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Studies in the Synthesis of Vindoline

by

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To my

mother and father.
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I. INTRODUCTION
INTRODUCTION

The indole alkaloids vinblastine* and vincristine,* isolated from the leaves of the plant *Vinc a rosea* Linn. of the family apocynaceae, are of interest in medicine because of their striking oncolytic activity against a variety of neoplasms.¹ Investigations by a group at the Lilly Research Laboratories led to the discovery of the antitumor activity** of these compounds.¹ The alkaloid vindoline, also from *Vinc a rosea*, itself inactive, has been investigated because of its structural relationship to vinblastine and vincristine.¹ The results of a study of some aspects of the synthesis of vindoline are reported in this thesis.

The structure determinations of vinblastine and vincristine were carried out at the Lilly Research Laboratories. Spectral and chemical evidence indicated the structure (1a) for vinblastine and (1b) for vincristine.³⁴ The stereochemical details of these structures were elucidated by an X-ray crystallographic analysis of vincristine methiodide.⁵ Correlation of the two compounds showed that they possessed the same absolute configuration,³ and therefore the configuration of vinblastine was also established.

The "dimeric" nature of these alkaloids and their relationship to vindoline (2a) was suggested by physical data,⁶ and strongly supported by acidic cleavage (concentrated hydrochloric acid, stannous chloride,

*Generic names approved by the American Medical Association Council on Drugs. These drugs are available from Eli Lilly and Co. under the brand names "Velban" and "Oncovin" respectively.

**The Pharmacology of vinblastine and vincristine has been extensively reviewed¹¹ elsewhere.
tin, reflux) which, in the case of vinblastine, yielded desacetylvinodoline (2b), as one of the products. Thus vindoline constitutes the dihydroindole moiety of the vinblastine molecule, and the elucidation of its structure was an important aspect of the vinblastine problem.

![Chemical structure of vindoline](image)

(1a) $R = \text{CH}_3$

(1b) $R = \text{CHO}$

Vindoline (2a), the most abundant alkaloid of the leaves of the plant, was determined to be a $C_{25}H_{32}N_2O_6$ dihydroindole compound. The nature of the six oxygens was determined by the formation of suitable derivatives. Brief treatment of vindoline with acid gave desacetyl vindoline (2b), $C_{23}H_{30}N_2O_5$, corresponding to loss of acetyl. Presence of a carbomethoxy group was shown by lithium aluminum hydride reduction of the alkaloid with removal of acetyl to give vindolinol, $C_{22}H_{28}N_2O_4$ (2c). The infrared spectrum of vindoline showed that the fifth oxygen was present as hydrogen bonded hydroxyl. Acetylation gave a diacetate with loss of the hydroxyl absorption in the infrared.
was found to be an aromatic methoxyl group attached to a dihydroindole chromophore by consideration of the infrared and ultraviolet spectra.\textsuperscript{7} Confirmation of oxygen functional groups was obtained from the NMR spectrum.\textsuperscript{8}

![Chemical Structure](image)

(2a) $R_1 = \text{COOCH}_3$, $R_2 = \text{COOCH}_3$
(2b) $R_1 = \text{COOCH}_3$, $R_2 = \text{H}$
(2c) $R_1 = \text{CH}_2\text{OH}$, $R_2 = \text{H}$

Vindoline consumed one mole of hydrogen at atmospheric pressure, showing it to be a pentacyclic compound. The product, dihydrovindoline, could be converted to a hydrochloride. Pyrolysis of this salt at $195-200^\circ$ in vacuum gave a distillate from which compound (3), $C_{21}H_{28}O_2$, was isolated. The methoxydihydroindole portion of this compound was the same as that of vindoline and the second oxygen was shown to be a ketone ($\lambda_{\text{max}}^{\text{CHCl}_3} 5.85\mu$).\textsuperscript{8}

Mass spectral comparison of the pyrolysis ketone (3), dihydrovindoline, and N-methyldeacetylaspidospermine (4a), indicated that the ring system of the latter is present in vindoline and its derivatives. In all three compounds intense peaks were observed at $m/e$ 124, 174, 188, and 298.\textsuperscript{9}

The position of the carbonyl group in the pyrolysis ketone (3) was tentatively assigned to $C_3$ or $C_4$ on the basis of the $m/e$ 295 peak ($M - 42$,
loss of ketene) in the mass spectrum. Position 4 was chosen on the basis of NMR evidence which indicated the presence of three protons between the carbonyl group and nitrogen. Exchange with deuteromethanol-methoxide gave a dideutero derivative. If the carbonyl group had been at C₃, three hydrogens would be exchangeable instead of two.⁸

![Chemical structures](image)

(3)  
(4a) R = CH₃  
(4b) R = COCH₃

The position of the aromatic methoxyl was shown to be at C₁₅ or C₁₆ by inspection of the 1,2,4 aromatic splitting pattern in the NMR spectrum. Choice of C₁₆ was made on the basis of comparison of the ultraviolet and infrared spectra of vindoline with 6-methoxy-N-methylindoline (5). Isolation of N-methylnorharine (6) from soda-lime distillation of vindoline further substantiated the assignment. This derivative also indicated the position of the N-methyl group on the anilino nitrogen.⁸

Comparison of the mass spectra of vindoline (2a), its degradation product (3), and aspidospermine (4b) showed that all the oxygen functional groups except the aromatic methoxyl must be located at C₃ and C₄.⁸ The indicated arrangement of groups at C₃-₄ was determined on the basis of the unsplit proton on the carbon bearing the acetoxy function which appeared as a singlet at 5.438 in vindoline and was shifted to 4.076 in
desacetylvinblonine. Furthermore, this assignment allowed for a mechanistic explanation for formation of the pyrolysis ketone (5) (dehydration, hydrolysis, decarboxylation). 8

![Chemical structures](5)

![Chemical structures](6)

The stereochemistry of vindoline was tentatively assigned by the Lilly group. 8 Complete stereochemical assignment became available with the X-ray analysis of vincristine 5 since des-N-methyl-desacetyl vindoline was isolated as a product of cleavage of this compound.

Although no synthesis of vindoline has yet appeared in the literature, several routes to the aspidospermine ring system are now available. In 1963 Stork reported the first total synthesis of aspidospermine itself 10 as outlined in Chart I. Enamine addition of methyl acrylate to butyraldehyde gave the aldehyde ester (7), the enamine of which afforded the unsaturated ketone (8) on reaction with methyl vinyl ketone. Ketulation, ammonolysis of the ester, and hydride reduction, followed by treatment with acid and base converted (8) into the bicyclic amine (9). The two carbon bridge was added as chloroacetyl chloride, forming an amide which gave ketolactam (10a) on treatment with base. Ketolization of (10a) and subsequent lithium aluminum hydride reduction, followed by removal of
Chart I

(7)

(3)

(9)

(10a) \( R = O \)

(10b) \( R = H_2 \)

(11)

(hb)
the protecting group, afforded the amino ketone (10b). Fischer indole synthesis with 2-methoxyphenylhydrazine produced (11) which was reduced with lithium aluminum hydride and acetylated to complete the synthesis of aspidospermine (4b). A different but less stereospecific synthesis of the amino ketone (10b) has been reported.\textsuperscript{11}

While our investigation was in progress, several new routes to the aspidospermine system were reported. In 1965 Harley-Mason and Barton discovered that suitable β-carboline derivatives would yield rearrangement products of the aspidospermine type when treated with boron trifluoride etherate.\textsuperscript{12,13} Thus the aldehyde ester (12a) (Chart II), formed by successive enamine alkylation of butyraldehyde with methyl acrylate and allyl bromide, was condensed with tryptamine to give the lactam (13a). Treatment of (13a) with boron trifluoride etherate (no solvent, 100°C, five hours) gave the indolenine (14a) in 60% yield. Reduction gave 16-methylaspidospermidine (15a).\textsuperscript{12} Modification of this procedure led to a stereospecific synthesis of aspidospermidine itself.\textsuperscript{13} The aldehyde ester (12a) was protected as the dimethylacetal which, on ozonolysis with reductive workup, yielded the hydroxy-acetal (12b). Condensation with tryptamine gave (13b) which rearranged with boron trifluoride etherate or 40% sulfuric acid to the indolenine (14b). Reduction yielded a substance found to be identical with natural aspidospermidine (15b).

In 1964 Wenkert\textsuperscript{14} reported the conversion of the methiodide (16) with lithium and ammonia to the nine membered ring compound (17), a model for the synthesis of the alkaloid quebrachamine (24) (Chart III). This reaction became the basis for a general synthetic procedure for alkaloids of the quebrachamine and aspidospermine types.\textsuperscript{15,16} A recent modification\textsuperscript{17,18} involving ring opening by nucleophilic reagents such as...
Chart II

(12a) $R_1 = \text{CH}_2$  $R_2 = \text{CHO}$

(12b) $R_1 = \text{H}, \text{OH}$  $R_2 = \text{CH(OCH}_3)_2$

(13a) $R = \text{CH}_2$

(13b) $R = \text{H}, \text{OH}$

(14a) $R = \text{CH}_3$

(14b) $R = \text{H}$

(15a) $R = \text{CH}_3$

(15b) $R = \text{H}$
cyanide or acetate rather than reduction has allowed the introduction
of functional groups. The versatility of the procedure is well
demonstrated by the examples of Kutney and co-workers,\textsuperscript{19} outlined in

\[
\text{(16)} \quad \rightarrow \quad \text{(17)}
\]

Chart III. The ester (18) was alkylated with allyl bromide in the
presence of triphenylmethyl sodium to the allyl ester (19). Cleavage
of the double bond (osmium tetroxide-peridate) gave the aldehyde ester
(20). Condensation of (20) with tryptamine yielded the lactam (21).
Lithium aluminum hydride reduction followed by removal of the benzyl
group by catalytic hydrogenation afforded the amine (22). Treatment of
(22) with methanesulfonyl chloride resulted in spontaneous cyclization
of the intermediate methanesulfonate to the salt (23). Sodium-liquid
ammonia reduction of (23) gave $\text{\underline{d}l}$-quebrachamine (24).\textsuperscript{16,18} Earlier work
had established the conversion of this alkaloid to aspidospermidine (15b)
by oxidative cyclization with mercuric acetate, followed by borohydride
reduction,\textsuperscript{20,21} and thus a synthesis of the latter compound was also
completed. Opening of (23) with potassium cyanide in dimethylformamide\textsuperscript{19}
gave two isomeric cyano derivatives (25a and b) which were converted to
the corresponding methyl esters $\text{\underline{d}l}$-vincadine (26a) and $\text{\underline{d}l}$-epivincadine
(26b) by hydrolysis and esterification of the acids with diisomethane.
Chart III

(18)

(19)

(20)

(21) $R_1 = \text{O} \quad R_2 = \text{CH}_2\text{Ph}$

(22) $R_1 = \text{H} \quad R_2 = \text{H}$

(23)

(24)

(25a) $R_1 = \text{CN} \quad R_2 = \text{H}$

(25b) $R_1 = \text{H} \quad R_2 = \text{CN}$

(26a) $R_1 = \text{COOCH}_3 \quad R_2 = \text{H}$

(26b) $R_1 = \text{H} \quad R_2 = \text{COOCH}_3$

(27)
Oxidative cyclization of vincadine or epivincadine (mercuric acetate or oxygen over platinum/charcoal) gave dl-vincadifformine (27). Known conversions and choice of suitable starting materials have allowed the use of this basic synthetic route for the preparation of several other members of this series such as dihydrocleavamine (28),\textsuperscript{15} 16-carbomethoxy-dihydrocleavamine (29),\textsuperscript{18,22} and 16-hydroxydihydrocleavamine (30).\textsuperscript{23}

(28) \( R = H \)  
(29) \( R = COOCH_3 \)  
(30) \( R = OH \)

The importance of the dimeric alkaloids vinblastine and vincristine in clinical cancer research has suggested synthesis of these compounds as a suitable long range objective. Study of the synthesis of vindoline was undertaken as a part of this goal. The synthesis of the dimeric alkaloids was envisioned to consist of construction of suitable indole and dihydroindole moieties and joining these pieces by a coupling process. Such a coupling reaction must be involved in a tenable biogenetic explanation for these dimeric species.

