1970

Phenanthropiperidines and related compounds

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Recommended Citation
PHENANTHROPIPERIDINES AND RELATED COMPOUNDS

Thesis submitted in partial fulfilment of the requirements for the degree of Bachelor of Science with Honours

by

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Wollongong University College,
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November, 1970.
SUMMARY

Syntheses of variously substituted diphenylpiperidine derivatives were accomplished and their reactions, as intermediates in a new synthetic route to the physiologically active phenanthroindolizidine alkaloids and their analogues, were investigated.

The synthesis involves Michael addition of phenylacetonitrile donors to ethyl cinnamate acceptors, yielding a series of ethyl-3,4-diphenyl-4-cyanobutanoates bearing aromatic methoxy, methylenedioxy and iodo substituents. Reductive cyclisation of these cyanoesters with Raney-nickel or copper chromite catalysts gave, under exactly controlled conditions, either secondary or tertiary diphenylpiperidine derivatives or the corresponding d-lactams. The ratio of the cis- and trans- racemates formed in each reaction was found to vary with changes in reduction temperature and with the substituent pattern of the starting material.

A new method to distinguish between the cis- and trans- isomers of the diphenylpiperidine derivatives, by evaluation of their n.m.r. spectra, was developed. This investigation provided information on characteristic patterns of the aromatic proton signals of the 1,2-diphenyl system and established a process for the
determination of the stereochemistry of other puckered ring systems with vicinal aryl substituents.

In addition, three methods for the construction of the indolizidine system were investigated.

Attempts to form the corresponding phenthropiperidines (or their 9,10-dihydro derivatives) by a method based on the photolytic cyclisation of stilbene derivatives were of no avail. However the preparation of ortho-amino derivatives of both cyanoesters and diphenylpiperidines proved to be quite successful and these compounds are expected to cyclise to phenanthrene derivatives by a recent modification of the Pschorr synthesis. Work to complete this reaction sequence and to synthesise the indolizidine ring system is still proceeding.
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INTRODUCTION
A. DISTRIBUTION AND STRUCTURE OF THE ALKALOIDS OF THE FAMILY ASCLEPIADACEAE

There are over 320 genera, comprising 1700 individual species, in the family Asclepiadaceae. However relatively few of the species have been shown to contain alkaloids,\(^1,2\) e.g.:

nicotine (I) in *Asclepis syriaca*\(^3\)
cryptolepine\(^4,5\) (II) in *Cryptolepis triangularis*\(^4\) and *C. Sanguinolenta*.\(^5\)

\[
\text{\begin{tikzpicture}
\node at (0,0) [draw, shape=circle, inner sep=0.2cm] (A) {\text{CH}_3};
\node at (1.5,0.5) [draw, shape=circle, inner sep=0.2cm] (B) {\text{N}};
\node at (1.5, -0.5) [draw, shape=circle, inner sep=0.2cm] (C) {\text{N}};
\draw (A) -- (B);
\draw (B) -- (C);
\end{tikzpicture}}
\]

Species of the genus *Tylophora*, which contain the greatest number of alkaloids, are distributed over a wide area encompassing the Indian sub-continent, Indonesia, the Philippines and Northern Australia. The members are slender vines possessing emetic and vesicant activity while some have long been known as herbal remedies.

Hooper,\(^6\) in 1891, isolated a small amount of a crystalline base from *Tylophora indica* (formerly *T. asthmatica*) while Ratnagiriswaran and Venkatachalam\(^7\) obtained two alkaloids; tylophorine and tylophorinine. Tylophorine was also isolated, together with a lower
melting point base, from *T.indica* by Chopra et al.\(^8\)

Govindachari and co-workers\(^9,10,11\) reisolated tylophorine (III) and tylophorinine (IV), and confirmed their structures by synthesis in 1961\(^12,13\) and 1965\(^14\) respectively.

In 1962 Gellert et al\(^15\) isolated and synthesised tylocrebrine (V) a new alkaloid isomeric with tylophorine, both of which they obtained from *T.crebriflora*, a North Queensland vine.

Rao and Wilson\(^16\) have made an extensive study concerning the genus *Tylophora* and have isolated alkaloids as shown below;

*Tylophora crebriflora* yielded alkaloids:

*Tylophora indicas*:
"C\(^1\)", "D\(^1\)", "E\(^1\)", tylophorine and tylophorinine.

*Tylophora dalzellii*:
"C\(^1\)" and "E\(^1\)"

*Tylophora hirsut*:

Apart from compound "F", all these alkaloids possess the phenanthroindolizidine skeleton.

Other genera, apart from the genus *Tylophora*, have also been shown to contain phenanthroindolizidine alkaloids; e.g. antofine (VI) which has been isolated
from the following species;

Vincetoxicum officinale by Pailer and Streicher\textsuperscript{17}

Antitoxicum funebre by Platonova et al\textsuperscript{18}

Cyanchum vincetoxicum by Wiegbe et al\textsuperscript{19}

and a demethylated derivative (VII) of antofine isolated from C. vincetoxicum.

It is interesting to note that septicine (VIII), a secophenanthroindolizidine alkaloid which has been isolated from Ficus septica (family Moraceae) by Russell,\textsuperscript{20} is a probable intermediate in the biogenesis of tylocrebrine and tylophorine.

B. PHYSIOLOGICAL ACTIVITY OF THE TYLOPHORA ALKALOIDS

Rao and Wilson\textsuperscript{16} have found that most of the phenanthroindolizidine alkaloids show cytotoxic activity against Hela cells grown in culture. They claimed that this activity varies with the number and nature of substituents. The demethylated analogues were more active than the methoxy substituted compounds. The presence of a benzylic hydroxyl group at carbon 1\textsuperscript{4} also substantially increases the activity. Thus 1\textsuperscript{4}-hydroxytylocrebrine is more active than tylocrebrine which, in turn, is much more active than tylophorine. It was also found that, in general, alkaloids which exhibit cytotoxic behaviour are also active against Lymphoid Leukemia L1210.
Chopra found that tylophorine has a paralysing action on heart muscle but acts as a stimulant towards the muscle of blood vessels. Tests carried out on behalf of the National Cancer Institute of N.I.H., U.S.A. showed that tylocrebrine exhibits significant and consistent activity against L1210 leukemia in mice. However the toxicity of tylocrebrine, and its analogues, in humans has not yet been fully determined.

Thus an extensive testing programme is required and in order that this may be accomplished, a varied and commercially useful synthetic route to the phenanthroindolizidines is necessary.

C. BIODEGENESIS OF THE PHENANTHROINDOLIZIDINE ALKALOIDS

There is an obvious structural relationship between the phenanthroindolizidines and the phenanthroquinolizidine alkaloid cryptopleurine \(22,23,24\) (IX) which has been isolated from several plants unrelated to the genus Tylophora: Cryptocarya pleurosperma (family Lauraceae) by White and Francis. Boehmeria platyphylla \(^25\) and B. cylindrica \(^26\) (family Urticaceae).

Johns et al \(^27\) recently isolated cryptopleuridine (XI) and cryptopleurospermine (XII), in addition to the above
alkaloid and pleuropermine, from *C. pleurosperma*.

Due to the structural similarities between cryptopleurine and the alkaloids of the genus *Tylophora*, a biosynthetic scheme proposed should provide pathways to both types of alkaloids.

By extending Robinson's original ideas that cryptopleurine originated from two tyrosine units and one lysine unit, Marchini and Belleau\(^2\) proposed the mechanism outlined in figure 1. However the now generally accepted route is the one proposed by Wenkert\(^3\) (figure 2). This latter scheme is supported by the fact that two alkaloids, pleuropermine (X) and 0-methylpleuropermine (XIII), both closely related to the intermediate (XIV), have been isolated from *C. pleurosperma* and *B. platyphylla* respectively.\(^4\) The likelihood that compound (XV) is an intermediate is strengthened by the isolation of the secophenanthroquinolizidine alkaloid (XVI) from *B. platyphylla*\(^5\) and the base (XVII) from *B. cylindrica*\(^6\).

Barton\(^7\) has reported the cyclisation of intermediates of the type (XV) by oxidative coupling while Pauson et al\(^8\) have synthesised (+) cryptopleurine by a route similar to the biogenetic pathway previously proposed (figure 2).

The presence of the secophenanthroindolizidine alkaloid septicine in *Ficus septica*\(^9\) supports the correlation of
CRYPTOPLEURINE
the biosynthetic pathways of the *Tylophora* alkaloids\(^3^5\) (figure 3) and cryptopleurine. The variation in the two routes arises from the pyrrolidine ring being derived from ornithine,\(^3^6\) while the analogous ring of cryptopleurine comes from lysine.

**D. PREVIOUS SYNTHESSES OF THE ALKALOIDS AND THEIR ANALOGUES**

In 1958 Govindachari and co-workers\(^1^0\) successfully synthesised the phenanthroindolizidine skeleton (XVIII) using the scheme shown in figure 4. However they found that this method was not applicable to the synthesis of tylophorine.\(^1^3\) The difficulty was overcome by use of the route shown in figure 5, and the racemic base was resolved using (+)-camphor-10-sulphonic acid.\(^1^3\) Using the same approach Gellert *et al*\(^1^5\) were able to synthesise racemic tylocrebrine. Unfortunately the introduction of a 14-hydroxy group, as in tylophorinine was not possible by this method.

Govindachari *et al*,\(^1^4\) in 1965 were able to synthesise tylophorinine (figure 6) by a modification of the synthesis of (\(^\ddagger\) )-cryptopleurine reported by Marchini and Belleau.\(^2^9\) Using a further variation of this scheme, Chauncy *et al*\(^3^7\) prepared the parent ring system from phenanthroindolizidone (XIX) by the Huang-Minlon modification of the Wolf-Kishner reduction.
Figure 6

TYLOPHORININE IV
Racemic septicine, along with the unsubstituted compound (VIIa), has been prepared by Russell\textsuperscript{38} and also by Govindachari and Viswanathan\textsuperscript{39} using the scheme shown in figure 7.

Herbert and Moody\textsuperscript{40} have reported a novel synthesis of (\textpm)-tylophorine (figure 8) however reduction of the amide (XX) with triethylxonium fluoroborate and sodium borohydride represents an expensive step not applicable to large scale manufacture.

Recently Paton et al\textsuperscript{34} have reported the synthesis of (\textpm)-cryptopleurine along biogenetic lines (figure 9). However many of the reactions proceed with very poor yields.

Perhaps the most successful synthetic route so far is that developed by Chauncy and Gellert,\textsuperscript{41} who, although
FIGURE 8

CURE 8

OCH

YLOPHORINE
FIGURE 9

\[ \text{Pyridine-Li} + \text{MeO-OMe} \rightarrow \text{COOMe} \rightarrow \text{MeO-OMe} \rightarrow \text{NH} \rightarrow \text{MeO-OMe} \rightarrow \text{MeO-OMe} \rightarrow \text{MeO-OMe} \]
they were unable to effect a stereospecific synthesis (at carbon 13a), prepared (‡)-tylophorine, (‡) tylocrebrine, (‡)-antofine and the previously unknown (‡)-2,3-dimethoxyphenanthroindolizidine (XXI) in overall yields far greater than those reported previously.

\[
\text{CH}_3\text{O} \quad \text{OCH}_3 \\
\text{OCH}_3 \\
\text{XXI}
\]

A general outline of the method used is shown in figure 10.
THEORETICAL
A. AIMS AND PROPOSED SYNTHESSES

The aim of this project was to develop new and versatile synthetic methods for the preparation of the alkaloid tylocrebrine and its analogues. Tylocrebrine shows potential antileukemia activity and it is hoped that some of its synthetic analogues will not only exhibit enhanced behaviour but also show a reduction in side-effects. The development of a synthetic route applicable to large scale manufacture would facilitate the preparation of phenanthroindolizidines possessing different substitution patterns and allow the introduction of more significant structural changes. A systematic study of the relationship between chemical structure and physiological activity would then be possible.

All of the previous syntheses (figures 4-10) have limited use due to the high cost of starting materials and reagents and the poor overall yields encountered. The methods reported here were designed to eliminate at least some of these problems.

