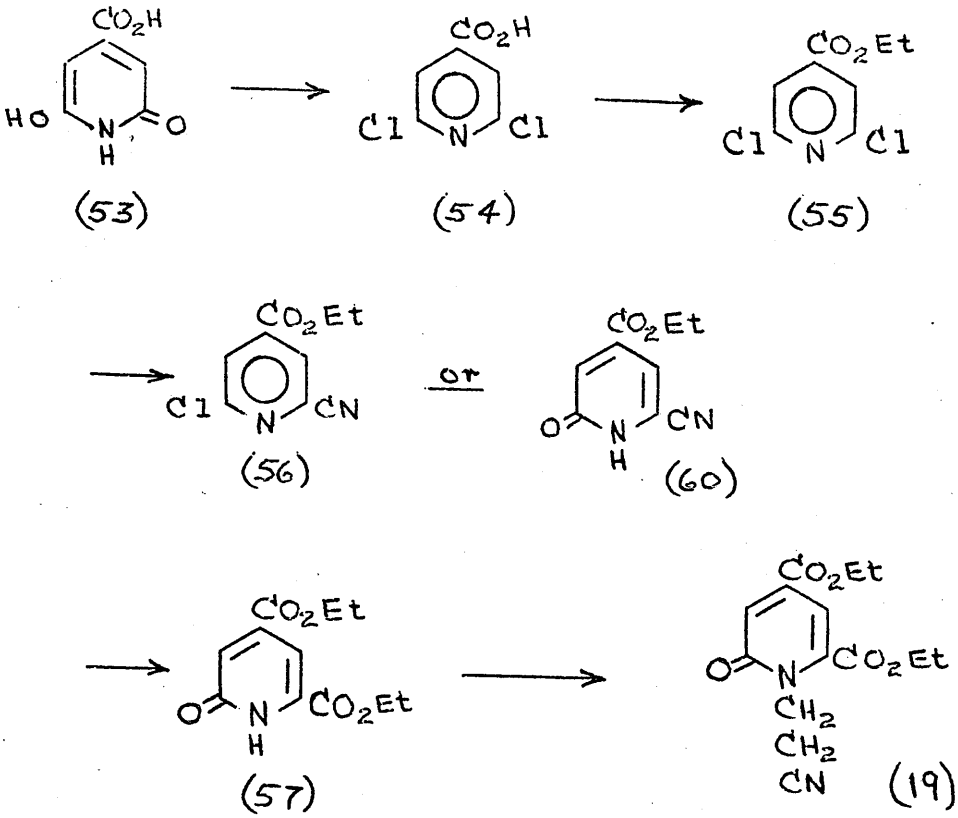
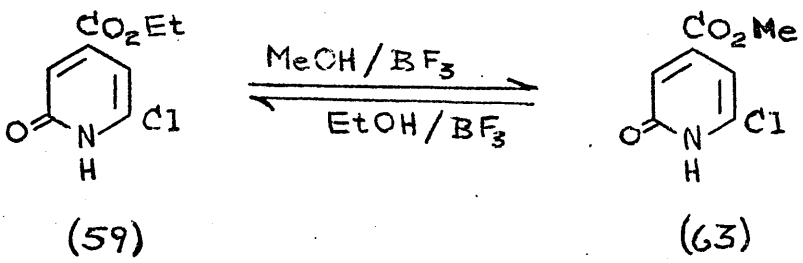


FIGURE 5.3-02



Chapter 5.3 Routes involving pyridone derivatives

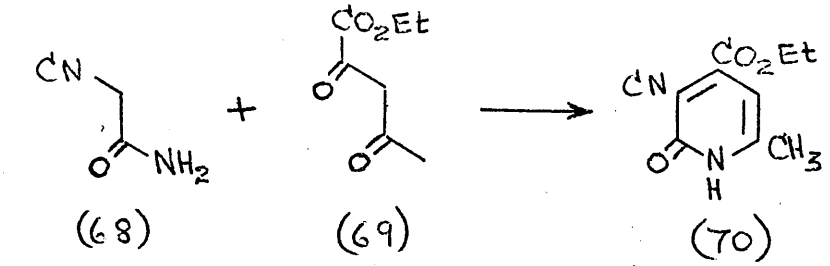
The immediate objective in the second synthetic approach to camptothecin was the tetracyclic compound (24) (as shown in Figure 5.1 -06, page 176). It was envisaged that this should be readily available from the pyridones (21) or (22) by conversion to (23) and Friedländer condensation [46] with o- amino benzaldehyde. It was anticipated that base - catalysed condensation of (19) or (20) would yield the required bicyclic type of compound (21),(22) and attention was therefore focused on a convenient preparation of either of these intermediates.

The first route attempted is outlined in Figure 5.3-01. At least two methods have been described for the conversion of citrazinic acid (53) to the dichloro derivative (54) (see below), and (following esterification) it was hoped that one of the chlorine atoms could be replaced by a cyano group. Hydrolysis followed by re-esterification and cyanoethylation would then yield the required pyridone (19).

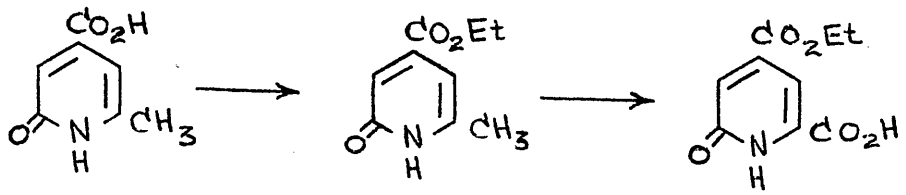
Attempted preparation of (54) by the method of Sell and Dootson involving prolonged heating with phosphorus oxychloride and phosphorus pentachloride [47] furnished moderate yields of the monochloro pyridone (58), only very little of the dichloro derivative (the alleged main product) being detected. The monochloro compound was esterified and the product (59) treated with potassium cyanide or cuprous cyanide in N- methyl- 2- pyrrolidone, [48] but cyano pyridone (60) was not isolated from these reactions.

In an attempt to form the alkoxy derivatives (61) and (62), which it was believed might be more reactive to nucleophilic attack by cyanide ion , the pyridone (59) was treated with triethyloxonium fluoroborate [49] and with boron trifluoride in methanol. Only in the latter case did a reaction take place, the sole product being the methyl ester (63), formed in high yield. This product can be simply explained by reference to the probable existence of a boron trifluoride - catalysed equilibrium as shown in Figure 5.3-02. With a large excess of methanol, as in the present case, the equilibium would lie very much to the right, and the met hyl ester would thus constitute almost all of the product.

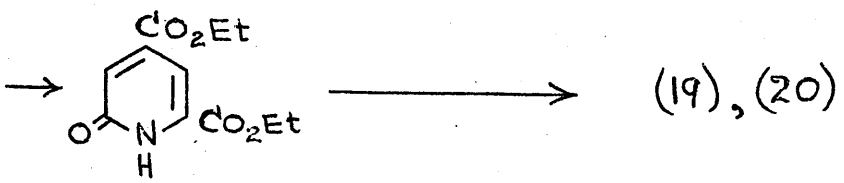
FIGURE 5.3-03



(68) (69) (70)



(71) (72) (73)



(75)

With acetic anhydride, the pyridone (59) was smoothly acetylated on oxygen to give the relatively volatile acetate (64). However, no attempt was made to react this with cyanide ion as it now appeared that the dichloropyridine (55) could be conveniently prepared by treatment of the acid (53) with phenyl phosphonic dichloride ($PhPOCl_2$) [50] followed by esterification with ethanolic hydrogen chloride. Treatment of this product (55) with methanolic potassium cyanide or sodium or cuprous cyanide in N - methyl - 2 - pyrrolidone yielded either the unreacted dichloropyridine or monochloropyridone (59), but no trace of a cyanopyridine.

The dichloropyridine was now converted to the 1-oxide (65) by reaction with hydrogen peroxide in trifluoroacetic acid cf. [51] in a further effort to increase the reactivity of such a system to nucleophilic substitution. [52] Again, however, no cyanopyridine resulted from treatment with cuprous cyanide in N - methyl - 2 - pyrrolidone, the only product to be isolated being the monochloro pyridone (59). The reaction mixture exhibited a strong odour resembling that of garlic : this is known to be characteristic of isonitriles ($R - \overset{+}{N}\equiv\overset{-}{C}$) [53] and it seems probable that a product of this type may have been formed, albeit in small yield.