Very recent reports of successful synthetic coupling reactions have demonstrated that vindoline is a useful starting material for the process. Harley-Mason\textsuperscript{23} has coupled 16-hydroxydihydrocleavamine (30) with vindoline to give vinblastine model (31\textsuperscript{a}) (Chart IV). This reaction apparently
Chart IV

(31a) \( R = H \)

(31b) \( R = COOCH_3 \)

(32)
involves solvolysis of the benzylic hydroxyl function and electrophillic attack of the resulting positive species on the 15-position of vindoline. Kutney\textsuperscript{24} has very recently reported a coupling reaction of 16-carbomethoxydihydrocleavamine (29) with vindoline. Oxidative chlorination of (29) with \textit{i}-butyl hypochlorite and exposure of the resulting chloroindolenine (32) to vindoline gave (31b), a dimeric product containing the carbomethoxy group at the point of attachment, necessary for completion of the natural dimeric vinca alkaloids. A synthesis of vindoline would thus nearly complete the total synthesis of vinblastine.
II. DISCUSSION
DISCUSSION

The goal of this investigation of the synthesis of vindoline was the ketone degradation product (3). This compound was considered a potential intermediate in the synthesis of dihydrovindoline since the C₄ carbonyl potentially allows for introduction of the three oxygen functional groups at C₃ and C₄. The ketone would also be a point of comparison with material derived from the natural base; and since vindoline is abundantly available as a byproduct of the manufacture of the active dimeric Vinca alkaloids, it would be a desirable relay point in the synthesis of dihydrovindoline. The determination of specific methods for the elaboration of the ketone (3) to dihydrovindoline and introduction of the double bond for vindoline (2a) itself was considered beyond the scope of this investigation.

Our first approach was based on the report of a successful synthesis of a strychnine-type system by van Tamelen²⁵ as shown in Chart V. Compound (33) was obtained from indole-3-acetic acid and the required amine, which was available from cyclopentadiene by a series of standard reactions. The cyclopentene double bond of (33) was hydroxylated with osmium tetroxide and the resulting diol cleaved with periodic acid. The intermediate dialdehyde (34) immediately cyclized to (35), as shown by hydroxyl absorption in the infrared. Crude (35) was heated in an acidic buffer solution (acetate or formate) and the aldehyde (36) was obtained. The mechanism of this reaction was considered by us to include ß-indole cyclization of the intermediate immonium species generated by the loss of water from (35) (Chart V). Addition of the aldehyde function to the resulting indolenine would give rise to (36), the reported
product. It appeared that this reaction might have an analogy in the synthesis of aspidospermine-type systems, most importantly the ketone (3). If compound (37) were treated with acid, it should eliminate water in analogy to (35). Cyclization of the resulting immonium salt with the indole and addition of the ketone moiety to the resulting indolene would give ketone (38), a model* for the vindoline pyrolysis ketone (3).

*For investigation of synthetic procedures, more readily available starting materials which did not possess the aromatic methoxy group necessary for the natural degradation product were used. All synthetic routes considered here could be modified in a straightforward manner to include this substituent in the final product.
The N-formyl derivative (46), Chart VI, was selected as a precursor to (37). In principle the N-formyl function could, after suitable activation, act as an internal Vilsmeier reagent. Cyclization toward the ketone would produce (37). There was a possibility of initial cyclization involving the indole, but the order of events seemed unimportant in view of the fact that the molecule could cyclize completely to (38) regardless of which occurred first.

The synthesis of compound (46) is outlined in Chart VI. The acetoacetic ester (39), prepared by ethylation of ethyl acetoacetate with ethyl bromide in the presence of sodium ethoxide, was converted to the glutaric ester (40) by Michael reaction with ethyl acrylate. Ester (40) was resistant to complete hydrolysis in acidic media but was smoothly hydrolyzed in base, and decarboxylation occurred spontaneously on acidification to give the ketoacid (41a). Fischer esterification with methanol proceeded smoothly to give the ester (41b). Treatment of (41b) with ethylene glycol and p-toluenesulfonic acid in benzene afforded the ketal ester (42a). Hydrolysis of this ester in dilute aqueous alcoholic sodium hydroxide followed by careful acidification and immediate workup produced the ketal acid (42b) as a nearly colorless oil. The NMR spectrum of the acid showed the loss of ester methyl signal at 3.688 in the starting material and the appearance of a one proton singlet at 2.758, assigned to the carboxyl group. The signal for ketal ring hydrogens (3.908, singlet) was retained in the acid. No evidence of appreciable ketal cleavage could be observed in the infrared or NMR spectra. The crude acid was condensed with tryptamine by the mixed anhydride procedure28 with ethyl chloroformate, giving a mixture of the amide (43) and the carbamic ester (44) which could be separated by chromato-
Chart VI

(39) → (40)

(41a) $R = H$
(41b) $R = CH_3$

(41b) $R = CH_3$

(42a) $R = CH_3$
(42b) $R = H$

(43) + (44b)

(45a) $R = H$
(45b) $R = CHO$

(46)
graphy on Fluorisil. The amide (43) was an oil which did not show any
tendency to crystallize. It showed indole N-H at 2.90μ and secondary
amide carbonyl absorption at 6.0μ in the infrared. Bands could be
found in the NMR for ketal (3.88μ) and amide N-H (6.05μ). The rest of
the NMR spectrum was consistent with the assigned structure. The car-
bamic ester (44) was easily identified by its NMR spectrum which showed
typical ethyl ester absorption (triplet, 1.26μ, 3H; quartet, 4.20μ, 2H).
The rest of the spectrum could be assigned to the tryptamine moiety of
the molecule. Despite obvious possibilities for improvement in the
yield of amide (43), the matter was not further investigated since
enough material could be obtained for further experiments.

Reduction of (43) with lithium aluminum hydride in refluxing
tetrahydrofuran proceeded smoothly to give the amine (45a), which,
without purification, was reacted with chloral in chloroform according
to the procedure of Blicke.27 The product, formamide (45b), was purified
by chromatography but could not be obtained in crystalline form. The
presence of the formyl group was indicated by a new band in the infrared
at 6.0μ (amide carbonyl) and a singlet at 8.0μ in the NMR characteristic
of the formamide proton. Ketal absorption in the NMR remained unchanged
from the keto amide (43). Treatment of (45b) with acetone containing
p-toluenesulfonic acid gave, after chromatography on alumina, ketone
(46), a non-crystalline substance which displayed unstrained ketone and
amide absorption at 5.83 and 5.98μ respectively, and indole N-H at 2.9μ.

Compound (46) was subjected to various acid conditions, both mild
and vigorous, but under no circumstances were identifiable products
obtained. For example, no reaction occurred on treatment of (46) with
boron trifluoride in benzene or p-toluenesulfonic acid in benzene;
concentrated hydrochloric acid with brief heating caused the material to decompose. Attempts to convert the formyl group to imidochloride with phosphorous oxychloride led only to tars. Imidoether formation with dimethyl sulfate similarly failed. Thionyl chloride in dimethylformamide, a reagent used by Corey to convert a secondary formamide to isonitrile,\textsuperscript{28,29} was tried with negative results. It was concluded that compound (46) could not survive the difficult formyl activation step and that the formyl carbonyl was not sufficiently active to condense with the ketone without activation.

While this series was being studied, an interesting reaction of compound (43) was discovered. When an NMR sample of this compound in deuterochloroform was rinsed out of the sample tube with reagent grade chloroform and evaporated on a steam bath, a crystalline solid was obtained, the infrared spectrum of which showed that it was not the amide (43). When a larger sample of (43) was exposed to \textit{p}-toluenesulfonic acid in benzene, a precipitate formed which was identical in the infrared with the solid from the accidental reaction. The new compound, mp 272-273\textdegree (sealed tube) gave elemental analysis and molecular weight (292, mass spectrum) for \textit{C}_{18}\textit{H}_{20}\textit{N}_{2}\textit{O}, corresponding to the loss of the ketal ring and two additional hydrogens from the starting amide. The infrared spectrum possessed indole N-H absorption at 2.89\textmu, verified by the ultraviolet spectrum which showed a typical indole pattern. There was also a band at 6.15\textmu in the infrared for amide or lactam carbonyl. The NMR data were poor due to the insolubility of the material in deuterated solvents available, but it was clear that the compound showed no singlet for ethylene ketal. A singlet at 1.53\textnu could also be easily discerned. Comparison of the integral of this band with that of the aromatic
pattern centered at 7.16 suggested the presence of four aromatic protons and an unsplit methyl group. The structure (47) was assigned to this compound on the basis of these observations and mechanistic considerations.

Formally, compound (47) may arise from acid assisted attack of the amide nitrogen on the ketal and nitrogen assisted elimination of the elements of ethylene glycol, followed by cyclization of the resulting immonium species into the indole 2-position.

Harley-Mason reported that the compound (48) rearranged to (49) when treated with hot concentrated hydrochloric acid (Chart VII). The mechanism of this reaction has not been investigated, but it formally appears to involve protonation and rearrangement of (48) to the indolenine (50) followed by nucleophilic attack by the phenolic para position on the indolenine, yielding (49). We have considered this process as a
Chart VII

(48) → (49) → (50) → (51) → (52) → (38)
possible means of obtaining the dihydroindole system found in the pyrolysis ketone (3). Thus if the ketone (51) rearranged in a similar manner, (38) would be the product, via the indolenine (52) (Chart VII).

Before attempting a synthesis of (51), a model study was carried out. The known ketone (53a)\textsuperscript{31} was chosen as a model for (51) since it was readily obtained from tryptamine and formylacetone sodium salt and possessed all the structural features which were believed to be involved in the rearrangement process. Treatment of (53a) with hydrochloric acid, however, gave only a dark tar from which no characterizable products could be obtained. Repeated attempts with other acidic conditions:

\begin{equation}
\begin{array}{c}
\text{(53)} \\
\text{a) } R = H, \text{HCl} \\
\text{b) } R = \text{Acetyl}
\end{array}
\end{equation}

failed to give any identifiable products other than starting material.

The possibility of cleavage of the side chain with participation of nitrogen was considered as a possible cause of the apparent instability of the molecule in acid. Accordingly, the compound was acetylated with acetic anhydride in pyridine, hopefully to stabilize it with respect to this cleavage possibility. The amide (53b), however, showed no tendency to rearrange in the desired manner. Vigorous acid treatment (boron trifluoride etherate, \textit{110°}) led to decomposition of the material and only
intractable tars were obtained. In view of these results with the model system, there seemed to be no incentive to synthesize compound (51) and attempt rearrangement of it; so the approach was abandoned.

Stevens and Wenkert\textsuperscript{32} have reported the cyclization of the vinylogous amide (55) to the keto ester (56) by treatment with ethereal hydrogen chloride. The mechanism of this interesting transformation probably involves the intermediate (57).\textsuperscript{32} An approach to the synthesis of the pyrolysis ketone (3) involving a similar cyclization occurred to us (Chart VIII). The ester (42a), available from the first series, was converted to the primary amide (58) with concentrated ammonia and then reduced with lithium-aluminum hydride to the amine (59). Both of these reactions proceeded smoothly. The amine was condensed with 3-formyl-N-methyloxindole in refluxing benzene, furnishing compound (60), mp 88-88.5\degree. The structure of compound (60) was confirmed by infrared and NMR spectra. The position of the double bond of the vinylogous amide system
Chart VIII

(58) → (59)

(60) → (61) → (62)

(63) → (64)
was assigned on the basis of the N-H absorption at 3.08 μ in the infrared. A single vinyl hydrogen was observed in the NMR at 7.48 δ.