The proposed synthesis was based on the preparation of N-alkyl diphenylpiperidines reported by Barr and Cook.\textsuperscript{43} This method is superior to that published by Kost and Terentyev\textsuperscript{44} who prepared 3,4-diphenylpiperidine by reductive cyclisation of the dinitrile obtained from Michael reaction between cinnamonitrile and phenylacetonitrile.
Spence encountered considerable difficulty in adapting this reaction sequence to the preparation of methoxy substituted diphenylpiperidines. However, Summons found that, by following the method of Barr and Cook, the desired derivatives could be obtained in high yield. The method used involves the preparation of ethyl 3,4-diphenyl-4-cyanobutanoates by Michael addition of phenylacetonitriles to ethyl cinnamate derivatives and cyclisation of these cyanoesters by catalytic hydrogenation. The work reported in this thesis represents a continuation of this approach.

Attempts to build the phenanthrene ring system were based on the well known photocyclisation reactions of stilbenes and their ortho-iodo derivatives. Routes involving the Pschorr synthesis and its modifications were also investigated.

Several methods for the construction of the indolizidine ring system were devised and examined. The general routes proposed are outlined in figure 11 (a and b).

B. CYANOESTERS: THE MICHAEL REACTION

The Michael reaction is the addition of a donor molecule (containing an active hydrogen to a carbonyl group) to the $\beta$-carbon of an enone acceptor in the presence of a base. The use of phenylacetonitriles is
an extension of the original scope of the reaction to include donors activated by both the nitrile group and the phenyl ring.

The major difference between the Michael reaction and other alkylation methods lies in the amount of base required. For the Michael reaction only catalytic amounts are normally used since the base which abstracts a proton from the donor molecule is later regenerated.

The substituted ethyl 3,4-diphenyl-4-cyanobutanoates (XXII) were prepared by Michael addition of phenylacetonitrile donors to ethyl cinnamate derivatives used as acceptors in the presence of catalytic amounts of sodium ethoxide.

Difficulties in obtaining the desired cyanoester arise through the reversible nature of the formation of the new carbon-carbon bond, the product itself being potentially capable of further transformations (figure 12). Because of this reversibility, a variety of products may be formed due to e.g., retrograde and/or abnormal Michael reactions. In fact if an excess of the acceptor (ethyl cinnamate derivative) is present, ethyl triphenylcyclohexanonecarboxylates\(^{43,64}\) (XXIII) are formed. These compounds have been found in the mother liquors of the Michael reactions and are readily recognised by their infrared spectra. The carbonyl band is extremely strong (with several symmetrical shoulders,
\( \nu_{\text{max.}} 1670\text{cm}^{-1} \) while absorbance due to the nitrile group (in the region 2200-2250\text{cm}^{-1}) is very weak and often absent. The cyanoesters on the other hand show absorbance at 1740\text{cm}^{-1} (\text{C}=\text{O}) and 2240\text{cm}^{-1} (\text{C} \equiv \text{N}).

Similarities in the physical properties of the products and starting materials present further difficulties in the isolation of the desired cyanoesters. However the following procedure enables these difficulties to be readily overcome and reduces side reactions to a minimum.

Sodium ethoxide catalyst (0.2-0.3 mole/mole) in ethanol solution is added with stirring to a melt of equimolar amounts of donor and acceptor at about 80\text{°C}. This initial temperature together with the heat evolved during the reaction assures rapid addition. The mixture is then immediately cooled to limit side reactions. The oil obtained usually solidifies at 0-25\text{°C} within several hours. These solids are then washed alternately with dilute acetic acid and water to remove both the catalyst and the coloured impurities. The remaining solid can then be crystallised from acqueous dioxan and finally from ethanol.

A series of nine cyanoesters has been prepared by this method and all were obtained in pure crystalline form with yields generally in the range of 80 - 97\% (Table I).

Since the cyanoesters contain two adjacent asymmetric centres (at \( C_3 \) and \( C_4 \)), two racemates are possible.
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXIIa</td>
<td>$R_1 = R_2 = R_3 = R_4 = R_5 = H$</td>
<td>97%</td>
</tr>
<tr>
<td>b</td>
<td>$R_1 = \text{OMe}; R_2 = R_3 = R_4 = R_5 = H$</td>
<td>85%</td>
</tr>
<tr>
<td>c</td>
<td>$R_1 = R_2 = \text{OMe}; R_3 = R_4 = R_5 = H$</td>
<td>87%</td>
</tr>
<tr>
<td>d</td>
<td>$R_1 = R_2 = R_3 = \text{OMe}; R_4 = R_5 = H$</td>
<td>85%</td>
</tr>
<tr>
<td>e</td>
<td>$R_1 = R_2 = R_3 = R_4 = \text{OMe}; R_5 = H$</td>
<td>93%</td>
</tr>
<tr>
<td>f</td>
<td>$R_1 = R_2 = R_4 = R_5 = H; R_3 = \text{OMe}$</td>
<td>88%</td>
</tr>
<tr>
<td>g</td>
<td>$R_1 = R_2 = R_5 = H; R_3 = R_4 = \text{OMe}$</td>
<td>73%</td>
</tr>
<tr>
<td>h</td>
<td>$R_1 = R_2 = H; R_3 = R_4 = R_5 = \text{OMe}$</td>
<td>90%</td>
</tr>
<tr>
<td>i</td>
<td>$R_1 = R_2 = R_5 = H; R_3, R_4 = \text{CH}_2\text{O}_2$</td>
<td>81%</td>
</tr>
<tr>
<td>j</td>
<td>$R_1 = R_3 = \text{OMe}; R_2 = R_4 = R_5 = H$</td>
<td>75%</td>
</tr>
</tbody>
</table>
The $\mathcal{L}$-racemate of ethyl 3,4-diphenyl-4-cyanobutanoate has been prepared by Barr and Cook and by Koelsch who has also reported the preparation of the $\beta$-isomer.

In our experiments the Michael reaction between ethyl cinnamate and phenylacetonitrile gave only the $\mathcal{L}$-racemate. This compound was chromatographically homogeneous and had a melting point identical to that reported in the literature. The other racemic cyanoesters were also homogeneous on thin layer chromatography using several adsorbents and in several solvent systems (cf. silica gel: light petroleum, benzene, chloroform/methanol, and mixtures of these; alumina: light petroleum, benzene, chloroform, and mixtures of these; cellulose: butanol/acetic acid/water). Reductive cyclisation of these cyanoesters (cf. section C) gives mainly the $\mathcal{L}$-(cis-) diphenylpiperidine derivatives. Hence all the cyanoesters are of the $\mathcal{L}$-configuration, i.e. they are racemic modifications of the erythro-isomers (XXIVa), while the $\beta$-isomers (not isolated here) are expected to be of the threeo-form (XXIVb).

\[
\begin{align*}
\text{XXIVa} & \quad \text{XXIVb} \\
& \quad R = \text{CH}_2\text{COOEt}
\end{align*}
\]
C. 3,4-DIPHENYLPIPERIDINE DERIVATIVES: REDUCTIVE CYCLISATION

The pharmacological interest attached to piperidine derivatives led Barr and Cook to investigate methods of synthesis of aryl substituted piperidines including N-alkyl 3,4-diphenylpiperidines. They prepared the latter compounds by reductive cyclisation of the cyanoester previously mentioned. Thus at 200°C and 175 atm. of hydrogen with copper chromite in ethanol, both $\mathcal{L}$- and $\beta$- racemates of N-ethyl-3,4-diphenylpiperidine (XXVa) were isolated (in the ratio 2:1 respectively). When dioxan was used as solvent, hydrogenation with copper chromite gave the $\mathcal{L}$- form of 4,5-diphenylpiperid-2-one (XXVI). The preparation of this lactam had been previously reported by Koelsch. In fact he was able to obtain a mixture of both $\mathcal{L}$- and $\beta$- lactams by reduction of the unsubstituted cyanoester in ethanol with Raney nickel at 165°C and 150 atm. of hydrogen.

Later Koelsch and Raffauf showed that the $\mathcal{L}$- lactam has the cis-configuration i.e. the phenyl groups are axial and equatorial with respect to the piperidine ring. This assignment was based on a new synthesis of the lactam by Beckmann rearrangement of the oxime of the known cis-form of 3,4-diphenylcyclopentanone.

We have repeated the reduction of the unsubstituted cyanoester ($\mathcal{L}$-form) using copper chromite in ethanol.
at 180°C under 150 atm. of hydrogen and isolated the \(\alpha\) - and \(\beta\) - racemates of N-ethyl-3,4-diphenylpiperidine in 55% and 42% yields respectively. The two isomeric bases were readily separated by fractional crystallisation of the \(\alpha\) - base from ethanol and the \(\beta\) - hydrochloride salt from ethanol/ether.

We have also reduced four of the methoxy substituted cyanoesters already listed, using the same reaction conditions. Treatment of the reduction mixtures as described above again yielded both \(\alpha\) - and \(\beta\) - racemates of the corresponding tertiary bases (Table 2). As can be seen from the table an increase in methoxy substitution leads to a decrease in the percentage of \(\beta\) - racemate formed. In fact, under the above conditions, no \(\beta\) - racemate was isolated from the reduction of the tetramethoxy cyanoester.

The homogeneity of the respective isomers can be readily determined by e.g. thin layer chromatography. The \(\alpha\) - and \(\beta\) - racemates have different Rf values in all the systems used for the cyanoesters; the \(\beta\) - isomer always has a slightly lower Rf than its \(\alpha\) - counterpart. This behaviour is attributed to the fact that in the \(\beta\) - isomer (where the phenyl rings are trans-diaxial) the phenyl groups are further apart giving rise to a more extended molecule which is therefore more likely to interact with the stationary phase. This property cannot
TABLE 2

N-Ethyl-3,4-diphenylpiperidine Derivatives

<table>
<thead>
<tr>
<th></th>
<th>( \alpha )-Racemate</th>
<th>( \beta )-Racemate</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXVa</td>
<td>55%</td>
<td>42%</td>
</tr>
<tr>
<td>b</td>
<td>62%</td>
<td>30%</td>
</tr>
<tr>
<td>c</td>
<td>60%</td>
<td>27%</td>
</tr>
<tr>
<td>d</td>
<td>65%</td>
<td>25%</td>
</tr>
<tr>
<td>e</td>
<td>81%</td>
<td>Nil</td>
</tr>
</tbody>
</table>

**Notes:**
- \( R_1 = R_2 = R_3 = R_4 = H \)
- \( R_1 = 0\text{Me}; R_2 = R_3 = R_4 = H \)
- \( R_1 = R_2 = 0\text{Me}; R_3 = R_4 = H \)
- \( R_1 = R_2 = R_3 = 0\text{Me}; R_4 = H \)
- \( R_1 = R_2 = R_3 = R_4 = 0\text{Me} \)

**Diagram:**

[Diagram of N-Ethyl-3,4-diphenylpiperidine Derivatives]
be due to differences in basicity since the \( \beta \) - racemates have lower Rf values on both silica and basic alumina. Halpern\(^6\) has shown that these compounds exhibit similar behaviour on gas chromatography i.e. the \( \beta \) - form has the longer retention time, using a column of 1% XE 60 on DMCS treated chromosome \( W \).

Barr and Cook\(^4\) proposed that the reduction proceeds via the lactams (XXVI) to the secondary piperidines (XXVII) which are then alkylated at the nitrogen by the alcohol present as solvent. The mechanism proposed is shown in figure 13.

We have now proved the correctness of this mechanism by breaking up the reaction into individual steps indicated in figure 13. The reaction sequence used to confirm the mechanism is shown in figure 14 (a and b). It must be pointed out however that this examination was only carried out with the unsubstituted derivatives, analogous behaviour being assumed for the methoxy substituted compounds.

Barr and Cook obtained the \( L \) - racemate of 4,5-diphenylpiperid-2-one by reduction of the cyanoester (XXII) in dioxan. The same lactam, together with the \( \beta \) - isomer, was also prepared by Koelsch using Raney nickel in ethanol. We have found that reduction of this cyanoester with copper chromite in cyclohexane yields
both racemic lactams (XXVI) and both secondary piperidines (XXVII) and that shortening the reaction time and lowering the temperature favours formation of the lactams (the $\mathcal{L}$ - isomer being by far the predominant product). We also found that these lactams could be prepared more conveniently by using Raney nickel in ethanol (the $\mathcal{L}$ - and $\beta$ - isomers being isolated in 50% and 40% yields respectively when the reduction was carried out at 180°C under 150 atm. of hydrogen) and that either of the isomers can be reduced to the respective secondary piperidines by copper chromite in cyclohexane at 150°C (ca 120 atm.). However at temperatures greater than 180°C (ca 150 atm.) interconversion of isomers occurs i.e. reduction of either $\mathcal{L}$ - or $\beta$ - 4,5-diphenylpiperid-2-one gives both $\mathcal{L}$ - and $\beta$ - forms of 3,4-diphenylpiperidine. The same reduction to the secondary amine can also be accomplished using diborane. If the secondary amines are subjected to the original reduction conditions i.e. copper chromite in ethanol at 180°C and 150 atm., the N-ethyl derivatives (respective isomer only) are obtained.