As a result of the difficulties experienced in the above studies, the alternative route shown in Figure 5.3-03 was also investigated. This involves the pyridone (71) which is available by condensation of cyanoacetamide (68) with ethyl acetylpyruvate (69), followed by hydrolysis and decarboxylation. [54] Various possibilities were open by means of which conversion tothe products (19) or (20) could be effected. cf. e.g. [55]

In view of the probable sensitivity of an N - cyanoethyl or N - carbethoxyethyl group [56] it was thought that oxidation of the methyl group should preferably be attempted before addition of this 3 - carbon unit was made. However selenium dioxide or chromic acid treatment of the pyridone (72) afforded no isolable oxidation products, complete recovery of unreacted material being made in the former case. Although the pyridone reacted smoothly with acryl-

onitrile under catalysis by sodium hydroxide to yield the cyanoethylated product (74), approaches to compounds (19) and (20) along the lines indicated above were curtailed at this point owing to the appearance in the literature of closely related work [20, 57] (see Chapter 6.1).

Finally some attention was given to the somewhat different approach depicted in Figure 5.1 - 07 (see page 176). The key compound here was to be the tetra-ester (28) which could be converted to (29) by a route similar to that discussed in connection with the previous approach (see page 176). Preparation of (28) depended on the reaction of β - alanine ethyl ester with the product of reaction of diethyl oxalate (or ethyloxalyl chloride) and 1, 1, 2 - tricarbethoxyprop - 1, 2 - ene (25).[59] It was felt that this product could exist either as the open-chain compound (26) or the α - pyrone (27). However, no condensation products were detected during attempts to carry out the first stage of the sequence employing a wide variety of bases and solvents, and no further work in this direction was undertaken.

(Considerable progress has now been made in the field of camptothecin synt hesis, culminating in the first total synthesis by Stork and Schultz. Highlights of recent work are briefly reviewed in an appendix to Part III, Chapters 6.1 and 6.2.)

Chapter 5.4 Experimental (with 5.2)

Acridinic acid anhydride (33)

A solution of acridinic acid (30) (200mg, prepared by Friedländer condensation of o-amino benzaldehyde and sodium diethyl oxaloacetate)[34] in dry benzene (10ml) containing oxalyl chloride (10ml) was refluxed for 3hr. Evaporation yielded acridinic acid anhydride (160mg, 80%) crystallising from xylene in long colourless needles, m.p. 224-228° with sintering from 180° (lit. m.p. 225°).[34]

IR ν_{max} (Nujol), cm^{-1} : 1840, 1765, 1195, 935, 905, 735.

This method was found to be superior to the reported dehydration with acetic anhydride, which afforded a 55% yield.[34]

Acridinic acid imide (15)

A suspension of acridinic acid amide (35) (1g, prepared either via the acid ester (34) and aqueous ammonia in 50% yield or via the anhydride (33) and dry gaseous ammonia in 65% yield)[34] in dry benzene (10ml) containing oxalyl chloride (20ml) was refluxed for 2hr and stirred overnight at room temperature. Evaporation furnished a colourless crystalline solid (1.20g), ν_{max} (Nujol), cm^{-1} : 1800, 1745, 1710, 1300, 805, 785, 775.

Treatment with hot glacial acetic acid converted this intermediate to acridinic acid imide (15), which crystallised in almost colourless needles (0.51g, 55% from acid amide), decomp. ~ 300° (lit. m.p. 314-315° decomp.)[34]

IR ν_{max} (Nujol), cm^{-1} : 3250, 1765, 1710, 1110, 770.
ν_{max} (KBr), cm^{-1} : 3200, 1775, 1765, 1710, 1300, 1110, 765.

ANAL Found, % : C, 66.70; H, 3.25; N, 14.17.
Calc. for $C_{11}H_6N_2O_2$: C, 66.65; H, 3.05; N, 14.14.

Utilisation of the reported method for converting amide to imide with 100% sulphuric acid afforded a much inferior yield of 10 - 15%.[34] Heating acridinic acid

anhydride in molten urea in an alternative approach towards the imide gave only tarry products, while prolonged refluxing of acridinic acid with phosphorus pentachloride in ether [60] failed to yield the di-(acid chloride) which it was hoped might have furnished the imide on treatment with ammonia.

Action of sodium borohydride on the imide (15)

Slow addition of acridinic acid imide (2g) to a slurry of sodium borohydride (0.8g) in dry ethanol (40ml) resulted in an exothermic reaction with evolution of gas, giving a yellow solution. Following ice-cooling to moderate the reaction, the mixture was stirred for 20hr at room temperature, poured into cold water (40ml), partially evaporated to remove some of the ethanol , and constantly extracted with ether for 4 days.

A quantity of a colourless crystalline solid (116mg) suspended at the ether-water interface in the constant extraction flask was obtained as small plates, m.p. 242-246° decomp. Although successive crystallisations from ethanol afforded small colourless needles, great variation in melting point and analysis figures was observed, and it became apparent that decomposition was taking place. The following data refer to the original material, compound A (37).

TLC Rf (10% MeOH -$CHCl_3$) : 0.2(brown).

IR ν_{max} (K Br), cm^{-1} : 3340, 3220, 3100, 3040, 2920, 1660, 1625, 1610, 1530, 1090, 750.

UV λ_{max} (EtOH), nm (log ε) : 203 (4.24), 227 (3.81), 231 (3.82), 240 (3.70), 335 (3.90).

NMR See Chapter 5.2.

MS M^+ at m/e 202; $C_{11}H_{10}N_2O_2$, MW 202.

After standing for 2 days at room temperature, a methanolic solution of the oily yellowish solid (1.84g) resulting from evaporation of the ether extract deposited almost colourless semi-crystalline material (0.60g), shown by TLC (10% methanol-chloroform) to consist of two main products

with Rf's 0.2 (compound B) and 0.6 (compound C). Minor constituents of this two-component mixture were eliminated by rapid crystallisation from benzene-methanol (99: 1), and a solution of the product (200mg) in hot benzene (3ml) containing a few drops of methanol was now allowed to cool very slowly to room temperature. The alcohol amide B (41) (71mg) which separated after 2 days crystallised from ethyl acetate-chloroform-methanol (7:2:1) in small colourless prisms, m.p. 197-200° with sintering from 190°.

TLC Rf (10% MeOH-$CHCl_3$) : 0.2 (brown).

IR ν_{max} (KBr), cm^{-1} : 3530, 3420, 3330, 3260, 3170, 2920, 1665, 1595, 1580, 745.

UV λ_{max} (EtOH), nm (logε) : 208 (4.54), 249 (4.22), 300 (3.64).

N M R See Chapter 5.2.

ANAL Found, % : C,63.91; H, 6.86; N, 13.33; M^+ at m/e 206.
$C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.58; MW 206.

After a further 3 days, the less polar alcohol amide C (43) was obtained (22mg), crystallising from methanol-ethyl acetate (1:4) in small colourless needles, m.p. 193-195°.

TLC Rf (10% MeOH-$CHCl_3$) : 0.6 (brown).

IR ν_{max} (K Br), cm^{-1} : 3440, 3250, 3170, 1690, 1630, 1560, 1010, 780, 750.

UV λ_{max} (EtOH), nm (logε): 211 (4.62), 236 (4.72), 287 (3.46), 319 (3.30).

NMR See Chapter 5.2.

ANAL Found, % : C,65.11; H,4.88; N, 13.66 ; M^+ at m/e 202.
$C_{11}H_{10}N_2O_2$ requires C,65.34; H, 4.98; N, 13.85; MW202.

A third crop of crystalline solid (needles and prisms, 60mg) taken 3 days later was shown by TLC to consist of at least 4 components, and isolation of these was not undertaken.

The methanolic mother liquors from which the crystalline mixture containing alcohol amides B and C was originally obtained, afforded upon evaporation the lactone D (44), crystallising from chloroform-light petroleum (b.p.60-80°) in small colourless prisms (85mg), m.p. 155-157° with sintering from 150°.

TLC Rf (10% MeOH-$CHCl_3$) : 0.8 (brown).

