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Cyclization of *N*[2-(3-indolyl)acetyl]-5-aminovaleraldehydes and *N*[2-(3-indolyl)ethyl]-5-aminovaleraldehydes

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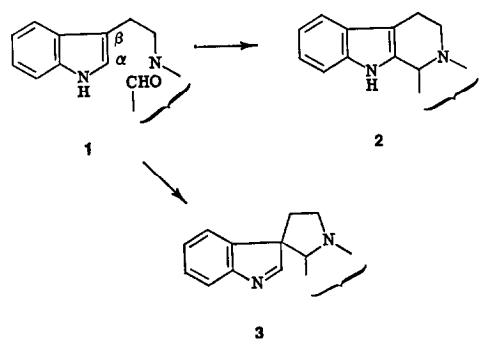
Various model cyclizations related to the organic or biological synthesis of diverse indole alkaloids, are described and discussed, including: **18** → **20**, **23** → **25**, **28** → **31** and **29** → **35**, **37**, **38** and **39** (as aldehydes).

Basic to the entire problem of indole alkaloid organic and biological synthesis in the yohimbine, strychnine, and related areas is the question of α-(**2**) versus β-cyclization (**3**) of tryptamine derivatives (**1**) possessing an aldehyde group (or equivalent) which



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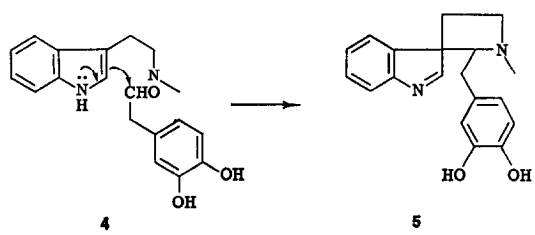
permits ring closure of the Pictet-Spengler type (*1*). Of obvious relation is interconversion of the α- and β-types. β-cyclizations were brought to the fore in this connection by Woodward, who featured this reaction pattern in both his strychnine biosynthesis hypothesis (**4** → **5**) (*2*) as well as his subsequent total laboratory synthesis of this



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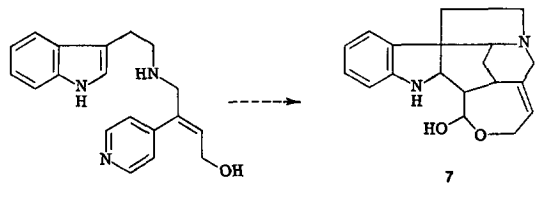
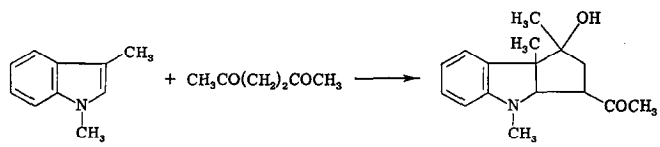
alkaloid (*3*). An awareness of the importance of the β-cyclization process in strychnine synthesis matters is also evident in the writings of Robinson and Saxton, who outlined

a proposed synthesis of strychnine based on the ring closure (**6** → **7**) (*4*) and accomplished in fact the suggestive condensation (**8** → **9**). Somewhat later, and contemporaneous with our own early synthetic efforts in this area, Harley-Mason and Waterfield



6 **7**



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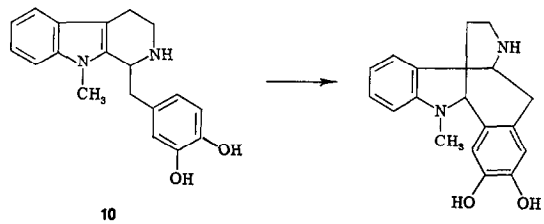
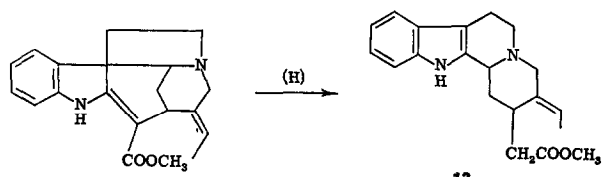
(*5*) described the isomerization of the tetrahydro-β-carboline derivative (**10**) to the pentacyclic indoline **11**, of obvious relation to the strychnine system. More recently,



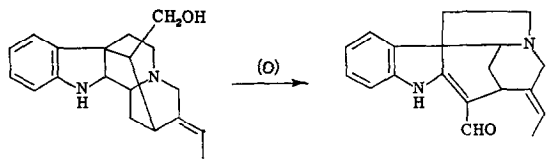
10 **11**

Le Men and associates reported the reverse phenomenon, the conversion by reductive means of akuammicine (**12**) to the corynantheine derivative, methyl geissoschizoate (**13**) (*6*). Also pertinent is the oxidative transformation of desformopicralinol (**14**) to



12 **13**

nor-C-fluorocurarine (**15**) (*7*); and, e.g., the conversion of indolic species stemmadenine or dihydrostemmadienine *O*-acetate to precondylcarpine acetate (**16**) and to (±)-pseudocatharanthine (**17**), respectively (*8*).



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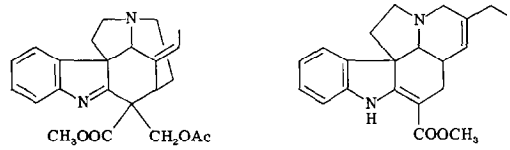

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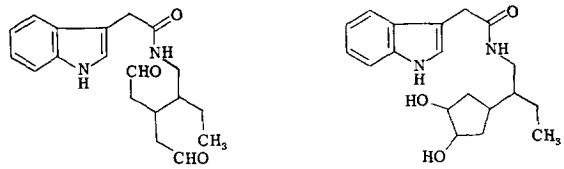
Our own interest in the fundamentals of such cyclization phenomenon centered around ring closure reactions exhibited by the dialdehyde (**18**), produced by the periodate cleavage of the cyclopentandiol (**19**).



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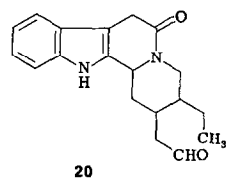
In connection with our reports on the formation of tetra- and pentacycles (*9*, *10*) from the indolic dialdehyde **18**, a broader study of α/β cyclization patterns was initiated in the hope that results obtained would be of value, not only in understanding reaction pathways per se but also in the design and execution of total syntheses (see accompanying and other publications).

Although under the comparatively drastic conditions of several hours refluxing in acetic acid–sodium acetate or formic acid–sodium formate, β-cyclization of indole dialdehyde **18** is dominant (*9*, *10*), this starting material generates with the same reagent, but under milder conditions, the α-cyclized product, apparently unaccompanied by the β-isomer. On the basis of the various chemical and spectral data collected, this new cyclization product is assigned the gross structure **20**.



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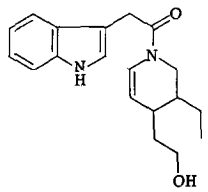
After brief treatment with dilute aqueous acetic acid at room temperature or below, the crude dialdehyde resulting directly from cleavage of diol **19** was converted to a new

product, which was not isolated but after workup was reduced as soon as possible with sodium borohydride. After chromatography, a seemingly homogeneous but non-crystalline lactam alcohol was secured. Monomeric, as indicated by its chromatographic behavior as well as by its sublimability, the transformation product possessed the molecular formula $C_{19}H_{24}N_2O_2$. Both the Ehrlich and nitrite tests for α-unsubstituted indoles were negative. That the substance retained an intact indole nucleus was indicated by its ultraviolet spectrum, which featured maxima at 221, 273, 280, and 290 nm. Catalytic hydrogenation attempts did not reveal any olefinic bonding, which might have been expected for an alternative structure **21**. The presence of lactam function was



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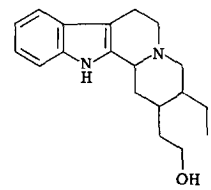

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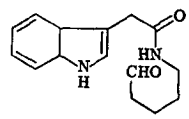
confirmed by infrared absorption at 6.10 μm, while that of the hydroxyl group was substantiated by formation of an *O*-tosylate. Since all stereoisomers corresponding to the gross structure **22** are known, chemical correlation of lactam **20** with such a tetracycle would corroborate the structure and establish stereochemistry as well. Unfortunately, lithium aluminum hydride reduction of the lactam failed, in that there was formed only a poorly defined product which gave strong Ehrlich and nitrite tests. Despite this correlation, it is clear that the β-cyclization course previously described (*9*, *10*) is preceded by α-cyclization to tetracycle **20**, which, under the more drastic conditions of the earlier experiments, rearranges to β-cyclization product.

In order to assess the role of the second aldehyde function in the overall cyclization of amide dialdehyde **18**, the behavior of the amide monoaldehyde **23** was observed under similar reaction conditions. Preparation of the desired amide type was carried out



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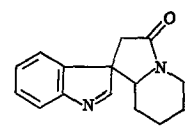

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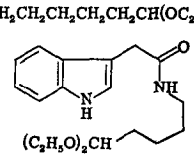
by reaction of indoleacetate ester and 5-aminopentaldehyde diethyl acetal, obtained by cyanide ion displacement of halogen from 4-chloro-butyraldehyde diethylacetal

A. $ClCH_2CH_2CH_2CH(OC_2H_5)_2 \longrightarrow NC-CH_2CH_2CH_2CH(OC_2H_5)_2 \longrightarrow$

$NH_2CH_2CH_2CH_2CH_2CH(OC_2H_5)_2 \longrightarrow$



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(*11*), followed by catalytic hydrogenation or lithium aluminum hydride reduction (sequence A).

