Organic and Biological Chemistry

Total Synthesis of Yohimbine

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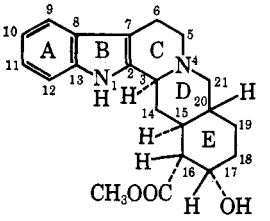
Abstract: The total synthesis of the venerable indole alkaloid yohimbine (**1**), described earlier in preliminary form, is detailed. The over-all sequence (**7** → **1**) involves the following individual intermediates: **9, 10, 11, 15, 23, 25, 26, 32, 39, 40, 41** (R = H), **41** (R = Ac), **42, 43, 44,** and **48**.

I. Background and Introduction

No class of natural products has received more chemical attention during the last decade than the indole alkaloid group. Following painstaking and ofttimes prodigious feats of isolation and characterization, structures of the greatest variety and novelty have come to light within this category of plant products.[2] In consequence, subtle, veiled biosynthetic pathways required clarification, and synthetic challenges of the first magnitude had to be met. In a utilitarian vein, the indole family remains a rich source of medicinally important agents, the most notable thus far being reserpine.

In this paper, we describe the first total synthesis of yohimbine (**1**),[3] historically the most important of the complex indole alkaloid type.[2] Known since ancient times in an impure state and regarded by African natives as a potent aphrodisiac, yohimbine occurs naturally in the bark of various trees, for example, *Pausinystalia yohimba* Pierre and *Aspidosperma quebracho-blanco* Schlecht. The alkaloids, first isolated and characterized by Spiegel in 1900, remained an object of chemical scrutiny for many years. Following laborious structural studies by various workers, Witkop suggested



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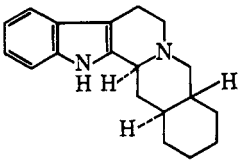
the correct constitution in 1943.[4] Subsequently, stereochemical proposals appeared,[2] and the entire three-dimensional structure (**1**) of yohimbine was put on a secure basis by definitive, stereospecific syntheses of the key degradation products, *dl*-yohimbane (**2**)[5] and *dl*-alloyohimbane (**3**).[6] At this point the stage was set for



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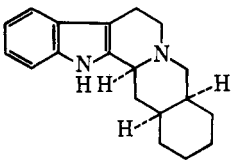

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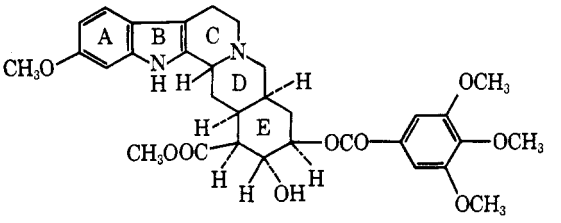
total synthesis performances.

Our synthesis program commenced in 1954 and was completed and published as a Communication to the Editor in 1958. In the meantime, the well-known hypotensive and tranquilizing agent reserpine (**4**) appeared on the scene; and after structure and stereochemistry were established, its synthesis was pursued forthwith by Woodward, who rapidly attained a solution to this out-



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standing problem.[7] Although structurally similar, the two cases of yohimbine and reserpine in fact pose quite different problems in synthesis, largely a consequence of the very different arrangement of asymmetric centers in the two natural products. Being committed to our original, stereospecific synthesis plan aimed at yohimbine, we continued to follow it and saw no convenient way to modify it so as to lead to the newer, D/E *cis*, reserpine case. Similarly, the Woodward reserpine synthesis has not been refashioned so as to embrace the D/E *trans* type, of which yohimbine is a member. The synthesis problems were, and remain, distinctly different.

In the yohimbine case, one had to contend with the problem of five asymmetric centers (**5**), in addition to a

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(2) For reviews, see L. Marion in "The Alkaloids," R. H. F. Manske and H. Holmes, Ed., Vol. II, Academic Press, New York, N. Y., 1952, p 371; J. E. Saxton in "The Alkaloids," R. H. F. Manske, Ed., Vol. VII, Academic Press, New York, N. Y., 1960, p 4; R. H. F. Manske "The Alkaloids," Vol. VIII, Academic Press, New York, N. Y., 1960, pp 1–814.

(3) First reported in a Communication to the Editor by E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich, *J. Am. Chem. Soc.*, **80**, 5006 (1958).