IR ν_{max} (KBr), cm^{-1} : 3380, 1750, 1600, 1580, 980, 740.

NMR See Chapter 5.2.

ANAL Found, % : C, 69.72; H, 5.99; N, 7.28; M^+ at m/e 189.
$C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40; MW189.

Careful chromatographic monitoring of a parallel experiment involving gradual treatment of the imide with an equimolar quantity of borohydride revealed that the alcohol amide B was one of the first products formed in any quantity. This suggested that di- or tetrahydroquinoline derivatives would be produced even if a shorter reaction time were employed.

Attempted conversion of alcohol amides B and C to lactams (50) and (51)

Before separation of B from C had been achieved, the mixture was treated with various dehydrating agents (e.g. thionyl chloride-pyridine, tosyl chloride-pyridine, trifluoroacetic anhydride) in the hope that a mixture of lactams would result which would be capable of further elaboration towards the amine (16). However complex mixtures of products were invariably produced and this approach was not investigated further (although it is reported that concentrated sulphuric acid has been used successfully for this type of transformation).[61]

Lactone E (47)

A solution of alcohol amide B (41) (12mg) in xylene (3ml) containing palladium on charcoal (10%, 12mg) was refluxed under nitrogen for 20hr. After removal of catalyst, evaporation yielded the lactone E (47), crystallising from ethyl acetate-light petroleum in very small colourless needles (7mg, 65%), m.p. 180 - 190° with sintering from 160° .

TLC Rf (10% MeOH-$CHCl_3$) : 0.7 (brown).

IR ν_{max} (K Br), cm^{-1} : 3330, 3300, 1740, 1660, 980, 740, 730.

UV λ_{max} (EtOH), nm (log ε) : 207 (3.94), 238 (3.86), 291 (3.08).

ANAL Found, % : C,69.78; H, 5.77; N, 7.53; M^+ at m/e 189.

$C_{11}H_{11}NO_2$ requires C, 69.83; H, 5.86; N, 7.40; MW 189.

Lactone F (49)

A solution of lactone D (44) (20mg) in diphenyl ether (2ml) containing palladium on charcoal (10%, 40mg) was refluxed under nitrogen for 3hr 30 min. After filtration through glass paper, light petroleum (20ml) was added and the solution set aside at 0°. After 7 days the resulting crystalline product (5mg, m.p. 210-215°) was removed, washed with light petroleum (2 x 10ml portions) and dissolved in hot methanol. The lactone F (49) crystallised on cooling in small flat plates (3mg, 15%), m.p. 175-185° decomp.

TLC Rf (10% MeOH-$CHCl_3$) : 0.8 (greyish brown).

IR ν_{max} (Nujol), cm^{-1} : 1745; no absorption in "N-H stretch" region (3000-4000cm^{-1})

MS M^+ at m/e 185; $C_{11}H_7NO_2$, MW 185.

Attempted total conversion of crude imide-borohydride reaction mixture to lactone (49) or lactam (51)

A solution in xylene (10ml) containing palladium on charcoal (10%, 160mg) of a portion (130 mg) of crude product obtained from constant ether extraction of the reaction mixture resulting from treatment of acridinic acid imide with sodium borohydride was refluxed for 24 hr under nitrogen. Removal of catalyst followed by evaporation afforded an almost colourless mixture of products (63mg), a methanolic solution of which deposited colourless needles (2mg) with no definite m.p. (decomp. ~260°), possibly containing some lactam (51). cf. 32, 45

TLC Rf (10% MeOH-$CHCl_3$) : 0.4 (grey).

IR ν_{max} (K Br), cm^{-1} : 3180, 3060, 1715, 1695, 1635, 1415, 1235, 790.

MS M^+ at m/e 184 ; $C_{11}H_8N_2O$, MW184.

Acridinic acid dimethyl ester (31)

Treatment of acridinic acid (30) with excess diazomethane in ether-methanol was found to be a more

convenient method for preparation of the dimethyl ester (over 90% yield) than those previously reported.[34] The ester crystallised from methanol in colourless prisms, m.p. 107-108°. cf[34]

TLC	Rf (10% MeOH-$CHCl_3$)	: 0.9 (greyish brown).
IR	ν_{max} (Nujol), cm^{-1}	: 1725, 1715, 1290, 1265, 1055, 810.
NMR	60MHz (DMSO), τ	: 0.94 (1H, s, H_4), 1.7-2.3 (4H, m, H_5-H_8), 5.97 (3H, s, 2-CO_2CH_3), 5.99 (3H, s, 3-CO_2CH_3).

Action of reducing agents ($LiAlH_4$, $NaBH_4$, B_2H_6) on acridinic acid derivatives

As with the sodium borohydride reduction described earlier, it was originally hoped in these reactions that the amine (16) or even intermediate lactams such as (51) could perhaps be obtained from the imide (15); the diol (32) from the anhydride (33) or more soluble dimethyl-ester (31); and the amino alcohol (36) from the acid amide (35). Mixtures of products (usually complex) were obtained in all cases, however, despite the variety of conditions of solvent and temperature, etc., under which the reactions were attempted. Moreover, means of isolating the products were severely limited due to the difficulty experienced in applying the common chromatographic procedures to the separation of these mixtures of highly polar compounds on a preparative scale. (The only product actually isolated in pure condition (2% yield) was from a reaction involving the acid amide (35) and diborane. As this had ν_{max} at 1690cm^{-1} and TLC and MS behaviour (m/e 202) very similar to that of alcohol amide C, perhaps this compound has structure (52)). cf.[45]

Chapter 5.5 Experimental (with 5.3)

4- Carbethoxy - 6 - chloro - 2 - pyridone (59)

Following overnight treatment of 4-carboxy-6-chloro-2- pyridone (58) [47] with ethanolic hydrogen chloride, evaporation furnished the ester (59) in excellent yield, crystallising from ether-light petroleum in colourless needles, m.p. 145° with sintering from 135°.

TLC Rf (5% MeOH-$CHCl_3$) : 0.5 (grey).

IR ν_{max} (Nujol), cm^{-1} : 1735, 1720, 1660, 1620, 1580, 1330, 1265, 785.

NMR 60 MHz ($CDCl_3$), τ : -0.40 (1H, bs, NH), 2.78 and 2.80 (2H, 2d, J= 1Hz, ArH), 5.61 (2H,q,J= 7Hz, CH_2), 8.61 (3H, t, J= 7Hz, CH_3).

ANAL Found, % : C, 47.75; H, 4.04; N, 6.72; M^+ at m/e 201, 203. $C_8H_8NO_3Cl$ requires C, 47.64; H, 3.97; N, 6.95; MW 201, 203.

Attempted preparation of 4- carbethoxy - 6 - cyano - 2 - pyridone (60) : (i)

Unreacted pyridone (59) was recovered following treatment with potassium cyanide or cuprous cyanide in N - methyl - 2 - pyrrolidone at 150- 170°. The latter reaction also yielded an unstable semi-solid product of Rf 0.3 in 10% methanol-chloroform, whose mass spectrum (M^+ at m/e 279) suggested that dimerisation had occurred. In neither case was the cyanopyridone (60) detected.

Attempted preparation of ethyl 4-carbethoxy - 6 - chloro-2 - pyridone - 1 - (β- propionate) (66)

Unreacted pyridone (59) was recovered following treatment with ethyl β - bromopropionate and sodium hydride in toluene. In an attempted preparation of the alternative compound (67) via cyanoethylation of the pyridone (59) with acrylonitrile and sodium hydroxide with or without added dioxane, the pyridone (59) again failed to react (TLC) and was also recoverable from the reaction mixture.

Attempted alkoxylation of the pyridone (59)

Unreacted 4-carbethoxy - chloro - 2 - pyridone (59) was recovered following treatment with triethyloxonium fluoroborate [49] in methylene chloride at room temperature. Ester exchange occurred on reaction with boron trifluoride in refluxing methanol, a high yield of 4 - carbomethoxy - 6-chloro - 2 - pyridone (63) being obtained, which crystallised from ether in colourless needles, m.p. 190° with sintering from 135°.

TLC Rf (5% MeOH-$CHCl_3$) : 0.5 (grey).

IR ν_{max} (Nujol), cm^{-1} : 1735, 1655, 1610, 1570, 1270, 775.

