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TOTAL SYNTHESIS OF (±)-EBURNAMONINE,
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VINCADEFORMINE, (±)-QUEBRACHAMINE, AND
(±)-ASPIDOSPERMIDINE.
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TOTAL SYNTHESIS OF (+)-EBURNAMONINE, (+)-DEHYDROASPIDOSPERMIDINE, (+)-VINCADIFFORMINE, (+)-QUEBRACHAMINE, AND (+)-ASPIDOSPERMIDINE

by

Tomáš Hudlický

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

THESIS DIRECTOR'S SIGNATURE

Ernest Wender

HOUSTON, TEXAS

MAY, 1977
A tree as great as a man's embrace
springs from a small shoot;
A terrace nine stories high
begins with a pile of earth;
A journey of a thousand miles
starts under one's feet.

Lao Tsu
(from "Tao Te Ching")
To my parents
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INTRODUCTION

A study of β-aminocyclopropylcarbonyl systems is to be undertaken in order to test their hydrolytic conversion into 1,4-dicarbonyl monoimines. Such compounds possess the necessary reactive centers to combine with indole or substituted indoles to form alkaloids of the eburnamnine and Aspidosperma types. Cyclopropanations of N-acylenamines are to be investigated in this connection.
A. HISTORICAL

I. INTRODUCTION

Four major families of terpenoid indole alkaloids are represented in *Vinca rosea*¹, *Aspidosperma quebracho blanco*², *Rhazya stricta*³, and other sources⁴,⁵. Some characteristic members of these families are ajmalicine ⁹, (Heteroyohimbines), akuammicine ¹⁰, (Strychnos), catharanthine ¹¹, (Iboga), and vindoline ¹², (Aspidosperma), Fig. I.

![Chemical structures](Diagram)

**Fig. I**

The biosynthetic pathways to these alkaloids have been elucidated through the combined efforts of many research groups and have been reviewed⁸. The experimental evidence suggests that the original biogenetic hypotheses of Thomas⁶ and Wenkert⁷,¹⁰ were essentially correct,
i.e., the terpenoid alkaloids arising by an encounter of tryptamine with terpene-like precursors.

By carefully controlled germination it was possible to obtain various intermediates at different oxidation levels\(^9\). The simplified biosynthetic scheme of the terpene indole alkaloids, thus, is represented in Fig. II.

\[ \text{CH}_3\text{CO}_2\text{H} \rightarrow \text{13} \rightarrow \text{14} \rightarrow \text{15} \]

\[ \text{17} \rightarrow \text{16} \rightarrow \text{Fig. II} \]
Legend:
14 loganin
15 secologanin
16 vincoside
17 geissoschizine
18 preakuammicine
R = CO₂Me throughout

Fig. II (continued)
II. Alkaloids of the Aspidosperma Structure Type:

Despite their isolation beginning as early as 1880\textsuperscript{11}, the Aspidosperma alkaloids, Fig. III, eluded structure elucidation for nearly eighty years. The pentacyclic skeleton of aspidospermine 29, isolated from \textit{Aspidosperma quebracho blanco}\textsuperscript{12}, finally yielded to the combined efforts of chemical degradation\textsuperscript{13a,b} and x-ray crystallography\textsuperscript{13c}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{alkaloids}
\caption{Fig. III}
\end{figure}

Other members of this family were soon to follow, much of the subsequent structure determination having succeeded largely due to the characteristic mass fragmentation pattern observed for all alkaloids of this class\textsuperscript{14,34}.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{mass_fragmentation}
\caption{Mass fragmentation}
\end{figure}
There are many alkaloids substituted by various functionalities on the basic skeleton portrayed in Fig. III. The most common of these substituents are the N-acetyl group, 16-carbomethoxy group, and 11- or 12-methoxy group. Furthermore, recent isolations have brought the C-14, C-15 unsaturated analogues to almost every member of this group. They proved to be of great significance in the field of biosynthesis as well as in the rapidly expanding field of dimer alkaloid synthesis.

The structures in Fig. IV show biosynthetically related alkaloids based on skeleton 20 pertinent to the following discussion. Stork\textsuperscript{15} achieved the first total synthesis of an Aspidosperma skeleton in which he utilized an enamine alkylation in the construction of the tricyclic intermediate 37. The stereochemistry of 37 was left unexamined as it was felt that an equilibration would occur at the indolenine stage 38 giving rise to the more stable cis-fused system\textsuperscript{16}. The intramolecular \( \beta \)-addition of amine 36 avoided problems encountered earlier. On omission of the reduction step of 27 amide 41 (scheme 1, Fig. V) had been obtained, Fischer indole cyclization of which had given both 39a and 39b.

\[
\begin{align*}
\text{41} & \quad \rightarrow \quad \text{39a} \quad + \quad \text{39b}
\end{align*}
\]

Fischer cyclization of 37 gave indolenine 38 which was reduced to (\( \tau \))-aspidospermine. Employing phenylhydrazine extended this scheme to (\( \tau \))-dehydroaspidospermidine which was reduced to either (\( \tau \))-aspidospermidine or (\( \tau \))-quebrachamine according to methods used previously on the
Fig. V
optically active systems\textsuperscript{16,31}.

Ban\textsuperscript{17,18} also prepared Stork's intermediate \textsuperscript{37}, albeit by a different route. After sample comparison it was discovered that the two groups had obtained different stereoisomers. A detailed NMR analysis yielded the correct assignment of all four stereoisomers of \textsuperscript{40}. Utilization of Ban's intermediate led also to trans-aspidospermine while that of Stork led to the natural cis system. Ban's synthesis of \textsuperscript{40} made use of exhaustive Michael addition of an enolate to acrylonitrile in forming the tetrahydroquinolone \textsuperscript{37}. Reduction of the enone \textsuperscript{41} yielded two isomeric alcohols \textsuperscript{42a} and \textsuperscript{42b} which on Oppenauer oxidation yielded \textsuperscript{37}, an aminoketone of opposite stereochemistry from that of Stork.

Introduction of the five-membered ring as well as the remainder of the synthesis was performed in exactly the manner of Stork's synthesis.

NMR analysis of \textsuperscript{40} as well as the synthesis of both, trans- and cis- \textsuperscript{29b} and \textsuperscript{29a}, established the relative configurations of Stork's

\[ \text{Diagram of 40a and 40b} \]
and Ban's intermediates as 40a and 40d, respectively.

![Chemical structures](image)

Prolonged heating of either isomer of aspidospermine in HOAc resulted in their equilibration (scheme 2, Fig. VI).

Kuehne\(^{19}\) reported another preparation of the tricycle 40. Starting with proline, he constructed the indolizidine 43, which was transformed into the vinylogous amide 44 by a Robinson annelation (scheme 3, Fig. VII). This compound yielded the all cis-tricycle 40a as the only product (identical in all respects with that of Stork) on reduction with lithium aluminum hydride, while a new stereoisomer, 40b, was obtained on hydrogenation (and alcohol oxidation) of amide 44. Complete stereo-analysis was performed on all isomers of 40.

Cyclopropylimine rearrangement was the key transformation in the Stevens\(^{20}\) synthesis of 40. Suitably functionalized imine 45 yielded pyrroleine 46 on controlled pyrolysis (scheme 4, Fig. VIII). Acid
Scheme 2

Reagents: i)acrylonitrile; ii)H$_2$SO$_4$/H$_2$O; iii)Pd/H$_2$/OH$^-$, LiAlH$_4$; iv)Ni/H$_2$, LiAlH$_4$; v)K$^+$/OCMe$_3$/acetone; vi)HOAc

Fig. VI
treatment of 46 resulted in intramolecular ring closure yielding indolizidine 47, which was transformed by a base/acid sequence to a mixture of enones 48a and 48b. The major isomer 48a afforded trans-40d. Enamine alkylation led Stevens⁰⁰b to prepare 37 by yet another route, now applicable to the synthesis of Aspidosperma alkaloids oxygenated at C-18. Piperidone 49a yielded enamine 50 on controlled reduction with diisobutyl aluminum hydride. Annelation with methyl vinyl ketone and hydrogenation gave an aminoketone of trans stereochemistry. Use of lactone 51 as a starting point gave piperidone 49b, a precursor for guinolone 52 (scheme 5, Fig. IX). This was the compound which Ban had
Scheme 4

Reagents: i) NH₄Cl/Δ; ii) HCl/EtOH; iii) aq K₂CO₃; iv) MeOH/MeONa; v) MeOH/HCl; vi) LiAlH₄; vii) H₃O⁺; viii) H₂/Pd

Fig. VIII
Scheme 5

Reagents: i)H₂/Ni; ii) benzyl bromide, DMSO, K; iii) DIBAL; iv) CH₂=CHCOCH₃/glycol/Δ; v) H₂/Pd

Fig. IX

used in an attempt to synthesize limasperine 99. Increased interest in the 14,15-dehydro Aspidosperma alkaloids led to a synthesis of 14,15-dehydroaspidospermine 53, as a possible model for approaches to vindoline 12, and eventually to vinculeucoblastine, whose oncological properties received recent attention. Stork's original synthesis 15 was repeated, but the unsaturated relative of 40 was prepared in a different manner (scheme 6, Fig. X). A different approach to the pentacyclic nucleus of 5 was undertaken by Kutney 21-26. In his study, the conversions of nine-membered ring compounds such as quebrachamine 4 and 16-carbomethoxy-dihydrocleavamine 54 into the corresponding Aspidosperma pentacycles
14,15-dehydroaspidospermine 53

Scheme 6

Reagents:  i)tBuO⁻⁺/tBuOH;ii)piperidine/HOAc/PhH;iii)(OHCH₂)₂;iv)LiAlH₄; v)SO₂,DMSO,pyridine;vi)ClCH=PPH₃;vii)BuO⁻⁺/HMPA;viii)Li,salt;CH₂O;ix)PtO₂/EtOAc/NET₃;xi)MeLi/PhH/MeSO₂Cl; xii)NaNO₃; xiii)Al,Fe;xiv)H⁺;xv)Al₂O₃,chromatography

were achieved. The main emphasis was placed on the synthesis of Iboga bases together with Aspidosperma compounds for possible use in the partial synthesis of dimeric indole alkaloids. 1,2-Dehydroaspidospermidine²⁶,²⁷, aspidospermidine ²⁴,²⁷, quebrachamine ⁴,²⁷, vincadine ³⁷,²⁸,⁵⁴, vincadifformine ³,²⁸,⁵⁴ and various relatives and epimers of the above alkaloids were synthesized from a common intermediate. The transannular cyclization portrayed in Fig. XI proceeded stereospecifically to give the natural configurations in all cases.
Fig. XI

The way to the quebrachamine-type intermediates was realized by taking advantage of the ease with which the indolyl-\(\alpha\)-carbinyl substituents are cleaved\(^{27,29}\). Synthesis of the required intermediate 57 was carried out as outlined in scheme 7, Fig. XII. The simplest case of
model study:

$$\text{EtO}_2\text{C} - \text{CO}_2\text{Et} \xrightarrow{\text{i-iii}} \phi \xrightarrow{\text{iv}} \phi \xrightarrow{\text{v}} \phi \xrightarrow{\text{vi-x}} \phi \xrightarrow{\text{x}} \phi \xrightarrow{\text{xi}} 4$$

Reagents: i) EtI/NaOEt; ii) OH⁻; iii) EtOH/HCl; iv) Ph₃C⁺Na⁺/BrCH₂CO₂Et; v) tryptamine; vi) LiAlH₄; vii) Hg(QAc)₂; viii) NaBH₄; ix) BrS₃; x) MeSO₂Cl/pyridine; xi) Na/NH₃

Scheme 7

Fig. XII
an indolycloazanone 59 was prepared by Wenkert 29b by reduction of 58 with sodium-ammonia, to serve as a model for the synthesis of quebrachamine, Fig. XII. Kutney's synthesis was improved later by the substitution of the aldehyde function 61 for an ester 60. Thus, exposure of 61 to tryptamine yields 62, thereby avoiding a sequence of oxidation-reduction reactions.

\[
\text{61} \xrightarrow{1 \text{ step}} \text{62}
\]

Displacement of the quaternary salt 57 by nucleophiles, such as cyanide ion, yielded a mixture of epimers, which were functionalized suitably for latter transformation to alkaloids of the vincadifformine type. Thus, treatment of 57 with potassium cyanide in dimethylformamide, followed by hydrolysis and esterification, yielded vincadine 32 and its epimer 32a, scheme 8, Fig. XIII. Oxidation of either isomer with mercuric acetate or oxygen over platinum yielded vincadifformine 3 through stereospecific transannular cyclization.

Quebrachamine and related alkaloids with various degrees of substitution 4 were converted into aspidospermines via dehydroaspidospermines through controlled permanganate oxidation 30, followed by reduction. In
one case was generated also by zinc dust distillation of quebrachamine.$^{31}$

Scheme 8

Reagents: i)KCN; ii)OH$^-$; iii)CH$_2$N$_2$; iv)Hg(OAc)$_2$

**Fig. XIII**

The latter was synthesized by Ziegler,$^{32}$ in whose approach ring D was prepared fully functionalized by the alkylation of tetrahydropyridine 50. Condensation with indolylacetyl chloride introduced the remaining carbon atoms of 4. Polyphosphoric acid-catalyzed ring closure and reduction gave racemic 4, scheme 9, Fig. XIV. The relatively high yield of the nine-membered ring 68, (87%), was justified on the basis of the preformation of the N-acyllactam salt 67 and subsequent transacylation.
Scheme 9

Reagents: i)piperidine; ii)CH₂=CHCN; iii)HOAc/H₂O; iv)(CH₂OH)₂; v)LiAlH₄; vi)PhCHO; vii)H₂/Pd; viii)H₂O; ix)CH₃CO₂Me; x)NaBH₄; xi)H₂/Pd; xii)indolylacetyl chloride; xiii)NaOH; xiv)polyphosphoric acid; xv)LiAlH₄.

Fig. XIV
Reduction of 68 gave 69 in addition to 4. Strangely, the double bond in 69 proved resistant to further reduction.

Extension of the above work led to 14,15-dehydroquebrachamine\textsuperscript{33} 70, an Aspidosperma alkaloid related to tabersonine\textsuperscript{34}. The synthesis followed the pattern of preparation of 4. The unsaturated equivalent of enamine 50 was prepared in several steps from N-benzyl glycine. A crucial reaction involved a Claisen rearrangement for the introduction of the double bond and quaternary center (scheme 10, Fig. XV).

Tabersonine 75 was prepared by Ziegler\textsuperscript{35} using the transannular cyclization employed by Kutney\textsuperscript{21-26}. The 14,15-dehydro analog of quebrachamine led to vincadine and epivincadine also. The compound 71 was converted into the ketone amide 72. Reduction and mesylation generated the quaternary salt 73 which was taken to the vincadine relative 74 and eventually to tabersonine 75. The preparation of 71 made it possible to extend Kutney's and Ziegler's studies to the synthesis of 14,15-dehydro compounds, scheme 11, Fig. XVI.

The most recent synthesis of quebrachamine and tabersonine by Takano\textsuperscript{56} employed some novel chemistry in the synthesis of quaternary salt 57 and its unsaturated relative 73. Thioketal 76 was prepared by known methods. Base cleavage gave the thioacetal acid 77, which was condensed with tryptamine. Hydrolysis of the thioacetal functionality afforded an aldehyde, which provided the electrophilic site for condensation of the α position of indole. Reduction of the lactam ester 78, a mixture of isomers, and mesylation yielded a quaternary salt 57, identical with that obtained by Kutney, and transformed into quebrachamine by the earlier method. Unsaturated quaternary salt 73 was prepared in ten steps from lactam 78 and taken to tabersonine by the
Scheme 10

Reagents: i) several steps; ii) NaBH₄; iii) dimethylacetamide, dimethylacetal; iv) ClCO₂Me; v) KOH/methyl cellosolve; vi) MeOH/HCl

Fig. XV
Scheme 11

Reagents: i) LiAlH₄; ii) MeSO₂Cl/pyridine; iii) KCN/DMF; iv) KOH/DEG; v) CH₂N₂; vi) Pt/O₂

Fig. XVI
aforementioned methods, scheme 12, Fig. XVII.

Ziegler's synthesis\textsuperscript{36,37} of minovine 31 was modeled biogenetically\textsuperscript{7,10}. An entirely novel approach in the construction of the Aspidosperma alkaloid skeleton was investigated. Metalation of 1-methylindole proceeded well to give indolyglyoxylic acid 79. The $\alpha,\beta$-unsaturated ester 80 and the previously reported enamine 50 interacted in a Michael addition to afford the tetracyclic ester 81 as a mixture of epimers in 55% yield. NMR analysis of the esters and the corresponding alcohols indicated that the ring junction was cis. The C-16 isomerism was of no consequence for the needed stereochemistry of the final product, as this center was destroyed by the generation of the vinylogous amide 31. The tryptamine two-carbon unit was introduced in one operation by the use of ethylene dibromide and sodium carbonate in dimethylformamide. The last step afforded racemic minovine in 25% yield, scheme 13, Fig. XVIII.