The amide **24**, a viscous oil, was used directly in cyclization experiments, usually carried out by heating for 1 hr in aqueous formic acid–sodium formate on a steam bath. Under these conditions, acetal hydrolysis occurred followed by cyclization of the intermediate amide aldehyde. The product, isolated in 78% yield after column chromatography on silica gel, was shown by tlc to be a ca. 1 : 1 mixture of two components having similar R_f values. After separation and isolation on a preparative scale, each component revealed ir absorption at 5.95–5.97 μm (strong) and at 6.27 μm (weak). The lactams exhibited identical uv spectra, with peaks at 213, 251, 260 (shoulder), 283, and 289 nm. Both oils, the lactams did not react with picric acid in cold chloroform but were converted to salts *on being heated with picric acid in boiling ethanol.* One picrate remained an oil, but the other appeared as a well-defined crystalline product (mp 198–199°C). Free base regenerated from picrate possessed a uv spectrum with maxima at 242 and 297 nm, different from that of the original material. Comparison of the uv spectra of the original lactams with the spectra of various types of indole alkaloids indicated that neither lactam could be an indolenine or an indole (Table 1). However, the spectral data were compatible with the presence in both lactams of an indole, an indolenine trimer, or an *N*-formyl indoline chromophore, the last being an especially satisfactory assignment.

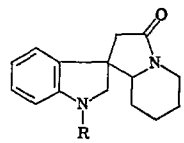
TABLE 1

ALKALOID ULTRAVIOLET SPECTRA

Compound	λ_{max} (nm)
Cyclization products **25 a–b**	213, 251, 260(sh), 283(sh), 289
Indolines (dihydroindoles)	
Quebrachidine (*12*)	242, 291
Kopsinine (*12*)	244, 295
Dimethylindolenine trimer	254, 298
Indoles	
Yohimbine (*12*)	226, 291
Amide acetal **24**	274, 281, 289
N-formyl indoline	
Aspidofractine (*12*)	253, 289
Refractidine (*12*)	254, 279, 288
Indolenine	
Vomilenine (*12*)	218, 257

That the pair of lactams fell in the *N*-formyl indoline category was confirmed by nmr spectral studies. The nmr spectrum of each isomer revealed the presence of the *N*-formyl proton by displaying in one case a doublet at 8.85 and 8.43 δ and in the other a doublet at 8.43 and 8.88 δ, both sets being due to rotomers having carbonyl oxygen *syn* and *anti* to the neighboring aromatic proton. Consistent with this explanation is

the presence of a small multiplet in the aromatic region, downfield from the aromatic envelope, centered at 7.98 δ and equal in area to the smaller of the two signals in each *N*-formyl doublet. This 7.98 δ absorption undoubtedly corresponds to the *N*-formyl rotomer having oxygen *syn* to the hydrogen *ortho* to the indoline nitrogen, causing it to be deshielded with respect to the remaining aromatic protons (*13*). Other nmr data

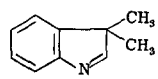


25a, R = H
25b, R = CHO

were completely consistent with behavior expected for the proposed structures, stereoisomers corresponding to the gross structure **25b**.

With the structure of the *N*-formyl lactam established, certain puzzling observations described above became interpretable. That the immediate product of cyclization is neither indolic nor basic to any detectable degree is understandable. The drastic conditions utilized for formation of picrates from **25b** clearly are required for preliminary hydrolysis of formamide to parent indoline **25a**. It is the latter entity that is regenerated from picrate and is responsible for the altered uv spectrum at this point. The elemental analysis of the picrate would fall within limits acceptable for either the indolenine or the indoline salt, while the single observable peak in the carbonyl region of the ir can be ascribed to overlapping butyrolactam and *N*-formylindoline absorption.

Although hardly predictable, the reaction course leading to primary product **25a** is almost self-evident. Subsequent to the β-cyclization process leading to intermediary indolenine lactam **26**, there must occur a Leuckart-type reduction, brought about by solvent formic acid and affording free indoline **25a**, which is formylated under the conditions of the reaction. In agreement with this interpretation are (i) the observed reduction of 3,3-dimethyl indolenine (**27**) by hot formic acid to indoline (*14*) and (ii)



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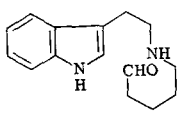
the efficient conversion of anilines to *N*-formylanilines under conditions similar to those used for cyclizations described herein, viz., heating in aqueous formic acid–sodium formate (*14*).

Of the various structural factors that might influence the cyclization course, the amide unit was thought to be of prime importance. Although ring closure of indoles with appropriately sited amide and aldehyde units within the molecular framework had been investigated and found to involve invariably the α-position, no cyclizations of β-indole acetamides (or other aromatic acetamides) had been reported up until the time of this work. Thus it seemed important to compare, in respect to *intramolecular* cyclization course, the β-indoleacetamide with the corresponding β-indole ethylamine type. Again, as far as we were aware, an intramolecular Pictet–Spengler reaction

had not been previously described. In view of these considerations, there were selected for study two representatives *N*(indole-β-2-ethyl)-5-aminovaleraldehydes: **28**, the



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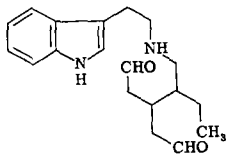

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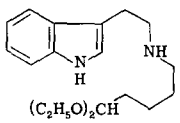
parent case and amine counterpart of β-indole acetamide **23**, and **29**, the more complex, dialdehyde parallel of amide dial **18**.

In the most direct production of amine aldehyde **28**, the available amide acetal **24** was reduced with lithium aluminum hydride and was thereby converted to the amine acetal **30**. It was observed that the same single product was generated from the acetal



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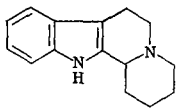

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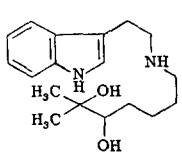
when treated with a variety of acidic agents, including chloroform—1% aqueous sulfuric acid, methanol—concentrated aqueous hydrochloric acid, and aqueous formic acid. In the hydrochloric acid experiment, for example, there was produced a 50% yield of crystalline material which, after recrystallization from *n*-hexane, melted at 153–155°C. By means of spectral data and mp's of free base, picrate, and hydrochloride, the substance was identified as the known hexahydroindolo[2,3a]quinolizine **31** (*15*).

It is worth noting that simple modification of an established synthetic sequence failed to provide the same target base in acceptable yield. Periodate cleavage was planned for the amine diol **32**, which was expected to yield the desired amine aldehyde **28**, along with acetone, an innocuous (in contrast to formaldehyde, for example), second cleavage product (normally, amide dialdehyde preparations from cyclopentandiols are carried out in aqueous acetone). In order to secure the diol **32**, 5-methyl-4-hexen-1-ol (**33**, $X = OH$) was converted to the corresponding tosylate, which was subjected to a displacement reaction with cyanide ion in dimethyl sulfoxide. The



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$(CH_3)_2C{=}CHCH_2CH_2CH_2X$

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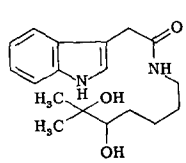

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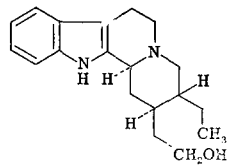
resulting nitrile (**33**, $X = CN$) was reduced with lithium aluminum hydride to the primary amine, which was converted to the corresponding β-indole acetamide. Osmylation produced the diol **34**; and a second hydride reduction afforded the desired secondary amine **32**. After treatment with an appropriate amount of sodium metaperiodate under the usual conditions, the diol was transformed in part into a mixture of *N*(β-indolyl-2-ethyl)2-piperidone (*16*) and other, basic products, including the aminealdehyde **28**.

After the basic component was subjected to cyclization conditions, a complex set of products was isolated, including original starting diol and the tetracycle **31** in small yield. Further study of the periodate reaction revealed that the cleavage rate is considerably slower than that of the cyclopentandiol utilized on other occasions in this laboratory. Apparently, in the primary–tertiary diol case, cleavage is sufficiently slow as to permit overoxidation, most noticeably amine aldehyde or the cyclic alkanolamine to piperidone.

With the amine dial **29**, it became possible (i) to determine whether a second acetaldehyde substituent might be effective in promoting cyclization to the pentacyclic level and (ii) to examine certain stereochemical features not present in the simpler cases. The most attractive precursor for the key dialdehyde was the available amide cyclopentanediol (**19**); and, despite the multiplicity of active hydrogens, the amide function in this molecule was reduced satisfactorily to secondary amine by means of lithium aluminum hydride. Following the periodate cleavage–acid cyclization pattern already established, it was found that the diol was not converted to any well-defined product, and all such attempts had to be judged as total failures. On the other hand, if the diol was allowed to stand for some hours in a solution of periodic acid buffered with sodium acetate–acetic acid (*17*), cleavage with ensuing cyclization occurred, giving a mixture of products which appeared as three zones on tlc. In most experiments, the mixture appeared to be stable to conditions which were effective in converting acetal **30** to tricycle **31**. Although the mixture could be separated by tlc into components which possessed uv, ir, and nmr spectral properties indicative of tetracyclic aldehyde structures, the entities as secured were quite labile, rapidly turning dark in various solvents. On this account, the aldehydes were not studied further but simply reduced with potassium borohydride to the corresponding alcohols. The aldehyde complex gave on reduction an alcohol mixture which appeared on tlc as three spots, corresponding exactly to the three single spots of varying R_f given by the aldehydes when each was reduced separately. By preparative tlc, individual alcohol fractions A, B, and C were obtained in yields of 36, 22, and 11%, respectively. By means of nmr spectral determinations on the A, B, and C acetates, it could be demonstrated that each was tetracyclic; invariant, the ratio of aromatic and methylene-bearing acetoxy was 4:2.