Thus from these experiments it appears that the interconversion of racemates occurs at the lactam stage. The only explanation we can offer is the possibility of temperature induced isomerisation.

The ultraviolet spectra of the unsubstituted compounds
show, as expected, that the lactams and secondary and tertiary piperidines have the same chromophoric system (cf figure 15a), while the spectra of the methoxy substituted N-ethyl-3,4-diphenylpiperidines (figures 15a and b) show a bathochromic shift in the absorption presumably due to extended overlap with the lone pair on the oxygen of the methoxy group(s).

We are grateful to Professor Pauson for supplying copies of the ultraviolet spectra (and n.m.r. spectra, cf: later) of the two racemates of the trimethoxy-quinolizidine XXVIII\textsuperscript{34} (cf also figure 9). These two spectra are practically superimposable with each other and with that of the stilbene derivative XXIX. Furthermore all three are very similar to the spectra of the methoxy-substituted diphenylpiperidine derivatives (figures 15a and b). Thus introduction of a $\Delta^3$ double bond does not increase the wavelength of absorption. Presumably
steric hindrance due to the aromatic substituents prevents the molecule from attaining planarity.

The most interesting and the most informative feature of the diphenylpiperidines lies in their n.m.r. spectra. The $\mathcal{L}$ - racemate of $4,5$-diphenylpiperid-2-one has been shown by chemical methods, to have the cis-configuration. N.m.r. spectroscopy, however, provides an easier, more convenient method for distinguishing between the cis- and trans- racemates of the substituted derivatives. Although the spectra were not sufficiently resolved to determine the coupling constants of the $C_3$ and $C_4$ protons in the piperidine ring, the aromatic proton signals are characteristic of either the cis- or the trans- configuration. The cis- compounds, as expected, show considerable interaction between the two phenyl groups whereas the trans- isomers show little or no interaction.

The data recently compiled by Ballantine and Pillinger for the theoretical calculation of shielding constants was used in interpreting the n.m.r. spectra. A selection of these substituent shielding values is reproduced in table 3.

Support for our method of configuration assignment is provided by the n.m.r. spectrum of the $\mathcal{L}$ - racemate of the unsubstituted lactam (XXVI), where the aromatic proton signals appear as a complex multiplet similar to that found for the $\mathcal{L}$ - racemate of the corresponding tertiary piperidine.
TABLE 3

Substituent Shielding Values
(measured in p.p.m. from benzene)*

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$S$-ortho</th>
<th>$S$-meta</th>
<th>$S$-para</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OH</td>
<td>-0.45</td>
<td>-0.10</td>
<td>-0.40</td>
</tr>
<tr>
<td>-OR</td>
<td>-0.45</td>
<td>-0.10</td>
<td>-0.40</td>
</tr>
<tr>
<td>-NH$_2$</td>
<td>-0.55</td>
<td>-0.15</td>
<td>-0.55</td>
</tr>
<tr>
<td>-Br</td>
<td>+0.10</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>-NO$_2$</td>
<td>+0.85</td>
<td>+0.10</td>
<td>+0.55</td>
</tr>
<tr>
<td>-CHR$_2$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

* A negative sign indicates a shift to higher field.
In the n.m.r. spectrum of the unsubstituted \textit{cis}-racemate (figure 16) the aromatic proton signals occur as a complex multiplet whereas in the corresponding \textit{trans}-compound (figure 16) all ten protons appear as one singlet. As all the protons should have approximately the same chemical shift in an undisturbed environment, the multiplet of the \textit{cis}- compound must therefore result from shielding and deshielding effects arising from the proximity of the two phenyl groups.

In the monomethoxy substituted compound the \textit{cis}-racemate shows complex splitting for ring A protons, the four protons of ring B being equivalent due to shielding effects, whereas the \textit{trans}-racemate shows the splitting pattern expected from well separated phenyl groups i.e. AA'BB' doublet of doublets for ring B and a singlet for ring A (figure 17). Theoretical calculation, using the constants listed in table 3, are carried out with $\delta$ 7.05 as base value (this being the chemical shift of all ten aromatic protons in the unsubstituted \textit{trans}- racemate; representing a shielding of c.a. 0.3 p.p.m. inherent in the molecule with respect to benzene).

Ring A:
all H; $\delta = 7.05 + 0.00 = 7.05$ (obs. 7.10)

Ring B:
$H_{2''}, H_{6''}$; $\delta = 7.05 + 0.00 - 0.10 = 6.95$ (obs. 6.99)
$H_{3''}, H_{5''}$; $\delta = 7.05 + 0.00 - 0.45 = 6.60$ (obs. 6.68)
According to the data reported by Ballantine and Pillinger the protons of ring B in the dimethoxy substituted compound (XXVc) should have approximately the same chemical shift; consequently no ABX splitting is expected.

Ring A:
all H; $\delta = 7.05 + 0.00 = 7.05 \quad \text{(obs. 7.20)}$

Ring B:

$H_2''; \delta = 7.05 + 0.00 - 0.45 - 0.10 = 6.50 \quad \text{(obs. 6.60)}$

$H_5''; \delta = 7.05 + 0.00 - 0.45 - 0.10 = 6.50 \quad \text{(obs. 6.60)}$

$H_6''; \delta = 7.05 + 0.00 - 0.40 - 0.10 = 6.55 \quad \text{(obs. 6.60)}$

This is observed in the trans- isomer (figure 18) where the aromatic proton signals appear as two singlets ($\delta 7.20$, 5H, ring A and $\delta 6.60$, 3H, ring B). In contrast, the cis- isomer shows the protons of ring B resolved into an ABX system, with further meta- splitting of $C_2''$ and $C_6''$, while the protons of ring A give rise to a complex multiplet.

Of the two trimethoxy substituted racemates (XXVd) the trans- compound (figure 19) shows the expected behaviour (a three proton singlet for ring B and an AA'BB' doublet of doublets for ring A).

Ring A:

$H_2''$, $H_6''; \delta = 7.05 + 0.00 - 0.10 = 6.95 \quad \text{(obs. 7.01)}$

$H_3''$, $H_5''; \delta = 7.05 + 0.00 - 0.45 = 6.60 \quad \text{(obs. 6.70)}$

Ring B:

$H_2''$, $H_5''; \delta = 7.05 + 0.00 - 0.45 - 0.10 = 6.50 \quad \text{(obs. 6.63)}$

$H_6''; \delta = 7.05 + 0.00 - 0.40 - 0.10 = 6.55 \quad \text{(obs. 6.63)}$
The cis-isomer shows an AA'BB' doublet of doublets for ring A protons. Ring B protons give rise to an ABX system as they are made non-equivalent by shielding effects.

Only the cis isomer of the tetramethoxy substituted compound (XXVe) has been prepared. In this racemate all aromatic protons are rendered non-equivalent by ring interaction thus giving rise to two ABX systems (figure 20). A calculated hypothetical n.m.r. spectrum of the trans-racemate is also shown, based on the following calculations.

\[ J' = 7.05 + 0.00 - 0.45 - 0.10 = 6.50 \]
\[ J'' = 7.05 + 0.00 - 0.40 - 0.10 = 6.55 \]

Thus the spectrum is expected to show either one singlet (six protons) or two closely spaced singlets (three protons each); probably the latter due to the slightly different shielding effects experienced by axial and equatorial substituents.

Using this same approach it is possible to at least suggest the appearance of the n.m.r. signals of the racemates of diphenylpiperidines with a variety of substitution patterns (cf also section E).

Interpretation of the n.m.r. spectra of the cis- and trans-racemates of compound XXVIII, prepared by Paton et al., is now possible. The trans racemate shows a three proton singlet (\( J' 6.7 \)) and a poorly resolved
four proton multiplet ($\int 6.2-6.8$) analogous to the pattern shown in figure 19 for the identically substituted diphenylpiperidine. The cis-isomer shows an ABX system ($\int 6.1$, 1H, d, $J=2$Hz; $6.4$, 1H, dd, $J=9$Hz, $2$Hz; $6.6$, 1H, d, $J=9$Hz) for ring B protons while ring A protons give rise to a doublet of doublets ($\int 6.6$ and $7.2$, $J=9$Hz).

D. DIPHENYLINDOLIZIDINES

The conversion of diphenylpiperidines to the corresponding diphenylindolizidine system entails bridging of the nitrogen and the six position of the piperidine ring by a three carbon straight chain. This can be achieved, at least in theory, by using appropriate 1,3-disubstituted propane derivatives. There are of course two possible orders of attachment (initial formation of the C-N bond and subsequent ring closure onto $C_6$ or vice versa, cf: figure 11). In the construction of this "fifth" ring our experiments were confined to the use of unsubstituted diphenylpiperidines, since it can be assumed that the methoxy-substituted analogues will exhibit similar behaviour.

The route initially proposed is outlined in figure 21. Of the several publications$^{71-75}$ referring to N-alkylation of amides, the original method of Fones,$^{71}$ i.e. treatment of the sodio derivative of the amide with
an alkyl halide, proved quite successful. Thus dropwise addition of excess allyl bromide to the sodio derivative of cis-4,5-diphenylpiperid-2-one gave, in 75-80% yield, the desired N-allyl derivative (XXX). We first intended to add (anti-Markownikov 76-79) hydrogen bromide across the isolated double bond of this N-allyl derivative. However, when dry hydrogen bromide gas 80 was passed into a n-pentane solution of XXX, a crystalline product which was chromatographically (but not by melting point/mixed melting point determination) identical with the starting material, immediately separated. The infrared spectrum of the compound eventually showed, by characteristic absorption in the region 2500-2750 cm⁻¹, it to be the hydrobromide salt of cis-N-allyl-4,5-diphenylpiperid-2-one.

In order to overcome the problems of hydrogen halide addition, the alkylation was repeated with 3-chloropropanol. However this reaction (using dimethylformamide, xylene or anisole as solvent) was unsuccessful; the alcoholic group presumably reacts with the sodio derivative.

As an alternative, the more complicated route shown in figure 22 was devised. This involves protection of both the lactam nitrogen 81,82 and the hydroxy group of chloropropanol 83,84 with dihydropyran, followed by Grignard reaction, hydrolysis and reductive cyclisation. However neither the protected lactam nor the protected halide could be prepared sufficiently pure so as to be
suitable for Grignard reaction. By the use of gas chromatographic analysis of the hydrolysed reaction product (chloropropanol protected with dihydropyran) we could show the presence of both the expected chloropropanol and a considerable amount of propane-1,3-diol in the mixture, indicating that partial hydrolysis of the carbon-chlorine bond had taken place. Attempts to purify this mixture either by chromatographic filtration using alumina or by treatment with tri-n-octylphosphine in carbon tetrachloride were unsuccessful, as were the attempts to prepare the benzyl ether of chloropropanol. Formation of a Grignard reagent from the crude protected halide could not be effected either by the usual method or by entrainment with 1,2-dibromoethane. In the hope of avoiding these difficulties, the lactam was treated directly with allyl magnesium bromide in tetrahydrofuran (figure 23). However only unchanged lactam could be isolated from the reaction mixture.

Our final attempt relied on a previous synthesis of substituted indolizidines involving addition of piperidine to divinyl ketone and subsequent ring closure by the prolonged action of dry hydrogen chloride gas. It was thought that this method could, by using acrolein in place of divinyl ketone, be modified to allow the preparation of the desired indolizidine system (figure 24). Thin layer chromatography (silica in chloroform-methanol 9:1)
showed that some initial reaction between trans-3,4-diphenylpiperidine and acrolein had taken place to give approximately 60% of a basic product. This compound appeared to be quite unstable and could not be isolated. In order to bypass this unstable intermediate, the same secondary piperidine was N-alkylated with 3-chloropropionaldehyde diethyl acetal (figure 24). However in this reaction, thin layer chromatography showed not only a major basic product (approximately 60-70%) but also several other compounds from which the desired product could not be separated. In order to effect ring closure of the "correct" material formed during the reaction, the crude mixture was treated with dry hydrogen chloride gas for 24 hours. Since the thin layer chromatography pattern remained unchanged after this period, it is unlikely that indolizidine formation had taken place.
E. PHENANTHROPIPERIDINES

Several routes for the synthesis of the phenanthrene system were devised and investigated (cf: figure 11).