Wenkert\textsuperscript{38,39} performed some model studies on an unique approach to the desethylaspidosperma system. Oxidative irradiation of nitrile 82 led to a mixture of 83a and 83b. Unfortunately, the desired isomer 83a was present in only 5% yield\textsuperscript{39} and the hindered pyridine nitrogen proved unreactive toward methiodide formation. Nitrile 82, however, was reduced and cyclized, in its hydrolyzed form to the amide 84 on catalytic hydrogenation in the presence of an acid\textsuperscript{38}. Introduction of the ethano bridge was achieved in low yield by means of bromoacetylation and solvolysis. The presence of a trans C/D junction was thought to cause the low yield ($\sim 10\%$) in the final cyclization, scheme 14, Fig. XIX.

There were several attempts to achieve total syntheses of oxygenated Aspidosperma alkaloids, especially vindoline 12, since this alkaloid constitutes a half of the drug vincaleucoblastine 85.
Scheme 12

Reagents: i) LDA,EtBr; ii) H₂SO₄; iii) pyrrolidine; iv) propane dithiol ditosylate; v) NaH/THF; vi) DCC, tryptamine; vii) MeI/CH₃CN/H₂O; viii) LiAlH₄; ix) MeSO₂Cl; x) ten steps

Fig. XVII
Reagents: i)n-BuLi; ii)(EtO₂C)₂; iii)KOH; iv)CH₂N₂; v)Ph₃P=CH₂; vi)Pd/C, H₂; vii)(CH₂Br)₂/Na₂CO₃/DMF

Fig. XVIII
Scheme 14

Reagents: 1)MeO\textsuperscript{"}Na\textsuperscript{+}; ii)I\textsubscript{2}/hv/EtOH; iii)NaBH\textsubscript{4}; iv)\textsubscript{2}O\textsubscript{2}/OH\textsuperscript{`}; v)MeOH/HCl/Pd/H\textsubscript{2}; vi)BrCH\textsubscript{2}COBr/Na\textsubscript{2}CO\textsubscript{3}/DMF

Fig. XIX
Büchi\textsuperscript{40a} completed the synthesis of vindorosine 87, which differs from vindoline by an aromatic methoxy group. The key transformation was the boron trifluoride catalyzed conversion of vinylogous amide 88 into the tetracyclic ketone 89. The reaction proceeded in 38\% yield and gave also the tetrahydro-β-carboline 90 in 20\% yield. Ketone 90 produced 89 under the reaction conditions only to the extent of 8\%. This fact demonstrated the operation of quite a different mechanism for the electrophilic substitution on β-alkylindoles than that proposed and utilized by Harley-Mason\textsuperscript{67}. Hydrolysis, condensation with acrolein and ethylation gave 91. Some further functionalizations of 91 deserve mentioning. The oxidation of keto-ester 92 with hydrogen peroxide gave the ketone 95 with complete stereochemical control. The authors rationalized this observation by proposing the hemiacetal epoxide 94 as an intermediate. Attack occurs on the ketone first giving rise to 93 which on opening gives the properly oriented hydroxylated keto-ester 95. Reduction and acetylation gave racemic 87, scheme 15, Fig. XX.

The general synthetic utility of 1-alkyl-3-acyl-tetrahydropyridines was extended to the synthesis of the desethyl Aspidosperma skeleton by
Reagents:  

i) Et₂N, EtOH;  

ii) AcCl;  

iii) BF₃·Et₂O/27 min/100°C;  

iv) HCl/H₂O;  

v) acrolein;  

vi) BF₃·OEt₂/HOAc;  

vii) tBuO⁻/K⁺/EtI;  

viii) NaH/Me₂CO₃;  

ix) H₂O₂/tBuO⁻/K⁺;  

x) LiAlH₄;  

xi) Ac₂O

Scheme 15

Fig. XX
Wenkert\textsuperscript{40c}, who previously utilized 1-alkyl pyridinium salts for the synthesis of β-carboline alkaloids in the Corynanthe\textsuperscript{field}\textsuperscript{40b}. This study paralleled Büchi's boron trifluoride catalyzed cyclization. Thus amide 96 gave the pentacyclic systems 97. Conversion to thiochetal and reduction/desulfurization afforded the saturated 98. In the absence of the C-20 ethyl group, the C/D ring junction prefers to be trans. This was observed also in the case of 98, scheme 16, Fig. XXI, although the cyclization with boron trifluoride etherate gives 97, stereospecifically.

The extension of Ban's work led to syntheses\textsuperscript{41-46} of some oxygenated alkaloids. An earlier attempt to prepare limasperine 99 and haplocine 100 failed because of unfavorable quaternarization of a precursor to 99.
Scheme 16

Reagents: 1) H₂/Pd(C); ii) DCC; iii) BF₃·Et₂O; iv) SH(CH₂)₃SH; v) LiAlH₄; vi) NiEtOH

Fig. XXI
The precursor was prepared using Stevens'\textsuperscript{20b} synthesis of \textbf{52}. The latter was carried forward as described by Stork\textsuperscript{15} to give \textbf{101}, which on attempted deprotection\textsuperscript{47} with hydrogen bromide gave salt \textbf{102}, thus establishing the unnatural stereochemistry not only in \textbf{101} but also in the original intermediate prepared by Stevens\textsuperscript{20a}.

\begin{center}
\textbf{101} \hspace{2cm} \textbf{102}
\end{center}

The desoxy analog of \textbf{104} of aspidodispermine \textbf{103} has been synthesized by Ban\textsuperscript{42} during a study of the utilization of a common intermediate for alkaloid synthesis. The syntheses of desethylaspidospermidine, \textbf{105} 7-ethyldesethylaspidospermidine\textsuperscript{45} \textbf{106}, and 4-hydroxyaspidofractinine\textsuperscript{43} \textbf{107} were accomplished as well.

The strategy of Ban's synthesis involved construction of tetracyclic intermediate \textbf{108} which could be modified at site A, to permit entry to the Aspidosperma/Iboga field, or at site B, to furnish the Strychnos skeleton\textsuperscript{43,44}, scheme 17, Fig. XXII.

The introduction of ring D was accomplished in two ways, both of which permitted entry to the Aspidosperma bases and/or 7-ethyl Iboga precursors. Alkylation of compound \textbf{109} (or \textbf{108}) with chloropropionyl chloride led to amide \textbf{110}. Hydrolysis and base treatment resulted in ring closure
to 111, which subsequently yielded the pentacycle 112. It was found that alkylation could be accomplished also by acryly chloride. The resulting amide 113 was converted to its imino ester which underwent intramolecular Michael addition to 111. There seemed to be some evidence that base treatment of chloroamide 110 afforded unsaturated amide 114, which reacted the same way as the imino ester, however in low yield. Varied substitution on either chloropropionyl chloride or acrylyl chloride permitted the synthesis of the 7-ethyl compounds, scheme 18, Fig. XXIII. Subsequently, all reactions were carried out on 10847,48. Use of this compound avoided the selectivity problems encountered on imino ester formation of 113.

A summary of the synthetic efforts in this study appeared recently47.
Reagents: i) HBr; ii) BF$_3$·Et$_2$O

**Fig. XXII**

Syntheses of desoxy-aspidodispermine 104, 4-hydroxyaspidofractinol 107, limapodine 125a, aspidofractinol 115, acetylaspidodialbine 116, fendleridine 117, and 1-acetylaspidospermidine 118 are described utilizing the N-tosylate of 112, 114, scheme 19, Fig. XXIV.

The reaction of 114 with such reagents as oxygen at low temperature, acrylonitrile, vinyl methyl sulfoxide and sulfide-sulfoxide 119 were noteworthy. Alkylation proceeded smoothly at C-20 with some degree of stereochemical control, opening the way to the hexacyclic Aspidosperma
Scheme 18

Reagents: i)\(\text{ClCH}_2\text{CH}(\text{R})\text{COCl}\); ii)\(\text{H}_2\text{O}^+\); iii)\(\text{NaOH}\); iv)\(\text{BF}_4^-\text{Et}_3\text{O}^+\); v)\(\text{CH}_2=\text{C}(\text{R})\text{COCl}\); vi)\(\text{NaH/DSMO}\); vii)\(\text{BF}_3\text{Et}_2\text{O}\)

Fig. XXIII
Reagents:  
i) NaH/DME/TsCl; ii) $\text{O}_2$/$\text{tBuO}^-\text{K}^+$/DMF/Et$_3$P; iii) LiAlH$_4$; iv) Pt/H$_2$;  
v) $\text{Ac}_2$O; vi) $\text{CH}_2=\text{CHCN}$ or $\text{CH}_2=\text{CHSOMe}$/tBuO$^-$K$^+$; vii) tBuO$^-$K$^+$;  
viii) DIBAL; ix) Ni/EtOH

Scheme 19

Fig. XXIV
alkaloids.

Treatment of tosylate 114 with oxygen and potassium tert-butoxide at low temperature in the presence of triethylphosphine gave 5-hydroxy ketone and its epimer, 119a and 119b, respectively. The cis compound, obtained in 57% yield gave 104 after reduction, scheme 19, Fig. XXIV. Curiously, the indolenine intermediate was reported \(^\text{47}\) as a stable enamine tautomer 120. 4-Hydroxyaspidofofractinine was synthesized \(^\text{43,47}\) from 114 by Michael addition to acrylonitrile \(^\text{43}\) in a model study, to afford 4-oxo-cyanoaspidofofractinine (123 - R=CN). Subsequently, the use of vinylmethylsulfoxide and base led to 122, together with some hexacyclic product 123, R=SOMe, which arose from 122 interacting with excess base. Reduction furnished 4-hydroxy-aspidofofractinine; however, there was no stereochemical control and the cis-isomers had to be separated from the reaction mixtures, scheme 19, Fig. XXIV. 4-Hydroxyaspidofofractinine was synthesized previously in a partial synthesis \(^\text{47}\) from minovicine 126, by the sequence below.
Compound 119 was utilized as an aldehyde synthon in the synthesis of fendlerine 117 and acetylaspidoalbine 116. The conjugate addition afforded two isomers of 124 in 40% yield each. Reduction gave 125 in 38% yield, which was taken to 117 and/or 116, scheme 20, Fig. XXV.

Treatment of 114 with methylvinylsulfoxide gave the conjugate addition product 122. The sulfoxide was reduced to 127 in 75% yield by the use of nickel along with the sideproduct. The latter could be converted into a mesylate and reduced to 118, scheme 21, Fig. XXVI.

A slightly different approach in the construction of the quaternary centers was employed in the final synthesis of aspidofractinine 115. Reduction of 114 to an allylic alcohol and its elimination gave diene 129. Diels-Alder reaction of 129 with nitroethylene gave the all cis system as a mixture of two isomers, 130. Removal of the nitro group was accomplished by its conversion into a diazo group and elimination. This afforded olefin 131 in 43% yield, together with an alcohol (38%) identical with epi-4-hydroxyaspidofractinine 132.

Racemic aspidofractinine was obtained by hydrogenation of 130, scheme 22, Fig. XXVII.

Saxton49 recently prepared some new Aspidosperma alkaloids bearing substituents on C-18, using the same strategy as Stork15 (i.e., preparation of tricycle 40 and Fischer indole synthesis). The substututed form of 40 was prepared from pent-4-enal 133. After the construction of the pentacyclic skeleton was completed, the original double bond in 133 served as a site for the introduction of the different functionalities of four related natural products, scheme 23, Fig. XXVIII. An analog 138 of quinolone 37, was prepared from 139 as a mixture of cis and trans isomers. The cis compound could be made more
Scheme 20

Reagents: i) LDA/DME; ii) HClO₄/CH₂CN/A; iii) separation; iv) LiAlH₄; v) H₂/Pt; vi) AcCl; vii) Hg(OAc)₂/CH₃COOH/H₂S

Fig. XXV
Scheme 21

Reagents: i)CH₂=CHSO₂Me/LDA; ii)Ni/EtOH; iii)LiAlH₄; iv)AcCl; v)PtO₂/H₂; vi)MsCl/Et₃N

Fig. XXII
Scheme 22

Reagents:  
i) NaBH₄; ii) PBr₃/benzene; iii) nitroethylene/Δ; iv) Pt/HOAc/H₂;  
v) NaN₃/ HOAc aq.; vi) Pt/EtOAc

Fig. XXVII

conveniently by a recent method of Stork⁵⁰.
Reagents: i) pyrrolidine; ii) CH₂=CHCO₂Me; iii) HOAc; iv) EtOH/NH₃; v) (CH₂OH)₂; vi) LiAIH₄; vii) H₂O; viii) C₆H₄(COCH₃)₂Cl/Na₂CO₃; ix) o-methoxyphenylezhydrine/HOAc; x) OsO₄/Na₂S₂O₄; xi) Ac₂O; xii) NH₂OH; xiii) H₂SO₄/MeOH; xiv) cinnamic acid

**Scheme 23**

*Fig. XXVIII*
Oxindole intermediates were used recently by LeMen\textsuperscript{57} in the synthesis of vincadifformine and aspidospermidine. Oxytryptamine was condensed with diester 140 to give 3-oxo-vincatine 141, scheme 24, Fig. XXIX.

![Chemical structure](image)

Scheme 24

Reagents: i)NaOAc; ii)Et\textsubscript{3}O\textsuperscript{+}BF\textsubscript{4}\textsuperscript{-}; iii)NaH; iv)P\textsubscript{2}S\textsubscript{5}; v)Ni/EtOH; vi)PPA/Δ; vii)LiAlH\textsubscript{4}

**Fig. XXIX**

The structure of vincatine 142 was proved by Harley-Mason\textsuperscript{58}, who prepared compound 141 by the method outlined above. Dilactam 141 reduced to an alcohol, which was identical in every respect with the reduction product of natural vincatine.

The search for antitumor agents led to partial syntheses of "dimeric" indole alkaloids\textsuperscript{52}. The total synthesis of vindoline 12 was
achieved by Büchi\textsuperscript{53} following much of the procedure developed in the synthesis of vindorosine. The crucial boron trifluoride-catalyzed ring closure failed to produce desired tetracycle \textsuperscript{144}, but afforded mostly tricycle \textsuperscript{143}.

This problem was solved by the use of a tosylxy group instead of the methoxy substituent and exchanging it at a later stage. The remainder of the scheme was as previously for vindorosine. The reduction of ketone \textsuperscript{145} with different hydrides gave epimeric alcohols; however, the use of DIBAL and aluminum chloride resulted in the formation of one stereoisomer presumably via a complex \textsuperscript{146}, the authors speculating that such complex would prevent hydride attack from the β-side, scheme 25, Fig. XXX.

Kutney published recently a series of papers\textsuperscript{54,55} which are extensions of his work on the Aspidosperma and Iboga bases\textsuperscript{22}. In addition to improvements of the past work, some dimer alkaloids were synthesized also.
Scheme 25

Reagents: i) AlCl$_3$/THF,DIBAL; ii) Ac$_2$O

Fig. XXX
III. Alkaloids of Vincamine Structure Type

The vincamine-like alkaloids possess the same non-tryptamine unit as Aspidosperma compounds, are characterized by pentacyclic system 147, and have been isolated from Rhazya stricta, Hunteria eburnea pichon, Aspidosperma quebracho blanco, Vinca minor, and other sources.

Co-occurrence of eburnamine and related alkaloids with major Aspidosperma alkaloids suggested a biosynthetic significance. Fig. XXXI lists the major alkaloids of this group.

The structure elucidation and first synthesis of eburnamonine was achieved by Taylor in 1960. However, the first synthesis of the basic pentacyclic ring system dates back to 1956. In a study connected with the curare alkaloids, Wieland synthesized scheme 26, Fig. XXXII. Taylor's synthesis utilized a Tiemann reaction in the construction of the substituted adipic acid derivative, which was condensed with tryptamine in acetic acid to the cis isomer, i.e., the natural stereochemistry, scheme 27, Fig. XXXIII.