We hoped that treatment of (60) with ethereal hydrogen chloride, in analogy to the Wenkert case, would effect cyclization to the amino ketone (61). Compound (61) was regarded as an important intermediate since alkylation at nitrogen and the oxindole α-position by means of a suitable two carbon piece would complete the necessary pyrrolidine ring and condensation of the ketone moiety with the oxindole carbonyl could lead to (62), a potentially useful intermediate for synthesis of the model ketone (38).

When compound (60) was exposed to ether saturated with hydrogen chloride overnight, however, and the reaction worked up according to the Stevens procedure only ketal cleavage, probably during workup, was observed. The position of the infrared carbonyl absorption due to vinyllogous amide was unchanged. When (60) was subjected to p-toluenesulfonic acid in refluxing benzene, starting material was recovered intact. In a parallel series of experiments (Chart VIII) the Schiff base (63), an oil, was obtained from (59) and indole-3-aldehyde in the same manner described for the synthesis of (60). Treatment of (63) with ethereal hydrogen chloride resulted in extensive amounts of cleavage of the imine instead of the desired cyclization to (64). Toluenesulfonic acid in benzene was without effect; starting material was recovered.

The difference in the successful cyclization discussed previously and the present case must be the mode of protonation. Compound (60) probably enolizes to the conjugated imine (65) by protonation on oxygen to give a stable hydroxyindole. The indole imine (63) also possesses the conjugated imine form. Decrease in reactivity of immonium species
toward nucleophilic attack by conjugation has been observed recently by the Wenkert group.\textsuperscript{33} Thus the tetrahydropyridine (66a) reacted with indole in the presence of acid to give (67a), whereas the aldehyde (66b) or ketone (66c) failed to give the corresponding products (67b) and (67c) under the same conditions. The ester (66a) was believed to protonate on carbon, giving the isolated immonium salt (68), whereas the aldehyde or keto derivatives enolized to conjugated immonium species of the type (69). This view was established by the ultraviolet spectra.
of compounds of both types in acid. The chromophore of (66a) was destroyed by addition of acid, whereas (66c) showed enhanced absorption. Apparently the conjugation of the imine moiety in (63) and (65) has

\[ \begin{align*}
\text{(68)} & \\
\text{(69)}
\end{align*} \]

similarly lowered the reactivity of these species to such an extent as to preclude successful cyclization with the ketal.

Oishe, Nagel, and Ben\textsuperscript{34} reported a successful synthesis of compound (76a) as outlined in Chart IX. Oxidation of the ketal alcohol (71a) with dimethyl sulfoxide-dicyclohexylcarbodiimide gave aldehyde (72a) which was condensed with hydroxytryptamine (73) in basic solution affording (74a). Acetylation and hydrolysis of the ketal resulted in (75a) which was treated with triethylloxonium fluoroborate and the imido ether-ketone thus obtained was treated with sodium hydride to give (76a). The corresponding ethylated compound (76b) was regarded as a very useful intermediate for the synthesis of the objective vindoline degradation product (3). For example, if the double bond of the vinylogous amide system could be reduced, possibly via borohydride treatment of the enol ether (77), one could obtain the ketone (78). Removal of the acetyl group and replacement by acrylate would lead to (79) which would be only an internal Michael reaction away from the desired model ketone (53). This approach had been considered previously but was set aside until the
Chart IX

(70) \[ \overset{\text{COOEt}}{\text{O}} \] \[ \overset{\text{O}}{\text{O}} \] \[ \overset{\text{R}}{\text{O}} \] \[ \overset{\text{H}}{\text{O}} \] \[ \overset{\text{CHO}}{\text{O}} \] (71) (72)

(73) \[ \overset{N}{\text{H}} \] \[ \overset{\text{O}}{\text{O}} \] \[ \overset{\text{NH}_2}{\text{H}} \]

(74) \[ \overset{\text{N}}{\text{H}} \] \[ \overset{\text{O}}{\text{O}} \] \[ \overset{\text{R}}{\text{O}} \] \[ \overset{\text{---}}{\text{---}} \]

(75) \[ \overset{\text{N}}{\text{H}} \] \[ \overset{\text{O}}{\text{O}} \] \[ \overset{\text{Ac}}{\text{R}} \]

(76) \[ \overset{\text{N}}{\text{H}} \] \[ \overset{\text{O}}{\text{O}} \] \[ \overset{\text{Ac}}{\text{R}} \] \[ \overset{\text{---}}{\text{---}} \]

\[ \text{a) } R = H \]
\[ \text{b) } R = \text{ethyl} \]
Chart IX contd.

(77) $\rightarrow$ (78)

(79) $\rightarrow$ (38)
success of the Japanese group prompted reconsideration by us. Indeed, the availability of the ethyl substituted intermediate (76b) seemed almost certain if the proper aldehyde starting material could be obtained.

Ketalization of the acetoacetic ester (39) followed by lithium aluminum hydride reduction of the resulting ketal ester (70) according to the procedures of Surber and Schinz\textsuperscript{35} gave the known ketal alcohol (71b). Oxidation of (71b) by the dimethyl sulfoxide procedure\textsuperscript{34} was unsuccessful in our hands. However, the ketal aldehyde (72b) was successfully obtained by oxidation with chromium trioxide-pyridine. The standard procedure for this reaction,\textsuperscript{36} involving the use of pyridine as reaction solvent, gave incomplete oxidation, and the mixture of aldehyde and alcohol could not be separated by ordinary distillation. A recent revision of the procedure\textsuperscript{37} involving a homogeneous solution of the complex in methylene chloride gave, after distillation, samples of the aldehyde which showed no hydroxyl in the infrared and were free of absorption at 3.55\textmu in the NMR, the position of the two proton doublet assigned to the hydroxymethyl group of (71b). Compound (72b), characterized as the semicarbazone, showed aldehyde absorption (3.68 and 5.79\textmu) in the infrared and ketal (4.05\textmu, singlet, 4H) and aldehyde (9.85\textmu, doublet, 1H, $J = 4$) absorption in the NMR. The remainder of the NMR spectrum was in accord with the assigned structure.

Attempts to condense the aldehyde (72b) with hydroxytryptamine (73) (available as the hydrochloride from isatin by the method\textsuperscript{*} of Harley-}

\textsuperscript{*}Reasonable yields of hydroxytryptamine hydrochloride were obtained by this procedure only if the experimental directions were strictly followed.
Mason and Ingleby)\textsuperscript{38} in aqueous ethanol were unsuccessful. Different conditions involving changes in the pH, reaction time and temperature were tried but under no circumstances could the desired product (74b) be obtained. These results were surprising in view of the close similarity of this reaction to the successful case reported by the Japanese group. In addition, benzaldehyde,\textsuperscript{38} 3,4-dimethoxyphenylacetaldehyde,\textsuperscript{39,40} and 3,4-diethyl-4-chlorobutyraldehyde\textsuperscript{41} have been condensed with hydroxytryptamine (73) to yield products analogous to (74b). Steric factors appeared to be the source of difficulty with aldehyde (72b).

Since a mechanism for the condensation of aldehydes with hydroxytryptamine has not been established to our knowledge, it is difficult to draw conclusions regarding the nature of the steric hindrance responsible for failure of the present example. However, (72b) readily formed a semicarbazone and reacted smoothly with tryptamine to give a Schiff base, indicating that the aldehyde carbonyl group is not seriously hindered. It seems likely that the condensation proceeds through a Schiff base intermediate which cyclizes with the oxindole to give the product, e.g. (80\textsuperscript{\textae}81). It would then appear that the ethyl group and dioxolane
ring of (72b) could cause crowding in the intermediate Schiff base which would hinder cyclization. The steric problem was considered unavoidable in this reaction and alternative methods for synthesis of (74b) were considered.

Finch and Taylor\textsuperscript{42} reported the conversion of yohimbine (82) to the imidoether (84) via the chloroindolenine intermediate (83). This reaction appeared to be a desirable alternative to direct condensation for the synthesis of the imidoether of (75b). The aldehyde (72b) was easily condensed with tryptamine to give the Schiff base (85) (Chart X). Treatment of (85) with methanolic hydrogen chloride gave the amino ketone (86a) containing some of the corresponding ketal. Most of the ketal was hydrolyzed, possibly by traces of water in the reaction mixture or during workup. The crude amino ketone was dissolved in aqueous acid to complete hydrolysis of the ketal and acetylated without
Chart X

(85) → (86a) R = H
(86b) R = Acetyl

(87) → (88)

(89) → (90)
purification. The keto amide (86b) was obtained as a crystalline solid, mp 168.5-169.5°, in poor overall yield due to inefficiency of the cyclization process. This compound showed expected ketone and amide absorption in the infrared and the NMR spectrum (figure 1) was consistent with the expected structure, but indicated that the product consisted of a mixture of diastereoisomers. One isomer possessed a doublet at 5.735; the other, a doublet at 6.185, assigned to the methine hydrogen adjacent to nitrogen in the carboline ring. The presence of stereoisomers was not surprising since no control over either asymmetric center had been anticipated. No attempt was made to separate the isomers at this point.

Reaction of compound (86b) with t-butyl hypochlorite was expected to produce the chloroindolenine (87) in analogy to the yohimbine case. Solvolysis of this intermediate with methanol would give the imidoether (88) which could be carried on as previously planned. However, when (86b) was exposed to t-butyl hypochlorite in methylene chloride according to the procedure of Finch and Taylor42 and the solvent removed in vacuum at room temperature, the material spontaneously decomposed. Chromatography of the resulting dark oil afforded a yellow crystalline substance, mp 174-175°, in nearly quantitative yield. The mass spectrum and elemental analysis of this compound provided the formula C_{18}H_{20}N_{2}O_{2}, corresponding to the loss of two hydrogens from (86b). It appeared that the chlorination was followed by the loss of hydrogen chloride. The infrared spectrum showed indole N-H at 2.95μ, extremely intense carbonyl absorption at 6.03μ, and absence of the ketone band of the starting material. The NMR spectrum (figure 2) was extremely complex, but showed the unsplit methyl signals for the two acetyl groups present in the starting material.
Moreover, there seemed to be a general downfield shift in the NMR pattern associated with the increase in unsaturation of the molecule. The ultraviolet spectrum indicated a complex chromophore and showed that the molecule was not a simple indole, and thus the new unsaturation must be in a conjugated system. Structure (89) (Chart X) was suggested as a possibility by the preceding data and supported by the following chemical evidence.

Treatment of (89) with either methanolic hydrogen chloride at room temperature, refluxing methanolic methoxide or aqueous hydroxide led to the same crystalline product, mp 177-180°C, shown to be compound (90) by infrared spectral comparison in chloroform with an authentic sample of 1-(n-propyl)-3,4-dihydro-β-carboline (90), prepared from tryptamine by the method of Spëth and Lederer. This product must be derived from (89) by hydrolysis (or solvolysis) of both amide and vinylogous amide acetyl groups and migration of the double bond to the imine position.

The initial product of the reaction of (86b) and t-butyl hypochlorite was assumed to be the chloroindolenine (87), in analogy to the yohimbine case. Migration of the double bond, giving the intermediate species (91), could lead to loss of hydrogen chloride ether by 1,4-elimination or by participation of the nitrogen electrons. Nitrogen participation was considered an unlikely possibility since the chloroindolenine from yohimbine (83) showed no tendency to lose hydrogen chloride on standing.

The postulated mechanism for the formation of compound (89) suggested that ketalization of (86b) might inhibit this undesired reaction. Cyclization of the imine (85) in hot acetic acid gave the ketal amine (92a) (Chart XI) without hydrolysis. Acetylation of crude (92a) afforded
crystalline ketal amide (92b), mp 167-168°. The infrared spectrum of (92b) showed the expected N-H and amide bands at 2.92 and 6.07μ, respectively. The NMR spectrum (figure 3) showed the presence of ketal

\[ \text{(91)} \]

\(4.01\delta, \text{4H, singlet}\) and acetyl \(2.21\delta, \text{3H, singlet}\) groups. The NMR spectrum showed the presence of diastereoisomers as was the case with the ketone (86b); the methine proton adjacent to the amide nitrogen appeared as two doublets, 4.88 and 5.34\δ, integrating to one hydrogen.