Alcohol A, a crystalline solid with mp 189–191°C, possessed the molecular formula $C_{19}H_{25}N_2O$ and was identified as DL-dihydrocorynantheol (**35**). In agreement with this result, one of the three original aldehyde tlc spots corresponded exactly to that given rise to by natural dihydrocorynantheal (*18*). Further, the synthetic alcohol could be dehydrogenated by means of palladium black–maleic acid (*19*) to the expected β-isocarboline, isolated and purified as the perchlorate salt **36**.

Alcohol fraction B could be separated by fractional crystallization means into two crystalline substances, one (B-1) melting at 114–116°C, and the other (B-2) at 198–



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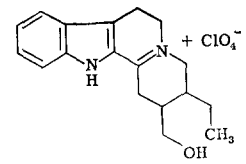

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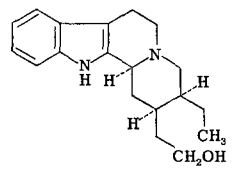
199.5°C (ratio 4:1). Various spectral and analytical data confirmed the isomerism of A and B materials. In separate dehydrogenation experiments alcohols B-1 and B-2 were converted to the same β-isocarbolinium perchlorate, which was found to be different from that derived from dihydrocorynantheol. On the basis of these results alcohols B-1 and B-2 had to be regarded as the diastereoisomeric pair of 15,20-*cis* isomers, i.e., DL-corynantheidol (**37**) and DL-isocorynantheidol (**38**). Wenkert, Dave



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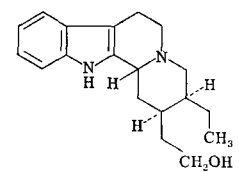

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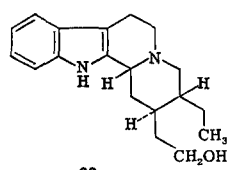
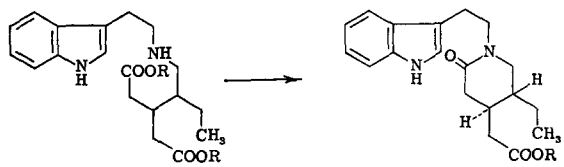
and Haglid (*20*) had synthesized both 15,20-*cis* isomers and reported melting points of 158–162 and 191–192°C for the two compounds. Despite the discrepancies, Wenkert's higher-melting isomer appeared to be identical (ir and mixed melting point) with our 198–199.5°C melting material. Further, the tetradehydroperchlorate obtained by Wenkert from his DL-isocorynantheidol was indistinguishable from that derived from our higher-melting isomer, which is therefore assigned stereostructure **38**. The two lower-melting products may be merely different crystalline modifications of the same alcohol, **37**.

Alcohol C, noncrystalline, difficult to purify, and available only in small amount, was not scrutinized as closely as its three congeners. A mass spectral determination on the acetate showed that the substance was in fact isomeric with its companion alcohols and further showed characteristics of the tetrahydro-β-carboline class. Dehydrogenation provided quaternary perchlorate which, apparently impure, displayed erratic melting behavior. Despite this unsatisfactory sequence of observations, the recrystallized perchlorate did generate on borohydride reduction DL-dihydrocorynantheol **35**. Since hydride reduction of β-isocarbolines involves generation of the more stable stereochemistry at C-3 and since no other asymmetric center is involved in the transformations described, isomer C apparently is indeed, despite its cryptic behavior, the only remaining possible racemate (**39**).



39

Certain stereochemical and reactivity aspects of this tetracyclic series deserve further treatment. First, the lack of stereochemical specificity in the cyclizations producing tetracyclic aldehyde from amine diol **29** is noteworthy, in that various other, similar ring closures studies in this laboratory have been more selective in this regard, e.g., amine diester **40** cyclizes without apparent formation of *cis*-fused isomer (*21*). It



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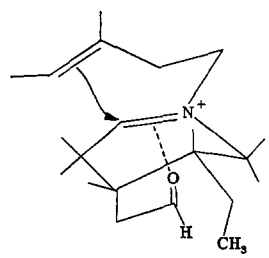
seems certain that conformational control based solely on steric effects of substituents, is not the determining factor in the cyclizations; else alcohol A would have been the product formed in overwhelming amount. Probably the operation, through, e.g., solvation or hydrogen bonding of various functional groups, is important in controlling the stereochemical outcome. Thus, formation of a sizeable amount of C-15,20 *cis* product may be due to a favorable interaction of iminium ion and axial acetaldehyde unit, as in **41**, an interaction which preserves the relative stereochemistry through the



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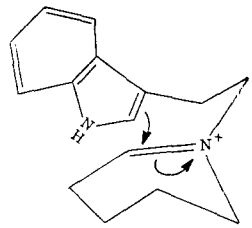
cyclization step and thus leads to formation of *cis* isomers, B_1 and B_2. However, because of the number of heteroatoms in the systems involved, analyses of this kind cannot be made with confidence; and we wish only to suggest that, because of the influences of such functions, there results a great energy leveling effect which permits formation of all four possible racemates in significant amounts. It is possible that similar chemical factors are at play in the biosynthesis of particular alkaloidal stereoisomers.

The amine mono- and dialdehyde cases, in clearly demonstrating that these intramolecular Mannich-type reactions occur without difficulty, serve as a foundation for consideration of the somewhat more unorthodox amide aldehyde cases. That is, there seems to be no obstacle to formation of a six-membered C-ring by attack of the indole ring presumably from a direction perpendicular (i.e., ca. axial) to the plane of the protonated piperideine C-ring (**42**). Whether these amine aldehyde cyclizations involve initial interaction at the β-position of the indole cannot be decided on the basis of our body of results.



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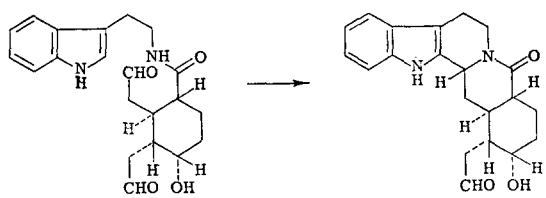
The outstanding feature of the amide aldehyde cyclizations is formation of a five-membered C-ring. The conformance of the simple monoaldehyde to this pattern shows unambiguously that neither the presence of a second aldehyde unit nor the ethyl substituent is of importance in determining the ultimate cyclization course. Similarly, the final, Leuckart-type reduction of indolenine to indoline is not decisive in forcing the equilibrium onto the side of β-cyclization product, since no such phenomenon was observable in the amine dialdehyde cases, where an equal opportunity should exist for such reduction. However, it does seem likely that the amide moiety per se plays an important role in directing cyclization along the β-pathway. In this connection, it should be mentioned that, in order to effect β-cyclization, the amide be β-indole acetic acid derived; the alternative tryptamide or β-phenethylamide type, e.g., **43** and **44**, leads to tetrahydro-β-carboline (*22*) *or* -isoquinoline (*23*) as the only



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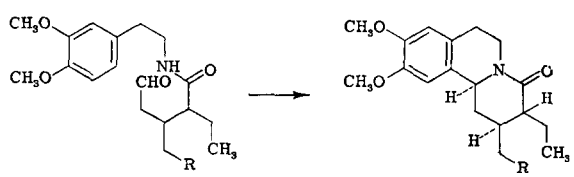
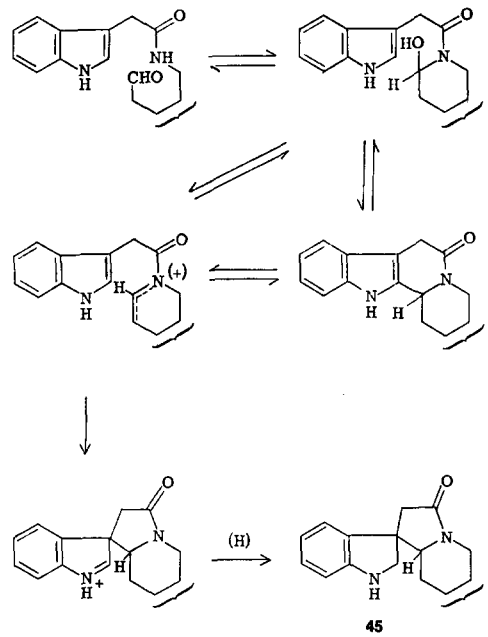


44

observable type of product. In view of the foregoing and in consideration of the well-known stability relationship of γ- and δ-lactams, the generation of five-membered ring-C product probably is merely a reflection of the greater stability of the γ-lactam system relative to the δ-lactam possibility. That the products formed reflect thermodynamic control is suggested by the observation that, under more mildly acidic conditions, the amide dialdehyde cyclizes to α-type **20**. As in the amine dialdehyde series, stereochemical control is low, there being formed a variety of racemate isomers by cyclization of amide dialdehyde **18** to the five-membered ring-C category. Pictorialized in sequence B (Chart I) is an interpretation of the cyclization sequence leading to final, observed

B Chart I



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product (**45**). Whether formation of the C-ring involves attack of indole directly on alkanolamide or on its product of dehydration is not known, and both possibilities are incorporated into the flow sheet.