(a) The photolysis of iodo aromatic compounds (in particular the derivatives of ortho-iodo stilbenes) has been extensively investigated and several papers and reviews have been published. With this method of ring closure in mind, the reactions leading to the preparation of the cyanoesters were repeated with the incorporation of ortho-nitro, amino and iodo substituents.

Direct nitration of veratraldehyde with conc. nitric acid at 5-10°C gave, in almost quantitative yield, 2-nitro-4,5-dimethoxybenzaldehyde which, on Doebner condensation with malonic acid gave 88% yield of 2-nitro-4,5-dimethoxycinnamic acid (XXXI). The ethyl ester (XXXII) of this compound was prepared by the Fischer Speier method. Although this method of esterification usually provides satisfactory yields, we found that by boiling off the solvent from the reaction mixture until the product began to crystallise (apparently shifting the equilibrium), yields of up to 92% could be obtained. Attempts to prepare the corresponding amino-acid by reduction of the nitro-acid (XXXI) with ferrous ammonia were of no avail. However under these conditions the nitro-ester (XXXII) gave ethyl 2-amino-4,5-dimethoxycinnamate (XXXIII) in 91% yield (34% yield reported in the literature93).
Both the nitro-ester and the amino-ester were reacted with phenylacetonitrile as described in section B (and also using triethylamine and piperidine as catalysts with ethanol, diethyl ether and benzene as solvent). However in all these reactions only unchanged starting materials could be isolated. The consistent failure of phenylacetonitrile derivatives to add to the nitro- and amino-ethyl cinnamates can be justified on mechanistic grounds. The nitro-group of XXXII is, through solvation effects, very bulky and is therefore expected to inhibit reaction. An amino-group in the same position, by virtue of its electron donating character, makes the β-carbon of the enone system less susceptible to attack by the anion formed from phenylacetonitrile.

\[
\begin{align*}
    &\text{XXXI} & R = H & R' = \text{NO}_2 \\
    &\text{XXXII} & R = \text{Et} & R' = \text{NO}_2 \\
    &\text{XXXIII} & R = \text{Et} & R' = \text{NH}_2 \\
    &\text{XXXIV} & R = \text{Et} & R' = \text{I}
\end{align*}
\]

This problem was partly overcome by diazotisation of XXXIII and treatment of the diazonium salt with sodium iodide to give 80% yield of the iodo-ester (XXXIV).
Michael reaction of this compound with phenylacetonitrile proceeded smoothly to give the iodo-cyanoester (XXXV) in 81% yield.

\[
\begin{align*}
\text{XXXV} \\
\end{align*}
\]

Unfortunately all attempts to reductively cyclise this cyanoester were unsuccessful. The compound was unaffected by high pressure hydrogenation over both copper chromite and a modified copper chromite catalyst containing 10% barium oxide,\(^9_4\) while with Raney-nickel a complex mixture of products was obtained, none of which were readily isolable. Furthermore irradiation of XXXV with ultraviolet light (with and without iodine initiator and in various solvents) was also unsuccessful.

(b) Stilbene derivatives are known to cyclise to phenanthrenes by irradiation with ultraviolet light.\(^9_5-9_8\) In order to use this method of ring closure it was first necessary to introduce a \(\Delta^3\) double bond into the
diphenylpiperidine system (figure 25). In view of the fact that both \( C_3 \) and \( C_4 \) are benzylic positions and that introduction of a double bond between these carbons should lead to a substantial increase in conjugation, the oxidation to 3,4-diphenyl-\( \Delta^3 \)-piperideines was expected to proceed smoothly. Thus chloranil appeared to be the first choice of oxidants. However both Spence and Summons were unable to effect oxidation of cis-N-ethyl-3,4-diphenylpiperidine with this reagent. Repetition of the reaction with both cis- and trans-isomers of the same compound and with the dimethoxy analogue (XXVc), using a variety of conditions (solvents: benzene, xylene, and also in benzene under a nitrogen atmosphere with ultraviolet light) confirmed these earlier findings. Summons also showed that selenium dioxide, an oxidising agent extensively used in the steroid field,\(^{99,100}\) was also ineffective as were lead tetraacetate, mercuric chloride and palladium dehydrogenation. We modified the reaction conditions as follows: oxidation of cis- and trans-forms of XXVc with selenium dioxide in ethanol; dehydrogenation of cis- and trans-forms of XXVa and XXVb with 5% palladium on charcoal using maleic anhydride, cyclohexene and diphenyl ether as solvents; but in all cases could only isolate unchanged starting material. Attempted oxidation of XXVa (cis-isomer) with peracetic acid\(^{63}\) was also unsuccessful.

The introduction of a \( \Delta^3 \) double bond in the diphenylquinolizidine system (XXVIII) apparently does not
increase the conjugation, due to steric hindrance from substituents in the aromatic rings (cf: section C). It is possible that these same steric factors excessively increase the activation energy required for the oxidation of diphenylpiperidines.

Benzylic bromination followed by dehydrobromination is a well established method of introducing a double bond in conjugation with an existing unsaturated system. Spence, and also Summons, reported that succinimide was formed in the attempted bromination of cis-N-ethyl-3,4-diphenylpiperidine with N-bromosuccinimide (N.B.S.), indicating that some bromination must have taken place, although, in their experiments, no other products were isolated. In our attempts to prepare the 4-(or 3-) bromo-derivative (XXXVI), this benzylic bromination was carried out with a number of the available diphenylpiperidines (table 2) using several different solvents and initiators (benzoyl peroxide and ultraviolet light). When carbon tetrachloride was used as solvent we obtained a thick brown oil (probably due to immediate formation of the hydrobromide salts) which was shown, by thin layer chromatography, to contain mostly the starting material. The hydrochloride salts of the diphenylpiperidines being readily soluble in chloroform, the bromination was repeated using chloroform as solvent, at various temperatures. In all cases either the starting material was recovered or the mixture obtained was shown (by t.l.c.) to
contain only non-basic products.

Molecular bromine has also been used for benzylic and allylic brominations. Addition of bromine, in chloroform, to the cis-forms of XXVb, d and e in chloroform, gave, in each case, a mixture of basic products. With the dimethoxy derivative (XXVc) t.l.c. showed the presence of only one product which was readily isolated as its hydrochloride. Its mass spectrum confirmed substitution by one bromine atom and examination of its n.m.r. spectrum indicated that bromination had taken place in one of the aromatic rings and not at one of the benzylic positions; C_6" (XXVc) being the aromatic position most susceptible to attack by bromine. The n.m.r. spectrum of the product shows the protons of ring B as two singlets, therefore substitution cannot have gone to C_2" (which requires a doublet splitting pattern) or to C_5" (meta-splitting of H_6" and H_2" is expected as for some of the cis-racemates of the diphenylpiperidines).

Using the data listed in table 3 the expected chemical shifts for ring B protons of cis-N-ethyl-3-phenyl-4-(2'-bromo-4',5'-dimethoxyphenyl) piperidine (XXXVII) would be:

\[
\begin{align*}
H_3" & \quad \delta = 7.05 + 0.10 - 0.45 - 0.10 = 6.60 \quad (\text{obs. 7.00}) \\
H_6" & \quad \delta = 7.05 - 0.10 - 0.45 \quad = 6.50 \quad (\text{obs. 5.67})
\end{align*}
\]

Thus at first sight the observed pattern does not correspond to the calculated values. However there is a major
structural feature still to be considered, viz. the bulky nature of the bromine substituent. We can assume that this bromine atom is removed as far as possible from ring A, i.e. placing the two phenyl rings almost perpendicular to each other. The initial shielding of 0.3 p.p.m. with respect to benzene (cf: section C) is lost, simultaneously, resulting a deshielding of $H_3$". The calculated chemical shift for $H_3$", adjusted accordingly, is then:

$$\delta_1 = 6.60 + 0.30 = 6.90 \text{ (obs. 7.00)}$$

Thin layer chromatography showed that bromine in chloroform had little or no effect on the trans- isomers of the methoxy-substituted racemates, while in the case of the unsubstituted compound (XXVa) neither the cis- nor the trans- isomers reacted.

As some aromatic bromo-derivatives are also known to undergo cyclisation and coupling reactions under the influence of ultraviolet light, we irradiated XXXVII.
Unfortunately no reaction occurred in any of the solvents used (chloroform, cyclohexane, t-butanol-benzene 9:1).

(c) The final stages of this project were devoted to the preparation of intermediates carrying aromatic amino-substituents for use in the modified version of the Pschorr synthesis recently developed by Chauncy and Gellert.\textsuperscript{61}

Attempts to prepare cyanoesters with nitro- or amino-substituents in ring B were unsuccessful as described earlier. It was however necessary to determine whether or not the Michael reaction would proceed with nitro- or amino-phenylacetonitriles.

Nitration of 3,4-dimethoxyphenylacetonitrile at 50°C with conc. nitric acid gave the required ortho-nitro derivative (XXXVII) in 88-90% yield (literature: 71\textsuperscript{101}). All attempts to add XXXVII to various ethyl cinnamate derivatives were unsuccessful and each time the starting material was recovered almost quantitatively. This can be explained by the fact that a nitro group in this position not only is highly solvated but also stabilises the anion formed to the extent that it is virtually unreactive.
In contrast, an amino group in the same position would eliminate the problem of solvation and at the same time activate the anion. Unfortunately reduction of $\text{XXXVIII}$ with ferrous ammonia gave a mixture of products and only a small amount (ca 5% yield) of the required amine ($\text{XXXIX}$) was obtained in pure form. Treatment of this 2-amino-4,5-dimethoxyphenylacetonitrile with ethyl cinnamate in the presence of sodium ethoxide catalyst gave a brown solid which was shown (t.l.c.) to contain starting material plus one product which could not be isolated. Experiments designed to give an acceptable preparation of the amino-nitrile ($\text{XXXIX}$) and to determine the feasibility of the above Michael reaction are still in progress.

In the hope that the amino cyanoesters may eventually be prepared, the cis- form of the dimethoxy diphenylpiperidine ($\text{XXVc}$) was nitrated directly with conc. nitric acid. We found that, by varying the reaction time and temperature, either the mono-nitro-derivative ($\text{XXXX}$) or its dinitro-analogue ($\text{XXXXI}$) or both could be obtained as the only reaction product(s).
These derivatives were identified by their n.m.r. spectra.
For the mono-nitro-compound the shielding constant calculations are:

\[
\begin{align*}
H_3'' & \quad \sigma = 7.05 + 0.85 - 0.45 - 0.10 = 7.35 \text{ (obs. 7.38)} \\
H_6'' & \quad \sigma = 7.05 + 0.10 - 0.45 - 0.10 = 6.60 \text{ (obs. 5.64)}
\end{align*}
\]

Both nitro-derivatives show \( H_6'' \) at very high field (\( \sigma 5.64 \) and \( \sigma 5.75 \), representing a shielding of approximately 1 p.p.m. with respect to the calculated values) due to steric factors similar to those discussed for the analogous bromo-derivative (XXXVII).

Reduction of XXXX with tin/hydrochloric acid or with Raney-nickel in ethanol (80°C, 60 atm. of hydrogen) gave, after extraction of bases and evaporation of the solvent, an oil containing one major product (80-90% by t.l.c.) which appeared to be light sensitive and, at present,
could not be isolated.

Attempts to isolate the amino-diphenylpiperidine (XXXII) and to cyclise this compound by the modified Pschorr method\textsuperscript{61} are proceeding.
EXPERIMENTAL
Melting points were determined on a micro-melting point apparatus and are uncorrected. All temperatures are expressed in degrees centigrade.

Ultraviolet absorption spectra were recorded on a Perkin-Elmer 137 Ultraviolet-Visible spectrometer and infrared spectra were recorded on a Perkin-Elmer 237 infrared grating spectrometer.

Adsorbents for thin layer chromatography were silica ("Merk, Kieselgel G. nach Stahl") and alumina ("Merk, Aluminium Oxide Type E").