Wenkert synthesized eburnamonine and its C-21 epimer in a study of general alkaloid synthesis. 1-Tryptophyl -3-acetylpyridinium bromide was hydrogenated to the vinylogous amide. Acid-catalyzed ring closure and reduction and reoxidation yielded enamine, condensation
of which with ethylidooacetate led to immonium salt 156. Reduction of 156 followed by base-catalyzed amide formation afforded eburnamonine 1 together with its epimer. Two methods of reduction, one with sodium borohydride and catalytic hydrogenation, were investigated. It was found that, while hydride reduction of either 156 or the immonium
Scheme 26

Reagents: i)EtOH/HCl;ii)K₂Cr₂O₇;iii)LiAlH₄;iv)HBr;v)NaOH;vi)NaBH₄

**Fig. XXXII**

perchlorate salt of \( \text{I} \) afforded a mixture of stereoisomers, catalytic hydrogenation of \( \text{156} \) gave a cis compound. Catalytic hydrogenation of the immonium salt of \( \text{I} \) gave the trans isomer, epi-burnamamine, scheme 28, Fig. XXXIV.

Harley-Mason\(^{65,66} \) synthesized eburnamine in a way which also set
Scheme 27

Reagents: i) CHCl₃/OH⁻; ii) H₂/Pd; iii) HNO₃; iv) H₂O/Δ; v) tryptamine, HCl/HOAc; vi) LiAlH₄; vii) CrO₃

Fig. XXXIII

A pattern for Aspidosperma-Eburnea alkaloid rearrangements. Condensation of aldehyde 157 with tryptamine led to the olefin 158. This compound rearranged smoothly into 3-methyl-19-oxo-1,2-didehydroaspidospermidine 159 on treatment with boron trifluoride. Oxidation of the
Scheme 28

Reagents: i) H₂/Pd/Et₃N; ii) HCl; iii) NH₂NH₂/KOH; iv) Hg(OAc)₂; v) HClO₄; vi) NaOH; vii) ICH₂CO₂Et; viii) H₂/Pd or NaBH₄; ix) EtO₂
olefin to the diol 160 followed by cleavage to an aldehyde gave 19-oxo eburnamine, 161, which was reduced to eburnamine with lithium aluminum hydride, scheme 29, Fig. XXXV. It was found that reduction and/or base treatment causes conversion of epieburnamine into the natural configuration, 149.

Extension of this work\textsuperscript{66} led to the synthesis of some functionalized Eburnea/Aspidosperma skeleta. Condensation of tryptamine with the substituted aldehyde 162 gave pentacycle 163. In analogy with the previous scheme this compound was taken to 164. It gave 165 with boron trifluoride, scheme 30, Fig. XXXVI. The stereochemistry was not mentioned in conjunction with this work. However, the acid-catalyzed reaction of 158 led to 159 which had the natural Aspidosperma stereochemistry. This point was proved by the synthesis of aspidospermidine\textsuperscript{67} by the same authors (see section IV). Stereochemical analysis of diol intermediates\textsuperscript{68} 160 showed that the compound 160 contained four stereoisomers. Either isomeric diol of the cis compound 160 gave eburnamine.

Saxton\textsuperscript{69-71} published a synthesis of eburnamine and homoeburnamenine 166, with full experimental details and stereochemical analysis\textsuperscript{71}.

The key step was the formation of tryptamine amide 167, which yielded 166 and epimer on oxidative cleavage cyclization and reduction, scheme 31, Fig. XXXVII. The necessary starting material, ester diol 168,
Scheme 29

Reagents: i) pyrrolidine; ii) CH₂=CHCH₂Br; iii) tryptamine; iv) BF₃·Et₂O; v) OsO₄; vi) NaIO₄; vii) LiAlH₄

Fig. XXXV
Scheme 30

Reagents:  i)tryptamine; ii)BF$_3$ Et$_2$O; iii)LiAlH$_4$; iv)OsO$_4$; v)NaIO$_4$

Fig. XXXVI

was prepared by reduction of 169. Either isomer of 166 could be epimerized to a cis-trans mixture on treatment with acetic acid. Prolonged treatment produced the all-trans compound. Acid-catalyzed closure of 173 gave approximately a 1:1 mixture of cis and trans fused systems. Oxidative cleavage of 166, followed by reduction gave a mixture of 149 and its epimer. Extension of this work led also to synthesis of vincamine 148 by oxidative cleavage of homoeburnamenine 166, scheme 32,
Reagents: i) NaBH₄; ii) P₂Os/PhH; iii) LiAlH₄; iv) DMSO/HOAc or Al(tBuO)/p-benzoquinone; v) Ph₂P=CHCO₂Et; vi) OsO₄; vii) H₂/Pd; viii) tryptamine; ix) NaIO₄; x) HÖAc; xi) Pb(OAc)₄; xii) K₂CO₃

Scheme 31

Fig. XXXVII
XXXVIII. Only the hydroxyamide 174 was obtained after vain attempts to get the corresponding keto compound. Oxidation of 174 with cupric acetate gave (±)-eburnamonine 1, while base cleavage, esterification, and reoxidation afforded vincamine 148.

![Chemical structure](image)

Reagents: i) OsO₄; ii) Me₂SO/Et₃N/pyridine/SO₃/H₂O; iii) Cu(OAc)₂, MeOH; iv) OH⁻; v) CH₂H₂

**Fig. XXXVIII**

A quite different approach to the Eburnea ring system was undertaken by Atta-Ur-Rahman. Reactions of the imine-enamine tautomers of harmaline 176 was investigated. Addition of 176 to methyl acrylate occurred readily to afford 177. Under harsher conditions more ester 179 could be obtained. The esters yielded the tetracyclic amides 178.
and 180, respectively, on exposure to base, scheme 33, Fig. XXXIX.

\[
\begin{align*}
\text{176} & \iff \text{177} \\
\text{178} & \iff \text{179}
\end{align*}
\]

Scheme 33

Reagents: i)CH$_2$=CHCO$_2$Me/RT; ii)MeOH/$\Delta$; iii)large excess of i

Fig. XXXIX

An interesting rearrangement of substituted quinuclidines led to the synthesis of dihydroeburnamine.$^{73}$ Acid treatment of 181 was found not to undergo an allylic rearrangement to 182, but afforded 183 in 75% yield.

This rearrangement was used to build up the Eburnea skeleton. o-Fluorobenzaldehyde was transformed into quinuclidine 184 which
rearranged smoothly into 185. The electron-withdrawing properties of fluorine helped to facilitate the collapse of the intermediate 186.

Introduction of the ethanamino bridge was accomplished in two ways, scheme 34, Fig. LX. Acrylamide was added to 185 to give 187, to which the aminooethyl group was added by the classical method of tryptamine synthesis. The amine 191 was pyrolyzed with a loss of ammonia. Subsequently it was found that the product, 189, could be generated by a simple sequence of reduction-oxidation and alkylation of imine 188.
Reagents:  
i) quinuclidone, HCl/NaEtO; ii) KAcO/Δ; iii) CH₂=CHCONH₂/tBuOK;  
iv) HOAc/CH₂O/HNMe₂; v) CH₂I; vi) NaCN; vii) H₂/Ni; viii) Δ; ix) LiAlH₄;  
x) Hg(ÖAc)₂/EDTA; xi) BrCH₂O/DMF/Na₂CO₃; xii) Zn/HOAc;  
xiii) Ag₂CO₃/Celite; xiv) NH₂NH₂/KOH

Fig. XL
with ethylene dibromide. Reduction of 189 gave dihydroeburnamonine as a mixture of isomers.

The procedure of Wenkert¹⁰ has been improved ⁷⁴ᵃ in yield by Potier. The approach uses an alkylation of enamine 171 with ethyl iodoacetate to give desethyliburnamonine 192 in 50% yield. Reduction of the immonium salt of 192 with borohydride gives the cis-fused system and with zinc and acid the trans compound. An alternate ring closure involved the Polonovski-Potier reaction⁷⁴ᵇ. Trifluoroacetic anhydride treatment of the N-oxide 192ᵃ gives the pentacycle 192ᵇ, which then was taken to eburnamonine.

A different approach was utilized recently by Martel⁷⁵. Tryptamine was condensed with bromoester 193. Bischler-Napieralski cyclization gave perchlorate 194, which subsequently yielded eburnamonine ¹, scheme 35, Fig. XLI.

Schlessinger⁷⁶ used a similar approach. The dianion of 195 was alkylated with methyl bromoacetate and cyclized yielding perchlorate salt 196. Reduction and ring closure gave eburnamonine and its epimer
Scheme 35

Reagents: i) K2CO3/tBuOH/Δ; ii) POCl3/PhNMMe2; iii) NH3·OH/EtOH; iv) benzoylperoxide, (EtO)2POCH2CO2Et/NaH; v) CuCl, EtMgI/THF; vi) EtO

in an overall yield of 60%, scheme 36, Fig. XLII. Eburnamonine was reduced to eburnamine and its epimer, and the mixture isomerized with base to natural steroisomer 149.

Many approaches were used in the synthesis of vincamine 14877, most cases involving oxidation of the keto-ester equivalent of 196.
Scheme 36

Reagents: i)LDA/THF,CH₂O₂CCH₂Br;ii)POCl₃/CH₃CN;iii)LiClO₄;iv)H₂/Pd;
v)MeO⁻;vi)Li₂AlH₄

Fig. XLII
IV. Interconversions of Aspidosperma and Eburnea alkaloid systems

In recent years some chemical rearrangements were brought to light interrelating the Eburnea and Aspidosperma alkaloid skeleta. A recent reviewer\textsuperscript{78} summarizes the efforts of a French group in this area. In 1967

Harley-Mason succeeded\textsuperscript{67} in converting the eburnamine-like skeleton into dehydroaspidospermidine via

intermediate \textbf{199}. Since that time alkaloids of the type \textbf{199} have been isolated\textsuperscript{4b}.

In the synthesis\textsuperscript{67} of dehydroaspidospermidine \textbf{2} the dimethylacetal of starting compound \textbf{157} had been ozonized and reduced to give alcohol \textbf{197} which now was condensed with tryptamine in acetic acid to the lactam \textbf{204}. In analogy with the previous scheme developed for 16-methyl aspidospermidine, \textbf{204} was cyclized stereospecifically to the pentacycle \textbf{198}. Reduction afforded natural aspidospermidine (scheme 37,
Fig. XLIII).

\[
\begin{align*}
\text{CH}_3O & \quad \text{OCH}_3 & \quad \text{i,ii} & \quad \text{HO} & \quad \text{CH(OCH}_3)_2 & \quad \text{CO}_2\text{Me} \\
\text{CH}_3 & \quad \text{CO}_2\text{Me} & \quad \text{iii} & \quad \text{197} & \quad \text{iii} \\
\text{198} & \quad \text{iv} & \quad \text{204} \\
5 & \quad \text{v}
\end{align*}
\]

Scheme 37

Reagents:  
\(1)\text{O}_3;\text{ii})\text{NaBH}_4;\text{iii})\text{tryptamine/HOAc;BF}_3/\text{Et}_2\text{O;v})\text{LiAlH}_4\)

Fig. XLIII

Levy and Le Men\(^{79}\) transformed vincadifformine 3 into vincamine 148 by peracid or lead tetraacetate oxidation.\(^{83}\) Compounds of the eburnamine type 149 were obtained also. The procedures for the above transformations as well as for the similar processes in the 14,15-unsaturated series are now developed to the point of commercial feasibility.\(^{83}\)

Peracid treatment of vincadifformine 3 yielded hydroxy ester 203 which upon decarboxylation gave 203a. This compound could be obtained also on peracid oxidation of dehydroaspidospermidine 2. N-Oxide 203a yielded (±)-eburnamine 149 and (−)-eburnamenine 206, by way of the vallesamine-like intermediate 205 (scheme 38, Fig. XLIV).
Reagents:  i)p-NO_2C_6H_4CO_2H; ii)HOAc; iii)Ph_3P, HOAc
Tabersonine 75 undergoes a similar rearrangement to furnish 200.

Tabersonine has been rearranged into valesamidine 201 and an ester 202, which could be transformed into vincamine\(^{83g}\) (scheme 39, Fig. XLV).

An interesting rearrangement of \((-\))-1,2-dehydroaspidospermidine N-oxide 207 was reported by Le Men\(^{80}\). Hydrolysis yielded 208 through the intermediates pictured in scheme 38, Fig. XLVIII. One of these, dihydorrhazinilam, 209, had been proposed previously as an intermediate in the oxidative conversion of dehydroaspidospermine of 2 into rhazinilam 210\(^{81}\). It is interesting to note that compound 212 (scheme 40, Fig. XLVI) could be obtained also by the reaction of \((-\))-vincadifformine 3 with an excess of m-chloroperbenzoic acid followed by acidic workup. Employment of only two equivalents of peracid gives vincamine 149\(^{82}\).

Rhazinilam 210 was the subject of a total synthesis\(^{81}\) in conjunction with the study of the oxidation of 2. In a partial synthesis, 210, occurring in Rhazya stricta, was generated from \((-\))-dehydroaspidospermidine 2 by oxidation with m-chloroperbenzoic acid in the presence of ferrous sulfate in 30\% yield. It was optically active and of the \((-\) form.
The total synthesis utilized pyrole 213 substituted with an ester grouping to direct subsequent alkylation in the desired direction. Condensation with lactone 214 gave 215 which closed intramolecularly under Friedel-Crafts conditions to generate the quaternary center in 216. Reduction of the nitro group, closure to the nine-membered lactam and decarboxylation yielded (±)-210. The lowest yielding step in the synthesis was the Friedel-Crafts reaction (50%), scheme 41, Fig. XLVII.

Scheme 39

Reagents: i)Zn,HAc/CuSO_{4}; ii)Hg(OAc); iii)NaBH_{4}; iv)NOC_{6}H_{4}NM_{2}; v)Pt/H_{2}
Scheme 40

Reagents: i) m-Cl-C₆H₄CO₂H; ii) Ph₃P/HOAc; iii) excess peracid; iv) 30% HCl

Fig. XLVI
Scheme 41

Reagents: i) NaH; ii) AlCl3/NO2CH3; iii) H2/Adams catalyst; iv) THF/DCC; v) MeOH/KOH; vi) Δ; vii) Fe(II)SO4/MCPBA

Fig. XLVII
Tabersonine has been the subject of many studies of rearrangement, most of which serve to furnish vincamine and eburnamine derivatives, useful in pharmacological research. Most of the references to these rearrangements are contained in the patent literature\(^{83}\).

An intriguing rearrangement by Levy and Le Men\(^{84}\) transformed tabersonine 75 into the esters 219 and 221. In a study\(^{85}\) aimed at the synthesis of alkaloids of meloscine type 218 (believed to be products of oxidative rearrangement of the Aspidosperma alkaloids), compound 221 (scheme 42, Fig. XLVIII) was isolated as the only product of sodium hypochlorite-induced rearrangement of 75. Quinoline 218 was not detected in the reaction mixture. The presence of 221 in the reaction mixture of a similar rearrangement\(^{84}\) of tabersonine, in which ester 219 was the major product, prompted the authors to investigate the reaction sequence in detail. Treatment of tabersonine 75 with sodium hypochlorite afforded the chloroindolenine 220. Solvolysis of 220 in tetrahydrofuran-water gave 219 and a small amount of 221, while solvolysis of 220 in water-acetone in the presence of silver perchlorate gave 221 as the major product. The following was a mechanism postulated for the above transformations. The chloroindolenine 220 is cleaved to the vincadine-type intermediate 217. Internal displacement of chloride leads to ester 219 which is transformed into 221 by an oxidation-reduction sequence.
Scheme 42

Reagents:  

i) NaOCl; ii) THF/H₂O/Δ; iii) H₂O/acetone/AgClO₄

Fig. XLVIII
V. Cyclopropanations of enamines

The strain of a cyclopropane ring and the ease with which it undergoes solvolytic opening in favor of more stable structures make substituted cyclopropanes potentially useful synthons. The many mechanistic studies of the cyclopropylcarbinyl cation system as well as its broad use in α- and β-oxycyclopropylcarbinyl rearrangements serve as examples thereof. The cyclopropanation of enol ethers and acid hydrolysis of the products have led to the development of methods for ring-enlargement, and syntheses of β,γ-unsaturated ketones, 1,4-diketones, dihydrofurans and cyclobutanones. The cyclopropylcarbinyl cation, Fig. XLIX, can be captured by nucleophiles, rearrange to a homoallylcation or cyclobutyl cation. By a choice of electron-donating substituents at various sites of the initial cation, it is possible to control the direction of unraveling.

Fig. XLIX
Rynbrandt and Dutton\textsuperscript{92} have prepared an amino-thio-cyclopropane \textit{222}, which opened on oxidation to an enaminosulfone equivalent of a 1,4-diketone, \textit{224}.

Burger\textsuperscript{93} studied the role of 2-phenyl-1-aminocyclopropane as a central nervous system agent, i.e., as a monoaminooxidase inhibitor\textsuperscript{94}, and found such a system underwent facile solvolysis in hot methanol; if the reaction was carried out in the presence of a secondary amine, the trapped species, the aminal \textit{225} could be isolated.