EXPERIMENTAL

All melting points were taken on a Buchi melting-point apparatus or microscope hot stage and are uncorrected. All boiling points are uncorrected.

Analyses were carried out in part at the Stanford University Microanalytical Laboratory by E. Meier and J. Consul and in part at Spang Microanalytical Laboratories.

The infrared spectra were recorded on a Perkin–Elmer Model 137 spectrometer or on a Perkin–Elmer Model 421 grating spectrometer. The ultraviolet spectra were measured on 95% ethanol solutions with a Bausch and Lomb Spectronic 505 or with a Cary Model 14M recording spectrometer. All nuclear magnetic resonance spectra were recorded by means of a Varian A-60 spectrometer, with tetramethylsilane as internal reference.

All compounds containing an asymmetric center, unless specifically designated "natural," are racemic, the prefix "DL" having been omitted.

The substrates for column chromatography were as follows: silica gel, 100–200 mesh, Davison Chemical; alumina, Merck A.G.; Florisil, Floridin Company. Preparative thin-layer chromatographies were carried out on 1-mm Merck silica gel GF_{254}.

Periodate cleavage and α-cyclization of N[*2*(cis-*3,4-dihydroxycyclopentyl*)*butyl*]*indole-β-acetamide.* Diol **19** (965 mg, 2.92 mmole), prepared from the corresponding cyclo-

pentene by osmium tetraoxide hydroxylation, was dissolved in 11 ml of acetone, to which 11 ml of water was subsequently added. This solution at 0°C was mixed with a solution of 775 mg (3.62 mmole) of sodium metaperiodate in 11 ml of water at 0°C and allowed to stand for 1 hr at 0°C. After evaporation of most of the acetone, 5–10 ml of 50% aqueous acetic acid was added. After shaking the mixture with chloroform until all residual oil had dissolved, the organic layer was separated, washed with water, and evaporated to give 519 mg of almost colorless foam. The product was chromatographed on 30 g of alumina–4% water, the fraction (396 mg) eluted with 100% chloroform being reduced directly with 278 mg of sodium borohydride in 14 ml of ethanol by mixing and allowing the reaction to proceed at 0–8°C for 15 hr. After addition of water, the organic product (395 mg) was extracted with chloroform and chromatographed on silicic acid. Material eluted with 100% chloroform was discarded; alcohol (302 mg, 35%) was eluted with chloroform–2% methanol.

In thin-layer chromatography on silicic acid with chloroform–5% aqueous (95%) acetic acid, different samples of α-cyclized alcohol showed roughly the same behavior: All migrated with a very strong tail, the fronts of three samples having R_f-values of 0.48, 0.46, and 0.45.

A sample showed uv maxima at 290, 280, 273, and 221 nm with a deep minimum at 249 nm. After sublimation the (analytical) sample showed maxima at 290, 280, 273 nm and (strongest) 221 nm, but a less pronounced minimum at 250 nm.

For analysis, a sample of alcohol of good quality was sublimed at 170°C Hg vacuum. The sublimate was a slightly colored, noncrystalline solid.

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 72.47; H, 7.52; N, 8.89.

γ-Chlorobutyraldehyde diethylacetal. In a 1-liter round-bottomed three-necked flask equipped with Teflon-paddle power stirrer, reflux condenser, and fritted-glass gas inlet were placed 80.0 g (0.567 mole) of γ-chlorobutyryl chloride, 450 ml of toluene, 80 g of 5% $Pd/BaSO_4$ catalyst, and 0.8 ml of sulfur–quinoline–xylene poison. With vigorous stirring, hydrogen gas was passed into the reaction mixture, and the toluene was heated to reflux. The reflux was continued for 20.5 hr.

To the cooled solution of γ-chlorobutyraldehyde were added 125 ml of absolute ethanol and 25 g of powdered calcium chloride. After stirring at room temperature for 24 hr, the reaction mixture was filtered, the two layers separated, and the upper (toluene) layer washed twice with saturated sodium bicarbonate solution and once with saturated sodium chloride solution. All the aqueous extracts were reextracted with ether, and the combined organic layers dried over anhydrous magnesium sulfate. After filtration, most of the toluene was removed by water-vacuum distillation. The residue was fractionated thru a 12-cm Vigreux column. After some toluene and a small forerun, there was obtained 63.5 g (62% from acid chloride) of γ-chlorobutyraldehyde diethylacetal ($n_D^{25°}$ 1.4294), bp 97–100°C (16 mm). Lit. (*11*): bp 89–92°C (14 mm).

γ-Cyanobutyraldehyde diethylacetal. In a 1-liter round-bottomed three-necked flask equipped with teflon-paddle power stirrer and reflux condenser were placed 63.5 g (0.352 mole) of γ-chlorobutyraldehyde diethylacetal, 34.3 g (1.5 × 0.352 mole) of potassium cyanide, 29.2 g (0.5 × 0.352 mole) of potassium iodide, and 400 ml of 80% ethanol. The mixture was heated at reflux for 24 hr and cooled. The precipitated

potassium salts were removed by filtration, and most of the ethanol was removed on a rotary evaporator. To the residue was added 200 ml of water, and this mixture was extracted with five 75-ml portions of ether. The combined ether extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 60.7 g of a liquid which was distilled through a 12-cm Vigreux column. The first fraction, 2.9 g, bp to 116°C (14 mm), was unreacted chloro acetal; the second fraction, 9.0 g, bp 116–124°C (14 mm), was 80% nitrile (vpc); the third fraction, 36.8 g, bp 124–127°C (14 mm), was pure γ-cyanobutyraldehyde diethylacetal. The total yield of nitrile was 73%.

δ-Aminovaleraldehyde diethylacetal. A solution of 36.0 g (0.210 mole) of γ-cyanobutyraldehyde diethylacetal in 250 ml of anhydrous ether was added dropwise over 45 min to a stirred suspension of 12 g (3 equiv) of lithium aluminum hydride in 800 ml of anhydrous ether placed in a 2-liter round-bottomed three-necked flask equipped with Hershberg stirrer, reflux condenser, pressure-equalized cropping funnel, and nitrogen inlet. During the addition the ether refluxed gently without external application of heat. After addition was complete, the reaction mixture was refluxed for 16 hr. After cooling, saturated sodium potassium tartrate solution was added dropwise to decompose excess hydride, and the precipitated aluminum salts removed by suction filtration and washed well with ether. The ether solution of amino–acetal was dried over anhydrous sodium sulfate, filtered, and evaporated to give 43.3 g of crude amino-acetal. Distillation under water vacuum thru a short Vigreux Claisen head gave 31.6 g (90%) of δ-aminovaleraldehyde diethylacetal, bp 109–110°C (14 mm).

N_b-[*5,5-Diethoxypentyl*]-*indoleacetamide* (**24**). To a solution of 12.6 g of *p*-nitrophenyl indoleacetate in 90 ml of chloroform was added 7.400 g (0.0423 mole) of δ-aminovaleraldehyde diethylacetal. After being stirred for 19 hr at room temperature, 50 ml of chloroform and 50 ml of water were added. After extraction with two 50-ml portions of 10% sodium hydroxide, the chloroform was evaporated; and 100 ml of methanol and 40 ml of 10% sodium hydroxide were added. This mixture was stirred for 1.5 hr at room temperature, poured into 400 ml of water, and extracted with five 100-ml portions of ether. The combined ether extracts were washed twice with 10% sodium hydroxide, three times with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield 14.0 g (99%) of oily amide acetal 24, which appeared as one spot by tlc. ($CHCl_3$–5% methanol).

The uv spectrum showed λ_{max} at 273 nm ($\varepsilon = 6500$), 280 nm ($\varepsilon = 6900$), and 289 nm ($\varepsilon = 6000$). For analysis, a small portion of amide was twice microdistilled.

Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.64; H, 8.49; N, 8.43. Found: C, 68.48; H, 8.44; N, 8.37.

N_b-[*5,5,Diethoxypentyl*]-*tryptamine* (**30**). To a refluxing suspension of 1.14 g (5 equiv) of lithium aluminum hydride in 200 ml of dry TNF in a 500-ml round-bottomed three-necked flask equipped with Teflon-paddle power stirrer, reflux condenser, pressure-equalized dropping funnel, and nitrogen inlet was added a solution of 1.99 g (0.006 mole) of amide acetal **24** in 50 ml of dry THF over a 40-min period. After a 24-hr reflux, the reaction mixture was cooled, and the excess hydride destroyed by slow addition of saturated sodium potassium tartrate solution. The precipitated aluminum salts were removed by suction filtration thru a pad of anhydrous magnesium sulfate and washed well with chloroform. Evaporation of solvent gave a dark brown oil which

was chromatographed on a Florisil column, 120 g, 31-mm diameter by 26-cm length. Nonpolar material was eluted by benzene and benzene–ether. Ether and ether–5% methanol eluted 700 mg of ca. 60% pure amine. Elution with ether–(10–50%) methanol gave 1.25 g of pure amine acetal **30**.