"T.l.c." refers to thin layer chromatography. The solvent and absorbent used are shown in brackets. Spots were developed with iodine or sulphuric acid spray.

Nuclear magnetic resonance (n.m.r.) spectra were measured on a Varian A 60 spectrometer by Mr. V. Pickels, using CDCl₃ as solvent and tetramethylsilane as an internal reference. Abbreviations used to describe the n.m.r. spectra are: s, singlet; d, doublet; dd, pair of doublets; as, asymmetric and m, multiplet.

Mass spectra were recorded on a M.S. 902 instrument by the Mass Spectrometry Unit of the University of Sydney.

Microanalyses were carried out by Dr. E. Challen of the University of New South Wales and by the Australian Microanalytical Service, Melbourne.
**3,4-Dimethoxycinnamic acid**

Doebner condensation of veratraldehyde (30g, 0.17 mole) and malonic acid (30g, 0.3 mole) in 60 ml. of pyridine and 6 ml. of piperidine at 80-90° for four hours gave, on precipitation with 300 ml. of 2N HCl and recrystallisation from ethanol, the required acid (37g, 97%) as white needles, m.p. 180° (lit. m.p. 182°).\(^{102}\)

**Ethyl 3,4-dimethoxycinnamate**

Fischer-Speier esterification of the above acid in absolute ethanol with dry hydrogen chloride as catalyst, gave the required ester as colourless prisms from ethanol, m.p. 53° (lit. m.p. 55°).\(^{103}\)

**Ethyl-4-methoxycinnamate**

Fischer-Speier esterification of 4-methoxycinnamic acid gave the required ester as colourless needles from ethanol, m.p. 50° (lit. m.p. 50°).\(^{103}\)

**Ethyl 3,4-diphenyl-4-cyanobutanoate (XXIIa).**

Sodium ethoxide catalyst (2 mmol) in ethanol (2 ml.) was added with stirring to a mixture of ethyl cinnamate (1.76g, 10 mmol) and phenylacetonitrile (1.2g, 10 mmol). Heat was evolved and after 30 min. the mixture solidified.
Recrystallisation from aqueous ethanol gave (XXIIa), (2.84 g, 97%) as colourless needles m.p. 102° (lit. m.p. 99°). Concentration of the mother liquors gave a small amount of solid which, after recrystallisation from acetone, formed colourless prisms m.p. 206°. This was evidently ethyl 4-cyano-3,4,5-triphenylcyclohexanone-2-carboxylate (XXIII), formed from 1 mol. of phenylacetonitrile and 2 mols. of ethyl cinnamate, (lit. m.p. 207-208°).

The L- Racemate of Ethyl 3-(4'-methoxyphenyl)-4-phenyl-4-cyanobutanoate (XXIIb).

A mixture of phenylacetonitrile (1.2 g, 10 mmol) and ethyl 4-methoxy cinnamate (2.1 g, 10 mmol) was warmed until molten, then sodium ethoxide catalyst (46 mg of sodium in 1 ml of absolute ethanol) was added to the melt with stirring. The mixture darkened, became quite viscous and solidified on cooling. The yellow solid was washed alternately with dilute acetic acid and water until the coloured impurities were removed. The solid remaining was dissolved in hot dioxan, precipitated with water and crystallised from ethanol to give (XXIIb), (2.75 g, 85%) as colourless needles, m.p. 108° (Found: C, 74.5; H, 6.6; N, 4.6. C_{20}H_{21}NO_{3} requires C, 74.3; H, 6.6; N, 4.3%). \( \nu \max \) (nujol) 1740 and 2240 cm\(^{-1}\).
The $L$- Racemate of Ethyl 3-(3',4'-dimethoxyphenyl)-4-phenyl-4-cyanobutanoate (XXIIc).

Using the procedure described for (XXIIb), ethyl 3,4-dimethoxycinnamate (2.36g, 10 mmol), phenylacetonitrile (1.2g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIc), (2.2g, 87%) as colourless needles from ethanol, m.p. 125° (Found: C, 71.7; H, 6.6; N, 4.2. $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.6; N, 4.0%). $\nu$ max (nujol) 1740 and 2240 cm$^{-1}$.

The $L$- Racemate of Ethyl 3-(3',4'-dimethoxyphenyl)-4-(4'-methoxyphenyl)-4-cyanobutanoate (XXIIId).

Using the procedure described for (XXIIb), ethyl 3,4-dimethoxycinnamate (2.36g, 10 mmol), 4-methoxyphenylacetonitrile (1.5g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIId), (3.26g, 85%) as colourless needles from ethanol, m.p. 128° (Found: C, 68.7; H, 6.6; N, 3.5; O, 20.9. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.6; N, 3.6; O, 20.9%). $\nu$ max (nujol) 1740 and 2240 cm$^{-1}$.

The $L$- Racemate of Ethyl 3,4-bis(3',4'-dimethoxyphenyl)-4-cyanobutanoate (XXIIe).

Using the procedure described for (XXIIb), ethyl 3,4-dimethoxycinnamate (2.36g, 10 mmol), 3,4-dimethoxyphenylacetonitrile (1.8g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIe), (3.85g, 93%) as colourless needles from ethanol, m.p. 113° (Found: C, 66.8;
The \( L \) -Racemate of Ethyl 3-phenyl-4-(4'-methoxyphenyl)-4-
 cyanobutanoate (XXIIf).

Using the procedure described for (XXIIb), ethyl cinnamate (1.76g, 10 mmol), 4-methoxyphenylacetoneitrile
(1.5g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIf),
(2.84g, 88%) as colourless needles from ethanol, m.p. 83°
(Found: C, 74.3; H, 6.5; N, 4.4. \( C_{20}H_{21}NO_3 \) requires
C, 74.4; H, 6.5; N 4.3%). \( \nu \) max (nujol) 1740 and
2240 cm\(^{-1}\).

The \( L \) -Racemate of Ethyl 3-phenyl-4-(3',4',5'-
trimethoxyphenyl)-4-
cyanobutanoate (XXIIg).

Using the procedure described for (XXIIb), ethyl cinnamate (1.76g, 10 mmol), 3,4-dimethoxyphenylacetoneitrile
(1.8g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIg),
(2.58g, 73%) as colourless needles from ethanol, m.p. 67°
(Found: C, 71.12; H, 6.60; N, 4.17. \( C_{21}H_{23}NO_4 \) requires
C, 71.36; H, 6.56; N, 3.96%). \( \nu \) max (nujol) 1740 and
2240 cm\(^{-1}\).

The \( L \) -Racemate of Ethyl 3-phenyl-4-(3',4',5'-
trimethoxyphenyl)-4-
cyanobutanoate (XXIIh).

Using the procedure described for (XXIIb), ethyl
cinnamate (1.76g, 10 mmol), 3,4,5-trimethoxyphenylacetonitrile (2.1g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIb), (3.45g, 90%) as colourless needles from ethanol, m.p. 104° (Found: C, 68.72; H, 6.43; N, 3.75. C_{22}H_{25}NO_5 requires C, 69.20; H, 6.63; N, 3.66%). ν max (nujol) 1740 and 2240 cm⁻¹.

The L- Racemate of Ethyl 3-phenyl-4-(3',4'-methylenedioxyphenyl)-4-cyanobutanoate (XXIII).

Using the procedure described for (XXIIb), ethyl cinnamate (1.76g, 10 mmol), 3,4-methylenedioxyphenylacetonitrile (1.64g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIIi), (2.73g, 81%) as colourless needles from ethanol, m.p. 101° (Found: C, 70.79; H, 5.65; N, 4.13. C_{20}H_{19}NO_4 requires C, 71.20; H, 5.68; N, 4.15%). ν max (nujol) 1740 and 2240 cm⁻¹.

The L- Racemate of Ethyl 3,4-bis(4'-methoxyphenyl)-4-cyanobutanoate (XXIIIj).

Using the procedure described for (XXIIIb), ethyl 4-methoxycinnamate (2.1g, 10 mmol), 4-methoxyphenylacetonitrile (1.5g, 10 mmol) and sodium ethoxide (2 mmol) gave (XXIIIj), (2.65g, 75%) as colourless needles from ethanol, m.p. 87° (lit. m.p. 88°).¹⁰⁴
Chromatographic Behaviour of the \( \alpha \)-Cyanoesters.

All of the cyanoesters (XXIIa-j) were examined on t.l.c. in the following systems:
silica; light petroleum (80-100\(^\circ\)), benzene, benzene-light-petroleum (1:1), chloroform, chloroform-benzene (5:1), chloroform-methanol (50:1, 19:1, 9:1), \( n \)-butanol-acetic acid - water (12:3:5).
alumina; light petroleum (80-100\(^\circ\)), benzene, chloroform, chloroform-benzene (5:1).
paper (Whatman No. 1); butanol-acetic acid-water (12:3:5).

(With silica and alumina, the adsorbent was spread, as a slurry with water, on glass plates (10 x 5 cm) and activated in a dry oven at 115\(^\circ\) for 30 min.)

In all cases, on developing with \( I_2/CHCl_3 \) spray, each compound appeared as one spot.

Preparation of Copper Chromite Catalyst. \(^{54}\)

Concentrated ammonia solution was added to a filtered solution of ammonium dichromate (50g, 0.196 mole) in 200 ml of water. The resulting yellow solution was added with stirring to cupric nitrate trihydrate (96.6g, 0.32 mole) in 120 ml of water and the immediate brown precipitate filtered, washed and dried overnight at 100\(^\circ\). The solid was then finely powdered and gently heated in a porcelain crucible until the evolution of fumes had ceased. The
residue, a fine black powder was then washed with a 10% acetic acid solution, filtered and washed with water. Twenty hours drying at 100° gave 47g of the copper chromite catalyst.

Preparation of Raney-Nickel Catalyst. 67

75g of nickel-aluminium alloy was added in small portions to a solution of 95g of sodium hydroxide in 375 ml of water at 0-20°. After the addition was complete (ca 1 hr.) the mixture was allowed to attain room temperature and then heated on a warm water bath until evolution of hydrogen ceased (ca 4 hr.). The solid was allowed to settle, the solution decanted and replaced with distilled water. This washing was repeated 20 times and a further 5 times with absolute ethanol. The catalyst was stored under absolute alcohol in tightly sealed bottles.

Preparation of Copper Chromite/10% Barium Oxide Catalyst. 94

Ammonium carbonate monohydrate (71g) in 400 ml of water was added to a solution of copper nitrate trihydrate (50g), barium nitrate (5.4g and chromium nitrate, (Cr₂(NO₃)₆·15H₂O), (77g) in 575 ml of water. The immediate blue precipitate was filtered and washed with 100 ml of water. The solid was dried overnight at 100°, ground to a fine powder and
heated to 230° to expel CO₂ and NH₃ fumes. The residual catalyst (a fine black powder) weighed 33g.

The \( \alpha^- \) and \( \beta^- \) Racemates of N-ethyl-3,4-diphenylpiperidine \( \text{XXVa} \)

The \( \alpha^- \) racemate of ethyl 3,4-diphenyl-4-cyanobutanoate (XXIIa), (5.9g, 20 mmol), and 4.5g of copper chromite catalyst in 80 ml of absolute ethanol were subjected to a hydrogen pressure of 150 atm. at 180° for 3 hr. in a high pressure cylinder. The cooled solution was filtered and the solvent removed under vacuum. The residue was dissolved in ether and the bases extracted into 1N hydrochloric acid. The acid layer was washed with ether, basified with conc. ammonia and the bases extracted into ether. The dried \( \text{MgSO}_4 \) ether solution was evaporated yielding 5.3g of a viscous oil which was shown, on t.l.c., to contain two bases. The oil was dissolved in ethanol and the solution on cooling deposited 1.9g of the \( \alpha^- \) racemate of (XXVa). The filtrate was evaporated to dryness and the oil obtained dissolved in 3 ml acetone, acidified with conc. hydrochloric acid and treated with ether. Within 20 min. the solution deposited 1.8g of the hydrochloride salt of the \( \beta^- \) racemate of (XXVa). The filtrate was concentrated and basified with conc. ammonia to give a further 1.1g of the \( \alpha^- \) racemate of (XXVa). Another 0.8g of the hydrochloride salt of the \( \beta^- \) racemate of (XXVa) was obtained, as before, from the filtrate. Recrystallisation
of the \( \alpha^- \) racemate from ethanol gave 2.9g (55\%) of colourless needles, m.p. 68° (lit. m.p. 71°).\(^43\) \( \wedge \) max (ethanol) 252 nm (log \( \varepsilon \) 2.62); 257 (2.69); 263 (2.62); \( \wedge \) infl 247 (2.53); 266 (2.51). N.m.r. signals at \( \delta \) 6.7-7.4 (10H, m, Ar protons rings A and B). The hydrochloride salt of the \( \alpha^- \) racemate crystallised as colourless needles from acetone-ether, m.p. 268° (lit. m.p. 268°).\(^43\) The hydrochloride salt of the \( \beta^- \) racemate was recrystallised from acetone-ether to give 2.53g (42\%) of colourless needles m.p. 273° (lit. m.p. 273°).\(^43\) The \( \beta^- \) racemate of (XXVa) was obtained as colourless needles from \( n \)-pentane, m.p. 35° (lit. m.p. 30°).\(^43\) \( \wedge \) max (ethanol) 252 nm (log \( \varepsilon \) 2.55); 257 (2.67); 263 (2.55); \( \wedge \) infl 247 (2.41); 266 (2.41). N.m.r. signals at \( \delta \) 7.05 (10H, s, Ar protons rings A and B).