NMR 60MHz ($CDCl_3$), τ : 2.68 (2H, 2s, ArH), 6.06 (3H, s, CH_3); (not scanned below 0 τ):

ANAL Found, % : C, 44.66; H, 3.19; N, 7.21. $C_7H_6NO_3Cl$ requires C, 44.80; H, 3.20; N, 7.47.

2 - Acetoxy - 4 - carbethoxy - 6 - chloropyridine (64)

A solution of 4 - carbethoxy - 6 - chloro - 2 - pyridone (59) (94mg) in acetic anhydride (3ml) was refluxed for 2 hr and left overnight at room temperature. Evaporation furnished the volatile acetate (64) (72mg, 65%) subliming at 70° - 0.05mm and crystallising from light petroleum in small clusters of colourless needles, m.p. 75-78°, with sintering from 70°.

TLC Rf ($CHCl_3$) : 0.7 (greyish brown).

IR ν_{max} (Nujol), cm^{-1} : 1770, 1730, 1590, 1575, 1540, 1280, 1155, 1020, 770.

NMR 60 MHz ($CDCl_3$), τ : 2.17 and 2.41 (2H, 2s, ArH), 5.55 (2H, q, J= 7Hz, CH_2), 7.62 (3H, s, $COCH_3$), 8.60 (3H, t, J= 7Hz, CH_3).

ANAL Found, % : C, 49.36; H, 4.16; N, 5.78; M^+ at m/e 243, 245. $C_{10}H_{10}NO_4Cl$ requires C, 49.28; H, 4.15; N, 5.75; MW 243, 245.

2, 6 - Dichloro - 4 - carbethoxypyridine (55)

A satisfactory yield of the dichloropyridine acid

(54) was not obtained from the reaction of 4 - carboxy - 6 - hydroxy - 2 - pyridone (53) with phosphorus oxychloride and phosphorus pentachloride, [47] only the monochloro derivative (58) being isolated in any quantity. A variant of the method by Sell and Dootson [47] involving quenching of the reaction mixture with dry ethanol instead of water also failed to provide dichloro derivatives.

Prolonged refluxing of the monochloro ester (59) with the phosphorus oxychloride - phosphorus pentachloride combination in the hope that the second chlorine atom could thus be introduced only furnished what appeared to be dimeric products (M^+ at m/e >300).

However the dichloro acid (54) was found to be conveniently prepared by reaction of the hydroxy acid.(53) with phenyl phosphonic dichloride ($PhPOCl_2$), [50] and smoothly converted by overnight treatment with ethanolic hydrogen chloride to the ester (55), which crystallised from ethanol in long colourless needles, m.p. 62-65° (lit. m.p. 65-66°). [47]

TLC Rf (5% MeOH-$CHCl_3$) : 0.8 (negative staining).

IR ν_{max} (Nujol), cm^{-1} : 1730, 1585, 1555, 1300, 1270, 780.

N M R 60MHz ($CDCl_3$), τ : 2.20 (2H, s, ArH), 5.58 (2H, q, J= 7Hz, CH_2), 8.59 (3H, t, J= 7Hz, CH_3).

MS M^+ at m/e 219 (Cl = 35); $C_8H_7NO_2Cl_2$, MW 219 (Cl= 35).

Attempted preparation of 4 - carbethoxy - 6 - cyano - 2 - pyridone (60) : (ii)

TLC examination of the reaction mixture obtained from treatment of 2, 6 - dichloro - 4 - carbethoxypyridine (55) with potassium cyanide in methanol suggested that, apart from highly polar acidic materials, the main product was the chloropyridone (59). This was also the only compound to be isolated in pure condition from a reaction involving sodium cyanide in N- methyl - 2 - pyrrolidone at 180°, and almost total recovery of unreacted 2, 6 - dichloro - 4 - carbethoxypyridine (55) was achieved following treatment with cuprous cyanide in N - methyl - 2 - pyrrolidone at 150°. [48]

2, 6 - Dichloro - 4 - carbethoxypyridine - 1 - oxide (65)

A solution of 2, 6 - dichloro - 4 - carbethoxy - pyridine (55) (1g) in trifluoroacetic acid (13ml) containing hydrogen peroxide (27.5%, 2ml) [51] was heated on the steam bath for 3 hr. On pouring the reaction mixture into cold water (100ml), chilling and filtering, a first crop (416 mg) of the amine oxide (65) was obtained. Evaporation of the filtrate, addition of solid anhydrous sodium carbonate and extraction with chloroform yielded a second crop (490 mg; total yield 906 mg, 85%), the amine oxide crystallising from ether - light petroleum in long colourless prisms, m.p. 108 - 110°.

TLC Rf (2% MeOH - $CHCl_3$) : 0.6 (very slightly grey).

IR ν_{max} (Nujol), cm^{-1} : 1735, 1600, 1535, 1280, 1035, 860, 785.

NMR 60 MHz($CDCl_3$), τ : 1.93 (2H, s, ArH), 5.60 (2H, q, J= 7Hz, CH_2), 8.60 (3H, t, J= 7Hz, CH_3).

ANAL Found, % : C, 40.69; H, 2.75; N, 5.94.
$C_8H_7NO_3Cl_2$ requires C, 40.71; H, 3.00; N, 5.94.

Action of cuprous cyanide on the amine oxide (65)

A solution of amine oxide (65) (100 mg) in N - methyl - 2 - pyrrolidone (13 ml) containing cuprous cyanide (180 mg) was heated for 20 hr at 160°. Evaporation and addition of water (3 ml) followed by saturation with hydrogen sulphide [62] and Soxhlet extraction of the resultant black precipitate with ethyl acetate for 48 hr afforded a slightly brownish semi-solid product (51 mg). This multi-component mixture (TLC) had a strong odour resembling that of garlic, which is known to be characteristic of isonitriles. [53] No cyanopyridine could be detected however, the only product to be isolated being 4 - carbethoxy - 6 - chloro - 2 pyridone (59) in about 5% yield.

4- Carbethoxy - 6 - methyl - 2 - pyridone (72)

A slurry of the acid (71) (132 g, prepared from the condensation product (70) of ethyl acetylpyruvate (69) [63]

and cyanoacetamide (68) via removal of the cyano group with hot concentrated hydrochloric acid) [54] in dry ethanol (500 ml) containing concentrated sulphuric acid (5 ml) was refluxed for 6 hr and stirred for 40 hr at room temperature. Filtration of the resulting thick crystalline slurry followed by partial evaporation of the filtrate furnished the ester (72) (111 g, 70%), crystallising from ethyl acetate in long colourless needles, m.p. 191 - 192°, with sintering from 150°.

TLC Rf (10% MeOH - $CHCl_3$) : 0.6 (greyish brown).

IR ν_{max} (K Br), cm^{-1} : 2800, 1738, 1672, 1642, 1265, 1208, 770.

NMR 60MHz ($CDCl_3$), τ : 2.97 and 3.41 (2H, 2s, ArH), 5.62 (2H, q, J= 7Hz, CH_2), 7.58 (3H, s, $ArCH_3$), 8.61 (3H, t, J= 7Hz, CH_3) ;(NH possibly responsible for a very broad signal at about -3 to - 4 τ, exchangeable with D_2O).

ANAL Found, % : C,59.41; H, 6.17; N, 7.68; M^+ at m/e 181. $C_9H_{11}NO_3$ requires C, 59.66; H, 6.12; N, 7.73; MW 181.

1 - (β - Cyanoethyl) - 4 - carbethoxy - 6 - methyl - 2 - pyridone (74)

A solution of the ester (72) (181 mg) in benzene (3 ml) containing acrylonitrile (200 mg) and sodium hydroxide (finely ground, 20 - 30 mg) cf. [64] was refluxed for 20 min and stirred overnight at room temperature. Evaporation followed by fractional crystallisation from acetone and PLC in 10% methanol - chloroform to remove unreacted ester (72) yielded the cyanoethylated pyridone (74) (55 mg, 25%), crystallising from ether in long colourless prisms, m.p. 92 - 94°.

TLC Rf (10% MeOH - $CHCl_3$) : 0.7 (greyish brown).

IR ν_{max} (Nujol), cm^{-1} : 2300 (CN), 1720, 1670, 1590, 1270, 780.