The uv spectrum showed λ_{max} at 274 nm ($\varepsilon = 5900$), 281 nm ($\varepsilon = 6200$), and 289 nm ($\varepsilon = 5500$).

Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 60.93; H, 6.30; N, 10.93. Found: C, 60.51; H, 6.30; N, 11.12.

The amine acetal **30** was characterized as its 3,5-dinitrobenzamide, which, recrystallized from ether, had mp 134–135.5°C (hot stage).

Cyclization of amine acetal **30**: *preparation of hexahydroindolo[2,3-a]quinolizine* (**31**). Ten drops of concentrated hydrochloric acid was added to a solution of 506 mg of amine acetal **30** in 150 ml of methanol. The mixture was refluxed under nitrogen for 3 hr. After cooling, most of the methanol was removed on a rotary evaporator; and the residue was made basic with concentrated ammonium hydroxide. Water and chloroform were added, and the aqueous layer was extracted with four 50-ml portions of chloroform. The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to give 390 mg of a brown oil. This oil was taken up in hot *n*-hexane, filtered, and allowed to cool. There was obtained a total of 175 mg (50%) of tetracyclic base **31** as a tan solid, mp 147–152°C. The melting point could be raised to 153–155°C (hot stage) by recrystallization from *n*-hexane. Lit. (*15*): 147–147.5; 148–151°C.

Infrared spectrum ($CHCl_3$): 2.88 μm, three "Bohlmann bands" between 3.5 and 3.65 μm. Ultraviolet spectrum: λ_{max} at 274 nm (sh) ($\varepsilon = 5300$), 279 nm (sh) ($\varepsilon = 5500$), 282 nm ($\varepsilon = 5600$), and 289 nm ($\varepsilon = 4600$).

The picrate was crystallized from ethanol, mp 229–230°C (hot stage). Lit. (*15*): mp 228–230°C.

The hydrochloride was crystallized from ethanol, mp 308–311°C (Buchi). Lit. (*15*): mp 311–312°C.

Hydrolysis and cyclization of amide acetal **24**. Amide acetal **24** (230 mg) was dissolved in a solution made up from 10 ml of water, 10 ml of 88% formic acid, plus 2.0 g of sodium carbonate and heated on a steam bath for 1 hr. The reaction mixture was made basic with 10% sodium hydroxide and extracted well with chloroform. The combined organic extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 167 mg of a nearly colorless oil. This material could not be extracted from chloroform with 5% sulfuric acid and was composed predominantly of two compounds in equal amount (by tlc) which had very similar R_f values. but could be separated using 10% methanol in chloroform, or ethyl acetate.

The total cyclization product, purified by column chromatography on silica gel–15% water and eluted therefrom with 40–80% chloroform in benzene was obtained as 143 mg (78%) of a light golden oil. The ir spectrum ($CHCl_3$) had bands at 5.97 and 6.26 μm.

A 1 : 1 molar mixture of the purified cyclization product and picric acid were mixed in chloroform; the chloroform was blown off with nitrogen, and the residue was taken up in absolute ethanol and cooled. No crystallization occurred. The ethanol was boiled

and concentrated; a mass of yellow crystals, mp 145–155°C deposited at room temperature. The melting point of this material did not change after one recrystallization from 95% ethanol.

The two-component cyclization mixture was separated by continuous (4–5 hr) preparative tlc, using 2% methanol in chloroform, into the pure components, obtained in equal amount (I, higher R_f; II, lower R_f). I and II had very similar ir spectra ($CHCl_3$), exhibiting absorption at 5.97 and 6.27 μm.

The ultraviolet spectrum of isomer I showed λ_{max} at 213 nm ($\varepsilon = 15{,}200$), 251 nm ($\varepsilon = 10{,}600$), 260 nm (sh) ($\varepsilon = 7900$), 283 (sh) nm ($\varepsilon = 3200$), and 289 nm ($\varepsilon = 3400$); isomer II showed λ_{max} at 213 nm ($\varepsilon = 16{,}100$), 251 nm ($\varepsilon = 11{,}300$), 260 (sh) nm ($\varepsilon = 8500$), 283 (sh) nm ($\varepsilon = 3200$), and 289 nm ($\varepsilon = 3400$).

When each pure isomer was mixed with 1 molar equiv of picric acid and warmed in chloroform, no precipitate formed upon cooling. An ethanol solution was boiled for a few minutes and then placed in a freezer, after which there was deposited a mass of yellow crystals. The picrate from isomer I became an oil upon being warmed to room temperature. The picrate from isomer II had mp 205–210°C (rapid heating, hot stage). After one recrystallization from ethanol, the picrate had mp 204.5–208.5°C (hot stage), 201–203°C (Buchi).

Anal. Calcd for $C_{21}H_{19}N_5O_8$: C, 53.73; H, 4.08; N, 14.92. Found: C, 53.77; H, 4.31; N, 14.79.

The nmr spectra were measured using carbon tetrachloride solutions.

Isomer I: 1.0 to 2.0 δ (6H), broad absorption assigned to the three methylenes of the six-membered nitrogen ring; 2.0 to 3.0 δ (3H), assigned to the methylene α to lactam carbonyl (AB system, $J = 17$ cps, centered at 2. 55δ) and one methylene proton alpha to lactam nitrogen; 3.0 to 4.5 δ (4H), complex absorption of at least six peaks, assignable to the remaining protons alpha to lactam nitrogen and the methylene α to *N*-formyl (AB system centered at 3.54 and 4.38 δ, $J = 13$ cps); most of the aromatic absorption (total of 4H) appeared at 6.9 to 7.4 δ, however, there was a small complex doublet at 7.98 δ; the *N*-formyl proton appeared as a doublet (1H) at 8.43 and 8.85 δ, ratio 5:2; the area of the 8.43 and 7.98 δ absorptions were equal.

Isomer II. 0.8 to 2.0 δ (6H), broad absorption assigned to the three methylenes of the six-membered nitrogen ring; 2.3 to 3.0 δ (3H), assigned to the methylene α to lactam carbonyl (sharp singlet at 2.56 δ) and one methylene proton α to lactam nitrogen; 3.2 to 4.4 δ, complex absorption assignable to the two remaining protons α to lactam nitrogen and the methylene α to *N*-formyl; most of the aromatic absorption (total of 4H) appeared at 6.9 to 7.35 δ, however, there was a small broad absorption centered at 7.98 δ; the *N*-formyl proton appeared as a doublet (1H) at 8.43 and 8.88 δ, ratio 8:3; the area of the 8.43 and 7.98 δ absorptions were equal.

5-Methyl-4-hexenoic acid. To 131 g (12 × 0.273 mole) of sodium hydroxide dissolved in 50 ml of water and maintained at −5 to −3°C was added with stirring 142 g (3.25 × 0.273 mole) of bromine in a dropwise fashion. This hypobromite solution was added gradually to a solution of 34.4 g (0.273 mole) of 6-methyl-5-hepten-2-one in 950 ml of dioxane–750 ml of water placed in a 3-liter round-bottomed three-necked flask equipped with a Hershberg stirrer and thermometer and cooled to 2°C. After a short induction period, the temperature started to rise but did not exceed 10°C. After addition was complete, the reaction mixture retained a yellow tinge. Stirring was continued 1 hr at

–5°C, 1 hr at 0 to 5°C, and 1 hr at 5°C. Some sodium sulfite was added to destroy any excess hypobromite; then 750 ml of water and some sodium chloride were added. Extraction was carried out with three 500-ml portions of ether. The aqueous portion was returned to the reaction vessel, and concentrated hydrochloric acid was added dropwise with stirring, the temperature maintained below 10°C. The acidic (pH 2) reaction mixture was extracted with four 300-ml portions of ether. The combined ether extracts were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 44.2 g (theoretical: 34.9 g) of crude acid, containing some dioxane. This material was used directly for alcohol preparation.

5-Methyl-4-hexene-1-ol (**33**, $X = OH$). To a suspension of 15.6 g of lithium aluminum hydride in 700 ml of anhydrous ether at room temperature in a 2-liter round-bottomed three-necked flask equipped with Hershberg stirrer, reflux condenser, pressure-equalized dropping funnel, and nitrogen inlet was added dropwise a solution of 5-methyl-4-hexenoic acid in 170 ml of anhydrous ether over 1.5 hr. After refluxing for 4 hr, the reaction mixture was cooled, and water was added to decompose excess hydride. After acidification by slow addition of 25% sulfuric acid to the cooled reaction mixture, the ether layer was removed, and the milky aqueous layer was extracted with three 150-ml portions of ether. The combined ether portions were washed with saturated sodium chloride solution, saturated sodium bicarbonate solution, and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 27.2 g of a colorless oil. Distillation under water vacuum gave 15.4 g (49.6% from ketone) of the alcohol, bp 86–88°C (21 mm), $n_D^{27^\circ}$ 1.4462. Lit. (*25*): bp 82–83°C (20 mm), $n_D^{15^\circ}$ 1.4520.

The α-naphthylurethane was recrystallized from methanol–water to give colorless needles, mp 59–60°C (Buchi), 59.5–61.5°C (hot stage). Lit. (*25*): mp 62–63°C.