The \( \alpha^- \) and \( \beta^- \) Racemates of N-ethyl-3-phenyl-4-(4'-methoxyphenyl) piperidine (XXVb)

Compound (XXIIb), (6.5g, 20 mmol), and 4.5g of copper chromite catalyst in 90 ml of absolute ethanol, under the conditions described for (XXVa) gave the \( \alpha^- \) racemate of (XXVb), (3.65g, 62\%) as colourless needles from ethanol, m.p. 73° (Found: C, 81.6; H, 8.6; N, 5.1. C\(_{20}\)H\(_{25}\)N\(_{0}\) requires C, 81.3; H, 8.5; N, 4.8\%) \( \wedge \) max (ethanol) 225 nm (log \( \varepsilon \) 3.62); 277 (3.07); 284 (3.03); \( \wedge \) infl 270 (2.96). N.m.r. signals at \( \delta \) 6.65 (4H, s, C\(_2^-\), C\(_3^-\), C\(_5^-\) and C\(_6^-\) - H); 6.9-7.4 (5H, m, Ar protons ring A);
The hydrochloride salt of the \( \text{L-} \) racemate of (XXVb) crystallised from acetone-ether as colourless needles, m.p. 257°.

The hydrochloride salt of the \( \beta^- \) racemate of (XXVb), (1.98g, 30%), was obtained as colourless needles from acetone-ether, m.p. 266°. The \( \beta^- \) racemate of (XXVb) crystallised as colourless needles from light petroleum (80-100°), m.p. 79°. (Found: C, 81.2; H, 8.4; N, 4.5. \( \text{C}_{20}\text{H}_{25}\text{NO} \) requires C, 81.3; H, 8.5; N, 4.8%). \( \lambda \) max (ethanol) 225 nm (log \( \varepsilon \) 4.01); 277 (3.29); 284 (3.22); \( \lambda \) inf 270 (3.18). N.m.r. signals at \( \delta \) 7.10 (5H, s, Ar protons ring A); 6.68 and 6.99 (4H, dd, J 9.0 Hz, C\(_3^-\), C\(_5^-\) and C\(_2^-\), C\(_6^-\) - H); 3.66 (3H, s, 0-CH\(_3\)).

The \( \text{L-} \) and \( \beta^- \) Racemates of N-ethyl-3-phenyl-4-(3',4'-dimethoxyphenyl) piperidine (XXVc).

Compound (XXIIc), (7.1g, 20 mmol) and 4.5 g of copper chromite catalyst in 100 ml of absolute ethanol, under the conditions described for (XXVa), gave the \( \text{L-} \) racemate of (XXVc), (3.9g, 60%), as colourless needles from ethanol, m.p. 86° (Found: C, 77.8; H, 8.4; N, 4.5. \( \text{C}_{21}\text{H}_{27}\text{NO}_2 \) requires C, 77.5; H, 8.4; N, 4.3%). \( \lambda \) max (ethanol) 227 nm (log \( \varepsilon \) 3.90); 280 (3.41); \( \lambda \) inf 284 (3.37). N.m.r. signals at \( \delta \) 7.0-7.4 (5H, m, Ar protons ring A); 6.67 (1H, as d, J 8.0 Hz, C\(_5^-\) - H); 6.51 and 6.36 (1H, dd, J 8.0 and 2.0 Hz, C\(_6^-\) - H); 6.07 (1H, as d, J 2.0 Hz,
The hydrochloride salt of the $\alpha$-racemate crystallised as colourless needles from acetone-ether, m.p. 214°.

The hydrochloride salt of the $\beta$-racemate of (XXVc), (1.96g, 27%), was obtained as colourless needles from acetone-ether, m.p. 112° (Found: C, 69.8; H, 7.7; N, 4.0. $\text{C}_{21}\text{H}_{28}\text{NClO}_2$ requires C, 69.7; H, 7.8; N, 3.9%). Basification of this salt gave the $\beta$-racemate as an oil which could not be crystallised. $\lambda$ max (ethanol) 227 nm (log $\varepsilon$ 3.81); 280 (3.43); $\lambda$ inf 284 (3.38). N.m.r. signals at $\delta$ 7.09 (5H, s, Ar protons ring A); 6.60 (3H, s, $C_2''$, $C_5''$ and $C_6''$ - H); 3.65 (3H, s, 0-CH$_3$); 3.60 (3H, s, 0-CH$_3$).

The $\alpha$- and $\beta$- Racemates of N-ethyl-3-(4'-(methoxyphenyl)-4-(3',4'-dimethoxyphenyl) piperidine (XXVd).

Compound (XXId), (7.7g, 20 mmol) and 4.5g of copper chromite catalyst in 100 ml of absolute ethanol, under the conditions described for (XXVa), gave the $\alpha$- racemate of (XXVd), (4.6g, 65%), as colourless needles from ethanol, m.p. 60° (Found: C, 74.6; H, 8.1. $\text{C}_{22}\text{H}_{29}\text{NO}_3$ requires C, 74.3; H, 8.2%). $\lambda$ max (ethanol) 226 nm (log $\varepsilon$ 4.19); 277 (3.65); $\lambda$ inf 283 (3.63). N.m.r. signals at $\delta$ 7.23 and 6.63 (4H, dd, J 9.0 Hz, $C_6'$, $C_2'$ and $C_3'$, $C_5'$ - H); 6.66 (1H, as d, J 9.0 Hz, $C_5''$ - H); 6.49 and 6.34 (1H, dd, J 9.0 and 2.0 Hz, $C_6''$ - H); 6.13
(1H, d, J 2.0 Hz, C_2'' - H); 3.81 (3H, s, O-CH_3); 3.72 (3H, s, O-CH_3); 3.57 (3H, s, O-CH_3). The hydrochloride salt of the \( \alpha \)-racemate crystallised as colourless needles from acetone-ether, m.p. 201°.

The hydrochloride salt of the \( \beta \)-racemate of (XXVd), (1.95g, 25%), was obtained as colourless needles from acetone-ether, m.p. 219° (Found: C, 67.3; H, 7.6; N, 3.8. \( \text{C}_{22}\text{H}_{30}\text{NClO}_{3} \) requires C, 67.4; H, 7.7; N, 3.6%). The \( \beta \)-racemate of (XXVd) could not be crystallised. \( \lambda \) max (ethanol) 226 nm (log 4.21); 277 (3.69); \( \lambda \) inf 383 (3.67). N.m.r. signals at \( \delta \) 6.63 (3H, s, C_2''', C_5''' and C_6''' - H); 7.01 and 6.70 (4H, dd J 9.0 Hz, C_2', C_6' and C_3', C_5' - H); 3.70 (3H, s, O-CH_3); 3.67 (3H, s, O-CH_3); 3.58 (3H, s, O-CH_3).

The \( \alpha \)-Racemate of N-ethyl-3,4-bis(3',4' -dimethoxyphenyl) piperidine (XXVe).

Compound (XXIIe), (8.3g, 20 mmol), and 4.5g of copper chromite catalyst in 100 ml of absolute ethanol, under the conditions described for (XXVa), gave the \( \alpha \)-racemate of (XXVe), (6.25g, 81%), as colourless needles from ethanol, m.p. 130° (Found: C, 72.1; H, 8.3. \( \text{C}_{23}\text{H}_{31}\text{NO}_4 \) requires C, 71.7; H, 8.1%). \( \lambda \) max (ethanol) 227 nm (log 3.92); 280 (3.54); \( \lambda \) inf 283 (3.52). N.m.r. signals at \( \delta \) 6.68 (1H, d, J 8.5 Hz, C_5'' - H); 6.47 and 6.34 (1H, dd, J 8.5 and 2.0 Hz, C_6'' - H); 6.21 (1H, d, J 2.0 Hz, C_2'' - H);
6.67 (1H, d, J 8.5 Hz, C\textsubscript{5}' - H); 6.73 and 6.87 (1H, dd, J 8.5 and 2.0 Hz, C\textsubscript{6}' - H); 7.10 (1H, d, J 2.0 Hz, C\textsubscript{2}' - H); 3.82 (6H, s, 2 x O-CH\textsubscript{3}); 3.67 (3H, s, O-CH\textsubscript{3}); 3.63 (3H, s, O-CH\textsubscript{3}). The hydrochloride salt of the \textit{L}-racemate crystallised as colourless needles from acetone-ether, m.p. 133°.

No \textit{\beta} racemate was isolated from the reduction mixture (either as the free base or as its hydrochloride salt).

The \textit{L}- and \textit{\beta}- Racemates of 4,5-Diphenylpiperid-2-one\textsuperscript{65} (XXVI)

(i) Compound (XXIIa), (5.9g, 20 mmol), and 1g of Raney-nickel\textsuperscript{67} in 100 ml of absolute ethanol, under the conditions described for (XXVa) gave the \textit{L}-lactam, (2.5g, 50%), as colourless prisms from ethanol, m.p. 194° (lit. m.p. 192-194°).\textsuperscript{65} The mother liquors were taken to dryness and the residue deposited the \textit{\beta}-racemate of (XXVI), (2.0g, 40%) as colourless needles from benzene, m.p. 176° (lit. m.p. 177°).\textsuperscript{65}

(ii) Compound (XXIIa), (4.4g, 15 mmol), and 1.5g of copper chromite catalyst in 100 ml of cyclohexane were subjected to a hydrogen pressure of 120 atm. at 150° for 3 hr. in a high pressure cylinder. The filtrate from the catalyst was evaporated to dryness, the oily residue dissolved in ether and the solution washed with 1N hydrochloric acid. The dried (MgSO\textsubscript{4}) ether layer gave
1.0g of the $\alpha$- racemate of (XXVI) as colourless prisms from ethanol, m.p. 194°; identical to that obtained from (i). T.l.c. (silica; chloroform-methanol 19:1) showed that the mother liquors contained mostly the $\alpha$- lactam together with a small amount of the $\beta$- racemate of (XXVI), chromatographically identical to that obtained from (i). The aqueous, acidic layer was basified with conc. ammonia and the bases extracted into ether. This dried (MgSO$_4$) ether solution gave 1.5g of the $\alpha$- racemate of (XXVII), (cf; below), as white plates from ethanol, m.p. 84° (lit. m.p. 84°). T.l.c. (silica; chloroform-methanol 19:1) showed that the only other base present was the $\beta$- racemate of (XXVII).

The $\alpha$- Racemate of 3,4-Diphenylpiperidine$^{65}$ (XXVII).

(i) Boron trifluoride etherate (7.0g, 4.8 mmol) in 10 ml of diglyme was added to a solution of the $\alpha$- lactam (XXVI), (0.5g, 2 mmol), and sodium borohydride (0.54g, 13 mmol) in 30 ml of diglyme at 0° over a period of 15 min. The mixture was stirred for 1 hr. at 25° and for a further 2 hr. at 70°, after which it was poured into 1N hydrochloric acid. The aqueous layer was basified with conc. ammonia and the bases extracted into ether. The dried (MgSO$_4$) ether solution gave the $\alpha$- racemate of XXVII, (0.4g), as white plates from ethanol, m.p. 84° (lit. m.p. 84°);$^{65}$ N-nitroso derivative, m.p. 109°.
(ii) The \( \alpha \)-lactam (XXVI), (0.3 g, 2 mmol), and 0.5 g of copper chromite catalyst in 20 ml of cyclohexane were subjected to a hydrogen pressure of 150 atm. at 150° for 3 hr. in a high pressure cylinder. After removal of the catalyst the solvent was distilled under vacuum and the residue obtained deposited the \( \alpha \)-racemate of XXVII, (0.4 g), as white plates from ethanol, m.p. 84° (lit. m.p. 84°). T.l.c. (silica; chloroform-methanol 9:1) showed only traces of the \( \beta \)-racemate of XXVII to be present. Repetition of the reaction at 180° (ca 150 atm.) gave an oil containing the \( \alpha \)- and \( \beta \)-racemates of XXVII in approximately equal proportions (by t.l.c., silica; chloroform-methanol 9:1).