Pandit and de Graaf\textsuperscript{95} studied the cyclopropanation of vinylogous
amides derived from β-keto-esters. The adducts 226 hydrolyzed readily to 1,4-dicarbonyl compounds 227.

Cyclopropanation of enamines with dihalocarbenes was reported to give ring-expanded, unsaturated ketones of the type 228\textsuperscript{95}.

The cyclopropylamines can be generated in a variety of ways from methylenes or carboalkoxycarbenes\textsuperscript{96}.
Wittig\textsuperscript{97} reported generation of cyclopropylamine 229 in 78\% yield by the action of zinc-copper couple on methylene iodide in the presence of the morpholine enamine of acetophenone.

\begin{center}
\includegraphics[width=0.5\textwidth]{reaction.png}
\end{center}

Wolinsky\textsuperscript{98} and Ohno\textsuperscript{99} reported conflicting results on cyclopropanation of the piperidine enamine of cyclohexanone with dichlorocarbene. The former investigators obtained 230 which proved identical to an authentic sample prepared in a different manner, while the ring-expanded product 231 was reported in the latter study. The cyclopropylamine exhibited a remarkable stability to acid.

\begin{center}
\includegraphics[width=0.5\textwidth]{reaction2.png}
\end{center}

Elkik\textsuperscript{100} reported the aldehyde 232 from a reaction of aliphatic enamine and dichlorocarbene, followed by hydrolysis. In their continuous studies on functionalized enamines Pandit and co-workers\textsuperscript{101,95} reported cyclopropanations of enamines and dienamines. In general, the use of morpho-
line enamines gave isolable cyclopropane adducts, except in the case of dienamines. Ring expansions to chloroolefins \textsuperscript{233}, \textsuperscript{234} were observed. Using Simmons-Smith reagents permitted the conversion of \(\beta\)-keto-esters into 1,4-dicarboxyl compounds. The cyclopropanation steps proceeded in 10-55\% yields.

\[ \text{Diagram showing chemical reactions and structures} \]
Muck and Wilson reported the reaction of enamines with diazomethane to give cyclopropyl amines in high yield. The cyclic enamines gave on exposure to two equivalents of diazomethane.

\[
\begin{array}{c}
\text{N}_2R \quad \text{2CH}_2\text{N}_2 \\
\text{235} \quad \text{236}
\end{array}
\]

The search for cyclopropene resulted in at least two procedures employing cyclopropyl amines as intermediates (with the amine serving as a potential leaving group). Simmons reported preparation of in low yield (\~10\%) by the use of methylene iodide and zinc-copper couple. The product was treated with alkyllithium reagents, but failed to give.

\[
\begin{array}{c}
\text{R}_2\text{N} \quad \text{236} \\
\text{237}
\end{array}
\]

In a different attempt to form a cyclopropene, the cyclopropyl-amine was treated with base, but gave acetylene instead of a cyclopropene.
Hydrolysis of 239 afforded amide 240.

An improved procedure\textsuperscript{105} appeared recently for phase-transfer catalysis in the cyclopropanation of aliphatic enamines with chloroform and potassium t-butoxide. Yields were reported in the range of 60-95%.

Merlini reported\textsuperscript{106} that the reaction of ethyl diazoacetate with enamines over cupric sulfate or copper affords 1,3-dipolar adducts, e.g. 241.

Wenkert\textsuperscript{88b} isolated the diazoester 242 from the thermal decomposition of ethyl diazoacetate and an enamine in good yield. A copper-catalyzed equivalent reaction led to an aminocyclopropane in poor yield\textsuperscript{88a}. The latter, 243, on hydrolysis gave aldehydoester 244.
French workers observed an unusual reaction between diazooacetic ester and an imine. With the uptake of two moles of the diazo compound a cyclopropylamine was formed, whose acid hydrolysis yielded a $\gamma$-aldehydoester, Fig. L.
Pandit\textsuperscript{101a} isolated $\alpha$- and $\gamma$-alkylated cyclohexenones \textit{246}, when a dienamine was subjected to diazoacetic ester over copper and the products hydrolyzed.

\begin{equation}
\text{\textbf{246 a}} \quad + \quad \text{\textbf{246 b}}
\end{equation}

The reactions of carbenes with aromatic heterocycles is now almost a century old and has been reviewed extensively\textsuperscript{96b,c}.

Treatment of pyrrole with chloroform and base resulted in the formation of 3-halo-pyridines\textsuperscript{108}.

A study of the Tiemann reaction on indole resulted in a solution of the sixty-year old mechanistic puzzle\textsuperscript{109-111}.

It was thought originally that $\beta$-haloquinolines arise from indolenines of the type \textit{247}. However, such indolenines synthesized independently are not converted to quinolines under the reaction conditions of the Reimer-Tiemann reaction. This suggested two separate pathways to the two products, Fig. LI. The demonstration that cyclopropanes are intermediates in the ring expansions of indoles shed much light on the analogous reactions of pyrrole, furan and thiophene with halocarbenes\textsuperscript{96c}.

Recently\textsuperscript{114}, a kinetic study of products from the reaction of pyrroles with dichlorocarbene showed that the rates of formation of ring-expanded products were solvent dependent. An increased acidity of the solvents favored an increase of the rate.
Fig. LI
Pyrrole and indole derivatives were subjected to α-carbalkoxy-carbenes, generated by the thermal, copper-catalyzed decomposition of dizaoacetic esters, as early as 1899\textsuperscript{112}.

Piccinini\textsuperscript{112} isolated 2- or 3-indolyl acetic esters depending on the substitution pattern on the indole nucleus. Thus, indole could be alkylated in yields up to 60\% at temperatures up to 150°C.

\[
\text{N} \xrightarrow{\text{CO}_2\text{Et}} \text{N} \quad \text{248}
\]

\[
\text{N} \xrightarrow{\text{CO}_2\text{Et}} \text{N}
\]

Nametkin, et al.\textsuperscript{113} obtained the indole 248 in 74\% using cuprous chloride as a catalyst. Skvortsov, et al.\textsuperscript{115} studied the alkylation of pyrrole derivatives and found that it occurs predominantly on carbon-2, in analogy with electrophilic substitutions. No cyclopropane intermediates were detected.

\[
\text{R} \xrightarrow{\text{CH}_2\text{CO}_2\text{Et}} \text{R} + \text{CH}_2\text{CO}_2\text{Et}
\]

Recently, cyclopropanation of the indole nucleus with the isolation
of a cyclopropane product was reported. Wenkert\textsuperscript{116} utilized N-carbo-
methoxyindole 249, and ethyl diazoacetate and Cu-bronze, and obtained 250 in good yield. This result is in accord with an earlier observation\textsuperscript{117} that N-carboethoxy pyrrole yields the adducts 251 and 252.

\[
\text{CO}_2\text{Me} \quad \rightarrow \quad \text{CO}_2\text{Et} \\
249 \quad \rightarrow \quad 250
\]

\[
\text{R} = \text{CO}_2\text{Et} \\
\text{R} \quad + \\
251 \quad 252
\]

The stereochemistry of adducts 251 and 252 was examined by means of high-
resolution \textsuperscript{1}H-NMR spectroscopy\textsuperscript{117} and was found to be entirely analogous
with the findings of Moser\textsuperscript{118} for cyclic olefin cases. The copper-
catalyzed thermal decomposition tends to favor the more stable exo pro-
duct 253. A summary of the results for cyclohexene is shown in Fig. LIII.

\[
\text{N}_2\text{CHCO}_2\text{Et} \quad \rightarrow \quad \text{H} \quad \text{CO}_2\text{Et} \quad + \quad \text{EtO}_2\text{C} \quad \text{H} \\
253 \quad 254
\]

<table>
<thead>
<tr>
<th>mode of decomposition</th>
<th>253</th>
<th>254</th>
<th>insertion products</th>
</tr>
</thead>
<tbody>
<tr>
<td>( h\nu )</td>
<td>1.8</td>
<td>1</td>
<td>2.36</td>
</tr>
<tr>
<td>( \Delta )</td>
<td>7.1</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>( \text{Cu/\Delta} )</td>
<td>9.6</td>
<td>1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

\textit{Fig. LII}
B. Discussion

While most syntheses of Aspidosperma alkaloids incorporate the basic tryptamino nitrogen into the alkaloid skeleton by the use of tryptamine itself as a starting material, the present approach was to exclude it initially from the indolyl-β-ethyl unit. It was envisioned that a suitable tryptophyl moiety could be acted upon by the nucleophilic nitrogen of the target compound, 255, to permit the synthesis of a vincamine-like skeleton 256, or that the ethano bridge could be introduced\(^{36,37,38}\) at the later stage of a tetracyclic compound, e.g., 257, for the synthesis of Aspidosperma-like compounds.

The presence of two electrophilic centers in 255, each of which possesses different degrees of reactivity, would permit one the choice
of acid- versus base-catalyzed operations. Thus, condensation of 255 with methyl α-indolyl-acetate 258 in the presence of acid might give 260, whose treatment with base could produce the tetracycle 261. The latter contains a double bond important for possible functionalization for the preparation of vindoline-like substances. On the other hand, base-catalyzed condensation of 255 with methyl α-indolylacetate would lead to 262. Photoisomerization of the double bond\(^{39}\) in the presence of an acid would lead to 261, or reduction and acid treatment might give the saturated tetracycle 257 (scheme 43, Fig. LIII).

It appeared that such imine-aldehyde could be constructed in analogy with its oxygenated relative 263, which had been synthesized from 3-ethyldihydropyran by the following reactions\(^{119}\).

Whereas cyclopropanation of an enamine with α-diazocarbonyl reagents could be expected to be difficult (see section A-V), an acylenamine might be enough olefin-like to behave normally toward the carbenoid species. Thus, for example, N-carbomethoxyindole had been cyclopropanated in high yield and had led then to 3-indolylacetic ester 248\(^{116}\), via the intermediate cyclopropane 250.
Scheme 43

Reagents: i)methyl α-indolylacetate; ii)base; iii)acid; iv)hv/H⁺; v)reduction

Fig. LIII
A suitable analog to 3-ethyldihydropyran appeared to be the N-acylenamine 8.

![Chemical Structure](image)

A possible synthetic scheme thus consisted of three stages: a) synthesis of 8, b) cyclopropanation and unraveling of the cyclopropane ester, and c) incorporation of the imine 255 or its equivalent into the alkaloid skeleton.

In analogy with the chemistry of 3-acylindoles\textsuperscript{120} the known tetrahydropyridine 265\textsuperscript{121} was considered to be reducible with hydrides to furnish 3-ethyl-1,4,5,6-tetrahydropyridine 266.

![Chemical Structures](image)

All early attempts to reduce 265 to 266 failed. Lithium aluminum hydride in different solvents (ether, tetrahydrofuran and morpholine) and temperatures furnished only saturated alcohols and/or starting material. The reaction of 265 with phosphorus penta-chloride or trimethylxonium tetrafluoroborate followed by treatment with sodium borohydride led to complex mixtures. Selective methods for amide reduction\textsuperscript{122,130} also failed.

Subsequently it was found that reduction with lithium aluminum hydride in refluxing dioxane affords the known enamine 266\textsuperscript{32} in low yield (ca. 15\%). On a large scale enamine 266 was prepared by a modification of a published procedure\textsuperscript{32}. Acylation with methyl chloroformate
gave the desired 8 in high yield, scheme 44, Fig. LIV.

Reagents: i)piperidine/PhH; ii)CH₂=CHCN/CH₃CN; iii)HOAc/H₂O; iv)(CH₂OH)₂/H⁺; v)LiAlH₄; vi)HCl/H₂O; vii)KOH; viii)ClCO₂Me/Et₃N/THF

Fig. LIV

When 265 was treated with methyl chloroformate, two compounds, 268 and 269, were obtained. The diacyl derivative 269 was convertible into 268 by treatment with aqueous hydrochloric acid. The diacyl compound was present in the reaction mixture, even when 265 was treated with sodium hydride prior to the addition of the acylating agent. The mechanism of the formation of 268 and 269 may be portrayed as follows:
Compound 268 resembled an \( \alpha, \beta \)-unsaturated ketone as evident from its infrared spectrum (acetyl carbonyl absorption at 1620 cm\(^{-1} \)) as well as from its behavior toward 2,4-dinitrophenylhydrazine. In contrast to the inertness of 265 the N-acyl derivative formed a crystalline adduct. In view of these observations an attempt was made to reduce the ketone carbonyl group of 268.

Although various reduction techniques were tried, including one via the tosylhydrazone\(^ {123} \) of 268, only traces of \( \beta \) were found in the reaction mixtures. However, it proved possible to ketalize 268 with propane-1,3-dithiol (conceivably via its hydrobromide 270) by a procedure used previously with \( \alpha, \beta \)-unsaturated ketones\(^ {124,125} \). The yield of this reaction was only ca. 50% in view of the liberation of sideproducts.
Thus, when 268 was exposed to the dithiol and boron trifluoride etherate at or above room temperature, a mixture of compounds 271 and 272 was observed (scheme 45, Fig. LVII). Compound 271 (m/e 263) lacked the ortho-thioester methine found at δ5.21 in the $^1$H-NMR spectrum of 272 (m/e 381) as well as the mass difference corresponding to the loss of one of the dithianyl units. Temperature variations produced only changes in the relative amounts of 271 and 272. A small amount of thioketal 273 was detected when the reaction was carried out at 0°C for 10 minutes. This unusual reaction may be the consequence of the mechanistic pathway portrayed in Fig. LV.

The conjugate addition of dithiol seems to be preferred at higher temperatures. The intermediate 268a is then transformed by a series of steps to 271. The formal loss of a carbon of the starting compound occurs at the ortho-ester stage.

The use of hydrogen bromide as an acid avoids partially the conjugate addition of dithiol by formation of hydrobromide 270 which is then ketalized to give 273. The yields of the three products and the conditions of their formation are summarized in Table 1, Fig. LVI and in scheme 45, Fig. LVII.

Compound 271 was converted into 272 in "wet" chloroform containing boron trifluoride etherate. The identity of 271 and 272, established by spectral methods, was supported by their degradation to $N$-carbo-methoxy-$n$-hexylamine with Raney nickel in ethanol.

The desulfurization of 273 was effected by Raney nickel$^{125}$ in ethanol or by the use of nickelous chloride and sodium borohydride$^{126}$. The yields of this transformation were, unfortunately, not reproducible and varied from 40-95%. When the sodium borohydride method was used,
Table 1

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>271</td>
<td>272</td>
<td>273</td>
</tr>
<tr>
<td>BF₃/CHCl₃/0°C</td>
<td>70%</td>
<td>10%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>BF₃/CHCl₃/80°C</td>
<td>&lt;5%</td>
<td>82%</td>
<td>---</td>
</tr>
<tr>
<td>HBr/SH(CH₂)₃SH</td>
<td>40%</td>
<td>&lt;5%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Fig. LVI

It was found that the starting ketone 268 was present in the reaction mixture, whenever nickelous chloride was employed as its hydrate! Anhydrous salt and absolute ethanol gave only deprotected product, 8 identical in all respects with the compound obtained by acylation of 266.

With the enamide 8 in hand cyclopropanations were carried out. Initial attempts of this reaction gave only low yields¹²⁷, but it was discovered later that lack of control of the concentration of reactants and of the temperature were responsible for the early failures. However, exposure of 8 to ethyl diazoacetate¹²⁸ over freshly prepared copper-bronze¹²⁹ catalyst in the absence of solvent led to isolation of 274 as a mixture of stereoisomers in 80-90% yield. The ratio of the exo, 274a, to endo, 274b, -isomer was found to be 2:1. While ¹H-NMR spectra of the two compounds differed only slightly, the carbon chemical shifts helped to pinpoint the correct stereochemistry. Marked differences
Reagents: 1)Cl\textsubscript{2}CO\textsubscript{2}Me/Et\textsubscript{3}N/THF; ii)HCl/H\textsubscript{2}O; iii)BF\textsubscript{3}/propane dithiol/0\textdegree{}C; iv)BF\textsubscript{3}/propane dithiol/80\textdegree{}C; v)HBr,Et\textsubscript{3}O; vi)BF\textsubscript{3}/H\textsubscript{2}O; vii)propane dithiol/RT; viii)NiCl\textsubscript{2}/H\textsubscript{2}O/EtOH; ix)NiCl\textsubscript{2}/EtOH

Fig. LVII
were observed for the chemical shifts of the methylene of the ethyl group, that of the \textit{exo} isomer being shielded by 7.2 ppm due to a \( \gamma \)-effect of the neighboring ester function. The \(^1\)H-NMR analysis of the 274 isomers was complicated by the presence of two N-acyl rotamers of each stereoisomer.