NMR 60 MHz ($CDCl_3$), τ : 2.95 and 3.40 (2H, 2s, ArH), 5.62 (2H, q, J= 7Hz, OCH_2), 5.67 (2H, t, J=6Hz, NCH_2), 7.07 (2H, t, J= 6Hz, CH_2CN), 7.42 (3H, s, $ArCH_3$), 8.61 (3H, t, J= 7Hz, CH_3).

ANAL Found, % : C, 61.34; H, 6.03; N, 11,70; M^+ at m/e 234 .

ANAL (contd.)

$C_{12}H_{14}N_2O_3$ requires C, 61.53; H, 6.02; N, 11.96; MW234.

Attempted oxidation of 4 - carbethoxy - 6 - methyl - 2 - pyridone (72)

With the ultimate aim of obtaining 4,6 - dicarbethoxy - 2 - pyridone (75) via the 6 - carboxy derivative (73), the 6 - methyl pyridone (72) was treated with selenium dioxide in ethanol, but was recovered unchanged after refluxing for 48 hr (with the addition of a few ml concentrated sulphuric acid for the final 24 hr).[65]

The only material recovered from reactions involving potassium dichromate in sulphuric acid was a small quantity of unreacted pyridone (72), although the amphoteric and water - soluble nature (and possible chelating ability)[66] of oxidation - hydrolysis products may have prevented isolation under the conditions used (these including thorough extraction of the reaction mixture with chloroform both before and after neutralisation with sodium hydrogen carbonate).

Attempted preparation of 3, 4, 6 - tricarbethoxy -α- pyrone

1, 1, 2 - Tricarbethoxyprop - 1, 2 - ene (25) (27) cf.[67], prepared by zinc chloride - acetic anhydride treatment of ethyl pyruvate and diethyl malonate,[59] failed to condense (TLC) with diethyl oxalate in the presence of potassium ethoxide in ether under reflux, sodium hydride in refluxing benzene or sodium hydride in dimethyl sulphoxide at room temperature. In the presence of sodium wire in refluxing light petroleum however, a yellow microcrystalline solid precipitated, believed to be the sodium salt (76) of the triester (25).

UV λ_{max}(EtOH), nm : 205, 270.
λ_{max}(EtOH + HCl), nm : 200.
λ_{max} (EtOH + HCl + XS NaOH), nm : 215, 268.

Cf. Ultraviolet spectrum of (25) :
λ_{max}(EtOH + NaOH), nm : 220, 266.
λ_{max}(EtOH or EtOH + HCl), nm : 220.

Condensation products were not detected when this yellow material (76) was treated with diethyl oxalate in refluxing ether, dimethylformamide at 80 - 90° or dimethyl sulphoxide at 80°, or with ethyloxalyl chloride in the absence of solvent at room temperature.

Attempted condensation of acridinic acid imide (15) with the triester (25) cf. [69]

Overnight treatment of the imide (15) with 1, 1, 2-tricarbethoxyprop -1, 2 - ene (25) [59] and dimsyl sodium [68] in dimethyl sulphoxide at room temperature afforded after dilution with water a crystalline solid shown by TLC to be unreacted imide (15) (over 50% recovery). No condensation products were detected in the aqueous mother liquor.

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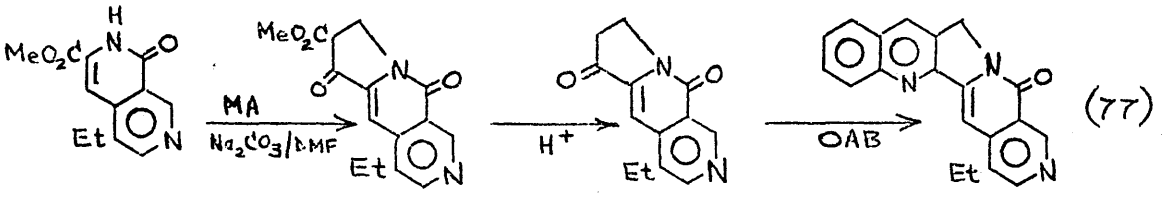
PART III (6)

Appendix: Published Synthetic Routes

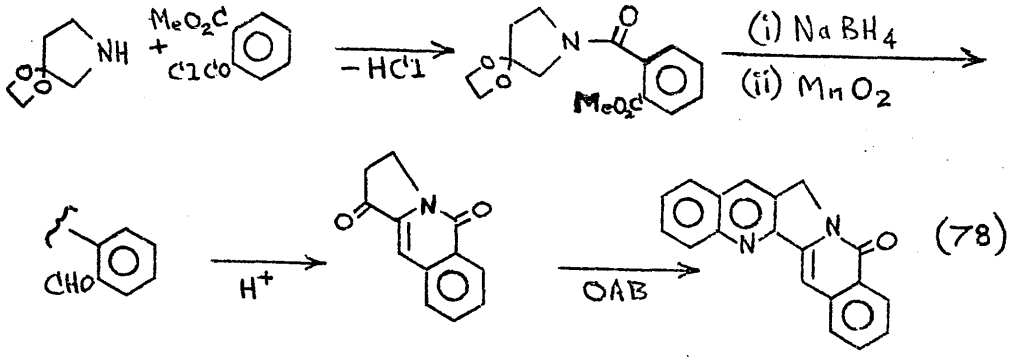
FIGURE 6.1-01

[MA = Methyl acrylate ; OAB = o-Aminobenzaldehyde]



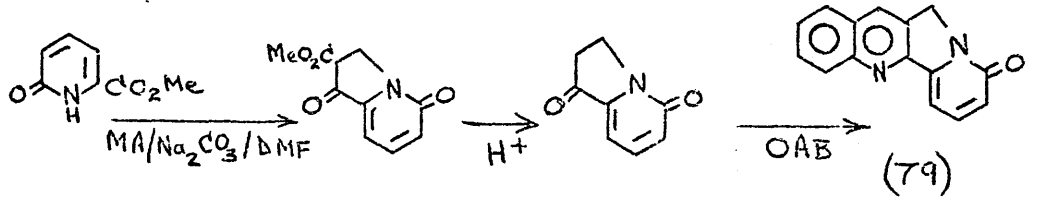
(77)

FIGURE 6.1-02



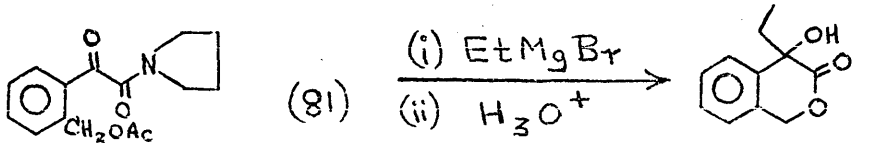
(78)

FIGURE 6.1-03



(79)

FIGURE 6.1-04



Chapter 6.1 Approaches to camptothecin, 1967 - 1971

Between 1967 and 1971 several publications appeared describing approaches to the synthesis of camptothecin, virtually all of them making use of the Friedländer condensation [1] with o- aminobenzaldehyde to form the pyrroloquinoline nucleus at some stage of the reaction sequence. Using this as the final step analogues (77), [2] (78) [3] and (79) [4] were prepared, as illustrated in Figures 6.1 - 01, 6.1 - 02, and 6.1 - 03.

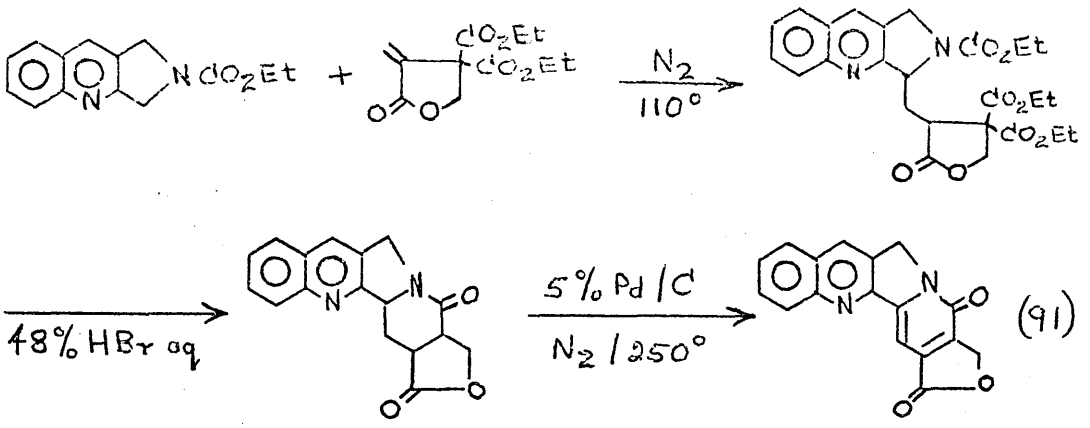
One abstract mentioned the facile preparation of a pentacyclic furan (80) and indicated that the method could readily be applied to give the camptothecin molecule. [5] Another allusion to a possible synthesis making use of a "bicyclic epoxidation " appeared in the literature but as in the case of (80) no further details were given. [6] (See Chapter 5 pp161-169 for all formulae).