The \( \beta \)-Racemate of 3,4-Diphenylpiperidine\(^{65}\) (XXVII).

The \( \beta \)-lactam (XXVI), (0.5 g, 2 mmol), and 0.5 g of copper chromite catalyst in 20 ml of cyclohexane were subjected to a hydrogen pressure of 150 atm. at 150° for 3 hr. in a high pressure cylinder. After removal of the catalyst the solvent was distilled under vacuum and the residue obtained deposited the \( \beta \)-racemate of XXVII, (0.45 g), as colourless needles from light petroleum (80-100°), m.p. 114° (lit. m.p. 115°). T.l.c. (silica; chloroform-methanol 9:1) showed only traces of the \( \alpha \)-racemate of XXVII to be present. Repetition of the reduction at 180° (ca 150 atm.) gave an oil containing
both $\alpha$- and $\beta$- racemates of XXVII in the ratio of approximately 1:2 (by t.l.c., silica; chloroform-methanol 9:1).

The $\alpha$- Racemate of N-ethyl-3,4-diphenylpiperidine (XXVa)

The $\alpha$- racemate of XXVII, (0.24g, 1 mmol), at 150°C and 120 atm of hydrogen with copper chromite in absolute ethanol, gave, in 90% yield, the $\alpha$- racemate of XXVa as colourless needles from ethanol, m.p. 68°C (lit. m.p. 71°C).

The $\beta$- Racemate of N-ethyl-3,4-diphenylpiperidine (XXVa)

As above, the $\beta$- racemate of XXVII gave, in 93% yield, the desired $\beta$- racemate of XXVa as colourless needles from n-pentane, m.p. 35°C (lit. m.p. 30°C).

Chromatographic Behaviour of the $\alpha$- and $\beta$- Racemates of the Diphenylpiperidines.

The $\alpha$- and $\beta$- racemates of compounds XXVa, b, c, d, e; XXVI and XXVII were examined in the following systems:

- **silica:** light petroleum 80-100°C ($R_f = 0$), benzene ($R_f = 0$), chloroform, chloroform-methanol (50:1, 19:1 and 9:1), n-butanol-acetic acid-water (12:3:5).
- **alumina:** light petroleum 80-100°C ($R_f = 0$), benzene, chloroform.
In all cases where the $R_f$ values were greater than zero, the $\alpha$-racemate had a higher $R_f$ than its counterpart.

The $\alpha$-Racemate of N-allyl-4,5-diphenylpiperid-2-one (XXX)

To a solution of the $\alpha$-racemate of 4,5-diphenylpiperid-2-one (XXVI), (2.5g, 10 mmol) in 50 ml of anisole (sodium dried) was added sodium hydride (0.25g, 10.5 mmol) and the mixture refluxed under a nitrogen atmosphere for 24 hrs. During this time the sodio derivative had precipitated from solution. The mixture was cooled to 70°, treated with allyl bromide, (2.4g, 20 mmol), and kept at this temperature, under nitrogen, until all suspended solid had reacted (ca 10 hr.). The solvent was removed under vacuum and the oil obtained deposited the required N-allyl derivative, (2.3g, 79%), as colourless needles from light petroleum (60-80°), m.p. 91° (Found: C, 82.23; H, 7.31; N, 5.05. $C_{20}H_{21}NO$ requires C, 82.39; H, 7.26; N, 4.81%). $\nu$ max 1640 (s) cm$^{-1}$.

Anti-Markownikov Addition of HBr.

Dry hydrogen bromide gas was passed into a n-pentane solution of the $\alpha$-racemate of XXX, (0.5g in 50 ml of solvent.) A white crystalline product immediately separated, m.p. 148-149°. This compound was
chromatographically identical to the starting material and was shown to be the hydrobromide salt of the \(L\)-racemate of XXX by examination of its infrared spectrum. \(\nu_{\text{max}} 1640, 2600, 2650 \text{ (broad)}, \text{cm}^{-1}\).

**N-alkylation with 3-Chloropropanol**

3-chloropropanol (1.9g, 20 mmol) was added to a suspension of the sodio-derivative of the \(L\)-racemate of XXVI (prepared as above from 2.5g of XXVI and 0.25g of sodium hydride) in anisole. The mixture was refluxed under nitrogen for 6 hr. and the solvent removed under vacuum. The oil obtained deposited 1.9g of unchanged starting material as colourless prisms from ethanol, m.p. 194°.

The reaction was repeated using dimethylformamide and xylene, however in all cases the starting material was isolated unchanged or an oil containing a complex mixture of products was obtained (t.l.c. silica; chloroform).

**Protection of the \(L\)-lactam (XXVI) with Dihydropyran.**

To a solution of the \(L\)-racemate of XXVI, (0.5g, 2 mmol) and dihydropyran (0.5 ml) in 5 ml of dry benzene was added 0.5 ml of ether saturated with HCl. The mixture was stirred at 40-50° for 1 hr. After this time, t.l.c.
(silica; chloroform-methanol 9:1) showed that no reaction had taken place. POCl₃ (2 drops) was added and the solution warmed for a further 2 hr. The solution was then poured into 50 ml of a saturated solution of sodium bicarbonate and the organic compounds extracted with ether (30 ml). Evaporation of the dried ether solution gave an oil which deposited 300 mg of colourless prisms from ethanol, m.p. 194°. Comparison of u.v. and i.r. spectra confirmed that it was unchanged starting material.

The reaction was repeated using benzene-dimethylformamide (1:1), dimethylformamide and xylene as solvent. In each case t.l.c. showed that little or no reaction had taken place and most of the starting material was recovered.

Protection of 3-Chloropropanol with Dihydropyran

Redistilled 3-chloropropanol (5.0g, 4.5 ml) was added dropwise to redistilled, sodium dried dihydropyran (5.0g, 5.5 ml) containing 2 drops of POCl₃. The mixture was stirred for 2 hr. The excess dihydropyran was distilled off and the residue fractionated under vacuum. A clear distillate, b.p. 94-96° (at 60 mm Hg) was collected; yield 6.0g. The i.r. spectrum (liq. film) of the product showed strong hydroxyl absorbance and t.l.c. (silica; chloroform) showed the presence of two compounds.
A portion (ca 0.25g) of this liquid was hydrolysed with methanolic sodium hydroxide. The distillate obtained from fractionation of the hydrolysed mixture was examined by g.l.c. Two peaks were observed. The major peak was enhanced by addition of 3-chloropropanol to the sample while the minor peak (longer retention time) was enhanced by the addition of propane-1,3-diol.

The mixture obtained from the protection reaction (0.5g) was dissolved in 10 ml of CCl₄ and the solution treated with tri-n-octylphosphine. The solution was stirred for 1 hr. and the solvent removed under vacuum. The residue was distilled (60 mm Hg) and the fraction boiling between 94 and 98° collected. T.l.c. (silica; chloroform) showed only slight improvement in the purity of the product. This distillate was dissolved in light petroleum (60-80°) and the solution filtered through an alumina column. However the hydroxy impurity was still present (t.l.c., i.r. spectrum).

This crude protected halide was dissolved in sodium dried ether and magnesium metal added to the solution. After 30 min. no reaction was apparent and addition of a crystal of iodine to the mixture produced no change. This attempted Grignard formation was repeated using a solution of the protected halide and dibromoethane (1:1). However in this case only half of the required amount of magnesium reacted.
Grignard Reaction on the \( \alpha \) Racemate of XXVI.

A solution of the \( \alpha \) racemate of XXVI, (500 mg in 20 ml of dry ether) was added to a solution of excess allyl magnesium bromide (prepared in the usual manner). The mixture was warmed to 40\(^\circ\) for 45 min. The white gum formed was decomposed with dilute sulphuric acid (40 ml of 1N). The acid layer was separated basified with conc. ammonia and extracted with ether. Evaporation of this ether solution showed that no bases were present. The non basic layer was taken to dryness and the oil obtained deposited 350 mg of unchanged starting material as colourless prisms from ethanol, m.p. 194\(^\circ\).

The reaction was repeated using tetrahydrofuran as solvent but again only unchanged starting material was isolated.

Reaction of the \( \beta \) Racemate of XXVII with Acrolein

A solution of the \( \beta \) racemate of XXVII, (0.24g, 1 mmol, in 5 ml of benzene) was added to a warm solution of acrolein (0.06g, 1.1 mmol, in 5 ml of benzene). The mixture was kept at 40-50\(^\circ\) on a water bath for 3 hr. The bases were extracted into 1N HCl and this acid layer basified with conc. ammonia and extracted with ether. The oil obtained from the dried ether layer was shown, by t.l.c., to contain a single product plus starting material. Attempts to crystallise the product were unsuccessful and
resulted in extensive decomposition (t.l.c.).

N-alkylation of the β-Racemate of XXVII.

The β-racemate of XXVII, (0.24 g, 1 mmol), fused K$_2$CO$_3$, (0.15 g, 1.1 mmol) and 3-chloropropionaldehyde diethyl acetal, (0.17 g, 1 mmol) were dissolved in 30 ml of acetone and the solution kept under reflux for 3 hr. After this time t.l.c. (silica; chloroform-methanol 9:1) showed the presence of one major product plus several minor components. The solution was filtered and taken to dryness. The oil obtained could not be crystallised.

This oil was dissolved in 20 mls of absolute ethanol and dry hydrogen chloride gas passed through the solution for 24 hr. T.l.c. showed that no change had taken place.

2-Nitro-4,5-dimethoxybenzaldehyde

Veratraldehyde (30 g, 0.17 mole) was added with stirring to 300 ml of conc. nitric acid at 5-10°. After a further 30 min. of stirring the mixture was poured into 4 l. of ice water, the product filtered and recrystallised from ethanol to give 37 g of yellow needles m.p. 131° (lit. m.p. 133°). 102

2-Nitro-4,5-dimethoxycinnamic acid

Doebner condensation of the above aldehyde (20 g) with
malonic acid (20g) gave 21g (88%) of the required nitro acid as pale yellow needles from glacial acetic acid, m.p. 294° (lit. m.p. 295°). 102

**Ethyl-2-nitro-4,5-dimethoxycinnamate**

Fischer Speier esterification of the nitro acid (44g) gave the corresponding ester (45g, 92%) as yellow needles from ethanol, m.p. 150° (lit. m.p. 152°). 102 The product was isolated directly from the reaction mixture by boiling off the solvent until crystallisation began.

**Ethyl-2-amino-4,5-dimethoxycinnamate**

A solution of the nitro ester (11g) in 250 ml of ethyl acetate and 170 ml of absolute alcohol was added, slowly to the hot reducing mixture consisting of FeSO₄·7H₂O (100g), conc. ammonia (200 ml) and water (300 ml). The mixture was kept on a boiling water bath for 2 hr., then cooled to room temperature. 600 ml of ethyl acetate was added and the mixture shaken thoroughly. The ethyl acetate layer was decanted, dried and the solvent removed under vacuum. The oil obtained deposited 9.0g (91%) of the required amino ester as yellow prisms from ethanol, m.p. 99-102° (lit. m.p. 92°). 93
Michael Reaction with the Nitro and Amino Esters

Michael reaction between phenylacetonitrile and ethyl 2-nitro-4,5-dimethoxycinnamate, as described for the preparation of XXIIb, gave an oil from which only unchanged starting material could be isolated. The reaction was repeated using the corresponding amino ester with similar results.

Ethyl-2-iodo-4,5-dimethoxycinnamate

The amino ester (5.0g) was dissolved in 200 ml of acetone, cooled to 5° and 11 ml of cold 20% H₂SO₄ added with stirring. 6 ml of iso-amyl nitrite was then added and the mixture kept below 5° for 30 min. After this time 12.0g of sodium iodide was added, in portions. The mixture was stirred until the evolution of N₂ had ceased then heated to 50° for 2 min., poured into 800 ml of water, the product filtered and crystallised, twice, from ethanol to give 7.4g (80%) of colourless needles m.p. 133°.