The selective reduction of the ester in preference to the carbamate never was accomplished despite the use of a large variety of reducing agents\(^{122}\) and conditions. Alcohol 275 (m/e 213) could be detected in the reaction mixtures by mass spectrometry, but no preparatively useful results were obtained.

At this stage it was thought that modification of the N-acyl group\(^{153}\) might be helpful. Thus, the benzoyl urethane 276 was prepared, cyclopropanated in comparable yields and 277 tested for removal of the carbamyl unit. Most cleavage reactions, hydrogenolysis, reduction with alkali metals in liquid ammonia, hydrolyses with hydrogen bromide in acetic acid or alkali hydroxides in alcoholic solvents\(^{131-133}\), led to cyclopropane ring opening. Thus, for example, hydrogenolysis in ethyl
acetate gave 278, (m/e 199), identified by the presence of two aminomethylene in its pmr spectrum (δ 2.8), by the appearance of a singlet for the α-methylene protons (δ 2.36), and an ester carbonyl absorption at 1730 cm⁻¹ in the infrared spectrum. The piperidine 278 is the ethyl ester equivalent of the methyl ester 65 used by Ziegler 32 in his synthesis of quebrachamine (see section A-II); its preparation above is shorter and higher yielding and, thus, of possible utility.

Finally, cyclopropane 280 was prepared by the N-acylation of 266 with p-nitrobenzoyl chloride and cyclopropanation of enamide 279.

Although hydrolytic cleavage again was unsuccessful, it proved possible to reduce 280 to 281 in good yield with aluminum hydride in tetrahydrofuran 132. However, despite the survival of the cyclopropane ester 281, (m/e 332), under these conditions, the removal of the N-benzyl group was expected to be troublesome, and, thus, the scheme was abandoned.

As a consequence efforts were directed to removal of the carbo-
methoxy group of 274 by non-reducing methods. Surprisingly, the carbamate of 274 proved exceptionally resistant to acid or base hydrolysis under a variety of conditions\textsuperscript{133} and yielded only lactone 282, but in nearly quantitative yield. The presence of the carbamate was evident from the infrared carbonyl band at 1700 cm\textsuperscript{-1} in addition to the lactone carbonyl absorption at 1770 cm\textsuperscript{-1}.

\[ \text{274} \rightarrow \text{282} \]

Only one isomer 282 was formed which was assumed to be cis-fused. Various methods of deprotection were tried, including lithium iodide/dimethylformamide\textsuperscript{133e} and lithium n-butylmercaptide/hexamethylphosphoramide\textsuperscript{133d} cleavage of methoxy groups, but were only marginally successful. Hydrolysis with potassium hydroxide in the presence of cerium (IV) bisulfate\textsuperscript{134} gave the desired amino lactone 283, characterized by its infrared frequencies at 3400 and 1740 cm\textsuperscript{-1}. Again, the compound was a single isomer assumed to be cis-fused. Irreproducible yields of this transformation (30-90\%) led finally to the use of potassium hydroxide and water in diethylene glycol\textsuperscript{33}. These conditions gave yields in the range of 65-95\%.

\[ \text{274 or 282} \rightarrow \text{283} \]
Treatment of 283 with methanolic hydrogen chloride gave iminoester 6 in high yield. Complete purification was not possible, as 6 decomposed into intractable materials on chromatography. The substance in ca. 85% purity had imine and carbonyl infrared bands at 1645 and 1730 cm\(^{-1}\), respectively, and a mass of m/e 183. It was suitable for direct use in subsequent steps. Both 283 and 6 were utilized in the construction of alkaloid skeletons. A summary of the synthetic scheme of these vital intermediates appears in scheme 46, Fig. LVIII.

Synthesis of (+)-eburnamonine and (+)-epieburnamonine

The amino lactone 283 was alkylated with tryptophyl bromide\(^{135}\) under a variety of conditions (Table 2, Fig. LXI), the most reproducible of which seemed to be the phase-transfer catalyzed reaction. This produced the indolyl-lactone 285 in up to 65% yields. The remainder of the reaction mixture contained products derived from further reaction of lactone 285, i.e., eburnamonic acids and eburnamonine. Only about 15% of the reaction contained products derived from the decomposition of tryptophyl bromide. The diminution of yield of lactone 285 being due to its decomposition into eburnamonine-like products was evident from the ca. 70% yield of eburnamonines produced in an acetic acid-induced cyclization. The carbinolamine lactone 285 showed infrared bands at 3500 and 1740 cm\(^{-1}\) and had an ultra-violet spectrum characteristic of a \(\beta\)-substituted indole. It was synthesized recently in this laboratory by the route\(^{136}\) shown in scheme 47, Fig. LIX. The final products of the two different routes proved identical in every respect.

It proved very difficult to purify the lactone 285, as it readily
Scheme 46

Reagents: i) $H_2/Pd(c)$; ii) $\text{ClCO}_2\text{Me}/\text{THF/Et}_3\text{N}$; iii) $\text{HCl}/H_2O$; iv) $\text{HBr}, \text{HS(CH}_2)_3\text{SH}$; v) $\text{NiCl}_2/\text{NaBH}_4$; vi) $\text{N}_2\text{CHCO}_2\text{Et/CU}$; vii) $10\% H_2\text{SO}_4/\text{dioxane}$; viii) $\text{KOH/DEG}$; ix) $\text{MeOH/HCl}$

Fig. LVIII
Scheme 47

Reagents:  i) N₂CHCO₂Et/Cu; ii) 10% H₂SO₄/dioxane; iii) BBr₃/CH₂Cl₂; iv) 2% HCl/dioxane; v) tryptamine/DMSO, 55°C; vi) tryptophyl bromide/NaOH, PhH, H₂O/PhCH₂(Et)₃NCl⁻
decomposed into eburnamonine on chromatography. When the chromatographic separation was effected using methanol/dichloromethane as the eluting solvent, good yields of methyl eburnamonate and 21-epiburnamonate, 286a and 286b, respectively, were obtained. Heating of 285 in glacial acetic acid at 100°C yielded a 3:2 mixture of eburnamonine 1 and epiburnamonine 1a in 80% yield. Crystalline (±)-eburnamonine, m.p. 200 - 201°C, showed a carbonyl infrared absorption at 1685 and enamine band at 1625 cm⁻¹, while its epimer, m.p. 132 - 134°C, had infrared bands at 1695 and 1650 cm⁻¹, respectively. The spectral properties of 1 and 1a were identical with those reported in the literature (section A-III)¹⁰.

Distillation of 285 resulted in its decomposition into 1 in good yield. As only an insignificant trace of 1a was present in the reaction mixture, this reaction constitutes a stereospecific synthesis of the natural compound.

Exposure of imine 6 to tryptophyl bromide, potassium iodide and dimethylformamide at elevated temperatures led to a mixture of 1, 1a, 286a, 286b, as well as acids 287a and 287b, which were formed by demethylation of the ester under the reaction conditions. The identity of the eburnamonic acids and their esters was established only by mass spectroscopy (m/e 312 and 326, respectively). Their treatment with acetic acid gave 1 and 1a. The above operation is inferior to the acetic acid-catalyzed closure of 285, as a large number of products is formed. However, it may be of some value in the preparation of esters of 1, which exhibit important pharmacological properties⁷⁷d. The summary of the reactions appears in scheme 48, Fig. LX and Table 2, Fig. LXI.
Reagents: i) MeOH/HCl; ii) KI/DMF/100°C, tryptophyl bromide; iii) tryptophylbromide/NaOH/PhH, PhCH₂(Et)₃N⁺Cl⁻; iv) HOAc or BF₃; v) Δ

Scheme 48
Table 2

<table>
<thead>
<tr>
<th>Product (Yield %)</th>
<th>1</th>
<th>2</th>
<th>286a</th>
<th>286b</th>
<th>287a</th>
<th>287b</th>
</tr>
</thead>
<tbody>
<tr>
<td>285</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>60%</td>
<td>60%</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 hr.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaOH/benzene/ H$_2$O</td>
<td>10%</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhCH$_2$(Et)$_3$Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO, 55°C, sieves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kugelrohr. distillation</td>
<td>60%</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250°C/0.01 torr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HOAc/100°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Starting materials:

- CO$_2$Me
- Br
- N
- H

Fig. LXI
In order to ascertain the origin of the eburnamone isomers, each compound was exposed to the various conditions used for its preparation (boron trifluoride etherate, glacial acetic acid, dimethylformamide/potassium iodide and thermolysis in a Kugelrohr apparatus). However, only starting material in 50% yield was recovered, the remainder being decomposition products. This implied that none of the three possible C(21) epimerization modes, i.e., C(21)-H, C(21)-C(2), and C(21)-N(4) cleavages\(^ {156}\), operates on N-acylindole systems.

**Synthesis of (+)-dehydroaspidospermidine, (+)-aspidospermidine, and (+)-quebrachamine**

Although the Mannich reaction has contributed to 3-substituted indoles, except in the case of aspidospermidine, it has been exploited only minimally for the synthesis of these indoles. Van Tamelen\(^ {139}\), Wenkert\(^ {140,121}\) and others have focused on the condensation of indole with 1- or 2-piperidines under acidic conditions.

\[
\begin{align*}
\text{R}_1 = \text{CH}_2\text{CO}_2\text{Me}, \text{H} \\
\text{R}_2 = \text{H}, \text{Me}
\end{align*}
\]
In order to ascertain the origin of the eburnamonine isomers, each compound was exposed to the various conditions used for its preparation (boron trifluoride etherate, glacial acetic acid, dimethylformamide/potassium iodide and thermolysis in a Kugelrohr apparatus). However, only starting material in 50% yield was recovered, the remainder being decomposition products. This implied that none of the three possible C(21) epimerization modes, i.e., C(21)-H, C(21)-C(2), and C(21)-N(4) cleavages, operate on N-acylindole systems.

**Synthesis of (±)-dehydroaspidospermidine, (±)-aspidospermidine, and (±)-quebrachamine**

Although the Mannich condensation is a common route to 3-substituted indoles, except for intramolecular reactions it has been exploited only minimally for the synthesis of indole alkaloids. Van Tamelen, Wenkert, and others have performed studies on the condensation of indole with 1- or 2-piperideines under acidic conditions.
The piperideine 288 was generated from its trimer by use of acid or was obtained by controlled reduction of piperidone 141. The conditions of such reactions ranged from carefully controlled pH operations 139 to the use of methanolic hydrogen chloride 140.

Exposure of the imine ester 6 or lactone 283 to indole in 10% aqueous acetic acid with a trace of dioxane brought about the desired reaction, yielding a mixture of epimeric acids 292 in excellent yield. The pH of the reaction medium was approximately 6.5, apparently sufficient to bring about the equilibrium below.

\[
\begin{array}{c}
\text{N} \\
\text{O} \\
\end{array} \quad \xleftrightarrow{} \quad \begin{array}{c}
\text{N} \\
\text{O} \quad \text{COOH}
\end{array}
\]

The acids were converted to their methyl esters, 295, for spectral characterization, as they were quite insoluble in common solvents. Treatment of the mixture of acids with polyphosphoric acid at 80°C resulted in a high yield of 2:1 cis-trans ketones 293. The ketones 293 exhibited infrared and ultra-violet spectra similar to those of the ketotetrahydrocarbazole 142,143 294 (infrared carbonyl and double bond absorptions at 1645 and 1605 cm\(^{-1}\), respectively).

\[
\text{294}
\]

Several attempts to reduce the carbonyl function in 293 failed. Lithium aluminum hydride in ether or tetrahydrofuran gave only alcohols...
and an elimination product. Wolff-Kischner reduction or sodium borohydride reduction of the tosylhydrazone of either isomer gave low yields of amines. However, in agreement with the earlier observations, clean reduction of 293 was accomplished using lithium aluminum hydride in refluxing dioxane. Although the tetracycle contains two indolylcarbiny1 substituents capable of hydrogenolysis, no epimerization or over-reduction of either isomer took place. Infrared spectra of amines showed no absorption in the carbonyl region. The summary of the reactions appears in scheme 49, Fig. LXII. At this point detailed stereochemical analysis became necessary. It was accomplished by a $^{13}$C-NMR analysis of the esters and amines, Fig. LXIII.

![Chemical Structures](image)

Fig. LXIII
Scheme 49

Reagents:  
i) indole/HOAc (10% H₂O)/dioxane; ii) MeOH/HCl; iii) PPA/80°C;  
iv) LiAlH₄/dioxane, reflux

Fig. LXII
The carbon shift assignment of the methylenes was achieved by their coupling characteristics. Carbons 14 and 15 showed secondary coupling and the C-16 signal revealed large residual coupling in view of C-16 being benzylic.

As the conformations 289 and 290 for the cis isomer and 291 for the trans isomer of the tetracyclic amines indicate, C-19 suffers from two 1,3-diaxial interactions in the cis system (from C-7 and C-16 in 289 and C-14 and N-4 in 290) and four in the trans system (from C-7, C-16, C-14 and N-4). Since such non-bonded interactions express themselves in $^{13}$C-NMR spectroscopy as shielding parameters ($\gamma$-effects)\textsuperscript{157}, C-19 of the trans compound would be expected to be over 5 ppm upfield of the same carbon signal of the cis isomer. Furthermore, the cis arrangement of H-21 and the ethyl group in the cis isomer permit C-18 to exert a

$\gamma$-effect on C-21, an effect not possible in the trans isomer. This would shield C-21 in the cis compound relative to the trans substance. These facts permit differentiation of the isomeric amines.

On the assumption of the indolyl unit being equatorial in both aminoester isomers 295 one compound must possess an axial ethyl group
and the other an axial acetic ester sidechain. Since the methylene of the axial substituent must be shielded relative to the same carbon in an equatorial orientation, the chemical shift relationship of the methylenes of the ethyl and acetic ester function are diagnostic of the stereochemistry of the aminoesters 295. This assignment fits the stereochemistry of the tetracyclic amines 296.

Although the ratio of the isomeric acids 292 in the initial condensation remained unknown, the ketones 293 were obtained in a ca. 2:1 cis-trans ratio.

The last stage of the synthesis consisted of the introduction of the ethano indole-N-4 bridge. Ziegler's\textsuperscript{36,37} method of alkylation with ethylene dibromide in dimethylformamide produced only trace amounts of dehydroaspidospermidine.

In view of Harley-Mason's experience with alcohol 204 (section A-IV and below), it was thought that an analogous reaction may take place in the case of alcohol 298.
Alkylation of 296a with bromoethanol, ethylene oxide or ethyl bromoacetate in dimethylsulfoxide or dimethylformamide also led to only traces of desired products. However, when methyl bromoacetate was used as both reagent and solvent, almost a quantitative yield of ester 299 was obtained, scheme 50, Fig. LXIII. This compound was reduced to alcohol 298 with lithium aluminum hydride in tetrahydrofuran in good yield. Alkylation with bromoethanol as reagent and solvent in the presence of sodium carbonate at elevated temperature gave an excellent yield of 298.

\[
\begin{array}{c}
\text{HO} \\
\text{296a} \\
\text{298}
\end{array}
\]

Whereas exposure of alcohol 298 to boron trifluoride etherate at 100°C gave a low yield of product, treatment of alcohol with methanesulfonyl chloride followed by solvolysis in refluxing acetic acid gave moderate yields of 2. Finally, alkylation of 296a with ethylene dibromide as reagent and solvent in the presence of sodium carbonate yielded 2 in 20-45%. The product exhibited an imine infrared band at 1590 cm\(^{-1}\) and was spectrally identical with dehydroaspidospermidine 2, obtained by the known decarboxylation of natural vincadifformine 147.

\[
\begin{array}{c}
\text{HCl} \\
\Delta \\
3 \\
\text{CO}_2\text{Me} \\
\rightarrow \\
2
\end{array}
\]
Scheme 50

Reagents:  
i) BrCH₂CO₂Me/Na₂CO₃; ii) HOCH₂CH₂Br/Na₂CO₃; iii) LiAlH₄;  
iv) NaCl/C₆H₅; v) H₂O; vi) BrCH₂CH₂Br/Na₂CO₃;  
vii) NaBH₄/80°C/EtOH; viii) NaBH₄/EtOH/0°C
Dehydroaspidospermidine was reduced by known methods\textsuperscript{15,148} to aspidospermidine as well as to quebrachamine.