Treatment of (92b) with \textit{t}-butyl hypochlorite, however, again led apparently to an unstable chloroindolenine (93), which decomposed spontaneously on evaporation of the solvent. Thin layer chromatography of the resulting dark oil showed it to be a complex mixture, and no characterizable products were obtained. The cause of the decomposition in this case was not clear, but it seemed obvious that the ketone function was not entirely responsible for the anomalous behavior of this series.

The presence of the N-acetyl group was considered as a possible cause of the difference in behavior of our series and yohimbine. Since the acetyl substituent served only as a protecting group, it was expendable. Replacement with benzyl would, for example, give a protecting
Chart XI

(92a) $R = H$

(92b) $R = Acety l$

(94) $\rightarrow$ (95)

(96)
group which would restore the nitrogen to tertiary amine as in yohimbine. In order to observe the difference in behavior of ketal amide (92b) and a corresponding ketal amine, reduction of (92b) to the amine (94) (Chart XI) with lithium aluminum hydride was carried out. Crystalline (94), mp 109-110°, was easily obtained. Treatment of (94) with t-butyl hypochlorite resulted in a stable, albeit noncrystalline indolenine chloride (95) which showed appearance of infrared absorption at 6.33μ, characteristic of indolenines, with concomitant loss of N-H absorption at 2.9μ. Treatment of (95) with methanol and one equivalent of base in the manner prescribed42 for the rearrangement of the yohimbine chloroindolenine (83) resulted only in recovery of starting material instead of rearrangement to the imidoether (96) as expected.

The surprising failure of the chloroindolenine (95) to undergo the rearrangement was not easily understandable. A mechanism for the rearrangement has been suggested42 which involves addition of methanol to the chloroindolenine to give an intermediate, e.g. (97), which undergoes concerted rearrangement as indicated by the arrows.

![Chemical Structure](image)

(97)

Such a process would require the chlorine to be equatorial so as to exist in a trans-coplanar relation to the migrating carbon-carbon bond. Chloroindolenines in which the chlorine is axial should not
rearrange. No experimental evidence appears to be available for this mechanism, however. There was no obvious reason to expect that the orientation of chlorine in the chloroindolenine (95) would be different from that of the yohimbine chloroindolenine (83). Our observations of this reaction indicate that its generality may be severely limited by electronic and, possibly, steric factors which are as yet not clear.

A study of a synthetic plan designed to utilize the reductive ring opening procedure first reported by Wenkert\textsuperscript{14} and recently used by Harley-Mason\textsuperscript{15} and Kutney\textsuperscript{16,19} in successful syntheses of quebrachamine and aspidospermine type systems (see introduction) was undertaken. The basic plan is shown in Chart XII. Methods for the conversion of (98) to (99), cyclization to (100), and reduction to (101) were available from syntheses described in the introduction of this thesis. Attention was focused on the development of a synthesis of a system of the type (98), oxygenated in the proper position for elaboration to the vindoline pyrolysis ketone model (38) by the route indicated in Chart XII.

Our first exploration of this approach involved study of a model series as outlined in Chart XIII. The keto aldehyde (104a) was expected to undergo normal Picket-Spengler cyclization with tryptamine to give the amino ketone (105a). Completion of the five-membered ring by means of an internal Mannich reaction with formaldehyde would lead to (106), which, after alkylation to a quarternary salt and treatment with sodium in ammonia,\textsuperscript{15,16} should afford the ketone (107). An oxidative cyclization with mercuric acetate\textsuperscript{20,21} would complete synthesis of the basic ring system (108). Choice of a suitable three carbon unit for the R-group of (107) could allow for completion of the aspidospermine skeleton oxygenated as necessary for the degradation product series, e.g. (38).
Chart XII

(98) → (99)

(100) → (101)
Chart XIII

\[ \text{(102)} \]

\[ \text{(103a) } R = O \]
\[ \text{(103b) } R = \text{NOH} \]

\[ \text{(104a) } R = O \]
\[ \text{(104b) } R = \text{NOH} \]

\[ \text{(105a) } R = O \]
\[ \text{(105b) } R = \text{NOH} \]

\[ \text{(106)} \]

\[ \text{(107)} \]

\[ \text{(108)} \]
Condensation of methyl dimethoxyacetate, available commercially, and methyl butyrate afforded the keto ester (102), which was hydrolyzed with aqueous base and decarboxylated by acidic workup to yield the keto acetal (103a) according to known procedures.\textsuperscript{44} The hydrolysis of (103a) to the corresponding aldehyde, reported to proceed in low yield,\textsuperscript{44} was unsuccessful in our hands. Refluxing of (103a) in 5% aqueous sulfuric acid caused extensive decomposition, and none of the desired aldehyde was isolated by distillation of the crude product. Hydrolysis of α-keto aldehydes is expected to be difficult for mechanistic reasons. In this system the carbonyl group causes destabilization of the positive charge in the intermediate leading to formation of the hemiacetal. Oximino acetals, on the other hand, can be hydrolyzed much more easily,\textsuperscript{45} apparently due to assistance by the oxime group as shown.

Oxime formation was regarded as a solution to the acetal hydrolysis problem. After cyclization to (105b), the no longer needed oxime function could be removed and the rest of the sequence could be carried out as previously planned. Accordingly keto acetal (103a) was converted to
the oxime (103b) with hydroxylamine in basic solution and hydrolysis in an aqueous alcoholic buffer (pH 3.75) gave the oximinoaldehyde (104b), bp 54-55°/0.45 mm, in 61% yield. The NMR spectrum of this compound showed a singlet at 9.50δ, characteristic of aldehyde protons. The oxime proton was present as a broad band at 10.6δ. The infrared spectrum possessed the expected absorption for hydroxyl, 3.0μ, and C-N, 6.10μ, of the oxime, and conjugated carbonyl, 5.38, 5.9μ. The apparent splitting of the carbonyl band suggested the presence of syn and anti isomers at the oxime group.

Reaction of oxime (104b) with tryptamine in aqueous acidic buffer solution (pH 3.75) did not produce the expected oxime (105b); instead a white crystalline substance, mp 124-125°, precipitated from the reaction mixture. The molecular weight (354, mass spectrum*) and elemental analysis of the product indicated the formula C20H26N4O2, corresponding to the condensation of tryptamine with two molecules of aldehyde (104b) with loss of two molecules of water.** We theorized that the desired product (105b) was formed initially and condensed with a second molecule of aldehyde to give (109), which may form the tetracyclic compound (110) on loss of water. The ultraviolet spectrum indicated an indole chromophore. The infrared spectrum was not in contradiction to the proposed structure but contained little confirmatory information. Extreme

*Assistance in obtaining this spectrum by the Lilly Research Laboratories is gratefully acknowledged.

**This product could also be isolated from reaction of (104b) with tryptamine in dry benzene at room temperature. Attempts to find conditions which would avoid formation of this product were unsuccessful.
insolubility of the material in organic solvents made determination of the NMR spectrum difficult. The analytical and mass spectral data clearly indicated, however, that the desired oxime (105b) had not been obtained.

\[ \text{(109)} \quad \rightarrow \quad \text{(110)} \]

While considering possible modifications of the preceding plan which would avoid the formation of (110), a more attractive approach occurred to us, as shown in Chart XIV. If the ketodiester (140), previously synthesized in connection with earlier work (see Chart VI), could be converted to the ketoaldehyde (112), subsequent reaction with tryptamine would be expected to give compound (113). Lithium aluminum hydride reduction of (113) should give the diol (114) which, after selective activation of the primary hydroxyl group with methane sulfonyl chloride, should cyclize to the salt (115). This compound could then be elaborated to the desired model ketone (35) by the plan indicated in Chart XII.

Bromination of the ketodiester (40) with one mole of bromine proceeded smoothly to give bromoketone (111a). Attempts to convert (111a) to (112) by means of the dimethyl sulfoxide-dicyclohexylcarbodiimide procedure were not successful, so the longer Kendall method was
Chart XIV

(40)

(111a) \( R_1 = H, R_2 = Br \)
(111b) \( R_1 = H, R_2 = OAc \)
(111c) \( R_1 = Br, R_2 = OAc \)

(115)

(114)

(115)
resorted to. Thus acetolysis of (111a) in alcoholic potassium acetate
gave the acetoxy ketone (111b). The product was easily characterized by
its NMR spectrum, showing appearance of acetoxyacetyl methylene absorp-
tion at 4.78δ.48 The rest of the spectrum and its integration was in
accord with the assigned structure. Bromination of (111b) with excess
bromine gave bromoacetoxy ketone (111c) which was hydrolyzed without
purification with 80% aqueous pyridine47 to the ketoaldehyde (112). The
NMR spectrum indicated presence of a mixture of free aldehyde (9.15δ,
singlet) and hydrate (4.98δ, singlet; 5.32δ, broad (OH)) in reasonably
pure condition. The crude aldehyde was condensed with tryptamine in
benzene without further purification to give an oily Schiff base which
was not isolated. Treatment of this oily material with hot acetic acid
gave, on workup, crystalline compound (113), mp 150-153° (after re-
crystallization from methanol).

Confirmation of the structure of (113) was available from physical
data. The infrared spectrum possessed N-H absorption at 2.9µ and three
carbonyl bands at 5.68, 5.81, and 5.94µ assigned to the five-ring ketone,
ester, and five-ring lactam groups respectively. The ultraviolet spec-
trum contained an indole chromophore. The NMR spectrum (figure 4) was
very complex due to the presence of nonequivalent diastereoisomers.† The
ratio of these isomers was estimated by integration of the spectrum to
be 7:3.** The predominant of the two displayed a triplet at 0.42δ for

*No attempt was made to separate the isomers since the planned ring
opening (Chart XIV) would destroy the asymmetric center at the
ring fusion.

**The predominance of one of these isomers may have arisen by
selective cyclization.
the methyl of the ethyl side chain. The abnormally high field position of this signal may be due to interaction with the indole system. The ethyl group of the ester function of this isomer appeared as a triplet at 1.22° and quartet at 4.11°. The less abundant isomer similarly showed side chain methyl as a triplet at 0.86° and the ester ethyl group as a triplet at 1.02° and quartet at 3.88°. Aromatic absorption for both isomers appeared as a complex pattern centered at 7.36°, and the broad band at 8.85° was assigned to indole N-H. The rest of the spectrum was complex and further definite assignments could not be made. A singlet at 5.16° was probably due to the ring fusion methine hydrogen of the predominant isomer, but the presence of overlapping bands made this assignment uncertain. The mass spectrum showed a parent ion at m/e 368, confirming the molecular weight and formula obtained from elemental analysis. Prominent ions of mass 339 and 267 were observed corresponding to loss of the ethyl and carboethoxyethyl side chains respectively. The most intense peaks, however, occurred at m/e 170 and 169. Such ions could be accounted for by cleavage of the five-membered ring to give dihydrocarboline ion (a, M=170) which would give the protonated carboline ion (b, M=169) on loss of hydride.

Attempts to reduce the keto lactam (113) to the diol (114) with lithium aluminum hydride in tetrahydrofuran were not successful. Crude material could be obtained which was free of carbonyl absorption in the infrared but thin layer chromatography of the product showed that it was a complex mixture. Furthermore, the crude product was unstable, darkening on standing in the refrigerator.

Other less direct methods for the conversion of compound (113) to (114) were considered. Stepwise reduction of the oxygen functional
groups by milder and more selective reagents may be more successful. Such an alternative course would introduce several additional steps into the synthetic plan, making it less attractive. Since time was not available to prepare more starting material for an investigation of the reduction steps the decision was made to conclude the investigation at this point.