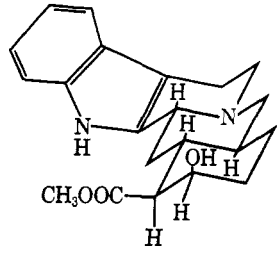
(4) B. Witkop, *Ann.*, **554**, 83 (1943).

(5) E. E. van Tamelen, M. Shamma, and P. Aldrich, *J. Am. Chem. Soc.*, **76**, 950 (1954); **78**, 4628 (1956).

(6) G. Stork and R. K. Hill, *ibid.*, **76**, 949 (1954).

(7) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *ibid.*, **78**, 2023, 2657 (1956); *Tetrahedron*, **2**, 1 (1958).

pentacyclic ring system featuring two heteroatoms. In each of four of these five centers (3, 15, 16, 20) the more stable of two possible stereochemical arrangements is involved—a simplifying feature, provided that means



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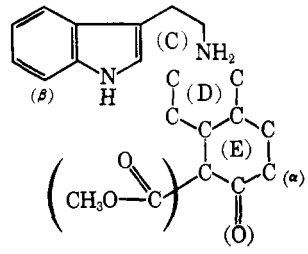
are available for epimerization, if necessary, at said centers. In more general terms, the synthetic problems centered around the stereospecific construction of actual or potential D and E rings (α unit) (**6**), with provision for C-16 and C-17 substituents and also attachment (with ring-C formation) to tryptamine, an almost ob-



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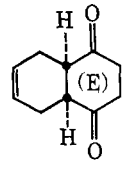
ligatory, available, second major structural component (β unit). The reduced quinone–1,3-butadiene Diels–



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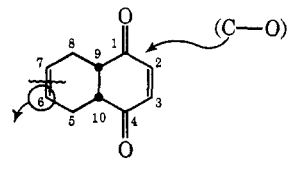
Alder adduct (**7**)[8] was selected as the actual starting material since it incorporated intrinsically all the structural requirements of component α or offered means for the controlled materialization of each. Given diketone **7**, specifically we were required (**8**) to (a) attach to C-1 a carbon atom in a partially oxidized form so as to permit at some stage connection with the N_b of tryptamine, (b) reduce C-4 carbonyl to axial (less stable) hydroxyl, (c) ring open between C-6 and C-7, while allowing for ultimate bond formation between C-7 and the α position of the indole ring in β, (d) remove literally C-6 and permit final appearance of C-5 as a carbomethoxyl func-



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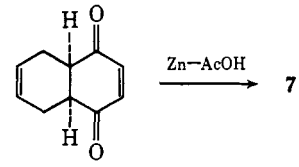
tion, and (e) adjust stereochemistry at C-1, C-7, C-9, and C-10 so that these centers possess the relative stereochemistry in yohimbine. This paper is largely concerned with the reduction to practice of the above plan of action.

(8) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).

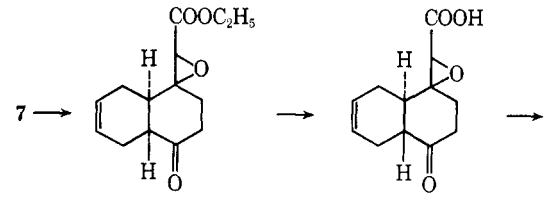
II. Synthesis of the Skeletal Precursor of the α Unit

1,4,5,8,9,10-*cis*-Hexahydronaphthalene-1,4-dione, the well-known Diels–Alder adduct derived from *p*-benzoquinone and 1,4-butadiene, was prepared conveniently



and in good yield (>90%) by minor modification of the original directions, thus permitting runs with 0.5–1 kg amounts of starting quinone. Selective reduction of the conjugated double bond was handled, as previously reported,[8] by means of zinc metal and acetic acid, which reagents provided (80–90%), again by slight alteration of the original descriptions, the octahydronaphthalenedione (**7**), in somewhat impure state but of sufficiently good quality to permit utilization in the succeeding step.