Ethyl-3-(2'-iodo-4',5'-dimethoxyphenyl)-4-phenyl-4-
cyanobutanoate (XXXV).

Ethyl-2-iodo-4,5-dimethoxycinnamate (3.6g, 10 mmol), phenylacetonitrile (1.2g, 10 mmol) and sodium ethoxide (2 mmol), using the procedure described for XXIIb, gave (XXXV), (3.88g, 81%), as colourless needles from ethanol,
m.p. 113° (Found: C, 52.6; H, 4.9; N, 3.3. C₂₁H₂₂NO₄I requires C, 52.7; H, 4.6; N, 2.9%). V max (nujol) 1740 and 2240 cm⁻¹.

Reduction of XXXV with Copper Chromite

Compound XXXV, (2.0g) and copper chromite catalyst (2g) in 30 ml of absolute ethanol were subjected to a hydrogen pressure of 150 atm at 180° for 6 hr. After this time t.l.c. showed that no reaction had taken place. Evaporation of the filtrate from the catalyst gave an oil which deposited 1.5g of starting material as colourless needles from ethanol, m.p. 111°.

The reaction was repeated with the modified copper chromite catalyst (containing 10% barium oxide). Again no reaction occurred.

With Raney-nickel in ethanol (180°, 150 atm.), evaporation of the solvent gave a dark oil which was shown, on t.l.c. (silica; chloroform-methanol 19:1) to contain at least seven products. No attempt was made to isolate these compounds.

Irradiation of XXXV with U.V. Light

The iodo cyanoester XXXV (2.0g), benzoyl peroxide (50 mg) and iodine (200 mg) in chloroform solution (250 ml)
were irradiated with the internally mounted U.V. lamp for 24 hr. After this time, t.l.c. showed that no reaction had taken place.

Identical results were obtained when cyclohexane or t-butanol-benzene (9:1) was used as solvent.

**Attempted Oxidation of the Diphenylpiperidines**

(i) To a solution of the L- racemate of XXVa (100 mg, in 5 ml of benzene) was added chloranil (90 mg) in 5 ml of benzene. The solution kept under reflux for 1 hr., cooled, washed with 100 ml of 1N NaOH solution, and the bases extracted into 1N HCl. The acid layer was basified with conc. ammonia and the bases extracted into ether. Evaporation of the dried ether solution gave an oil which deposited 90 mg of the starting material as colourless needles from ethanol, m.p. 68°.

The reaction was repeated with the β-racemate of XXVa and the L- racemate of XXVc using xylene and benzene (under nitrogen atmosphere) as solvents.

(ii) Selenium dioxide (100 mg) was added to a solution of the L- racemate of XXVc (100 mg, in 30 ml of absolute ethanol). The mixture was kept under reflux for 4 hr. After this time, t.l.c. (silica; chloroform-methanol 19:1) showed that no reaction had taken place. The
reaction was repeated with the \( \beta^- \) racemate of \( \text{XXVc} \) and again no oxidation occurred.

(iii) To 10 ml of maleic anhydride was added the \( \alpha^- \) racemate of \( \text{XXVb} \) (100 mg) and 100 mg of 5\% Pd/Charcoal. The mixture was refluxed for 1 hr., cooled and the solid mass dissolved in 100 ml of water, basified with conc. sodium hydroxide, extracted with ether and the ether solution washed, dried and evaporated. Crystallisation, of the oil remaining, from ethanol gave 75 mg of unchanged starting material, m.p. 73\(^\circ\). This reaction was repeated with the \( \beta^- \) racemate of \( \text{XXVb} \) in cyclohexane and with the \( \alpha^- \) and \( \beta^- \) racemates of \( \text{XXVa} \) in diphenyl ether. In each case only unchanged starting material was isolated.

(iv) 15 ml of 30\% hydrogen peroxide and 4 drops of conc. sulphuric acid were added to a solution of the \( \alpha^- \) racemate of \( \text{XXVa} \) (0.5g) in 15 ml of glacial acetic acid, and the solution heated under reflux for 3 hr. After this time t.l.c. (silica; chloroform-methanol 19:1) showed that no reaction had occurred.

**Benzylic Bromination with N.B.S.**

The \( \alpha^- \) racemate of \( \text{XXVd} \), (200mg) and benzoyl peroxide (50 mg) were dissolved in 50 ml of chloroform and the solution stirred for 30 min. T.l.c. (chloroform-methanol
19:1) showed only starting material to be present after this time. The solution was then kept under reflux for 2 hr., extracted with 1N HCl, the acid layer basified with conc. ammonia and washed with ether. Evaporation of this ether layer gave an oil which deposited 90 mg of starting material as colourless needles from ethanol, m.p. 60°. T.l.c. showed that the mother liquors contained no other bases but that the chloroform solution contained two coloured products. Neither of these non basic products could be isolated.

The reaction was repeated with the \( \alpha \)-racemates of XXVa and XXVb. In both cases no basic products were isolated.

The \( \alpha \)-Racemat of N-ethyl-3-phenyl-4-(2'-bromo-4',5'-dimethoxyphenyl) piperidine (XXXVII).

A solution of bromine (1.0g) in 50 ml. of chloroform was added dropwise to a solution of the \( \alpha \)-racemate of XXVb (2.2g) in 50 ml of chloroform, with continuous stirring. After the addition was complete the mixture was stirred for a further 90 min., concentrated to a volume of 20 ml and extracted with 1N HCl. The acid layer was basified with conc. ammonia and the bases extracted into ether. The ether solution was washed, dried and evaporated to an oil which could not be crystallised. The oil was dissolved in 5 ml of acetone and the solution treated with 2 drops of conc. HCl, and
then 5 ml of ether. Within 20 minutes the solution deposited the hydrochloride salt of the \( L \)-racemate of XXXVII, (1.0g 82\%), as colourless needles, m.p. 217° (Found: C, 56.9; H, 6.3; N, 3.3. \( \text{C}_{21}\text{H}_{26}\text{N}\text{O}_{2}\text{Br} \) requires C, 57.1; H, 6.5; N, 3.2\%). N.m.r. signals at \( \delta \) 5.67 (1H, s, \( C_6'' - H \)); 7.00 (1H, s, \( C_3'' - H \)); 7.05-7.40 (5H, m, Ar protons ring A); 3.69 (3H, s, O-CH\(_3\) ); 3.30 (3H, s, O-CH\(_3\) ).

**Irradiation of XXXVII with U.V. Light**

No reaction could be induced under any of the conditions used for the irradiation of XXXV.

**2-Nitro-4,5-dimethoxyphenylacetonitrile (XXXVIII)**

3,4-Dimethoxyphenylacetonitrile (20g) was nitrated in conc. nitric acid at 5°. The acid solution was poured into ice water (500 mls), the yellow precipitate filtered and crystallised from methylated spirits to give 22.5g (90\%) of the nitro derivative as yellow needles, m.p. 113° (lit. m.p. 113°).\(^{101}\)

Michael reaction of XXXVIII with ethyl cinnamate using the procedure described for XXIIIb gave only unchanged starting material. An examination of the reaction mixture by t.l.c. (silica; chloroform) showed that no product had been formed.
2-amino-4,5-dimethoxyphenylacetonitrile (XXXIX)

Using the procedure described for the preparation of ethyl-2-amino-4,5-dimethoxycinnamate, ferrous/ammonia reduction of XXXVIII gave, after evaporation of the ethyl acetate layer, an oil which was shown (t.l.c.: silica; chloroform-methanol 50:1) to contain two main products. Crystallisation of this oil from ethyl acetate gave a small amount (ca 5% yield) of (XXXIX) as pale cream needles, m.p. 96° (lit. m.p. 95-98°). 101

Michael Reaction with XXXIX and Ethyl Cinnamate.

Compound XXXIX (0.2g) and ethyl cinnamate (0.18g) using the procedure described for XXIIb gave a dark oil. T.l.c. (silica; chloroform-methanol 19:1) showed the presence of one product plus starting material. Attempts to complete this reaction and isolate the product are still proceeding.

The L- racemate of N-ethyl-3-(4'-nitrophenyl)-4-
(2'-nitro-4',5'-dimethoxyphenyl) piperidine (XXXXI)

The L- racemate of XXVc (3.25g, 10 mmol) was added in portions (over a period of 45 min.) to 30 ml of conc. nitric acid at 5-10°. After addition was complete the yellow solution was stirred (5°) for 20 min., then poured into an excess of ice cold sodium hydroxide solution and this mixture washed thoroughly with 60 ml of chloroform
(2 x 30 ml). The dried chloroform layer was evaporated and the oil obtained crystallised from ethanol to give the \(L\)-racemate of (XXXI), (3.26g, 78%), as cream needles, m.p. 120° (Found: C, 60.67; H, 6.18; N, 9.75.

\(\text{C}_{21}\text{H}_{25}\text{N}_{3}\text{O}_{6}\) requires C, 60.71; H, 6.07; N, 10.11%).

N.m.r. signals at \(\delta\) 5.75 (1H, s, \(\text{C}^1 - \text{H}\)); 7.32 (1H, s, \(\text{C}^3 - \text{H}\)); 7.0-7.4 (4H, m, Ar protons ring A); 3.78 (3H, s, \(0-\text{CH}_3\)); 3.35 (3H, s, \(0-\text{CH}_3\)).

The \(L\)-racemate of \(N\)-ethyl-3-phenyl-4-(2'-nitro-4',5'-dimethoxyphenyl) piperidine (XXX)

The \(L\)-racemate of XXVc (3.25g, 10 mmol) was added in portions (over a period of 25 min) to 30 ml of conc. nitric acid at 0-5°. Immediately after the addition was complete the yellow solution was poured into an excess of ice cold sodium hydroxide solution and this mixture washed with 60 ml of chloroform. The dried chloroform layer was evaporated and the oil obtained deposited the \(L\)-racemate of (XXX), (3.14g, 85%) as cream needles from ethanol, m.p. 141° (Found: C, 67.55; H, 6.96; N, 7.85. \(\text{C}_{21}\text{H}_{26}\text{N}_{2}\text{O}_4\) requires C, 68.09; H, 7.07; N, 7.56%). N.m.r. signals at \(\delta\) 5.64 (1H, s, \(\text{C}^6 - \text{H}\)); 7.38 (1H, s, \(\text{C}^3 - \text{H}\)); 7.0-7.4 (5H, m, Ar protons ring A); 3.81 (3H, s, \(0-\text{CH}_3\)); 3.30 (3H, s, \(0-\text{CH}_3\)).
The \( \text{L-} \) Racemate of N-ethyl-3-phenyl-4-(2'-amino-4',5'\-
dimethoxyphenyl) piperidine (XXXII).

(i) The \( \text{L-} \) racemate of (XXX), (100 mg), was dissolved in 3 ml of conc. HCl. Granulated tin (100 mg) was added slowly and the mixture allowed to stand for 20 min. After this time the yellow colouration had disappeared and all the metal had dissolved. The solution was then poured into a large excess of saturated sodium hydroxide solution and the bases extracted into ether. Evaporation of the dried ether layer gave an oil which could not be crystallised. T.l.c. (silica; chloroform-methanol 9:1) showed the presence of one major product (ca 80-90\% of the mixture).

(ii) Reduction of the \( \text{L-} \) racemate of (XXX) with Raney-nickel in ethanol (80°, 60 atm of hydrogen) also gave an oil containing a product chromatographically identical to that obtained above. Attempts to isolate this product are still proceeding.
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ACKNOWLEDGMENTS

The author wishes to thank Associate Professor E. Gellert for his expert guidance and supervision throughout the Honours year, 1970.

Thanks are also due to Mr. R. Rudzats, Mr. R. E. Summons, Dr. B. Chauncy and the staff of the Chemistry Department of Wollongong University College for their interest and assistance during the course of the project.

The author is also indebted to Professor P. L. Pauson for copies of the n.m.r. and u.v. spectra of three diphenylquinolizidine derivatives and to Professor B. Halpern for helpful discussions relating to the g.l.c. analyses.

Finally, the author gratefully acknowledges the financial assistance of the Australian Research Grants Committee and the Leukemia Research Foundation.