This study has involved the experimental investigation of five different synthetic approaches to the vindoline pyrolysis ketone (3). Our synthetic objective has not been reached, but the results described here should be of value in determining the future course of work on the vindoline problem.
III. EXPERIMENTAL
EXPERIMENTAL*

Preparation of Ethyl-2-ethylacetoacetate (39). The general procedure for alkylation of ethyl acetoacetate\textsuperscript{49} was followed. Sodium, 115 g (5.0 moles), was dissolved in 2.5 liters absolute ethanol. Ethyl acetoacetate, 650 g (5.0 moles), was added, and the solution was stirred mechanically as ethyl bromide, 595 g (5.47 moles), was dripped in over 1.5 hours. The resulting mixture was stirred and heated under reflux overnight. Heating was stopped when the reaction mixture became neutral to litmus. (The precipitation of sodium bromide is heavy and efficient stirring must be maintained to prevent bumping.) The flask was allowed to cool, and the sodium bromide was removed by filtration. The solution was concentrated by distillation (with efficient stirring) to a volume of approximately 800 ml. The residue was distilled through a 50 cm spinning band distilling column. After a forerun of approximately 80 g containing some starting material, pure product, 422 g,

\*Melting points were determined on a Ficher-Johns melting point apparatus and are uncorrected. The sealed tube melting points were measured on a Mel-Temp apparatus. Boiling points are uncorrected. Infrared spectra were determined using a Beckman IR-5A or IR-8 infrared spectrophotometer. Ultraviolet spectra were obtained with a Bausch and Lomb Spectronic 50S ultraviolet spectrophotometer. Nuclear magnetic resonance (NMR) spectra at 60 megacycles were measured with Varian A-60 and A-56/60 instruments using tetramethyl silane as the internal standard. Certain NMR spectra at 100 megacycles were obtained with a Varian HA-100 spectrometer through the courtesy of Professor M. R. Wilcott, University of Houston. Mass spectra were determined on a Consolidated Electrodynamics analytical mass spectrometer. Elemental analyses were carried out by Elek Microanalytical Laboratories, Torrence, California and Scandanavian Microanalytical Laboratories, Herlen, Denmark.
bp 98°/30 mm (lit 196-198°) was collected. The tail fraction, 89 g (98-102°/30 mm) was determined to be 98% pure by gas chromatography and was suitable for further processing. Total yield of ethyl-2-ethylacetoacetate (39) was 511 g (65%).

Preparation of 2-Acetyl-2-ethylglutaric Acid Diethyl Ester (40).

A modification of Eschenmoser's procedure for addition of ethyl acrylate to ethyl acetoacetate was used. To ethyl-2-ethylacetoacetate (39), 139 g (0.88 moles), heated to 110° was added a solution of sodium ethoxide (0.3 g sodium dissolved in 15 ml absolute ethanol). Ethyl acrylate, 88 g (0.88 moles), was added with stirring over 20 minutes, no rise in temperature being observed. The mixture was heated (110°) for 6.5 hours before being cooled to room temperature. The reaction mixture was taken up in ether, 500 ml, and the ether solution washed with 0.05 N hydrochloric acid (250 ml), 5% sodium bicarbonate, water, saturated sodium chloride and dried over anhydrous sodium sulfate. The ether and unreacted ethyl acrylate were removed by distillation at reduced pressure and the colorless residue distilled yielding 141.6 g (62.5%) 2-acetyl-2-ethylglutaric acid diethyl ester (40), bp 95°/0.05 mm.

\[ \text{film} \]
\[ \lambda_{\text{max}} \quad 5.78, 5.84 \mu. \]

\[ \text{NMR (CCl}_4) \]
\[ 0.88 \delta \quad \text{triplet} \quad (3H) \]
\[ 1.23 \delta \quad \text{triplet} \quad (3H) \]
\[ 1.27 \delta \quad \text{triplet} \quad (3H) \]
1.86\textsuperscript{\textdegree}  
2.10\textsuperscript{\textdegree}  
4.12\textsuperscript{\textdegree}  

**Preparation of 4-Acetylcaproic Acid (41a).** To 2-Acetyl-2-ethyl-

Preparation of 4-Acetylcaproic Acid (41a). To 2-Acetyl-2-ethyl-
glutaric acid diethyl ester (40), 15 g (70 mmoles) was added 2.5 N-
aqueous sodium hydroxide, 75 ml. Ethanol was added until the mixture
was just homogeneous. The mixture was heated under reflux overnight.
On cooling the reaction mixture was concentrated to about 75 ml in
vacuum so that most of the alcohol was removed. Acidification with
concentrated hydrochloric acid to pH 2 was followed by extraction with
er. The ether extracts were washed with water, saturated sodium chloride, and dried over magnesium sulfate. Evaporation of the ether
afforded crude 4-acetylcaproic acid (41a), 9.46 g (85\%). The acid could
be distilled (bp 95°/0.13 mm; lit. 151-152°/5 mm); but the crude pro-
duct, shown to be free of starting ester by NMR, was suitable for
esterification.

\[ \lambda_{\text{film}} = 5.83\mu \text{ (broad).} \]

**Preparation of 4-Acetylcaproic Acid Methyl Ester (41b).** A solution
of 4-acetylcaproic acid (41a), 34.4 g (0.218 moles), in absolute
methanol, 80 ml, containing concentrated sulfuric acid, 3 drops, was
heated under reflux for 8 hours. About 50 ml of the alcohol was dis-
tilled and the reaction mixture was further concentrated by vacuum
evaporation. The residue was taken up in ether and the ether solution
washed with 5% sodium bicarbonate, water, saturated sodium chloride and
dried over magnesium sulfate. Evaporation gave nearly pure 4-acetyl-caproic acid methyl ester (41b), 29.6 g (80%). Distillation afforded pure product, bp 50°/0.13 mm (lit 52 101-102°/5 mm).

\[ \lambda_{\text{max}} \text{film} = 5.76, 5.84 \mu. \]

Preparation of 4-Acetylcaproic Acid Methyl Ester Ethylene Ketal (42a). A solution of 4-acetylcaproic acid methyl ester (41b), 26 g (0.15 mole), and ethylene glycol, 10 g (0.16 mole), in benzene, 100 ml, containing a catalytic amount of p-toluenesulfonic acid was heated under a water separator overnight. Slightly more than the theoretical amount of water (2.7 ml) was collected. The reaction mixture was cooled, washed with 5% sodium bicarbonate solution, water, saturated sodium chloride and dried over sodium sulfate. (Magnesium sulfate was found to be unsatisfactory for this purpose.) The solvent was removed in vacuum and the product distilled through a 25 cm glass helices packed column. After a short forerun (45-63°/0.1 mm), the pure ketal ester (42a), 12.95 g (40%), was collected, bp 66°/0.12 mm. The analytical sample was taken directly from this fraction without additional purification.

\[ \lambda_{\text{max}} \text{film} = 5.73, 6.91, 7.20, 8.50, 8.95, 9.32, 10.48, 11.5 \mu. \]

\begin{align*}
NMR \text{ (CCl}_4) \\
1.06 & \text{ poorly resolved triplet (3H)} \\
1.20 & \text{ singlet (3H)} \\
1.35-1.85 & \text{ multiplet (5H)}
\end{align*}
2.42₈ broadened triplet (2H)
3.68₈ singlet (3H)
3.91₈ singlet (4H)

Analysis
Calc. for C₁₁H₂₀O₄: C, 61.08; H, 9.32
Found: C, 61.10; H, 9.67

Preparation of 4-Acetylcaproic Acid Ethylene Ketal (42b). A mixture of 4-acetylcaproic acid methyl ester ethylene ketal (42a), 6.73 g, and 15 ml 1 N sodium hydroxide was made homogeneous by addition of methanol. The resulting solution was heated under reflux in an atmosphere of nitrogen for 9 hours, cooled and concentrated in vacuum to a volume of about 35 ml. The concentrated solution was placed in a separatory funnel and ice was added. Ether, 100 ml, was added and the aqueous layer neutralized by addition of ice cold 2 N hydrochloric acid in portions until the pH of the water layer was about 2. The funnel was shaken immediately and the layers separated. The water layer was extracted twice more with ether and the extracts quickly combined and washed with water, saturated sodium chloride, and dried over sodium sulfate. Evaporation of the solvent gave the product as a clear, nearly colorless oil, 4.59 g (73%). The acid was carried through the following reaction without further purification. Spectral data are for the crude material.

\[ \lambda_{\text{max}} \text{film} \]
\[ 3.2 \text{ (broad), } 5.36, 6.9, 7.1, 7.25, 8.10, 9.3, 9.5, 10.5, 11.5 \mu \text{.} \]
<table>
<thead>
<tr>
<th>NMR (CCl₄)</th>
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<tbody>
<tr>
<td>1.03 ppm</td>
<td>poorly resolved triplet</td>
<td>(3H)</td>
</tr>
<tr>
<td>1.20 ppm</td>
<td>singlet</td>
<td>(3H)</td>
</tr>
<tr>
<td>1.3-1.98 ppm</td>
<td>multiplet</td>
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<td>3.90 ppm</td>
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</tr>
<tr>
<td>8.75 ppm</td>
<td>singlet</td>
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**Preparation of Compound (43).** To a solution of the ketone acid (42b), 4.59 g (22.7 mmole), and triethylamine, 2.40 g (5.22 ml; one equiv.), in tetrahydrofuran, 25 ml, (freshly distilled from lithium aluminum hydride) maintained at -10⁰ in an ice-salt mixture was added ethyl chloroformate, 2.47 g (22.7 mmole), with stirring. The precipitate of triethylamine hydrochloride was observed immediately. Tryptamine, 3.64 g (22.7 mmole), in tetrahydrofuran, 30 ml, was added dropwise to the cooled reaction mixture. After being kept at -10⁰-0⁰ for one hour the mixture was allowed to warm to room temperature overnight. The precipitate was filtered and washed with additional tetrahydrofuran. The filtrate was concentrated to remove most of the tetrahydrofuran and the residue taken up in ether. The ether solution was washed with 0.5 N hydrochloric acid, water, 5% sodium bicarbonate, water, saturated sodium chloride and dried by filtration through magnesium sulfate. Evaporation of the ether afforded the crude product, 6.13 g, as an oil which was purified by chromatography on Fluorisil. Elution with benzene containing increasing amounts of ether up to 20%
ether gave the byproduct carbamic ester (44), 2.0 g. By increasing the benzene-ether ratio rapidly to 100% ether the desired ketal amide (43), 3.85 g (49% based on tryptamine) was obtained. Both products were colorless but showed no tendency to crystallize.