Incorporation of the additional required carbon atom at C-1 was obligatory at this stage and was accomplished by execution of a Darzens glycidic ester condensation, subsequent hydrolysis to the glycidic acid, and final decarboxylation to the expected unsaturated keto



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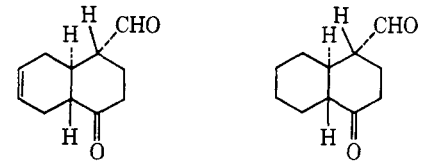
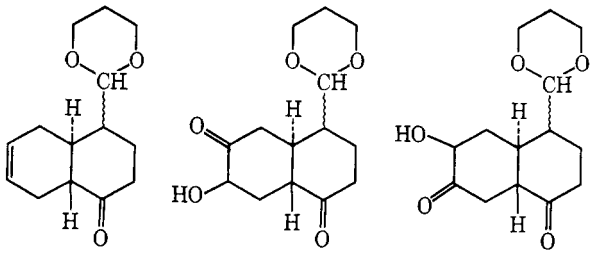


11a 11b

aldehyde system. The condensation was carried out with ethyl chloroacetate and potassium *t*-butoxide in benzene, and provided in 70–80% yield a mixture of diastereoisomeric α,β-epoxy esters (**9**). In fractional distillation, there was observed partial separation of the racemates, one of which was obtained in crystalline form (mp 92–94°). In the normal synthetic operation no effort was made to achieve separation, but the mixture was saponified directly to glycidic acid **10**.[9] This step was accomplished by means of hot aqueous sodium hydroxide (under nitrogen) and afforded in 79–87% yield the corresponding acids as a crystalline mixture (mp 140–148°). Optimal decarboxylation (70–76%) of the acids was observed when the mixture was heated with copper powder in diethylene glycol at

(9) Saponification of each of the partially purified glycidic ester racemates provided the separate glycidic acid (mp 138–140 and 210–211°). These substances were not investigated further, and their stereochemistry remains unknown. The same ketoaldehyde mixture was obtained from each, as shown by boiling point and refractive index comparison as well as by lithium aluminum hydride reduction to enediol.

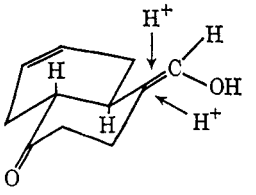
155–160°, after which the acetal product was hydrolyzed with hydrochloric acid and worked up. Although in itself a liquid, bp 107–109° (0.01 mm), keto aldehyde (**11**) formed a crystalline dioxime (mp 175–175.5°). Execution of the reaction in a trimethylene glycol instead of a diethylene glycol medium permitted formation of a crystalline acetal (mp 115.5–116.5°) (**12**), which on acid hydrolysis generated the parent keto aldehyde in high yield. Potassium permanganate oxidation of this acetal led to a crystalline ketol, presumably possessing structure **13a** or **13b**.



12 **13a** **13b**

At this stage in the synthesis, an intermediate possessing three asymmetric centers with counterparts in the natural product target was in hand; and it became important to confirm the anticipated relationship of these centers. Base-promoted isomerization of the *cis*- to the *trans*-octahydronaphthalendione under the conditions of the Darzens reaction was expected, and this change was confirmed by observing the solitary behavior of the *cis* isomer with aqueous sodium hydroxide: by infrared spectroscopy, the conversion to the crystalline *trans* isomer (mp 94.0–94.5°) was essentially complete (≥95%). Similar observations were made in the decalindione series.

Information on the stereochemical homogeneity of the unsaturated keto aldehyde was aquired by studying the nature of dioxime produced from material prepared under varying conditions. Keto aldehyde made by simple pyrolysis (no glycol solvent present) provided in 55% yield dioxime melting over the range 145–155°. After being equilibrated in a basic medium, a derivative of mp 165.5–170.5° was formed in 71% yield. Acid-treated material, as evolved from the aforementioned glycol solvent preparation, was converted in good yield (81%) to dioxime of mp 171–173°, a value not much below that (mp 175–175.5°) of pure material. It is evident that the aldehyde exposed to an acid medium is a reasonably pure racemate, presumably the desired one possessing the equatorial formyl group (**11a**). It is also clear that simple thermal decarboxylation generates a stereochemical mixture of unknown composition, ap-



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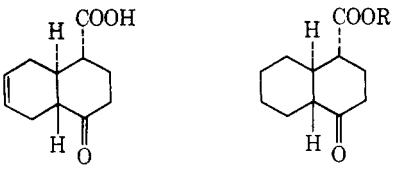
parently arising by stereochemically unselective protonation of the intermediary enol (**14**) or by partial conversion to equatorial isomer of axial product formed by preferred equatorial protonation of enol.