Considerable progress towards camptothecin itself (rather than analogues) was made during this period, however, by the original workers in this field, M. E. Wall and M. C. Wani, inter alia. Overcoming one of the major difficulties [3] they devised an elegant and efficient synthesis of the unusual lactone ring in a model compound (82) from a suitably protected precursor (81), as shown in Figure 6.1 -04. [7, 8]

Whereas, in keeping with the findings in the present thesis (Chapter 5.2), attempts to prepare the pyrroloquinoline (16) by reductive methods were fraught with difficulties, only the N- benzyl compound (83) being attained, [9] Wall and Wani finally succeeded in obtaining (16) although experimental details were not made available. [10] However on condensing (16) with (84) to give (85) and refluxing the corresponding ketone (86) with triethyl orthoformate in acetic anhydride in the hope of securing the key intermediate (87), compound (88) was formed instead. [8, 10] Methods of converting the polyfunctional compound (89) into another potentially important intermediate (90) were also studied. [8, 11]

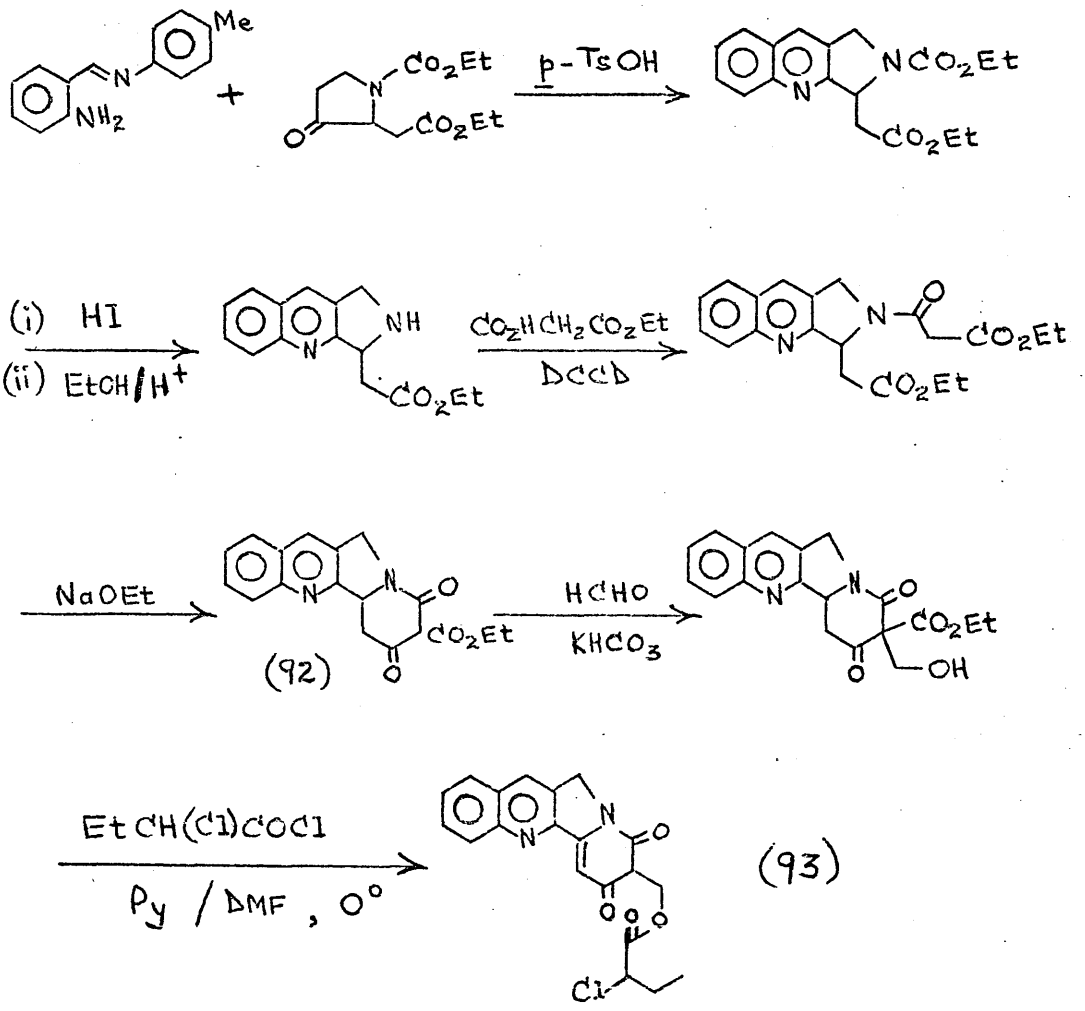
A later approach by Wall and Wani [12] depicted in

FIGURE 6.1–05



(91)

FIGURE 6.1–06



(92)

(93)

Figure 6.1 -05 afforded a structure (91) with suitable functionality for conversion to camptothecin and appeared to be one of the most promising attempts made towards a total synthesis up to this point.

A further synthetic route worthy of mention was that undertaken by Liao, Nyberg and Cheng (Figure 6.1 - 06), who claim that their tetracyclic product (93) is a suitable intermediate for camptothecin synthesis.[13] This approach is remarkably similar in its earlier stages to the work conducted by Stork and Schultz which eventually led to the first total synthesis : see following chapter.