5-Methyl-4-hexen-1-yl tosylate. To a nitrogen-saturated solution of 15.5 g (0.136 mole) of alcohol **33** ($X = OH$) in 75 ml of dry pyridine cooled in an ice–salt bath was added 28.5 g (10% excess) of tosyl chloride. After stirring for 0.5 hr at ice-bath temperature and 1 hr at room temperature, stirring was continued overnight (18 hr) in the cold room. The slightly colored reaction mixture was poured with stirring into 1 liter of an ice–water mixture and then extracted with five 150-ml portions of ether. The combined ether extracts were washed twice with 100-ml portions of 10% hydrochloric acid, 100 ml of water, twice with 100-ml portions of saturated sodium bicarbonate solution, and 100 ml of saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, filtration and evaporation gave 30.2 g (82.5%) of crude oily tosylate, which resisted crystallization attempts but appeared as one spot on tlc ($CHCl_3$). This material was used directly for nitrile preparation.

6-Methyl-5-heptonitrile (**33**, $X = CN$). In a 1-liter round-bottomed three-necked flask equipped with Teflon-paddle power stirrer, reflux condenser, nitrogen inlet, pressure-equalized dropping funnel, and thermometer was suspended 11.0 g (50% excess) of potassium cyanide in 250 ml of dimethyl sulfoxide. The mixture was heated to 90°C, and a solution of the crude tosylate (33, $X = CN$) (30.2 g, 0.112 mole) in 70 ml of dimethyl sulfoxide was added dropwise over 1.25 hr. The reaction mixture was heated at 90–95°C for 2.25 hr, cooled, poured into 900 ml of water, and extracted with five 150-ml portions of petroleum ether (60–68°C). The combined organic layers were washed with water and saturated sodium chloride solution, dried over anhydrous

magnesium sulfate, filtered, and evaporated to give 13.4 g of liquid. Distillation under water vacuum gave 12.48 g (90.6% from crude tosylate, 74.6% from alcohol) of the pure nitrile (**33**, $X = CN$), bp 94° (21 mm). Lit: (*26*) bp 89–91° (8 mm).

Anal. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.64. Found: C, 77.70; H, 10.54.

6-Methyl-5-heptenylamine. To a stirred suspension of 3.4 g (2.5 equiv for 0.0278 mole of nitrile) of lithium aluminum hydride in 200 ml of anhydrous ether at room temperature in a 50-ml round-bottomed three-necked flask equipped with Teflon-paddle power stirrer, reflux condenser, pressure-equalized dropping funnel, and nitrogen inlet was added dropwise a solution of 3.43 g (0.0278 mole) of the nitrile **51** in 80 ml of anhydrous ether over 0.5 hr. The reaction mixture was refluxed for 11 hr, cooled in an ice–water bath, and saturated sodium potassium tartrate solution was added slowly to decompose excess hydride. The precipitated aluminum salts were removed by suction filtration and washed well with ether. The combined ether portions were extracted with four 100-ml portions of 5% sulfuric acid. The acidic extracts were cooled, made basic with 10% sodium hydroxide, and extracted with four 75-ml portions of ether. The combined ether extracts were washed twice with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to a small volume. This concentrated solution of crude amine was used directly for amide preparation.

The α-naphthyl thiourea of the amine was prepared. Crystallization from *n*-hexane–ether gave colorless needles, mp 65.5–66.5°C.

Anal. Calcd for $C_{19}H_{24}N_2S$: C, 73.03; H, 7.74; N, 8.97. Found: C, 72.61; H, 7.71; N, 8.56.

N_b-[*6-methyl-5-heptenyl*]-*indoleacetamide.* The concentrated solution of crude 6-methyl-5-heptenyl amine was added to a solution of 8.24 g (0.0278 mole) of *p*-nitrophenyl indoleacetate in 70 ml of chloroform. After stirring for 1 hr, the reaction mixture was allowed to stand in the dark at room temperature for 42 hr. Then 50 ml of water was added, and the mixture was extracted twice with 50-ml portions of 10% sodium hydroxide. The chloroform solution was washed with saturated sodium chloride solution, 10% hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution, and the solvent was removed on a rotary evaporator. The residue was dissolved in 90 ml of methanol, and 25 ml of 10% sodium hydroxide was added. The mixture was allowed to stand at room temperature for 1 hr. The methanolic solution was poured into 200 ml of water and extracted with five 60-ml portions of ether. The combined ether extracts were washed twice with 50-ml portions of 10% sodium hydroxide and three times with 50-ml portions of saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, filtration and evaporation of solvent gave 6.88 g (84.8% from nitrile **33**, $X = CN$) of a light golden oil, homogeneous by tlc ($CHCl_3$–5% methanol). The amide was not purified further before osmylation.

Trinitrobenzene complex, dark orange needles, mp 104.5–105.5°C, after recrystallization from *n*-hexane-chloroform.

Anal. Calcd for $C_{24}H_{27}N_5O_7$: C, 57.94; H, 5.47; N, 14.08. Found: C, 59.31; H, 5.49; N, 14.14.

Infrared spectrum (CCl_4): indole N–H at 2.94 μm, amide N–H at 3.05 μm, vinyl H at 3.28 μm, amide carbonyl at 6.04 μm (amide I), and amide II band at 6.60 μm.

The uv spectrum showed λ_{max}: 274 nm ($\varepsilon = 5400$), 280 nm ($\varepsilon = 5700$), 289 nm ($\varepsilon = 4900$).

N_b-[*6-methyl-5,6-dihydroxyheptyl*]-*indoleacetamide* (**34**). A solution of 2.263 g (7.87 mmole) of the unsaturated amide in 80 ml of 1 : 1 dry pyridine–dry THF was placed in a 1-liter round-bottomed three-necked flask equipped with magnetic stirring bar, pressure-equalized dropping funnel, drying tube, and nitrogen inlet and was cooled in a dry ice-acetone bath to −75°C. A solution of 1.94 g of (7.66 mmole) osmium tetroxide in 95 ml of dry THF was added dropwise with stirring over 2 hr. After stirring for 0.5 hr at −75 to −70°C, 500 ml of anhydrous ether was added through the dropping funnel, and the precipitated brown osmate ester–pyridine complex was collected by suction filtration, washed with ether, and rapidly transferred to an Erlenmeyer flask containing 200 ml of 1 : 1 $CHCl_3$–95% ethanol. Hydrogen sulfide was passed into the dark brown solution for 7 min, and the mixture was allowed to stand at room temperature for 4 hr. After suction filtration through a pad of Celite, evaporation of solvent gave a golden oil.

A total of 5.376 g of crude diol **34** obtained in the above manner was chromatographed on 200 g of silica gel–15% water, using a column diameter of 9 cm. Elution with chloroform–1 and 2% methanol gave, after evaporation of solvent, 297 mg of nonpolar material. Elution with 3–5% methanol in chloroform gave, after removal of solvent, 4.10 g (87%) of a viscous golden oil, the diol-amide **34**.

The uv spectrum showed λ_{max}: 274 nm ($\varepsilon = 5100$), 281 nm ($\varepsilon = 5400$), 289 nm ($\varepsilon = 4600$).

N_b-[*5,6-dihydroxy-6-methylheptyl*]-*tryptamine* (**32**). A solution of 1.69 g (5.25 mmoles) of diol-amide **34** in 45 ml of dry THF was added dropwise over 1 hr to a refluxing suspension of 2.4 g (8 equiv.) of lithium aluminum hydride in 235 ml of dry THF in a 500-ml round-bottomed three-necked flask equipped with power stirrer, reflux condenser, pressure-equalized dropping funnel, nitrogen inlet, and heating mantle. The reaction mixture was refluxed for 23 hr and cooled, and the excess hydride was decomposed by slow addition of saturated sodium potassium tartrate solution. The precipitated white aluminum salts were removed by suction filtration thru a pad of anhydrous sodium sulfate and washed well with chloroform. The combined organic portions were evaporated to give 1.78 g of a viscous golden-brown oil, containing some residual solvent.

The crude amine-diol **32** was chromatographed on 105 g of Florisil (28.4-mm diameter × 27-cm length). After application in chloroform, elution with chloroform–methanol (4–8%) removed 390 mg of recovered diol-amide **34**; continued elution (8–30% methanol in chloroform) gave, after removal of solvent, 0.98 g (79% from unrecovered diol-amide) of amide-diol **32**.

The uv spectrum showed λ_{max}: 274 nm ($\varepsilon = 4800$), 281 nm ($\varepsilon = 5200$), and 289 nm ($\varepsilon = 4500$).

Cleavage and cyclization of amine-diol **32**. A solution of 208 mg of amine-diol **32** in 10 ml of 1 : 1 acetone–water was cooled in an ice–water bath under nitrogen, and 145.6 mg (1 equiv) of sodium metaperiodate in a total of 10 ml of 1 : 1 acetone–water was added in a slow dropwise manner over 15 min. The reaction mixture was stirred for 0.5 hr, the bath was allowed to warm slowly, and the reaction mixture was poured into 150 ml of water and extracted well with chloroform. The combined chloroform extracts

were washed with saturated sodium chloride solution, filtered, and evaporated with benzene to give 137 mg of golden oil.

This crude cleavage product was dissolved in 10 ml of chloroform in a 50-ml round-bottomed flask, and 25 ml of 2.5% sulfuric acid was added. The mixture was heated under nitrogen with a reflux condenser at 105°C for 1 hr. After cooling, some water was added, and extractions were made with three 15-ml portions of chloroform. The combined chloroform extracts were washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, filtered, and evaporated with benzene to give 23 mg of neutral material.