Data for the carbamic ester (44):

\[ \text{CH}_2\text{Cl}_2 \]
\[ \lambda_{\text{max}} \quad 2.9, 5.30 \mu. \]

NMR (CCl₄)

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Data for the ketal amide (43):

\[ \text{CHCl}_3 \]
\[ \lambda_{\text{max}} \quad 2.90, 6.0 \mu. \]

NMR (CDCl₃)

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<td>2.20 δ</td>
<td>triplet</td>
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</tbody>
</table>
Preparation of Compound (45b). The ketal amide (43), 1.25 g, in absolute tetrahydrofuran was added slowly to a slurry of lithium aluminum hydride, 0.5 g, in tetrahydrofuran, 65 ml, and the mixture was refluxed for 24 hours. After cooling, the excess hydride was destroyed by addition of wet ether and the inorganic material removed by filtration. The filter cake was washed thoroughly with ether. The filtrate was evaporated affording crude amine ketal (45a), 1.04 g, as an oil which did not crystallize (IR showed N-H at 2.9, 3.0μ but no carbonyl). The material was not purified further before formylation which was carried out by the procedure of Blickle.27 Thus the amine was dissolved in 15 ml dry chloroform and cooled to 0° under nitrogen. Chloral, freshly distilled, 450 mg (1 equiv.) was added slowly and the reaction mixture allowed to stand at 0° for one hour. After 24 hours at room temperature the mixture was heated on a steam bath for 30 minutes to complete the reaction. After cooling, the solution was diluted with ether and washed with 5% acetic acid, 5% sodium bicarbonate, water, saturated sodium chloride solution, and dried over sodium sulfate. Evaporation of the solvent gave the crude oily formamide (45b), 1.04 g, an oil. Chromatography on activity I alumina, 20 g, and elution with benzene-ether 1:1 gave 680 mg (60%) purified formamide (45b), as an oil which did not crystallize. Attempts to crystallize this compound were
unsuccessful.

\[ \text{CH}_2\text{Cl}_2 \quad \lambda_{\text{max}} = 2.9, 6.0 \mu. \]

NMR (CDCl₃)

1.12 \delta \quad \text{singlet} (3H)

3.80 \delta \quad \text{singlet} (4H)

8.05 \delta \quad \text{singlet} (1H)

(integration estimated)

Preparation of Compound (46). The purified ketal amide (45b), 668 mg, was dissolved in dry acetone, 15 ml, and a catalytic amount of p-toluenesulfonic acid was added. The reaction was kept at room temperature for 24 hours. The acetone was evaporated and the residue taken up in a mixture of ether and a little methylene chloride. The ether solution was washed with 5% sodium bicarbonate, water, saturated sodium chloride, and dried over sodium sulfate. Evaporation of solvent gave the crude product, 533 mg. Chromatography on activity I alumina and elution with ether-benzene 1:1 gave 470 mg (80%) of the purified keto formamide (46) as an oil which did not crystallize.

\[ \text{CH}_2\text{Cl}_2 \quad \lambda_{\text{max}} = 2.9, 5.33, 5.98 \mu. \]

Acid Catalyzed Cyclization of Compound (45) to Compound (47).

A sample of the ketal amide (45), 1.7 g, was dissolved in benzene, 20 ml, and a catalytic amount of toluenesulfonic acid was added. After the solution had been heated to just below reflux temperature (in about 10
minutes) a crystalline solid precipitated, and the solution had become deep red in color. Heating was stopped and the solid material, 0.88 g, isolated by filtration. Recrystallization from ethanol gave analytically pure compound (47), mp 272-273° (sealed tube). This compound was found to be insoluble in most organic solvents. It was sparingly soluble in dimethyl sulfoxide and chloroform.

\[ \lambda_{\text{max}}^{\text{CHCl}_3} = 2.89, 6.15\mu. \]

\[ \lambda_{\text{max}}^{\text{CH}_3\text{OH}} = 223\mu (\log \epsilon 4.59), 2.73\mu (\log \epsilon 3.89), 282\mu (\log \epsilon 3.89), 290\mu (\log \epsilon 3.81). \]

Molecular weight: 282 (mass spectrum).

**NMR** (DMSO-\(d_6\))

- 1.08\(\delta\) multiplet \((3H)\)
- 1.53\(\delta\) singlet \((3H)\)
- 4.83\(\delta\) multiplet \((1H)\)
- 6.8-7.5\(\delta\) complex multiplet \((4H)\)
- 9.6\(\delta\) broad \((1H)\)

**Analysis**

Calc'd. for C\(_{18}\)H\(_{22}\)N\(_2\)O: C, 76.56; H, 7.85; N, 9.32.

Found: C, 76.64; H, 7.91; N, 10.04.

**Preparation of Compound (53a).** In general, the procedure of Schut\(^{31}\) was followed. Thus to a solution of sodium hydroxymethylene acetone,
1.53 g (14.2 mmoles), in water, 50 ml, was added dropwise an aqueous solution of tryptamine hydrochloride, 2.80 g (14.2 mmoles). Reaction was rapid but no heat evolution was noticed on this scale. The oily insoluble vinylogous amide intermediate was extracted into ethyl acetate and the organic solution washed with water, saturated sodium chloride, and dried over sodium sulfate. Evaporation of the solvent gave about 3.45 g of oily vinylogous amide. A portion of the oil, 2.0 g, was taken up in absolute methanol, 20 ml, and the solution was saturated with hydrogen chloride with cooling in an ice bath, whereupon the product precipitated from the solution.* Ether was added and the precipitate, 1.5 g, was filtered off. Processing of the rest of the intermediate vinylogous amide, 1.45 g, gave an additional 1.0 g of crude material. Recrystallization of the combined crude product from methanol gave 1.65 g (43%) of compound (53a) (mp 205-215° dec; lit.31 220-230° sintering).

\[ \lambda_{\text{max}} \text{Nujol} = 5.35 \mu \text{ (lit.}^{31} \lambda_{\text{max}} \text{KBr} = 5.85 \mu \text{).} \]

**Acetylation of Compound (53a).** The hydrochloride (53a), 1.0 g, was suspended in acetic anhydride, 8 ml, and pyridine, 6.4 ml, was added. After one hour at room temperature the mixture was homogeneous. After one additional hour the excess acetic anhydride was destroyed by cautious addition of water. The reaction mixture was diluted with ice water and extracted with ether. The ether layers were combined and washed with

*If the methanol solution is too dilute, the product does not tend to precipitate as the solution becomes saturated with hydrochloride and the yield is greatly reduced.*
water, 1 N hydrochloric acid, water, 1 N sodium hydroxide, water, saturated sodium chloride, and dried over sodium sulfate. Evaporation of the ether gave 0.5 g of an oil which crystallized. Recrystallization from aqueous methanol gave the keto amide (53b), mp 131-132°C.

\[ \lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2} = 2.95, 5.85, 6.10 \mu. \]

**Analysis:**
Calc'd. for C_{18}H_{18}N_{2}O_{2}: C, 71.07; H, 6.74; N, 10.36.

Found:
C, 71.07; H, 6.84; N, 10.16.

**Preparation of 4-Acetylcaproamide Ethylene Ketal (58).** A mixture of 4-acetylcaproic acid methyl ester ethylene ketal, 6.7 g, and concentrated ammonia (sp. gr. 0.90), 67 ml, was stirred in a stoppered flask at room temperature overnight. The flask was opened and heated on a water bath until the ammonia had been driven off. The solution was concentrated at reduced pressure and the residue extracted with ether. The ether layers were washed with saturated sodium chloride and dried over sodium sulfate. Evaporation of the solvent gave 5.6 g (90%) crude amide as a yellow oil. It was carried to the next step without further purification.

\[ \lambda_{\text{max}}^{\text{film}} = 3.0, 3.15, 5.99 \mu. \]

**Preparation of 4-Acetyl-n-hexylamine Ethylene Ketal (59).** To a slurry of lithium aluminum hydride, 3.5 g, in absolute tetrahydrofuran,
100 ml, was added 4-acetylcaproamide ethylene ketal (58), 5.6 g, in tetrahydrofuran, 30 ml, dropwise, with stirring. The reaction mixture was heated to reflux overnight, cooled, and the excess hydride destroyed by addition of wet ether. The mixture was then diluted with ether and the solution partially decanted from the inorganic material. The remaining suspension was filtered with suction and the filter cake washed thoroughly with ether. The decantate and the filtrates were combined, washed with saturated sodium chloride and dried over sodium sulfate. Evaporation of the solvent and distillation gave 3.33 g (74%) 4-acetyl-n-hexylamine ethylene ketal (59), bp 76-79°/0.32 mm.

$\lambda_{\text{max}}$ film 3.0 (broad), 6.86, 6.96, 7.21, 8.0-8.20, 8.65, 9.35, 9.6, 10.5, 11.5 $\mu$.

**NMR (CCl$_4$)**

- 1.08 $\delta$ multiplet (3H)
- 1.18 $\delta$ singlet (3H)
- 1.3-1.6 $\delta$ multiplet (9H)
- 2.62 $\delta$ triplet (2H)
- 3.92 $\delta$ singlet (4H)

*Naphthyl urea:* mp 120-120.5°.

**Analysis of the naphthyl urea:**

Calcul'd. for C$_{21}$H$_{26}$N$_2$O$_3$: C, 70.75; H, 7.91; N, 7.86.

Found: C, 70.80; H, 7.99; N, 7.91.
Preparation of Compound (60). A solution of \(3\)-formyl-N-methyl-oxindole, 646 mg (3.74 mmoles), and \(4\)-acetyl-n-hexylamine ethylene ketal (59), 725 mg (3.88 mmoles), in benzene, 10 ml, was refluxed under a water separator for 6 hours. Upon cooling, the solvent was evaporated under vacuum and the oily residue crystallized on standing for several hours. Recrystallization of the material from aqueous ethanol gave the product, compound (60), mp 86-87\(^\circ\), 773 mg (60\%). The analytical sample melted at 88-88.5\(^\circ\).

\[\text{CHCl}_3 \max \quad \lambda = 3.08, 6.0, 6.21, 7.2, 7.4, 8.9, 9.02 \mu.\]

\[\text{EtOH} \max \quad \lambda = 224 \mu (\log \varepsilon 4.31), 274 \mu (\log \varepsilon 4.34), 278 \mu \]
\[\text{(log \varepsilon 4.38), 322 \mu (log \varepsilon 4.28), 330 \mu (log \varepsilon 4.28).}\]

NMR (CDCl\(_3\)):

| \(1.08\delta\) | multiplet | \(3\H\) |
| \(1.2\delta\) | singlet | \(3\H\) |
| \(1.3-1.8\delta\) | broad multiplet | \(7\H\) |
| \(3.20\delta\) | unresolved | \(2\H\) |
| \(3.26\delta\) | singlet | \(3\H\) |
| \(3.82\delta\) | singlet | \(4\H\) |
| \(6.7-7.3\delta\) | complex | \(4\H\) |
| \(7.48\delta\) | singlet | \(1\H\) |
| \(8.7\delta\) | broad | \(1\H\) |
Analysis:
Calc'd. for C_{20}H_{28}N_{2}O_{3}:  C, 69.74;  H, 8.19;  N, 8.14.
Found:  C, 69.78;  H, 8.19;  N, 8.03.

Preparation of Compound (63). Indole-3-aldehyde, 388 mg (2.64 mmol), and 4-acetyl-n-hexylamine ethylene ketal (59) 570 mg (2.78 mmol), were dissolved in toluene, 25 ml, with heating and the solution was heated to reflux overnight under a water separator containing calcium hydride. The mixture was cooled, and the solvent removed by vacuum evaporation furnishing the crude imine (63), as a light brown oil, 940 mg, (quantitative) which did not crystallize. Attempts to purify the product by chromatography on Fluorisil were unsuccessful.

\[ \lambda_{\text{max}}^{\text{CHCl}_3} \quad 2.92, 6.10 \mu. \]

NMR (CDCl$_3$):

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<td>8.605</td>
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</table>

Preparation of Ethyl-2-ethylacetoacetate Ethylene Ketal (74)\textsuperscript{75}.

Ethyl-2-ethylacetoacetate (39), 90.5 g (0.58 mole), and ethylene glycol,
47.5 g (0.76 mole), were dissolved in benzene, 200 ml, and a catalytic amount of p-toluenesulfonic acid (0.3 g) was added. The solution was refluxed under a water separator for 19 hours. The theoretical amount of water (10.4 ml) was collected. The reaction mixture was cooled and a small amount of solid potassium carbonate was added to neutralize the p-toluenesulfonic acid. The benzene solution was then washed with 5% sodium bicarbonate solution, water, saturated sodium chloride, and dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation gave 89.7 g (84%) ethyl 2-ethylacetoacetate ethylene ketal (70), bp 100.5°/9 mm (lit: 35 107°/11 mm).

\[ \lambda_{\text{max}}^{\text{film}} = 5.73 \mu \text{m}. \]

Preparation of 3-Hydroxymethyl-2-pentanone Ethylene Ketal (71b) 35.