Exposure of the trans amine 296b to ethylene dibromide led to compound 2b, which was believed to be the 20,21-trans isomer of dehydroaspidospermidine\textsuperscript{18}.

\[
\begin{align*}
296b & \xrightarrow{\text{BrCH}_2\text{CH}_2\text{Br}} 297 & \rightarrow & 2b
\end{align*}
\]

Reduction of this compound with sodium borohydride at elevated temperature afforded quebrachamine. Unfortunately the small amount of 2b prevented its full spectral analysis. Its identity rests so far only on the mass spectrum (identical with that of the cis isomer) and infrared spectrum which has an imine absorption at 1580 cm\textsuperscript{-1}, but possesses a different band pattern in the fingerprint region.

**Synthesis of (±)-vincadifformine**

An alternate approach to the Aspidosperma nucleus involved the interaction of the substituted tryptophyl halide 301 with the imine 7.
Although the enamide 303 did not undergo cyclopropanation with diazoacetate ester in high yield, it was highly receptive to the Simmons-Smith reagent. Showalter\textsuperscript{149} carried out the series of reactions depicted in scheme 51, Fig. LXIV, in good yield. Opening of cyclopropane 304 with pyridinium perbromide\textsuperscript{150} occurred with ease. The products were dibromide 305 or bromoalcohol 306 depending on the quality of the bromine-furnishing reagent. Much lower yields were obtained, when bromine in carbon tetrachloride was used for the ring opening. Exposure of imine 7 to indole 301\textsuperscript{151} under conditions similar to those used in the synthesis of eburnamonine from 6 gave a moderate yield of a compound, which exhibited a molecular ion peak of 338 and the typical fragmentation pattern of vincadifformine in its mass spectrum. Its ultra-violet and infrared spectra were similar to those of akuammicine-like alkaloids\textsuperscript{152}, e.g. infrared- 1650 cm\textsuperscript{-1} absorption of the double bond and a 1600 cm\textsuperscript{-1} intense peak for the vinylogous ester carbonyl group. However, the comparison with authentic vincadifformine showed major differences in the R\textsubscript{f} values of the two compounds. However, heating of the reaction product in dimethylformamide for a short time or raising the reaction temperature to 25\textdegree{C} led to a substance spectrally identical with vincadifformine.

Unfortunately the paucity of material prevented the \textsuperscript{13}C NMR analysis of the stereochemistry of the vincadifformine isomer (scheme 52, Fig. LXV).

A known method of imine alkylation\textsuperscript{155} was used for the possible conversion of dehydroaspidospermidine into vincadifformine. Treatment of dehydroaspidospermidine 2 with methylmagnesium iodide and then methyl chloroformate gave a mixture of products. A TLC analysis indicated that vincadifformine was present therein, but conclusive evidence must await
Scheme 51

Reagents: i) Ac₂O/CHCl₃; ii) CH₂I₂, Zn, CuCl₂/Δ; iii) pyridinium perbromide/CH₂Cl₂; iv) 5% aq. H₂SO₄/dioxane

Fig. LXIV
Scheme 52

Reagents: i) KI/DMF, 100°C; ii) KI/DMF, 125°C; iii) DME/130°C, 15 min; iv) MeMgI; v) ClCO₂Me, THF
repetition of the experiment with a larger quantity of starting material.

* *

It has been shown that cyclopropanation of an enamide and solvolysis can lead to β,β-dialkylated piperideines useful in the synthesis of indole alkaloids. As an extension of the diazoacetate-induced cyclopropanation of enamide 8, the copper-catalyzed reaction of the latter with ethyl diazopyruvate was attempted. Compound 307 was isolated in good yield.

![Chemical structure of 307](image)

Exposure of 307 and indole to methanolic hydrochloric acid led to the tetracyclic compound 308. This preliminary observation portends an even more direct synthesis of vincadifformine in the future.
C. Experimental

Melting points were determined on a Reichert micro hot stage and are uncorrected; infrared spectra were recorded on Beckman IR-8 and Perkin-Elmer 137 spectrophotometers, \(^1\)H-NMR and \(^{13}\)C-NMR spectra on Varian XL-100-15 spectrometers, mass spectra on Finnigan Model 3300 (low resolution) and C.E.C. 21-11013 (high resolution) instruments, ultraviolet spectra on a Cary-17 spectrophotometer. The financial support from the National Science Foundation in the purchase of NMR and mass spectrometers is gratefully acknowledged. Microanalyses were performed by Galbraith Laboratories, Inc.

All solvents were distilled prior to use from common drying agents. Chromatographic separations were effected by silica gel 60-PF-254 and alumina type-T PF-254, both supplied by EM reagents.
3-Acetyl-1-carboxemthoxy-1,4,5,6-tetrahydropyridine 268

3-Acetylpyridine (10 g; 0.082 m) was converted to the vinlylogous amide 265 in 98% yield \(^{121}\). A solution of the crude product (10.1 g; 0.0808 m) in 100 ml tetrahydrofuran was cooled to 0°C and triethyl-amine (8.16 g; 0.0808 m) was added. This was followed by a dropwise addition of methyl chloroformate (15.6 g; 0.1616 m) over 10-15 min. The resulting mixture, containing a voluminous white precipitate was stirred for four hours at room temperature. The reaction mixture was washed with concentrated hydrochloric acid, extracted with dichloromethane and the organic portion filtered through a short silica gel column. Evaporation of the solvent yielded 13.4 g (91.1%) of liquid 268 (Kugelrohr distillation) at 130-140°C/0.3 torr: ir(neat) C=O 1710 (carbamate), 1620 (acetyl), C=C 1650 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.84 (m, H\(_2\)-4), 2.26 (m, H\(_2\)-5), 2.28 (s, 3, Me), 3.62 (m, 2, NCH\(_2\)), 3.85 (s, 3, OMe), 7.98 (s, 1, olefinic H); uv(MeOH) \(\lambda_{\text{max}}\) 280 nm, \(\epsilon\) (34000); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 183(M\(^+\))(27), 168(B)(100), 81(29), 58(24), 43(73), 42(45).

Anal. Calc. for C\(_9\)H\(_{13}\)NO\(_3\): C 59.00, H 7.15, N 7.65.

Found: C 58.90, H 7.20, N 7.66.

Omission of the acidic washing in the above procedure gave a ca. 2:1 mixture of 268 and 269. Preparative TLC on silica gel with dichloromethane gave 269 (Kugelrohr) distillation at 140-160°C/0.5 torr: ir (CHCl\(_3\)) C=O 1760 (carbonate), 1700 (carbamate), C=C 1640, C=CH\(_2\) 850 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.8-2.3 (m, 4, H\(_2\)-4, H\(_2\)-5), 3.59 (t, 2, J = 6 Hz, NCH\(_2\)), 3.76 (s, 3, carbonate OMe), 3.85 (s, 3, OMe), 4.83 (ABq, 2, J = 3 Hz, vinyl CH\(_2\)), 7.1 - 7.3 (broad s, 1, olefinic NCH); uv (MeOH) \(\lambda_{\text{max}}\) 277 nm, \(\epsilon\) (16700); mass spectrum (70 eV) m/e (relative intensity, >20% of base
peak) 241(M⁺)(14), 165(B)(100), 54(75), 47(48).

**Anal. Calc. for C₁₁H₁₅NO₅: C 54.77, H 6.27, N 5.81.**

**Found: C 54.65, H 6.40, N 5.73.**

1-Carbomethoxy-3-{2'-(2'-methyl-1',3'-dithianyl)}-1,4,5,6-tetrahydropyridine 273

Gaseous hydrogen bromide was bubbled into a solution of 268 (1 g; 0.0055 m) in 200 ml of ether at 0°C for 10 min, at which time no more precipitate seemed to be generated. One gram (0.0098 m) of 1,3-propanedithiol was added and the reaction mixture kept at room temperature for 4 hr. The clear yellow solution was made neutral with sodium bicarbonate, extracted with dichloromethane and the oily extract chromatographed on silica gel. This led to 710 mg (48%) of 273. The rest of the reaction mixture contained 271 (≈40%), 272 (≈5%), and starting material (≈2%). Kugelrohr distillation at 160°C/0.5 torr gave 273: ir(CHCl₃) C=O 1700, C=C 1650 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.60 (s, 3, Me), 1.7-2.1 (m, 4, (CH₂)₂), 2.21 (m, 2, H₂-4), 2.78 (m, 4, (SCH₂)₂), 3.57 (t, 2, J = 6 Hz, NCH₂), 3.77 (s, 3, OMe), 7.33 (s, 1, olefinic H); uv (MeOH) λ_max 232 nm, ε (26000); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 273(M⁺)(10), 199(B)(100), 167(60), 106(100), 79(65), 59(100).

**Anal. Calc. for C₁₂H₁₉NO₂S₂: 273.0857.**

**Found: 273.0853.**

1-Carbomethoxy-4-{2'-(2'-methyl-1',3'-dithianyl)}-1-{2''-(1''',3'''-dithianyl)}

butylamine 271

One gram (0.0055 m) of 268 was dissolved in 5 ml of chloroform and
1 g of 1,3-propanedithiol and 10 drops of boron trifluoride etherate added at 0°C. The mixture was kept at room temperature for 1 hr. and then washed with sodium bicarbonate solution and extracted with dichloromethane. Chromatography of the extract on silica gel gave 1.4 g (66.9%) of 271. The rest of the reaction was 272 (10%) and starting material (20%). Crystallization of 271 from dichloromethane and hexane gave a solid, m.p. 118-124°C: IR(CHCl₃) ν= 1700 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.56 (s, 3, Me), 1.6 - 2.4 (m, 10, (CH₂)₅), 2.7 - 3.1 (m, 8, (SCH₂)₄), 3.32 (broad t, 2, NCH₂), 3.75 (s, 3, OMe), 5.21 (s, 1, S₂CH); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 381(M⁺)(48), 306(55), 279(15), 133(100), 128(100), 119(100), 59(95).

Anal. Calc. for C₁₅H₂₇NO₂S₄: 381.0924.

Found: 381.0919.

1-Carbomethoxy-4-{2'-(2'-methyl-1',3'-dithianyl)} butylamine 272

A mixture of 1 g (0.0055 m) of 268, 1 g (0.0098 m) of 1,3-propanedithiol and 10 drops of boron trifluoride etherate were heated on a hot plate at ~ 80-90°C for 1 hr. The reaction mixture was cooled, diluted with dichloromethane and neutralized with sodium bicarbonate and evaporated. Chromatography of the residue on silica gel using dichloromethane as the eluting solvent gave 1.17 g of 272 (81.8%) as a viscous oil: IR(CHCl₃) ν= 1705 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.60 (s, 3, Me), 1.6 - 2.0 (m, 8, (CH₂)₄), 2.8 (m, 4, (SCH₂)₂), 3.2 (m, 2, NCH₂), 3.64 (s, 3, OMe), 5.2 (broad s, 1); mass spectrum (70 eV) m/e (relative intensity > 20% of base peak) 263(M⁺)(72), 249(40), 200(35), 188(65), 167(80), 133(100), 119(92), 88(75), 59(64).

Anal. Calc. for C₁₁H₂₁NO₂S₂: C 50.19, H 8.04, N 5.32.
Found: C 49.80, H 7.91, N 5.31.

1-Carbomethoxy-3-ethyl-1,4,5,6-tetrahydropyridine 8

A. By acylation of 3-ethyl-1,4,5,6-tetrahydropyridine 266

Ketal 267\(^{32}\) (5 g; 0.0289 m) and 5 ml H\(_2\)O were cooled to 0°C and concentrated hydrochloric acid (5 ml) added over 10 min. The reaction mixture was stirred for an additional 15 min. and brought to pH 9 with solid potassium hydroxide. Extraction with dichloromethane and evaporation of the solvent at <35°C under reduced pressure gave 3.2 g (100%) of 266. The latter was dissolved immediately in 100 ml of tetrahydrofuran and subjected to the acylation procedure on p. 116. Work-up as before gave 4.6 g (94.2%) of 8, (Kugelrohr) distillation at 60-80°C/0.1-0.5 torr: ir(neat) C=O 1700 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.02 (t, 3, J = 7 Hz, Me), 1.8 - 2.2 (m, 6, (CH\(_2\))\(_3\)), 3.54 (m, 2, NCH\(_2\)), 3.73 (s, 3, OMe), 6.60 (broad s, 1, olefinic H); uv (MeOH) \(\lambda_{max}\) 225 nm, \(\epsilon\) (19000), 285 (1300); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 169(M\(^+\))(45), 153(B)(100), 140(38), 110(30), 95(38), 94(40), 59(55), 55 (72).

\textbf{Anal. Calc. for C\(_9\)H\(_{15}\)NO\(_2\):} C 63.88, H 8.93, N 8.28.

Found: C 63.52, H 8.85, N 8.37.

B. By desulfurization of 273

Either W-2 Raney nickel\(^{125}\) or active nickel generated from nickel dichloride-sodium borohydride\(^{126}\) were used. Thioketal 273 (150 mg: 0.00055 m) in 1 ml of 35% ethanol was added to a tenfold excess of Raney nickel in 25 ml of 95% ethanol. The mixture was refluxed for 12 hr. under nitrogen. Filtration and evaporation gave 110 mg of oil (93%)
identical in all respects with the material obtained by acylation of 266. The yields, however, were not reproducible easily and varied from 40 to 95%.

C. By reduction of 265

Amide 265 was added into a refluxing mixture of excess lithium aluminum hydride in dioxane. A Dry Ice/acetone trap was connected to the reflux condenser and the mixture refluxed for 8-12 hr. It then was cooled and quenched sequentially (water, 15% sodium hydroxide, water). The organic layer was combined with the materials from the trap. Acylation of this mixture produced 8 in less than 15% yield.

1-Carbobenzoxy-3-ethyl-1,4,5,6-tetrahydropyridine 276

276 was prepared in the manner described for the carbamate 8. It was obtained as an oil: ir(neat) C=O 1700 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 1.00 (t, 3, J = 7 Hz, Me), 1.7 - 2.1 (m, 6, (CH\(_2\))\(_3\)), 3.55 (m, 2, NCH\(_2\)), 5.16 (s, 2, benzylic H\(_2\)), 6.62, 6.72 (broad s, total 1, olefinic H of each rotamer), 7.35 (s, 5, aromatic H\(_5\)); mass spectrum (70eV) m/e (relative intensity >20% of base peak) 245(M\(^+\))(6), 186(40), 91(100).

Anal. Calc. for C\(_{15}\)H\(_{19}\)NO\(_2\): C 73.44, H 7.81, N 5.71.

Found: C 73.10, H 7.88, N 5.90.

3-Ethyl-1-(p-nitrobenzoyl)-1,4,5,6-tetrahydropyridine 279

279 was prepared in the fashion described for 8. It was obtained as yellow needles from dichloromethane-hexane, m.p. 74-75\(^{\circ}\)C: ir(CHCl\(_3\)) C=O 1625, C=C 1600 cm\(^{-1}\), NO\(_2\) 1520 and 1350 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 0.92 and 1.10 (t, total 3, J = 7 Hz, Me of each rotamer), 1.8 - 2.2 (m, 6,
(CH₂)₃, 3.45 and 3.8 (m, total 2, NCH₂ of each rotamer), 6.08 and 7.08 (broad s, total 1, olefinic H of each rotamer), 7.6 - 8.2 (m, 4, aromatic H₄); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 260(8)(10), 150(100), 120(22), 104(52), 76(60).

Anal. Calc. for C₁₄H₁₆N₂O₃: C 64.60, H 6.20, N 10.76.
Found: C 64.53, H 6.39, N 10.62.

2-Aza-2-carbomethoxy-7β-carboethoxy-6β-ethylbicyclo(4.1.0)heptane 274a and its 7α-isomer 274b

A mixture of enamide 8 (8 g; 0.047 m) and 400 mg of freshly prepared copper-bronze 129 was stirred under nitrogen in an oil bath at 135°C. Ethyl diazoacetate 154 (17.2 g; 0.151 m) was added through a constant addition funnel at a rate of 1 drop/3-4 sec. (The addition required ca. 1.5 hr.) The reaction mixture was stirred an additional 30 min., and filtered and the resulting oil was distilled in a Kugelrohr at 110°C/1 torr. This afforded ca. 6 g of ethyl maleate and fumarate. A second fraction (92-95°C/0.008 torr) yielded 11.4 g (95.1%) of a mixture of 274a and 274b. This mixture was used as such in subsequent steps. Careful chromatography on silica gel with dichloromethane and ethyl acetate separated the endo- and exo- isomers, which were present in a 1:2 ratio.

274a, exo: ir(neat) C=O 1710 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.88 (t, 3, J = 7 Hz, Me), 1.27 (t, 3, J = 7 Hz, Me of OEt), 1.6 (m, 6, (CH₂)₃), 2.05 (m, 1, COCH), 2.65 (m, 2, NCH₂), 3.35 (d, 1, J = 3.5 Hz, NCH), 3.70 (s, 3, OMe), 4.13 (q, 2, J = 7 Hz, OCH₂).