FIGURE 6.2-01

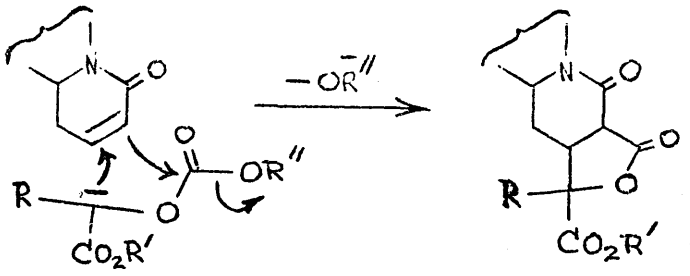


FIGURE 6.2-02

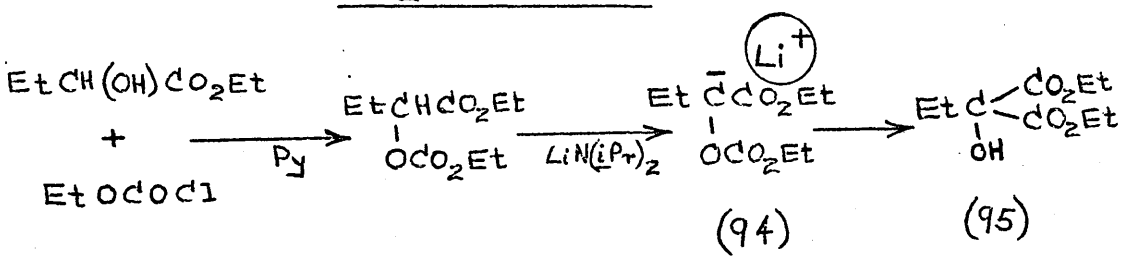


FIGURE 6.2-03

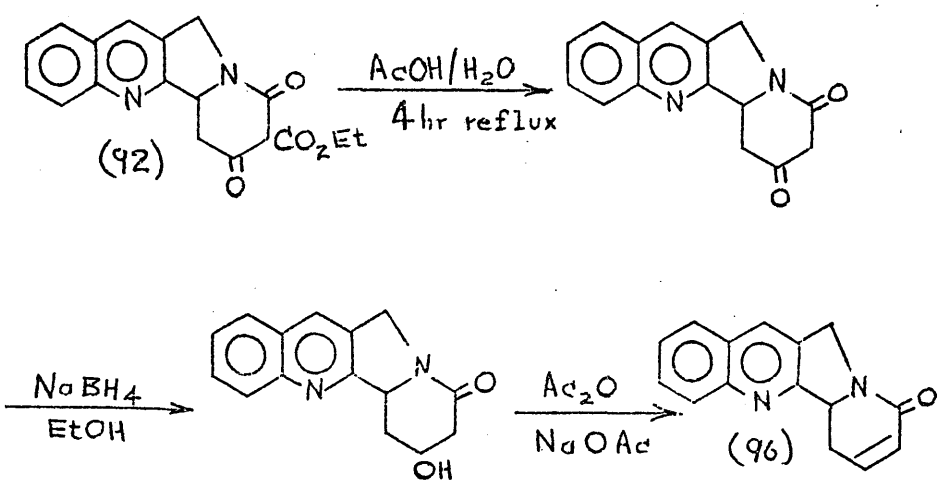


FIGURE 6.2-04

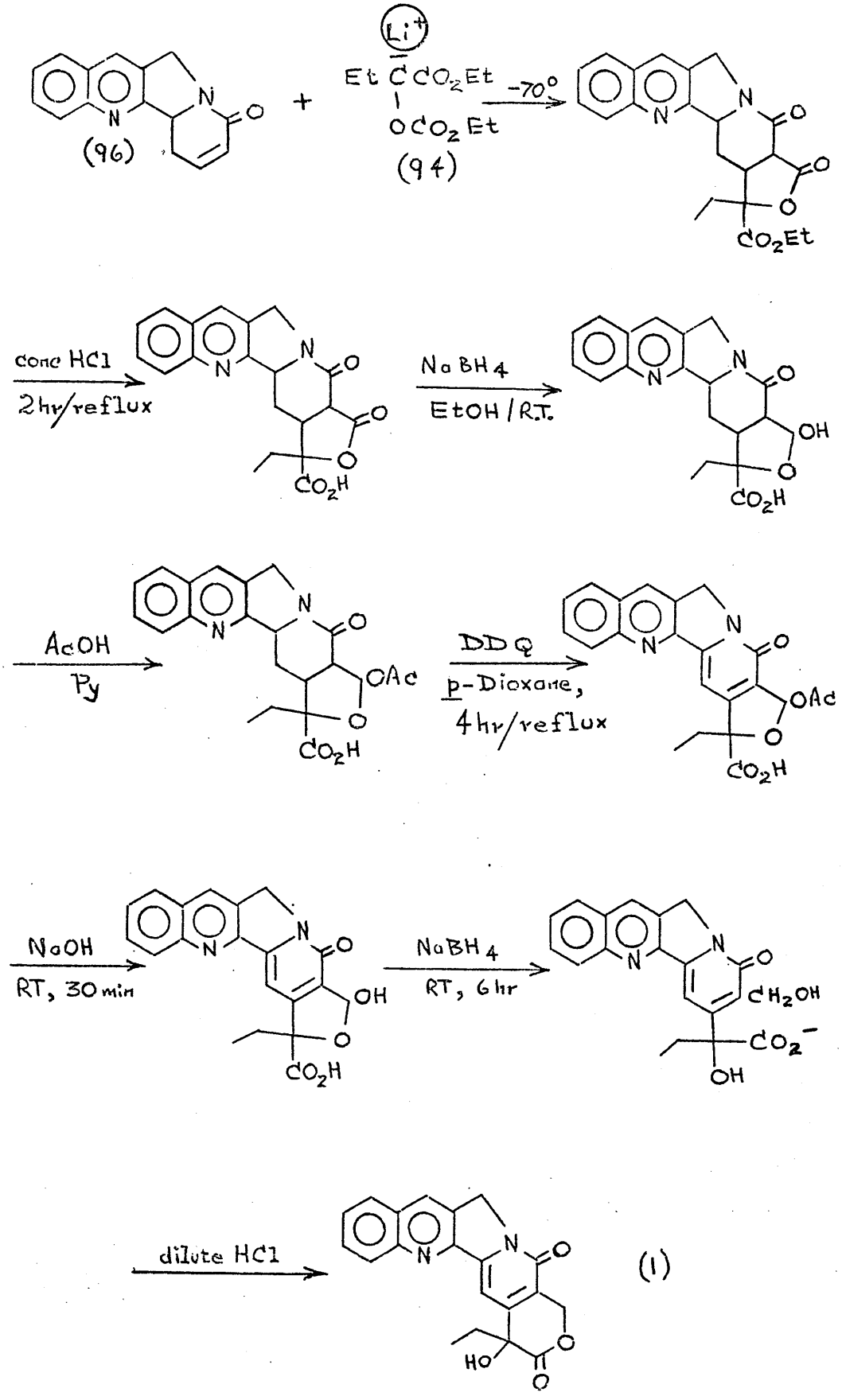
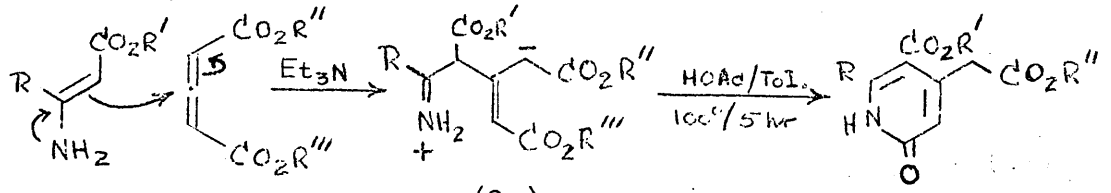
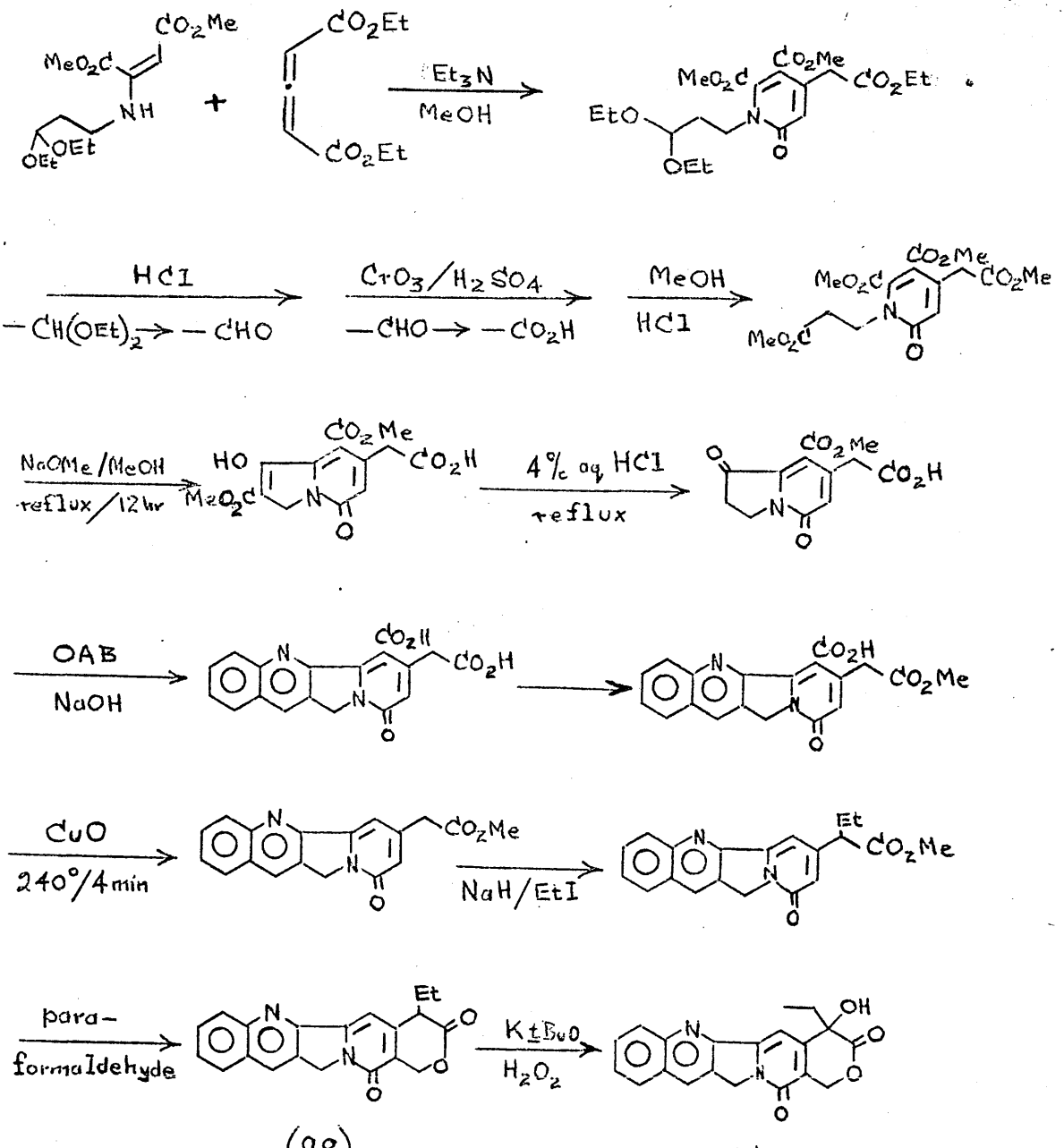