To a slurry of lithium aluminum hydride, 9 g, in absolute ether, 200 ml, was added dropwise a solution of ethyl 2-ethylacetoacetate ethylene ketal (70), 64.85 g, in an equal volume of ether. The addition was complete in 2 hours. The reaction was stirred at room temperature for one additional hour and refluxed for one hour. The excess hydride was destroyed by careful addition of water. The inorganic material was filtered with suction and the filter cake washed thoroughly with ether. The filtrate was washed with water, saturated sodium chloride, and dried over anhydrous sodium sulfate. Evaporation of solvent and distillation gave 40.50 g (79%) 3-hydroxymethyl-2-pentanone ethylene ketal (71b), bp 103°/13 mm (lit: 35 98.5°/12 mm).

\[ \lambda_{\text{max}}^{\text{film}} = 2.92 \mu \text{m}. \]
Preparation of 3-formyl-2-pentanone Ethylene Ketal (72b). A slurry of the chromium (VI) oxide-pyridine complex in pyridine was prepared by the Sarett procedure\(^*\) (90 g chromium trioxide was added slowly to 1 liter pyridine kept below \(20^\circ\)).\(^*\) The yellow slurry of the complex was allowed to stand at room temperature for several hours, and stirring was resumed, whereupon a change to a red macrocrystalline form of the complex was observed.\(^\text{37}\) The red material was filtered and dried in a vacuum desiccator.

A portion of the complex, 148 g, was dissolved in 1500 ml anhydrous methylene chloride,\(^\text{37}\) forming a dark red solution. The solution was stirred vigorously as 3-hydroxymethyl-2-pentanone ethylene ketal (71b), 15.0 g, in methylene chloride, 50 ml, was added. The solution changed immediately from red to dark brown upon addition of the alcohol and a black tarry precipitate coated the walls of the flask. The reaction mixture was stirred for 15 minutes and allowed to stand for two hours. The mixture was filtered and concentrated to about 50 ml. The residue, a very dark liquid, was distilled. After removal of pyridine, the

\(^*\)Note: This reaction was found to be hazardous when conducted on a large scale. A minor explosion occurred when chromium trioxide was added to a slurry of the complex which had become too thick to be stirred well by a motor driven stirrer. If the slurry becomes thick, additional pyridine should be added. The chromium trioxide must mix immediately with the pyridine. In a second case, a powder funnel in one neck of the reaction vessel, through which the chromium trioxide was being added, accumulated small amounts of the material during the course of addition. The funnel suddenly inflamed as pyridine vapor apparently came in contact with it. It is recommended that such a funnel not be used.
3-formyl-2-pentanone ethylene ketal (72b), 8.32 g (56%), bp 80-86°/9 mm, was collected.

\[
\lambda_{\text{max}} \quad 3.68, 5.79 \mu\text{m}.
\]

**NMR (CCl₄):**

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<th>(in Hz)</th>
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**Semicarbizone:** mp 175-177°.

**Analysis of semicarbizone:**

Calc'd. for C₉H₁₇NgO₅: C, 50.21; H, 7.96; N, 19.52.

Found: C, 50.50; H, 8.10; N, 19.05.

**Preparation of Compound (86b).** Tryptamine, 7.46 g (46.6 mmoles), and 3-formyl-2-pentanone ethylene ketal (72b), 7.46 g (47.2 mmoles), were dissolved in benzene, 200 ml, and anhydrous potassium carbonate, 35 g, was added. The mixture was stirred at room temperature overnight. The carbonate was filtered off and the benzene removed by vacuum evaporation. The residue, the crude imine intermediate (85), was dissolved in absolute methanol, 200 ml, and acetyl chloride, 10 ml, was slowly added with ice cooling. The mixture was allowed to stand at room
temperature for 5 hours, after which it was very dark. The methanol was removed at reduced pressure and the residue taken up in water. The aqueous solution was washed with ether, made alkaline with 10% sodium hydroxide solution, and extracted with ether. The ether layers were combined and washed with water, saturated sodium chloride, and dried over anhydrous sodium sulfate. Evaporation of the ether gave the crude amino ketone (86a), 6.9 g, which was acetylated without further purification.

The crude amino ketone (86a) was dissolved in 100 ml methylene chloride containing triethylamine, 18 ml, and cooled to 0° in an ice bath. Acetyl chloride, 2.54 g, in 25 ml methylene chloride was added dropwise, with stirring, over 15 minutes. The mixture was allowed to warm up to room temperature slowly over 4 hours. The reaction mixture was washed with 1 N hydrochloric acid, water, 5% sodium bicarbonate, saturated sodium chloride, and dried over sodium sulfate. The solvent was evaporated at reduced pressure and the residue dissolved in a mixture of 50 ml ethanol and 30 ml water. Concentrated hydrochloric acid, 5 drops, was added and the solution allowed to stand at room temperature overnight to complete hydrolysis of the ketal. The solution was concentrated under vacuum and the residue taken up in ether-ethyl acetate. The resulting solution was washed with 5% sodium bicarbonate solution, water, saturated sodium chloride, and dried by filtration through sodium sulfate. The dried ether-ethyl acetate solution was filtered through a column of 30 g activity I neutral alumina. After washing the alumina with an equal volume of ether, the solvent was removed by vacuum evaporation; and the residue, an oil, was triturated with ether, causing part of the material to crystallize. Recrystallization from ethanol gave the
keto-amide (86b), 1.75 g, mp 168-169\degree. A second alumina filtration of the mother liquor afforded an additional 2.50 g of the product. The total yield was 4.5 g (31\% based on tryptamine). The analytical sample melted at 168.5-169.5\degree.

\[
\begin{align*}
\chi_{\text{max}}^\text{CHCl}_3 & = 2.90, 5.85, 6.10\mu. \\
\chi_{\text{max}}^{\text{EtOH}} & = 223 \mu (\log \varepsilon 4.54), 274 \mu (\log \varepsilon 3.91), 281 \mu \\
& (\log \varepsilon 3.91), 290 \mu (\log \varepsilon 3.85). \\
\end{align*}
\]

**NMR**: see figure 1

**Analysis:**

Calc'd. for C_{18}H_{22}N_{2}O_{2}: C, 72.45; H, 7.43; N, 9.39.

Found:

C, 72.47; H, 7.56; N, 9.43.

**Reaction of Compound (86b) with t-Butyl Hypochlorite.** This reaction was carried out according to the procedure of Finch and Taylor.\(^{42}\) Thus to a solution of the keto-amide (86b), 2.158 g (7.24 mmole), in 50 ml methylene chloride containing triethylamine, 1.01 ml (7.24 mmole), cooled to -10\degree in an ice salt bath was added dropwise a solution of t-butyl hypochlorite, 800 mg (7.25 mmole), in 25 ml carbon tetrachloride. After stirring for 30 minutes at -10\degree, the mixture was washed with ice water, saturated sodium chloride, and dried over sodium sulfate. After removal of the solvent in vacuum at room temperature, the oily residue spontaneously darkened to an orange-
red color. Addition of a few drops of chloroform accelerated the darkening process. After standing for about one hour, the darkened material was purified by chromatography on activity III neutral alumina. Elution with ethyl acetate-cyclohexane 1:10 afforded 1.86 g (96%) crystalline compound (89), mp 169-174°C. Recrystallizations from 95% ethanol gave a pure sample, mp 174-175°C, yellow in color.

\[
\begin{align*}
\lambda_{\text{max}}^{\text{CHCl}_3} & = 2.95, 6.03, 7.25, 7.41, 7.62, 8.60, 8.90, 10.10, 10.55, 10.9, 11.0 \mu. \\
\lambda_{\text{max}}^{\text{EtOH}} & = 228 \mu (\log \epsilon = 4.32), 250 \mu (\log \epsilon = 4.05), 336 \mu (\log \epsilon = 4.06).
\end{align*}
\]

NMR: see figure 2

Molecular weight: 296 (mass spectrum).

Analysis:
Calc'd. for C\textsubscript{18}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2}: C, 72.95; H, 6.80; N, 9.45.
Found: C, 72.83; H, 6.88; N, 9.55.

Treatment of Compound (89) with Sodium Methoxide. To a solution of sodium methoxide in methanol prepared by addition of 0.4 g sodium to 45 ml absolute methanol was added compound (89), 200 mg, and the solution refluxed for 2 hours. After cooling, the methanol was removed in vacuum, and the residue was taken up in ether and the ether solution
washed with water, saturated sodium chloride, and dried over sodium sulfate. Evaporation of the solvent gave 86 mg of an oil. This material was combined with samples of other runs which had the same infrared spectra, and the resulting sample, 150 mg, was chromatographed on activity IV neutral alumina. Elution with 30% ether in cyclohexane gave several oily fractions followed by 112 mg of a yellow foam which crystallized when triturated with a small amount of ether. After two recrystallizations from aqueous methanol, a sample melting at 178-180° (sealed evacuated tube) was obtained. The infrared spectrum of this material in chloroform was found to be identical with a sample of 1-(n-propyl)-3, 4-dihydro-β-carboline (90) prepared from tryptamine by the method of Späth and Lederer,43 mp 177-180° (sealed evacuated tube, lit:43 182-183°). The molecular weight was found to be 212 (mass spectrum).

**Preparation of Compound (92b).** To a solution of tryptamine, 3.90 g (2.44 mmoles), and 3-formyl-2-pentanone ethylene ketal (72b), 3.90 g (2.47 mmoles) in benzene, 100 ml, was added anhydrous potassium carbonate, 17 g. The mixture was stirred at room temperature for 24 hours before filtration and removal of the solvent in vacuum. The resulting oil was dissolved in dry acetic acid, 50 ml; and the solution was stirred at 50° for 24 hours. After concentration of the solution in vacuum, the residue was taken up in water, the aqueous solution washed with ether, and then made alkaline with 10% sodium hydroxide. The basic product was extracted with ether and the ether layers combined and washed with water, saturated sodium chloride, and dried over sodium sulfate. Evaporation of the solvent gave 5.4 g crude amine ketal (92a) (no carbo-
nyl in infrared) as an oil. This intermediate was acetylated without further purification. The crude amine was dissolved in 100 ml methylene chloride containing 12 ml triethylamine, and the solution was cooled to 0° in ice. Acetyl chloride, 2.10 g (1.5 equiv.), in 25 ml methylene chloride was added dropwise with stirring. The reaction mixture was stirred at 0° for one additional hour, then allowed to warm to room temperature over two hours. The reaction mixture was washed with water, 1 N sodium hydroxide, water, saturated sodium chloride, and dried by filtration through sodium sulfate. The solution was filtered through activity I neutral alumina, 75 g, and the solvent removed in vacuum. A small amount of ether was added to the oily residue and, on standing, crystallization occurred, giving 2.8 g of compound (92b) melting at 158-160° (33.5% based on tryptamine). Two recrystallizations from methanol gave the analytical sample, mp 167-168°.

\[
\begin{align*}
\lambda_{\text{max}}^{\text{CHCl}_3} & \quad 2.92, 6.07 \mu. \\
\lambda_{\text{max}}^{\text{EtOH}} & \quad 224 \mu (\log \varepsilon 4.64), 274 \mu (\log \varepsilon 3.95), 279 \mu (\log \varepsilon 3.97), 290 \mu (\log \varepsilon 3.85). \\
\text{Molecular weight:} & \quad 342 \ (\text{mass spectrum}).
\end{align*}
\]

NMR: see figure 3

Analysis:
Calc'd. for C_{20}H_{25}N_{2}O_{3}: \quad C, 70.17; \quad H, 7.65; \quad N, 8.18.

Found: \quad C, 70.05; \quad H, 7.67; \quad N, 8.08.
Preparation of Compound (94). Compound (92b), 200 mg (0.585 mmole), was dissolved in 5 ml absolute tetrahydrofuran and added slowly to a suspension of lithium aluminum hydride, 100 mg, in 25 ml absolute tetrahydrofuran. The mixture was refluxed for 9.5 hours, cooled, and the excess hydride was destroyed by cautious addition of a few drops of water. The suspension of inorganic material was diluted with ether and filtered. The filtrate was evaporated to dryness in vacuum. The crude product obtained, 210 mg, showed no carbonyl in the infrared. It was taken up in ether and filtered through a short column of activity III neutral alumina. The purified product, 175 mg (92%) crystallized on standing for 2 days in a refrigerator, mp 106-109°. Recrystallization from hexane gave material melting at 109-110°.