274b, endo: ir(neat) C=O 1718 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.97 (t, 3, J =
7 Hz, Me), 1.24 (t, 3, J = 7 Hz, Me of OEt), 1.9 - 2.2 (m, 6, (CH₂)₃), 2.93, 3.00 (d, 1, J = 6.5 Hz, NCH of each rotamer), 3.30 (m, 2, NCH₂), 3.67 (s, 3, OMe), 4.05 (q, 2, J = 7.0 Hz, OCH₂); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 255(M⁺)(3), 226(50), 182(72), 132(82), 41(B)(100).

**Anal. Calc. for C₁₉H₂₅NO₄:** C 61.16, H 8.29, N 5.49.
**Found:** C 61.00, H 8.23, N 5.25.

2-Aza-2-carbobenzoxy-7β-carboethoxy-6β-ethylbicyclo(4.1.0)heptane 277
and its 7α-isomer

277 was prepared in the same manner as 274. The epimer mixture was obtained as an oil; ir(neat) C=O 1710 cm⁻¹ (both carbonyls); ¹H-NMR (CDCl₃) δ 0.88 (t, 3, J = 7 Hz, Me), 1.20 (t, 3, J = 7 Hz, Me of OEt), 1.2 - 2.0 (m, 6, (CH₂)₄), 2.6 - 3.1 (m, 2, cyclopropyl H₂), 3.4 (m, 2, NCH₂), 4.2 (q, 2, J = 7 Hz, OCH₂), 5.08, 5.24 (s, 2, benzylic H₂), 7.3 (s, 5, aromatic H₅); mass spectrum (70 eV), m/e (relative intensity >20% of base peak), M⁺ absent, 258(6), 91(100).

**Anal. Calc. for C₁₉H₂₅NO₄:** 331.1784
**Found:** 331.1792.

2-Aza-2-(p-nitrobenzoyl)-7β-carboethoxy-6β-ethylbicyclo(4.1.0)heptane 280 and its 7α-isomer

280 was prepared in the same manner as 274 and obtained as an oil; ir(neat) C=O 1720 (broad), C=O 1645 (amide), C=C 1610, NO₂ 1535 and 1350 cm⁻¹; mass spectrum (70 eV) m/e (relative intensity >20% of base peak), 346(M⁺).
Anal. Calc. for C_{10}H_{22}N_{2}O_{5}: 346.1529.
Found: 346.1529.

2-Carbomethoxy-7-carboethoxy-9-ethyl-piperidino(2,3-b)-8,9-dihydrofuran 307

A mixture of enamide 8 (0.8 g; 0.0047 m) and 300 mg of freshly prepared copper bronze was heated under nitrogen at 130°C, while a solution of ethyl diazopyruvate (1.44 g; 0.01 m) in (4 g; 0.024 m) of enamide 8 (total amount of 3 eq.) was added at a rate of 1 drop/5 sec. (The addition required 2 hr.) The reaction mixture was stirred an additional 30 min., cooled, filtered and the resultant oil chromatographed on silica gel with dichloromethane to give 3.2 g of the unreacted enamide followed by 2.71 g (95%) of 307 as a oil: ir(neat) C=O 1720, C=C 1635 cm\(^{-1}\); \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 0.94 (t, 3, J = 7 Hz, Me), 1.34 (t, 3, J = 7 Hz, Me of OEt), 1.4 - 1.8 (m, 6, (CH\(_2\))\(_3\)), 3.4 and 3.74 (m, 2, NCH\(_2\)), 3.74 (s, 3, OMe), 4.28 (q, 2, J = 7 Hz, OCH\(_2\)), 5.76 (s, 1, NCH), 6.2 (broad s, 1, olefinic H); uv (MeOH) \(\lambda_{\text{max}}\) 253 nm, \(\varepsilon\) (8300); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 283(M\(^+\))(15), 254(25), 225(45), 210(32), 208(60), 182(50), 73(B)(100).

Anal. Calc. for C\(_{14}\)H\(_{21}\)NO\(_5\): C 59.35, H 7.47, N 4.94.
Found: C 59.32, H 7.62, N 4.78.

7-Carbomethoxy-piperidino(2,3-b)-9-ethyl-2-oxotetrahydrofuran 282

A mixture of esters 274 (5 g; 0.019 m) was refluxed in 10% aqueous sulfuric acid (100 ml) and dioxane (20 ml) for 18 hr. Neutralization with sodium bicarbonate and extraction with dichloromethane gave after evaporation 4 g (90%) of 282 as a clear oil which solidified on standing. (The analytical sample was crystallized from dichloromethane-hexane),
m.p. 75°C: ir(CHCl₃) C=O 1770 (lactone), 1700 cm⁻¹ (carbamate);
¹H-NMR (CDCl₃) δ 0.93 (t, 3, J = 7 Hz, Me), 1.3 - 1.8 (m, 6, (CH₂)₃),
2.45 (ABq, 2, J = 16 Hz, COCH₂), 2.8 - 3.2 (m, 1) and 3.98 (d, 1, J =
13 Hz, NCH₂), 3.76 (s, 3, OMe), 6.02 (s, 1, NCH); mass spectrum (70 eV)
m/e (relative intensity >20% of base peak) 227(M⁺)(10), 196(65), 183(25),
154(100).

Found: C 58.07, H 7.46, N 6.12.

9-Ethyl-7H-piperidino(2,3-b)-2-oxotetrahydrofuran 283

A mixture of esters 274 (1 g; 0.0039 m), 1 g of potassium hydroxide,
5 ml of diethylene glycol and 1 ml of water was heated at 100-110°C for
12 hr. The cooled reaction mixture was poured onto 10 ml of concentrated
hydrochloric acid and ice and the resulting acidic solution brought
to pH 7 with sodium bicarbonate. Extraction with dichloromethane and
evaporation gave clear oil which later solidified. Crystallization
from dichloromethane-hexane gave 0.580 g (88%) of 283, m.p. 72°C:
ir(CHCl₃) N-H 3400, C=O 1740 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.90 (t, 3, J = 7 Hz,
Me), 1.2 - 1.8 (m, 4, (CH₂)₂), 1.81 (q, 2, J = 7 Hz, CH₂ of Et), 2.34
(ABq, 2, J = 16 Hz, COCH₂), 2.64 (broad s, 1, NH), 2.88 (m, 2, NCH₂),
5.12 (s, 1, NCH); mass spectrum (70 eV) m/e (relative intensity >20% of
base peak) 169(M⁺)(18), 140(32), 96(8)(100), 95(40).

Found: C 64.00, H 8.86, N 8.29.

The same results could be obtained when lactone 282 was used.
Reproducibility varied from case to case in the 60-90% yield range.
Methyl[3-(3-ethyl-3,4,5,6-tetrahydropyridyl)]acetate 6

Pure lactone 283 (1 g) was stirred at room temperature in methanol (100 ml) saturated with hydrogen chloride for 12 hr. Neutralization and extraction with dichloromethane gave an oil which resisted all attempts of purification, decomposing into intractable materials. It, therefore, was used without purification in subsequent reactions:

\[ \text{ir(neat) } C=O \ 1730, \ C=N \ 1645 \ \text{cm}^{-1}; \ \text{\textsuperscript{1}H-NMR (60 MHz) (CDCl}_3) \ \delta \ 0.86 \ (t, \ 3, \ J = 7 \ Hz, \ Me), \ 1.2 - 1.6 \ (m, \ 6, \ (CH}_2}_3), \ 2.48 \ (s, \ 2, \ COCH}_2), \ 3.4 \ (m, \ 2, \ NCH}_2), \ 3.53 \ (s, \ 3, \ OMe), \ 5.08 \ \text{(broad s, 1, imino H)}; \ \text{mass spectrum (70 eV) } m/e \ \text{(relative intensity >20% of base peak) } 183(M^+)(18), \ 154(32), \ 110(100). \]

9-Ethyl-7-tryptophyl-2-oxotetrahydrafuran 285

A mixture of lactone 283 (200 mg; 0.00118 m), tryptophyl bromide \[ \text{\textsuperscript{135}} \] (300 mg; 0.0013 m), triethylbenzylammonium chloride (70 mg; 0.0003 m), benzene (10 ml) and aqueous sodium hydroxide 30\% (4 ml) was stirred mechanically at 35°C for 6 hr. and then kept at room temperature for 12 hr. Extraction with dichloromethane gave a crude mixture which was purified by preparative TLC on silica gel with dichloromethane-methanol (4:1) to give pure 285, 220 mg (60\%), as a solid (ca. 10\% of eburnamonines and eburnamonic acids was also present). 285 was crystallized from dichloromethane-hexane, m.p. 111-114°C; (The product was difficult to obtain in an absolutely pure state, as it readily formed eburnamonine. Thus, the m.p. is only an approximation.): \[ \text{ir(CHCl}_3) \ \text{NH} \ 3500, \ C=O \ 1740 \ \text{cm}^{-1}; \ \text{\textsuperscript{1}H-NMR (CDCl}_3) \ \delta \ 0.78 \ (t, \ 3, \ J = 7 \ Hz, \ Me), \ 1.2 - 1.8 \ (m, \ 6, \ (CH}_2}_3), \ 2.1 - 2.4 \ (m, \ 2, \ COCH}_2), \ 2.78 \ (m, \ 2, \ allylic H}_2), \ 2.96 - 3.1 \ (m, \ 4, \ (NCH}_2}_2), \ 5.06 \ (s, \ 1, \ NCH), \ 6.9 - 7.6 \ (m, \ 5, \ aromatic H}_5), \ 8.36 \ \text{(broad s, 1, NH)}; \]
uv (MeOH). λ<sub>max</sub> 274 nm, ε (9090), 282(9700), 292(9090), 320(3400);
mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 312(M<sup>+</sup>)
(18), 218(10), 239(40), 182(100), 138(72).
Anal. Calc. for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>: 312.1838.
Found: 312.1843.

B. Tryptamine route

A mixture of lactone bromide 300<sup>136</sup> (700 mg; 0.0028 m), tryptamine
hydrochloride (700 mg; 0.0036 m), 3 ml of dimethylsulfoxide (dry) and
dry 3 Å molecular sieves were stirred in a stoppered flask at 55-60°C
for 12 hr. The dark red reaction mixture was poured into water and
extracted with ether. The organic layer was washed repeatedly with
water, dried and evaporated. Preparative TLC on silica with ethyl
acetate gave 1.35 g (78%) of 285, identical in every respect with the
product in part A. The yields varied from 40 to 80%. Eburnamonine
and its acids were isolated in ca. 20% yield.

(±)-Eburnamonine 1 and (±)-epieburnamonine 1a

A. Acetic acid cyclization of 285

Lactone 285 (180 mg; 0.00057 m) was heated in glacial acetic acid
(12 ml) at 100-110°C for 48 hr. The mixture was cooled, neutralized
and the organic layer evaporated, yielding a crude mixture of eburna-
monines. Preparative TLC on alumina with chloroform gave 85 mg (50%) of
(±)-eburnamonine and 63 mg (37%) of (±)-epieburnamonine (total yield
87%). The compounds had physical and spectral characteristics identical
with those reported in the literature<sup>10</sup>. (±)-Eburnamonine, m.p. 200-201°C
(lit.<sup>10</sup> 200-202°C): ir(CHCl<sub>3</sub>) C=O 1685, C=C 1625 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>)
δ 0.90 (t, 3, J = 7 Hz, Me), 1.2 -2.6 (m, 6, \(\text{CH}_2\)_3), 2.6 (s, 2, COCH_2),
3.24 (t, 2, J = 7 Hz, NCH_2), 3.92 (broad s, 1, NCH), 7.2 -8.3 (m, 4,
aromatic H_4); uv (MeOH) \(\lambda_{\text{max}}\) 232 nm, ε (31300), 265(14200), 275(12700),
294(8300), 306(8300), 326(4900); mass spectrum (70 eV) m/e (relative
intensity >20% of base peak) 294(M^+)(42), 293(37), 265(25), 237(28),
180(45), 168(55), 167(62), 46(B)(100). (±)-Epiburnamonine, m.p. 132-
134°C (lit.\(^\text{18}\) 134.5 - 136°C): ir(CHCl_3) C=O 1695, C=C 1650 cm\(^{-1}\); \(^1\)H-NMR
(CDC_13) δ 0.86 (t, 3, J = 7 Hz, Me), 1.2 -3.1 (m, 10, (CH_2)_5), 2.62
(ABq, 2, J = 16 Hz, COCH_2), 2.66 (s, 1, NCH), 7.2 - 8.3 (m, 4, aromatic
H_4); uv (MeOH) \(\lambda_{\text{max}}\) 235 nm, ε (25700), 242(25100), 264(14500), 276
(12800), 305(9090); mass spectrum (70 eV) m/e (relative intensity >20%
of base peak) 294(M^+)(33), 293(42), 265(12), 264(12), 187(30), 115(40),
46(B)(100).

B. Thermolysis of 285

A sample of 285 was heated in a Kugelrohr apparatus at 250°C/0.01
torr for 30 min. The oily distillate crystallized to give pure eburna-
monine (60%), m.p. 200°C. Eburnamonine and eburnanonic acid could also
be detected in the distillation residue.

C. From imine 6

A mixture of tryptophyl bromide (400 g; 0.00164m; + 10% excess),
imine 6 (0.300 g, 0.00164 m), 1.2 g potassium iodide and dimethyl form-
amide (5 ml) was heated at 100-110°C for 5 hr. The reaction was cooled,
diluted with water and extracted with ether. The organic layer was
washed repeatedly with water, dried and evaporated. Preparative TLC
afforded 0.150 g of eburnamonines (31%), as well as 160 mg (30%) of the
methyl eburnamonates and the eburnamononic acids (ca. 10%).

{"3-(3-ethyl-2-(3'-indolyl)piperidyl)}acetic acid 292a and 292b

A mixture of lactone 283 (1.4 g; 0.0083 m), indole (1.2 g; 0.0102 m), 10% aqueous acetic acid (10 ml), dioxane (2 ml) and 2 drops of concentrated hydrochloric acid were stirred at 80°C for 18 hr. The reaction mixture was extracted with ether. The combined ethereal layers were washed with 10% aqueous acetic acid and evaporated under reduced pressure. Trituration of the resultant oil with acetone yielded crystalline acids 292, 2.1 g (89%), m.p. 170-220°C: ir(Nujol mull) N-H 3300, O-H 3600-3000 (broad), C=O 1520 cm⁻¹; uv (MeOH) λ_max 272 nm, ε (11000), 280(12000), 290(10000); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 286(M⁺)(15), 241(18), 172(40), 171(55), 144(95), 143 (B)(100), 130(55), 117(62).

Anal. Calc for C_{17}H_{22}N_{2}O_{2}: C 71.30, H 7.74, N 9.78.

Found: C 71.30, H 7.80, N 9.72.

Methyl{3-(3-ethyl-2-(3'-indolyl)piperidyl)}acetates 295

The mixture of acids 292 (1 g) was esterified by stirring with 100 ml of methanol saturated with hydrogen chloride overnight. The esters were separated as partial solids by TLC on silica gel with ethyl acetate.

295a, cis: ir(CHCl₃) N-H 3500, C=O 1725 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.84 (t, 3, J = 7 Hz, Me), 1.4 - 2.4 (m, 6, (CH₂)₃), 2.96 (ABq, 2, J = 16 Hz, COCH₂), 2.8 - 3.4 (m, 2, NCH₂), 3.80 (s, 3, OMe), 3.24 (s, 1, NCH); uv (MeOH) λ_max 272 nm, ε (11100), 280 (12000), 288 (9300); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 300(M⁺)(18), 271(15),
241(38), 222(36), 171(48), 144(80), 143(B)(100).

295b, trans: IR(CHCl₃) N-H 3500, C=O 1720 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.74 (t, 3, J = 7 Hz, Me), 1.2 - 2.6 (m, 6, (CH₂)₃), 2.30 (broad s, 2, COCH₂), 3.0 - 3.4 (m, 2, NCH₂), 3.78 (s, 3, OMe), 3.83 (s, 1, NCH), 7.4 - 8.3 (m, 5, aromatic H₅); uν (MeOH) λ max 270 nm, ε (12300), 280(13600), 286(11600); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 300(M⁺)(8), 241(10), 171(55), 144(95), 143(100).