The acidic aqueous layer was filtered, cooled, made basic with 10% sodium hydroxide, and extracted with four 20-ml portions of chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution, filtered, and evaporated with benzene to give 89 mg of basic material. This product was applied to two 20 × 20-cm plates for preparative tlc, and the plates were eluted with $CHCl_3$–20% methanol containing a small amount of ammonia (40 drops of concd NH_4OH/100 ml of solvent). There was obtained, after separation from the silica gel, 58.5 mg of material, separated into six bands. The results are summarized in Table 2 (I, highest R_f to VI, lowest R_f).

TABLE 2

PRODUCTS OF MODEL AMINE-DIOL **32** CLEAVAGE AND CYCLIZATION

I	8 mg	Infrared ($CHCl_3$) absorption at 6.01 μm; possibly enamine.
II	14 mg	Two spots on analytical tlc; ir ($CHCl_3$) showed bands at 3.5–3.7 μm: upper spot subsequently shown to be *a*-cyclized material (tetracyclic base **31**).
III	12 mg	Infrared ($CHCl_3$) showed weak absorption at 6.05 μm.
IV	8 mg	Infrared ($CHCl_3$) showed carbonyl absorption at 5.83 μm; possibly aldehyde.
V	16 mg	Thin-layer chromatography and infrared ($CHCl_3$) suggested recovered starting material, amine-diol.
VI	0.5 mg	Discarded.

The neutral cyclization product was combined with neutral material from other cleavage-cyclizations of amine-diol **32** and purified by column chromatography on silica gel–15% water. The pure compound could be eluted from this substrate with 1:1 benzene–$CHCl_3$. The material obtained in this manner solidified and had mp 153.5–157.5°C (hot stage). One crystallization from *n*-hexane-benzene gave colorless needles, mp 156–157.5° C(hot stage). The compound exhibited an indolic uv spectrum; the ir spectrum ($CHCl_3$) exhibited, among other bands, strong absorption at 6.15 μm.

Material known to have the structure *N[β-indolyl-2-ethyl]2-piperidone* (i) melts at 155–157°C (hot stage) after one crystallization from *n*-hexane-benzene (*16*). Its mixture melting point with the neutral cyclization product was 155–156.5°C (hot stage). The ir spectrum ($CHCl_3$) of tricyclic lactam (i) was superimposable with that of the neutral cyclization product.

N_b-*[2-(3',4'-Dihydroxycyclopentyl)-butyl]-tryptamine* (**19a**). A solution of 600 mg (1.80 mmoles) of amide diol **19** (*10*) in 30 ml of dry THF was added dropwise over 15 min to a refluxing suspension of 1.0 g (10 equiv) of lithium aluminum hydride in 100 ml of dry THF in a 250-ml round-bottomed three-necked flask equipped with Teflon-

paddle power stirrer, reflux condenser, pressure-equalized dropping funnel, and nitrogen inlet. The reaction mixture was refluxed for 24 hr and excess hydride was decomposed by slow addition of saturated sodium potassium tartrate solution. The precipitated aluminum salts were removed by suction filtration and washed well with chloroform. The filtrate was evaporated to dryness, taken up in chloroform, and extracted with three 30-ml portions of 5% sulfuric acid. The chloroform was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 155 mg of recovered amide diol.

The acidic extracts were cooled, made basic with 10% sodium hydroxide solution, and extracted well with chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution, filtered, and evaporated with benzene to give 438 mg of crude amine-diol, containing some starting amide (tlc). The crude amide was chromatographed on 31 g (19-mm diameter × 18-cm length of Florisil. The material was applied in chloroform, and 110 mg of additional amide-diol **19** was eluted with 6–10% methanol in chloroform. Chloroform containing 12–20% methanol eluted 268 mg of pure amine diol, an oil (85% yield, 55% conversion).

The uv spectrum showed λ_{max} at 275 nm ($\varepsilon = 5300$), 282 nm ($\varepsilon = 5700$), and 290 nm ($\varepsilon = 4900$).

The 3,5-dinitrobenzamide, after purification by column chromatography on silica gel–15% water, was recrystallized from ethanol, giving fine yellow needles, mp 168–172°C.

Buffered periodic acid cleavage of amine-diol **19a**. In 40-ml of a buffer solution 0.0025 *M* in both acetic acid and sodium acetate there was dissolved slowly with stirring 151 mg of amine-diol **19a**. The solution was cooled, and 109 mg (1 equiv) of periodic acid in 35 ml of the buffer solution was added. The resulting mixture was protected from the light and stirred for 24 hr at room temperature under nitrogen. The green–black reaction mixture was cooled, made basic with 10% sodium hydroxide, and extracted well with chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution, filtered, and evaporated with benzene to give 153 mg of a dark green foam. This material showed three spots on analytical tlc, R_f values (10% methanol in chloroform) 0.67, 0.60, and 0.25 (aldehydes I, II, and III). The ir spectrum ($CHCl_3$) of this crude material showed indole N–H at 2.88 μm, strong carbonyl absorption at 5.8 μm, and medium absorption at 6.15 μm.

On the basis of a number of experiments, it was determined that the optimum reaction time for this cleavage was 24 hr. In three separate small-scale experiments, cleaved material was heated with $CHCl_3$–1% sulfuric acid, 1 : 1 water–88% formic acid, and methanol–concentrated hydrochloric acid. In each case, the organic material, recovered in excellent yield, had the same tlc pattern as the pre-acid-treated material.

The 153 mg of crude aldehyde obtained above was purified by two tandem preparative tlc steps using $CHCl_3$–10% methanol as eluent. There were obtained 47 mg of aldehyde I, 29 mg of II, and 8 mg of III, each as a golden oil which appeared as one spot on analytic tlc.

Infrared spectra ($CHCl_3$): I. 2.88 μm (m), 3.55 μm (m), 3.65 μm (w), and 5.80 μm (s). II. 2.88 μm (m), 3.55 μm (m), 3.65 μm (sh), and 5.80 μm (s). III. 2.88 μm (m), 3.65 μm (m), and 5.80 μm (s).

Ultraviolet spectra: I. λ_{max} at 273 nm (sh) ($\varepsilon = 7000$), 282 nm ($\varepsilon = 7500$), and 289 nm ($\varepsilon = 6500$). II. λ_{max} at 275 nm ($\varepsilon = 6900$), 282 nm ($\varepsilon = 8100$), and 289 nm ($\varepsilon = 7700$). III. λ_{max} at 275 nm (sh) ($\varepsilon = 6900$), 282 nm ($\varepsilon = 7500$), and 290 nm ($\varepsilon = 5900$).

An nmr spectrum (CCl_4) of aldehyde I showed aldehyde proton at 9.43 δ and indole N–H at 8.88 δ; the remainder of the spectrum was not amenable to analysis.

The nmr spectrum (CS_2) of aldehyde III showed aldehyde proton at 9.65 δ and indole N–H at 8.05–8.2 δ.

In order to determine whether the cleavage-cyclization mixture might be an equilibrium mixture or whether some of the products might only be intermediates, aldehydes II and III were each subjected to 24-hr treatment at room temperature under nitrogen, protected from the light in the buffer solution. They were recovered, respectively, in quantitative and 75% yield, unchanged, as indicated by analytical tlc.

Natural dihydrocorynantheol (**35**). In a 50-ml round-bottomed flask was placed 100 mg of natural dihydrocorynantheine and a mixture of 20 ml of water and 2 ml of concentrated hydrochloric acid. This mixture was heated at 110°C with stirring under nitrogen. Within 1 hr, all the solid had dissolved; and a white precipitate began to appear soon thereafter. After 3 hr of heating, the misture was cooled, made basic with concentrated ammonia, and extracted with four portions of ether. The combined ether extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to give 80 mg of crude natural dihydrocorynantheal (*18*) (one spot on analytical tlc, corresponding exactly in R_f to synthetic aldehyde I).

The crude material above could be sublimed to give a low yield of purified natural dihydrocorynantheal, mp 184–188.5°C. Lit. (*18b*): mp 187–188°C (dec.). This purified material was not sufficiently soluble in any solvent to provide a satisfactory solution ir spectrum.

Although the nmr spectrum (acetone-D_6) showed an aldehyde proton at 9.73 δ, the remainder of the spectrum was very complex.

Crude natural dihydrocorynantheal (56 mg) was dissolved in 8 ml of methanol, and 60 mg of potassium borohydride was added. This mixture was stirred under nitrogen at room temperature for 27 hr. Addition of water, followed by chloroform extraction gave 47 mg of crude natural dihydrocorynantheol. This material was purified by preparative tlc ($CHCl_3$–10% methanol as eluent), giving 31 mg of a golden oil.

Crystalline natural dihydrocorynantheol, mp 182–185.5°C, could be obtained by crystallization of the crude material from *n*-hexane–methylene chloride.

Borohydride reduction of amine-diol cleavage–cyclization product. In the manner described above, 195 mg of amine-diol **19a** was treated with 141 mg of periodic acid to give 192 mg of crude product. After being dissolved in 10 ml of methanol, the crude aldehyde was reduced with 195 mg of potassium borohydride. After being stirred at room temperature under nitrogen for 18 hr, the reaction mixture was poured into water and extracted well with chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution, filtered, and evaporated with benzene to give 184 mg of a golden foam, appearing as three spots on analytical tlc, R_f values ($CHCl_3$–10% methanol) 0.4, 0.35, and 0.2. These were designated alcohols A, B, and C. Each pure aldehyde (I, II, and III) was reduced with potassium borohydride to give products which corresponded exactly to alcohols A, B, and C, respectively, by analytical tlc.