(96)
(94)
Li+
-70°
conc HCl
2hr/reflux
NaBH4
EtOH/R.T.
AcOH
Py
DDQ
p-Dioxane,
4hr/reflux
NaOH
RT, 30 min
NaBH4
RT, 6 hr
dilute HCl
(I)

FIGURE 6.2–05



(97)

FIGURE 6.2–06



(98) (1)

Chapter 6.2 Syntheses of camptothecin, 1971 - 1972

The first total synthesis of (±)- camptothecin was announced in August 1971 by G. Stork and A. G. Schultz.[14] Their route embodied a novel annelation reaction of the type depicted in Figure 6.2-01, which may in itself prove to be of general synthetic utility. As applied to camptothecin synthesis the two reactants required-(94) and (96)- were prepared as shown in Figures 6.2-02 and 6.2-03 respectively. The anion (94) proved to be moderately stable in tetrahydrofuran at-70°, whilst rearranging to the tartronic ester (95) even at 0°.

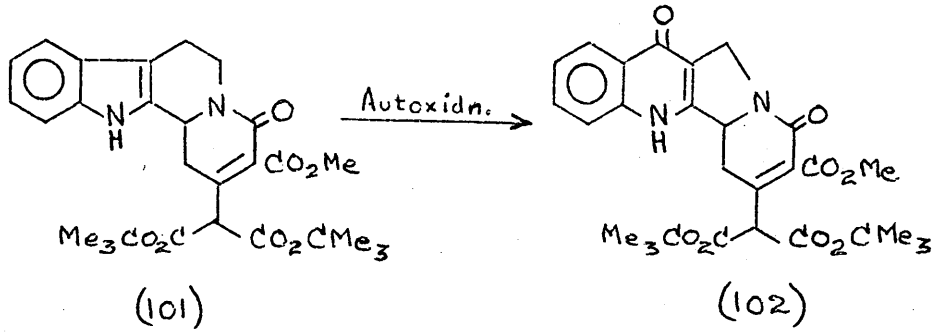
It is interesting to note that the tetracyclic ester (92) is also an intermediate in the rather different approach of Liao, Nyberg and Cheng [13] (see previous chapter), but is prepared here by a somewhat similar route.

Completion of the synthesis is illustrated in Figure 6.2 - 04, yields of up to 85% being claimed for the new cyclisation reaction. It is reported that attempts are presently underway to effect resolution of the (±) synthetic product, the natural isomer being (+) - camptothecin.[14]

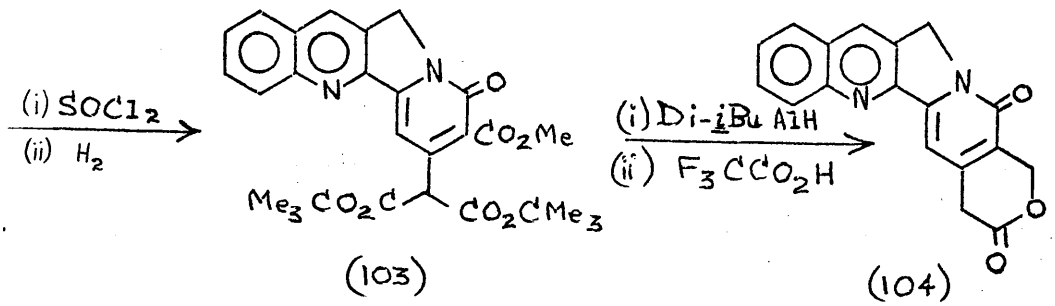
Several months later the second total synthesis appeared, this time by Danishefsky *et al.* at the University of Pittsburgh, Pennsylvania.[15] Like the above approach by Stork and Schultz, Danishefsky's route constituted the application of a novel type of reaction, in this case a new synthesis of α - pyridones *via* nucleophilic addition to an allene (see Figure 6.2 - 05),[16] the success of the reaction depending upon the stability of the intermediate glutaconate species (97).

The completed route is concisely drawn up in Figure 6.2 -06, showing how the new cyclisation was effectively utilised. Interestingly the last stage - conversion of desoxycamptothecin (98) to camptothecin (1) - was found to take place with remarkable facility, exposure of a methylene chloride solution to the atmosphere apparently being sufficient to cause this transformation (TLC and MS evidence).

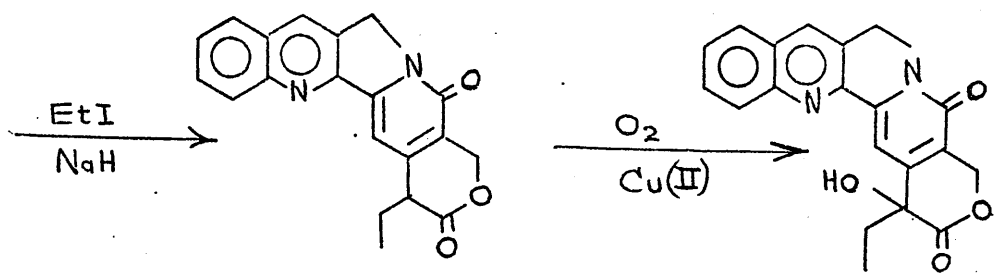
FIGURE 6.2 – 07



(101) (102)



(103) (104)



(98) (1)

The third approach to result in a total synthesis of camptothecin was that of Winterfeldt and his co-workers at Hannover.[17,18] As mentioned earlier (Chapter 5.1, page 174) Winterfeldt had met with considerable success in his earlier efforts to effect oxidative conversion of indoles to pyrroloquinolines along probable biogenetic-type pathways, and a later publication[19] describes the application of this work towards the synthesis of tetracyclic structures (99) and (100) containing the camptothecin chromophore (cf. (1) λ_{max}, nm: 254, 365).

For the complete synthesis (Figure 6.2 - 07), compound (101) was subjected to the aforementioned autoxidation process (potassium tert-butoxide in DMF), the product (102) treated with thionyl chloride to replace the resultant 4-oxy substituent by chlorine and dehydrogenate ring E, and finally hydrogenolysed to yield compound (103). The methyl ester was now selectively reduced to a primary hydroxyl group with di-iso-butyl aluminium hydride and lactonisation effected by trifluoroacetic acid treatment at room temperature. The product (104) was alkylated with ethyl iodide in dimethylformamide to yield desoxy-camptothecin (98), which was converted to camptothecin in high yield by passing oxygen through a solution in dimethylformamide containing copper (II) chloride.

Three further syntheses have been reported since the announcement of Winterfeldt's work : namely by (a) Wall and Wani[20] inter alia making use of the pyrroloquinoline ketotriester (105) obtained via (16); by (b) Sugasawa, Toyoda and Sasakura[21] using the quinoline lactam (106); and by (c) Tang and Rapoport[22] who claim an 11% overall yield of (±)- camptothecin from pyridine -2, 5-dicarboxylic acid (107).

Although the most recent clinical trials with camptothecin in the treatment of certain forms of cancer have apparently been rather less encouraging than was originally predicted,[20,23] it is to be hoped that the above work will perhaps enable larger quantities of the material to be made available for fuller trials, and possibly also pave the way for the preparation of more active analogues.

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