3-Ethyl-1-oxo-9H-piperidino[2,3-c]1,2,3,4-tetrahydrocarbazoles 293

A mixture of the acids 292 (1.5 g; 0.0052 m) and 150 g of polyphosphoric acid was swirled and heated at 80-90°C for 45 min. Cooling, basification with potassium hydroxide to pH 9-10, extraction of the aqueous layer with dichloromethane and evaporation gave crude ketones 293, 1.3 g (94%). Separation of 293a (65% of the mixture) and 293b (35%) was effected by TLC on silica gel with dichloromethane-methanol (9:1). Analytical samples were crystallized from dichloromethane-hexane.

293a, cis: m.p. 183-185°C; IR(CHCl₃) N-H 3350, C=O 1645, C=C 1605 cm⁻¹; ¹H-NMR (acetone-d₆) δ 0.82 (t, 3, J = 7 Hz, Me), 1.4 - 2.2 (m, 6, (CH₂)₃), 2.72 (AB q, 2, J = 16 Hz, COCH₂), 2.96 (m, 2, NCH₂), 4.18(s, 1, NCH), 7.2 - 8.2 (m, 4, aromatic H₄); uν (MeOH), 232 nm, ε (20500), 308(18900); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 268(M⁺) (20), 267(14), 211(70), 197(65), 130(60), 40(B)(100).


Found: 268.1584.
307b, trans: m.p. 226-229°C; IR(CHCl₃) N-H 3480, C=O 1650, C=C 1615 cm⁻¹; 
¹H-NMR (acetone-d₆) δ 0.72 (t, 3, J = 7 Hz, Me), 1.0 - 2.0 (m, 6, (CH₂)₃), 
2.44 (s, 2, COCH₂), 3.20 (m, 2, NCH₂), 4.36 (s, 1, NCH), 7.0 - 8.2 
(m, 4, aromatic H₄); UV (MeOH) λmax 226 nm, ε (48100), 310 (20700); 
mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 268(M⁺) 
(25), 267(22), 211(80), 197(70), 130(72), 40(B)(100).

3-Ethyl-9H-piperidino[2,3-c]1,2,3,4-tetrahydrocarbazoles 296

A solution of each isomer of 293 (350 mg; 0.0013 m) in dioxane 
(5 ml) was added with caution to lithium aluminum hydride (6g) in re- 
fluxing dioxane (150 ml). The mixture was refluxed for 18 hr., cooled, 
and decomposed with 6 ml of water, 6 ml of 15% sodium hydroxide, and 
18 ml of water. The aluminates were filtered and the filtrate evapor- 
ated, yielding 321 mg (97%) of crystalline amines 296.

296a, cis: m.p. 180-182°C (sublimation at ca. 140°C); IR(CHCl₃) 
N-H 3490 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.86 (t, 3, J = 7 Hz, Me), 1.1 - 2.0 
(m, 3, (CH₂)₄), 2.1 - 2.8 (m, 4, NCH₂, benzyl), 3.68 (s, 1, NCH), 
6.95 - 7.6 (m, 4, aromatic H₄); UV (MeOH) λmax 266 nm, ε (12900), 
278(12500), 286(10200), 326(2100); mass spectrum (70 eV) m/e (relative 
intensity >20% of base peak) 254(M⁺)(10), 253(8), 185(35), 130(25), 59 
(B)(100).

Anal. Calc. for C₁₇H₂₂N₂:  C 80.27, H 8.72, N 11.01.

Found:  C 80.04, H 8.92, N 11.01.

296b, trans: m.p. 175-177°C (sublimation point at 145°C); IR(CHCl₃) 
N-H 3490 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.80 (t, 3, J = 7 Hz, Me), 1.2 - 2.0 
(m, 8, (CH₂)₄), 2.6 (m, 2, benzylic H₂), 3.2 (m, 2, NCH₂), 3.94 (s, 1,
NCH), 6.9 - 7.9 (m, 4, aromatic H₄); uv (MeOH) λ_max 252 nm, ε (12500), 274(17900), 280(16900), 290(14500), 326(7700); mass spectrum (70 eV), m/e (relative intensity >20% of base peak) 254(M⁺)(12), 253(12), 185(40), 59(B)(100).

(±)-Dehydroaspidospermidine 2

A mixture of amine 296a (100 mg; 0.00039 m), 1,2-dibromoethane (3 ml), and anhydrous potassium carbonate (200 mg) was heated for 20 min at 140°C. It was poured onto 1 ml of concentrated hydrochloric acid and ice, and then made neutral with sodium bicarbonate. Extraction with dichloromethane, evaporation, and preparative TLC on alumina with chloroform gave 35 mg (32%) of 2 as a viscous oil (and 60 mg of unchanged 308a): ir(CHCl₃) C=N 1590 cm⁻¹; uv (MeOH) λ_max 222 nm, ε (22000), 254(12000), 264(12000); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 280(M⁺)(20), 251(15), 210(45), 184(30), 40(B)(100). The racemic alkaloid 2 was spectrally identical with the natural product obtained by treatment of vincadifformine with 4N hydrochloric acid at 100°C in a sealed tube according to a literature procedure. The product readily formed a carbonate (M⁺ 324) and decomposed on standing into air oxidation products 81.

(±)-Aspidospermidine

(±)-Dehydroaspidospermidine 2 was reduced with lithium aluminum hydride in ether at room temperature 15,51 of sodium borohydride in ethanol at 0°C 148 to (±)-aspidospermidine; mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 282(M⁺)(5), 254(15), 124(B)(100).
Quebrachamine

Amine 308b was treated with ethylene dibromide in the same manner as 308a. A 20% yield of trans-dehydroaspidospermidine 2b was obtained: \( \text{IR} (\text{CHCl}_3) \ C=\text{N} 1580 \text{ cm}^{-1} \); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 280(M⁺)(20), (40)(B)(100).

It was reduced without purification by treatment with sodium borohydride in refluxing ethanol for 3 hr\(^{148}\) to (±)-quebrachamine.; mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 282(M⁺)(20), 253(15), 156(20), 143(B)(100), 124(55).

Quebrachamine was obtained also from the reduction of 2. Detailed spectral analysis was not possible, since only minute amounts of material were available.

1-Acetyl-3-ethyl-1,4,5,6-tetrahydropyridine 303\(^{149}\)

A solution of enamine 266 (20 g; 0.130 m) in 150 ml chloroform was cooled to 0°C and 60 ml acetic anhydride added over 20 min. The resulting solution was stirred at room temperature for 1 hr. Kugelrohr distillation at 60°C/1-3 torr removed excess acetic anhydride. The second fraction (110-130°C/1 torr) gave 303 as an oil, 22.45 g (81.5%); \( \text{IR} \) (neat) C=0 1640 cm\(^{-1}\); \(^1\text{H-NMR} \) (CDCl\(_3\)) \( \delta \) 1.02 (t, 3, J = 7 Hz, Me), 1.6 - 2.2 (m, 6, \( \text{CH}_2 \))\(_3\), 2.12 (s, 3, acetyl Me), 3.6 (m, 2, NCH\(_2\)), 6.38 and 7.0 (s, total 1, olefinic H of each rotamer); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 153(M⁺)(15), 96(B)(100).


Found: 153.1150.
2-Acetyl-2-aza-6-ethylbicyclo(4.1.0)heptane \(^{304\text{149}}\)

Zinc (7.6 g; previously washed with 2N HCl), cuprous chloride (1.16 g), cuprous iodide (few mg) were refluxed in diethyl ether under nitrogen for 30 min. Diiodomethane (35 g) was added followed by a small crystal of iodine. Vigorous reaction ensued, indicating that the couple was being formed. The reaction mixture was refluxed 30 minutes and the enamide \(^{303}\) (1.5 g; 0.0098 m) was added. After the initial vigorous reaction subsided, the grey solution was refluxed for 18 hr. The cooled suspension was filtered, ethereal layer washed with ammonium chloride solution, 5\% sodium hydroxide solution, dried, and evaporated giving an oil whose TLC analysis showed it to consist of \(\sim 1:1\) mixture of \(^{303}\) and \(^{304}\). The entire process described above was repeated on this mixture. Identical workup afforded 1.31 g of \(^{304}\) (80.1\%) as clear oil, (Kugelrohr distillation) b.p. 110°C/0.5 torr: \(\text{ir(neat)}\) C=O 1650 cm\(^{-1}\); \(^{1}\text{H-NMR (CDCl}_3\) \(\delta 0.8 - 2.0 \text{ (m, 9, (CH}_2\)}_4 \text{ and CH}_3\), 2.06, 2.18 (s.each, total 3, COCH}_3 \text{ of each rotamer), 2.3 - 2.6 and 2.7 - 3.0 \text{ (m, total 2, NCH}_2\) \text{ of each rotamer), 3.3 - 3.7 and 4.0 - 4.3 (s, total 1, NCH of each rotamer); mass spectrum (70 eV) m/e (relative intensity >20\% of base peak) 167(M^+)(4), 138(20), 96(B)(100), 95(50).

Anal. Calc for C\(_{10}\)H\(_{17}\)N\(_2\): C 71.81, H 10.25, N 8.37.

Found: C 71.64, H 10.37, N 8.21.

3-(bromomethyl)-3-ethyl-3,4,5,6-tetrahydropyridine \(^{7}\)

A mixture of cyclopropylamide \(^{304}\) (1.22 g; 0.0073 m), and pyridinium perbromide (2.6 g) was stirred in 20 ml dichloromethane for 20 hr. The orange reaction mixture was washed with aqueous sodium thiosulfate, followed by a wash with copper sulfate solution. Evaporation of the
organic layer yielded a mixture of 305 and 306, which were characterized by spectral methods. The crude mixture was subjected to reflux in 30 ml of 5% sulfuric acid and 15 ml dioxane for 8 hr. Neutralization with sodium bicarbonate, extraction with dichloromethane and evaporation gave 1.35 g (91%) of 7 as an oil, (Kugelrohr) distillation 61°C/0.008 torr: ir(neat) C=N 1650 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.91 (t, 3, J = 7 Hz, CH₃), 1.4 - 1.9 (m, 6, (CH₂)₃), 3.38 (s, 2, CH₂Br), 3.4 - 3.7 (m, 2, NCH₂), 7.52 (broad s, 1, imino H); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 203, 205(M⁺)(4,4), 124(55), 69(70), 68(80), 55(B)(100).

Anal. Calc. for C₈H₁₄NBr: C 47.08, H 8.91, N 6.86.
Found: C 47.01, H 7.06, N 6.74.

Epivincadifformine 3b

A mixture of imine 7 (200 mg; 0.00098 m), chloride 301 (260 mg; 0.00104 m), 1 g potassium iodide, and dimethyl formamide (5 ml) were heated at 100°C for 3 hr. The reaction mixture was cooled, diluted with water and extracted with diethyl ether. Evaporation of the organic layer and preparative TLC on alumina/chloroform yielded 3b (noncrystalline); ir(CHCl₃) N-H 3390, C=C 1650, C=O 1595 cm⁻¹; uv (MeOH) λ_max 228 nm, ε (20000), 292(4000), 300(10500), 330(12500); mass spectrum (70 eV) m/e (relative intensity >20% of base peak) 338(M⁺)(10), 154(75), 126(B)(100), 124(45).

Vincadifformine 3a

3b was heated in DMF for 30 min. at 130°-140°C. Work-up was carried out as above to afford 3a: \( \text{ir(CHCl}_3) \ N-H \ 3390, \ C=C \ 1655, \ C=O \ 1590 \ \text{cm}^{-1}; \ \text{uv (MeOH)} \ \lambda_{\text{max}} \ 228 \ nm, \ \varepsilon(20000), 292(4000), 330(12500). \)

Vincadifformine 3a could also be obtained by carrying out the condensation of 7 and 301 at 125-130°C.

Marginal results were also obtained using iminoalkylation (see p. 111).
D. Spectra

TMS was used as an internal standard in the $^1$H-NMR spectra. Polystyrene film (1601 cm$^{-1}$ band) was used to calibrate the infrared spectra.
Summary

The copper-catalyzed reaction of ethyl diazoacetate with 1-carbomethoxy-3-ethyl-1,4,5,6-tetrahydropyridine led to 2-aza-2-carbomethoxy-7β-carboethoxy-6β-ethylbicyclo[4.2.1]heptane and its endo isomer, the hydrolytic unraveling of which afforded a desired intermediate for alkaloid synthesis, 9-ethyl-7H-piperidino[2,3-b]-2-oxotetrahydrofuran. The latter compound is alkylated by tryptophyl bromide to give the N-tryptophyl derivative, which produced eburnamonine on thermolysis.

Exposure of to indole and mild acid yielded the isomeric mixture of 2-{3-ethyl-2-(3-indoly1-)piperidyl}-acetic acid, whose sequential treatments with polyphosphoric acid and lithium aluminum hydride afforded a 2:1 mixture of cis and trans isomers of 3-ethyl-9H-piperidino[2,3-c]-1,2,3,4-tetrahydrocarbazole. Reaction of these compounds with 1,2-dibromoethane led to dehydroaspidospermidine, from which quebrachamine and aspidospermidine could be obtained.

A Simmons-Smith reaction of 1-acetyl-3-ethyl-1,4,5,6-tetrahydropyridine gave 2-acetyl-2-aza-6-ethylbicyclo[4.1.0]heptane, pyridinium perbromide treatment of which gave 3-(bromomethyl)-3-ethyl-3,4,5,6-tetrahydropyridine. Condensation of the latter with methyl 3-(β-chloroethyl-)indoly1-2-acetate afforded vincadifformine.
References


   b) Ref. 1b and 1c.


   d) A.I. Scott, in MTP International Review of Science, Ser. 1

e) Ref. 4b.


11. a) O. Hesse, Liebigs Ann., Vol. 211, 249 (1882).

12. Ref. 2a, 11c, 4a.


1700(1970) and following four articles.


   b) Ref. 4d.


61. Ref. 3a.


75. J. Martel, *German Offen.*, 2, 200259; *Chem. Abstr. 77*:152432.


77. Syntheses of vincamine:


   f) Ref. 80.

249(1973).


83. a) J. Levy, Belg. 763730 (1971), CA 76:P 127 223 z.
   (vincadifformine → vincamine on Pb(OAc)$_4$/CH$_2$Cl$_2$)

b) J. Levy, and J. LeMen, Belg. 772005, CA 77:152 433 w.
   (eburnamine from dehydroaspidospermidine by peracid)

c) C. Szantay, L. Sxabo, and G. Kalans, Ger. Offen, 2.203655,
   CA 77:152435 y. (epimerization of vincamines in xylene/Ag).

   (vincamine, apovincamine from Tabersonine by peracid).

e) J. Levy, Belg. 765 795 and Belg. 761628, CA: 77:19865x.
   (vincamine from vincadifformine)

   (vincine from Methoxy tabersonine)

g) J. LeMen, J. Levy and Fr. Demande, 2108947, CA:78:43817 z.
   (valesamidine, vincamine from Tabersonine)

84. J. Levy, C. Pierron, G. Lukacz, G. Massiot, and J. LeMen,


86. a) A. Streitwieser, Jr., *Solvolytic Displacement Reactions*, McGraw-

b) R. Breslow, Molecular Rearrangements, p. I, P. de Mayo, ed.,


c) K.J. Chou, ibid., 1975.


717, 728, 734, 743(1966).

b) E. Wenkert, R.J. Mueller, E.J. Reardon, Jr., S.S. Sathe, D.J.

c) E. Wenkert, B.L. Buckwalter, and S.S. Sathe, Syn. Comm., Vol. 3,
261(1973).

89. a) E. Wenkert, C.A. McPherson, E.L. Sanchez, and R.C. Webb, Syn.


c) Ref. 88,b,c.

d) Ref. 87b.

e) M. Jones, Jr. and R. A. Moss, Carbenes, Vol. I, J. Wiley and Sons

90. Ref. 87a.

Vol. 81, 6523(1959), and Ref. 104c.


93. A. Burger, C. Kaiser, L. Zirngibl, C.S. Davis, and C.L. Zirkle,
116. E. Wenkert and H.E. Gotlieb, unpublished observations.
119. E. Wenkert and H. Showalter, personal communication.
    b) E. Leete and L. Marion, *ibid.*, Vol. 31, 775(1953).
The author is indebted to L. Kwart for preparation of ethyl diazoacetate in large amounts.


   


145. Ref. 120c.

146. The author is indebted to M.S. Raju for a discussion of the $^{13}$C-NMR spectra.

147. a) B. Zsadon and K. Horvath-Otta, Herba Hung., Vol. 12, 133(1973); CA 82:150540 e.
   


149. Ref. 119.

   


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3. J.V. Hay, T. Hudlicky, J.F. Wolfe. The SR-1 mechanism in heteroaromatic nucleophilic substitution. Photostimulation and Entrainment of the reaction of Lithioacetone with 2-Chloro-


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