The 184 mg of crude alcohols were purified by continuous preparative tlc ($CHCl_3$–10% methanol), giving 70 mg (36%) of alcohol A, 43 mg (22%) of alcohol B, and 21 mg (11%) of alcohol C. These alcohols were not sufficiently soluble for solution ir spectra.

When obtained in sufficient amount, purified synthetic alcohol A solidified and could be recrystallized from benzene to give colorless needles, mp 182–183.5°C (hot stage).

Ultraviolet spectrum: λ_{max} at 274 nm (sh) ($\varepsilon = 7400$), 277 nm (sh) ($\varepsilon = 7500$), 282 nm ($\varepsilon = 7700$), and 290 nm ($\varepsilon = 7000$).

Infrared spectrum (KBr): "Bohlmann bands" at 3.57 and 3.64 μm.

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.86; H, 8.81; N, 9.22.

When recrystallized from ether, this material gave colorless needles, mp 189–191°C (hot stage); the mixture melting point with known synthetic dihydrocorynantheol, mp 188–192°C (hot stage) in our hands, was 188–190°C (hot stage). The ir spectrum (KBr) of alcohol A (crystallized from ether) was identical to that of known racemic dihydrocorynantheol (crystallized from ether).

Purified oily alcohol B (31 mg) was acetylated with acetic anhydride and pyridine, and the crude product was purified by preparative tlc, using $CHCl_3$–10% methanol as eluent. There was obtained 23 mg of semisolid acetate B.

Infrared spectrum ($CHCl_3$): 2.88 μm (w), 3.57 μm (w), 3.63 μm (sh), and 5.79 μm (s).

Nuclear magnetic resonance spectrum ($CDCl_3$): indole N–H at 8.72 δ; aromatic absorption (obvious $CHCl_3$ peak) at 7.0–7.55 δ, and methylene-bearing acetoxy (crude triplet) centered at 4.16 δ, relative intensity 4 (+): 2. There was a sharp peak at 2.07 δ, due to acetoxy methyl, superimposed on low-amplitude absorption. The remainder of the spectrum was complex but strikingly different from that of acetate of A. Of particular interest was a broad (almost plateau-like) low-amplitude absorption at 3.5–3.8 δ, relative intensity ca. 1H.

When sufficient amounts of material were on hand, alcohol B could be recrystallized from benzene with great difficulty. By fractional crystallization, there was obtained material melting at 114–116°C (alcohol B-1).

Infrared spectrum (KBr): at 3.57 and 3.62 μm.

Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.12; H, 8.59; N, 9.48.

The first crop obtained during recrystallization of alcohol B-1 from benzene melted, beginning at 117°C, over a very broad range. When crystallized from ether, this material easily gave tiny cubes of highly crystalline material, mp 198–199.5°C (hot stage). The mixture melting point with DL-3-isocorynantheidol (*27*) (hot stage mp in our hands, 192–199°C) was 195–200°C (hot stage). The ratio of B-1 and B-2 was ca. 4 : 1.

Ultraviolet spectrum. λ_{max} at 274 nm (sh) ($\varepsilon = 6000$), 283 nm ($\varepsilon = 6400$), and 290 nm ($\varepsilon = 5500$).

Infrared spectrum (KBr): 3.57 and 3.62 μm. The ir spectrum (Nujol) was identical to that of DL-3-isocorynantheidol.

Alcohol C, which had been purified by one preparative tlc, was taken up in chloroform and extracted with 5% sulfuric acid, and 24 mg of basic material was recovered. This was acetylated with acetic anhydride and pyridine, and the crude product was

purified by continuous preparative tlc ($CHCl_3$–10% methanol) to give 15 mg of acetate C as a golden oil.

Infrared spectrum (CCl_4): 2.93 μm (m), 3.57 μm (sh), 3.65 μm (sh), and 5.79 μm (s).

Nuclear magnetic resonance spectrum (CCl_4): indole N–H at 8.58 δ, aromatic absorption at 6.85–7.4 δ, and methylene-bearing acetoxy centered at 4.0 δ, relative intensity 1 : 4 : 2. There was a sharp singlet at 1.98 δ, due to acetoxy methyl, superimposed on other low-amplitude absorption. The remainder of the spectrum was very complex.

Alcohol C was never obtained crystalline. A mass spectrum of the acetate had molecular ion at *m/e* 340, corresponding to a monoacetate of $C_{19}H_{26}N_2$. The only other strong peak in this spectrum was the slightly larger M-1 peak.

Preparation of tetradehydro perchlorates. Alcohol A: Palladium black was prepared by dissolving 135 mg (ca. 0.75 mmole) of palladous chloride in 6 ml of water and adding 270 mg (ca. 4 mmoles) of sodium formate. Bubbling began immediately, and a black precipitate soon appeared. The mixture was stirred at room temperature under nitrogen until all bubbling had stopped (ca 0.5 hr). The water was removed by pipet, and the palladium black was washed four times with water.

To this Pd-black was added 45 mg (0.15 mmole) of crystalline alcohol A, 87 mg (0.75 mmole) of maleic acid, and 5 ml of water. This mixture was stirred until all organic material was in solution and then under a reflux condenser and nitrogen for 10 hr in an oil bath at 110°C. The reaction mixture was filtered by suction through a pad of Celite while still hot, and the filter cake was washed well with hot water. Most of the water was removed on a rotary evaporator. To the cooled residual solution were added a few drops of 60% perchloric acid. A cloudiness appeared immediately, and slowly a curdy, pale yellow precipitate formed. The solid was collected by suction filtration, washed with a small amount of water, and dried in a vacuum desiccator to give 47.5 mg of crude tetradehydro perchlorate. A.

This material was recrystallized from absolute ethanol. At first there appeared to be a double melting point, at ca. 130°C and ca. 160°C (hot stage). However, by fractional crystallization, less-soluble material could be removed which had mp 169–173°C (hot stage). The remaining material had a single melting point at 130–132°C (hot stage (fine, pale yellow needles).

Infrared spectrum (KBr pellet). 6.12 μm (m s).

Ultraviolet spectrum: λ_{max} at 253 nm ($\varepsilon = 31{,}500$), 307 nm ($\varepsilon = 22{,}500$), and 368 nm ($\varepsilon = 5000$). The uv spectrum of DL-alloyohimbine tetradehydro perchlorate showed λ_{max} at 253 nm ($\varepsilon = 20{,}400$), 307 nm ($\varepsilon = 14{,}100$), and 367 nm ($\varepsilon = 4070$).

Anal. Calcd. for $C_{19}H_{23}N_2O_5Cl$: C, 57.79; H, 5.87; N, 7.095. Found: C, 57.61; H, 5.84; N, 7.23.

Alcohol B-1. Tetradehydro perchlorate B-1 was prepared in the manner described above by heating Pd-black (30 mg of $PdCl_2$ and 60 mg of sodium formate) and 10 mg of crystalline alcohol B-1 in water for 8.5 hr. After recrystallization from absolute ethanol, there was obtained material with mp 160–164°C (hot stage).

The uv spectrum was the same as that of tetradehydro A, except for lower extinction coefficients, probably the result of weighing errors on the small amount of material.

Alcohol B-2. Tetradehydro B-2 was prepared in the manner described above by heating Pd-black (from 15 mg of $PdCl_2$ and 30 mg of sodium formate) and 5 mg of crystalline alcohol B-2 in water for 22 hr. After recrystallization from absolute ethanol

there was obtained material with mp 162–164.5°C (hot stage). The mixture melting point with tetradehydro B-1 was 159–162.5°C (hot stage). The mixture melting point with tetradehydrocorynantheidol perchlorate (*27*) (hot stage mp in our hands 158–161°C) was 158–163°C (hot stage).

Alcohol C. Tetradehydro A was prepared in the manner described above by heating Pd-black (from 45 mg of $PdCl_2$ and 90 mg of sodium formate) and 12 mg of oil alcohol C (recovered from the acetate) in water for 22 hr. There was obtained 8 mg of yellow solid. After two recrystallizations from absolute ethanol this material melted at 139–141.5°C (hot stage), and most of the material crystallized again up to 150°C, melting again at 163–171°C. The mixture melting point of this material with tetradehydro A was 157–164°C. After standing in a freezer for several weeks, the salt had mp 163–169°C.

Ultraviolet spectrum. λ_{max} at 254 nm ($\varepsilon = 31{,}800$), 307 nm ($\varepsilon = 23{,}800$), and 368 nm ($\varepsilon = 5500$).

To 1.7 mg of dehydrogenated alcohol C (mp 163–169°) dissolved in 2–3 ml of methanol were added three very small portions of potassium borohydride over a 45-min period. The methanol was removed under water vacuum, and saturated sodium chloride solution and chloroform were added. The mixture was extracted five times with chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, filtered and evaporated to give 1.2 mg of an amorphous colorless solid, mp 155–170°C, which was 95% one spot (same R_f as alcohol I) on tlc. This material was taken up in hot ether (0.2 mg, not soluble); the ether was evaporated to a small volume and placed in a freezer. Crystals deposited which had mp 180–181.5°C (hot stage); this mp was not depressed upon admixture of alcohol A (one crystallization from ether, mp 182–184°C).

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