\( \lambda_{\text{max}}^{\text{CHCl}_3} = 2.95\mu \) (no \( C = 0 \)).

\( \lambda_{\text{max}}^{\text{EtOH}} = 227 \mu_\lambda (\log \varepsilon 4.58), 275 \mu_\lambda (\log \varepsilon 3.94), 282 \mu_\lambda (\log \varepsilon 3.95), 290 \mu_\lambda (\log \varepsilon 3.88) \).

Molecular weight: 328 (mass spectrum).

Preparation of 1,1-Dimethoxy-3-carbomethoxy-2-pentanone (102)\(^{44}\). Sodium, 8.5 g (0.368 mole), was dissolved in about 100 ml methanol and the solution concentrated to about 20 ml. Absolute benzene was added and distilled until the boiling point was 78°, then cooled to room temperature. To the slurry of sodium methoxide thus prepared was added a mixture of methylbutyrate, 37.6 g (0.368 mole). The yellow mixture
was refluxed for 4 hours, cooled to 100, and poured into a mixture of glacial acetic acid, 36.8 ml, in an equal volume of water. After shaking, the aqueous phase was removed and extracted with ether in four 50 ml portions. The organic layers were combined and washed with water, 5% sodium bicarbonate, and saturated sodium chloride, and dried over sodium sulfate. The solvent was evaporated and the product distilled, yielding 25.4 g (34%) 1,1-dimethoxy-3-carboxemethoxy-2-pentanone (102), bp 115.3°/16 mm (lit: 106°/5 mm).

\[ \lambda_{\text{max}}^{\text{film}} = 5.72, 5.81 \mu. \]

Preparation of 1,1-Dimethoxy-2-pentanone (103a). To a solution of 1,1-dimethoxy-3-carboxemethoxy-2-pentanone (102), 25.4 g, in methanol, 40 ml, was added 2 N aqueous potassium hydroxide, 75 ml; and the mixture was heated to reflux under nitrogen for 1.25 hours. The reaction mixture was cooled and poured into 300 ml water and extracted with ten 25 ml portions of ether. The combined ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed under vacuum at room temperature and the product distilled, giving 14.03 g (78%) 1,1-dimethoxy-2-pentanone (103a), bp 70-70.5°/18 mm (lit: 66°/14 mm).

\[ \lambda_{\text{max}}^{\text{film}} = 5.78 \mu. \]

NMR (CCl₄):

0.98 \text{ triplet} \quad (3H)

1.68 \text{ multiplet} \quad (2H)
2.56    triplet    (2H)
3.408    singlet    (6H)
4.338    singlet    (1H)

Preparation of 2-Oximinovaleraldehyde Dimethylacetal (103b). A solution of 1,1-dimethoxy-2-pentanone (103a), 6.05 g (41.4 mmoles), in a mixture of methanol, 60 ml; water, 29 ml, and sodium carbonate, 3.1 g (60 meq), was added a solution of hydroxylamine hydrochloride, 2.96 g (41.4 mmoles) in water, 14 ml. The mixture was stirred at room temperature for 26 hours. The resulting clear solution was concentrated by vacuum evaporation to remove most of the alcohol. The residue was diluted with water, 100 ml, and extracted with ether (four times, 50 ml portions). The ether layers were combined and washed with saturated sodium chloride and dried over sodium sulfate. Removal of the ether and distillation gave 5.72 g (86.5%) 2-oximinovaleraldehyde dimethylacetal (103b), bp 69-70°C/0.45 mm.

film
\( \lambda_{\text{max}} \)
3.0, 6.78, 6.85, 7.40, 8.18, 8.32, 8.90, 9.26, 9.30, 10.2, 10.7, 11.25 μm.

Preparation of 2-Oximinovaleraldehyde (104b). A solution of 2-oximinovaleraldehyde dimethyl acetal, 5.45 g, in a mixture of methanol, 45 ml, and an acetate buffer solution (1 M in acetic acid; 0.1 M in sodium acetate), 45 ml, was heated to reflux under nitrogen for 4 hours. The solution was cooled to room temperature and concentrated at reduced pressure to remove most of the alcohol. The residue was diluted with water, 100 ml, and extracted with six 25 ml portions of
ether. Sodium chloride was added to the aqueous phase prior to the last two extractions. Removal of solvent and distillation gave 2.58 g (61%) 2-oximinovaleraldehyde, (104b), bp 61-65°/0.55 mm.

\[ \lambda_{\text{max}} \text{ film} \]
3.0 (broad), 5.88, 5.91, 6.10, 6.80, 6.95, 7.35, 8.18, 8.23, 9.20, 9.85\(\mu\).

**NMR (CCl₄):**

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Assignment</th>
</tr>
</thead>
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<td>0.96(\delta)</td>
<td>triplet</td>
<td>(3H)</td>
</tr>
<tr>
<td>1.56(\delta)</td>
<td>multiple</td>
<td>(2H)</td>
</tr>
<tr>
<td>2.56(\delta)</td>
<td>triplet</td>
<td>(3H)</td>
</tr>
<tr>
<td>9.50(\delta)</td>
<td>singlet</td>
<td>(1H)</td>
</tr>
<tr>
<td>10.6(\delta)</td>
<td>broad</td>
<td>(1H)</td>
</tr>
</tbody>
</table>

Condensation of 2-Oximinovaleraldehyde (104b) with Tryptamine.

Tryptamine, 510 mg (3.19 mmoles), was dissolved in an acetate buffer (1.0 M in acetic acid; 0.1 M in sodium acetate) and 2-oximinovaleraldehyde (104b) 500 mg, in methanol, 1 ml, was added dropwise with stirring. The mixture was stirred for 2.5 hours and filtered, giving 429 mg of a light tan crystalline solid. Recrystallizations from aqueous methanol gave the pure product, compound (110), mp 124-125°.

\[ \lambda_{\text{max}} \text{ nujol} \]
3.2, 6.22, 6.82, 6.85, 7.20, 7.60, 7.55, 7.80, 8.05, 8.10, 8.33, 8.52, 8.62, 8.82, 8.93, 9.00, 9.25, 9.45, 9.66, 9.80, 10.28, 10.82, 11.30, 12.60, 13.0, 13.45, 14.25, 14.95, 15.3, 15.75\(\mu\).
EtOH $\lambda_{\text{max}}$ 221 m$_\lambda$ (log $\varepsilon$ 4.60), 271 m$_\lambda$ (log $\varepsilon$ 4.00), 278 m$_\lambda$
(1 log $\varepsilon$ 4.00), 290 m$_\lambda$ (log $\varepsilon$ 3.89).

**Molecular weight**: 354 (mass spectrum).

**Analysis**:

Calc'd. for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_2$: C, 67.80; H, 7.34; N, 15.82.

Found: C, 67.79; H, 7.48; N, 15.68.

**Preparation of Compound (111b)**. The glutaric ester derivative (40), 18.50 g (71.6 mmoles), was dissolved in 10 ml carbon tetrachloride; and to this solution was added slowly with stirring 70 ml of a solution of bromine in carbon tetrachloride (1.02 M in bromine). When the addition was complete, the solution was stirred for 3 hours at room temperature. The reaction mixture was washed with water, 5% sodium bicarbonate, water, saturated sodium chloride, and dried over anhydrous magnesium sulfate. Evaporation of solvent gave the crude bromoketone (111a), 24.1 g (100%), as a clear, colorless oil (NMR: 4.12 s singlet, 2H bromoacetyl methylene) which was not further purified.

The bromoketone (111a), 24.1 g, was dissolved in 3 M ethanolic potassium acetate, 60 ml, and the solution refluxed for 1.5 hours. The reaction mixture was cooled and poured into water, 300 ml. The aqueous suspension was extracted with ether. The water layer was saturated with ammonium chloride and extracted repeatedly with ether until no color could be observed in the ether layer after shaking. The combined ether
layers were washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. Evaporation of the solvent and distillation gave the desired acetoxy ketone (111b), 14.89 g (66%) as a colorless oil, bp 106-109°/0.025 mm.

NMR (CCl₄):

0.88₈ triplet (3H)
1.21₈ triplet (3H)
1.27₈ triplet (3H)
1.91₈ quartet (2H)
2.08₈ singlet (4H)
2.28₈ singlet (3H)
4.11₈ quintet (4H)
4.78₈ singlet (2H)

Preparation of Compound (112). To a solution of the acetoxy ketone (111b), 14.89 g (47.2 mmole) in carbon tetrachloride, 5 ml, was added 1.07 M bromine in carbon tetrachloride, 48.5 ml (52 mmole), and the solution stirred at room temperature overnight. The reaction mixture was washed with water, 5% sodium bicarbonate solution, water, saturated sodium chloride, and dried over anhydrous magnesium sulfate. Evaporation of solvent gave the crude bromoacetoxy ketone (111c), 17.3 g (92%), as a yellow oil (NMR: 7.05₈, doublet J = 1, 1H, Bromoacetoxyacetyl methine proton).

The crude bromoacetoxy ketone (111c), 17.3 g, was dissolved in 80% aqueous pyridine, 70 ml; and the solution was allowed to stir at room temperature for 15 minutes. The reaction mixture was then poured
into 70 ml ice cold 10 N sulfuric acid. The aldehyde separated as an oil. After one extraction with ether, the aqueous phase was saturated with ammonium chloride and extracted repeatedly until no color appeared in the ether phase. The combined ether layers were washed with water, saturated sodium chloride, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude keto aldehyde (112), 12.3 g, as a mixture of free aldehyde (NMR : 9.15 s, singlet) and hydrate (NMR : 4.98 s, singlet; 5.32 s, broad).

The material was carried on to the next step without purification.

**Preparation of Compound (113).** The keto aldehyde (112), 7.30 g (25.8 mmol), and tryptamine, 4.13 g (25.8 mmol) were dissolved in benzene, 10 ml, and anhydrous potassium carbonate, 5 g, was added and the mixture allowed to stand at room temperature overnight. After filtration the benzene was removed by vacuum evaporation; and the crude imine, 11 g, was isolated as an oil which did not crystallize. The imine was dissolved in freshly distilled acetic acid, 40 ml, and the solution was heated (bath temperature 125°) for 3 hours. The reaction mixture was cooled, poured into 500 ml ice water and extracted with ether and chloroform until no color appeared in the organic layer. The combined organic phases were washed with 1 N hydrochloric acid, water, 5% sodium bicarbonate, water, saturated sodium chloride, and dried over anhydrous magnesium sulfate. Removal of the solvent at reduced pressure gave an oil, 7.3 g, which crystallized on trituration with benzene. Filtration and washing with cold benzene gave 1.73 g (18%) crude crystals. Recrystallization from ethanol gave pure compound (113), mp 150-153° (dec.).
CHCl₃
\( \lambda_{\text{max}} \) 2.9, 5.68, 5.81, 5.94\( \mu \).

EtOH
\( \lambda_{\text{max}} \) 222 \( \mu \) (log \( \varepsilon \) 4.50), 283 \( \mu \) (log \( \varepsilon \) 3.86), 290 \( \mu \) (log \( \varepsilon \) 3.81).

NMR: see figure 4

Mass spectrum: m/e 368 (M⁺); intense peaks also at m/e 339, 323, 267, 266, 251, 170, 169, 143, 115.

Analysis:
Calc'd. for C₂₁H₂₄N₂O₄: C, 68.46; H, 6.57; N, 7.60.
Found: C, 68.27; H, 6.63; N, 7.55.
IV. REFERENCES
REFERENCES


43. E. Späth and E. Lederer, Ber., 63, 2102 (1930).