Corroboration of the above stereochemical assignments appeared in the form of equilibration studies carried out on carboxylic ester derived from keto aldehyde **11a**. The unsaturated acid (**15**) itself (mp 146–147°)



15 **16**

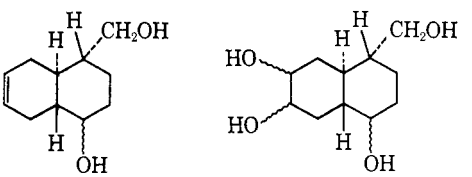
was best obtained in our hands by silver oxide oxidation in the presence of alkali. Chromium trioxide–pyridine or –acetic acid, dichromate–acetic acid or oxygen–acetic acid (in the presence of manganous acetate) were less effective in this operation. The new acid was characterized as a crystalline methyl ester, mp 72.5–73°, and a 2,4-dinitrophenylhydrazaone, mp 174–175°. Saponification of the methyl ester under mild conditions provided the original keto acid in 80% yield.

The saturated keto acid (**16**, R = H), mp 154–156°, was secured by (a) catalytic reduction of **15** over palladium on carbon, or (b) by manganese acetate catalyzed air oxidation of the saturated keto aldehyde, **11b**, itself prepared by catalytic reduction of the unsaturated keto aldehyde **11a**. After being subjected to epimerizing conditions (refluxing anhydrous sodium methoxide in absolute methanol), the saturated methyl ester (**16**, R = CH_3), mp 66–67°, was saponified, yielding as the only isolable product crystalline saturated acid identical with that (**16**, R = H) obtained from keto aldehyde **11** as already described.

III. Assemblage of the Gross Carbon–Nitrogen Framework

Synthesis of Keto Amide 23. Either (a) hydroxylation of the olefinic bond, preparatory to cleavage, and/or (b) attachment of the tryptamine unit became at this stage in the synthesis mandatory, in that generation of the required axial hydroxyl function at C-4 had best be done by catalytic reduction; and that operation could not be carried out while the olefinic linkage was still present. The experiments described next represent attempts to incorporate a tryptamine moiety, with or without olefin hydroxylation.

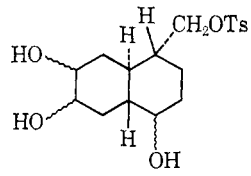
In disregard of the temporary fate at C-4, keto aldehyde **11a** or keto acid **15** was reduced by lithium aluminum hydride to a mixture of enediols (**17**), one of which was crystalline (mp 125–126°).[10] Treatment of this single product with performic acid resulted in for-



17 **18**

(10) Catalytic reduction of the crystalline enediol **17** afforded in high yield the corresponding saturated diol (mp 111.5–112.5°). Lithium aluminum hydride reduction of the saturated keto ester **16** (R = CH_3) generated saturated diol (mp 111.5–112.5°) identical with the product secured by reduction of aldehyde, as described. Thus the stereochemical formulation of the enediol is confirmed, although the configuration of the secondary hydroxyl function remains undefined.

mation of the amorphous tetrol (**18**), characterized as the crystalline tetrabenzoate. Tosylation of diol **17** under normal conditions with 1 mole of reagent afforded two monotosylates, mp 184–185 and 151–153°, the lower melting isomer being formed in lesser yield. Ready cleavage in each case by periodate denoted an intact, 1,2-glycol function. The more plentiful isomer was subjected to a displacement reaction with sodium thiophenoxide; and the resulting thioether, on being reductively desulfurized with Raney nickel, was converted to a triol which possessed a C-methyl group. Consequently, the higher melting tosylate must possess structure **19**, while the lower melting product corre-



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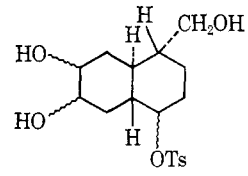

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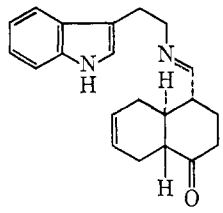
sponds to **20**. All attempts to achieve a displacement reaction between tosylate **19** and tryptamine were unsuccessful, since the derivative seemed only to solvolyze or suffer elimination.[11]

Attempts to incorporate a tryptamine unit by putting to use the keto aldehyde, either *per se* or in modified form, were unpromising. Treatment with tryptamine of the crude osmium tetroxide hydroxylation product of unsaturated keto aldehyde **11** led to ill-defined amorphous solids. Hydrolysis of the acetal **13a–b** or the corresponding acetal triol followed by exposure to tryptamine failed to produce characterizable products. Condensation of unsaturated keto aldehyde with tryptamine, carried out in refluxing benzene with water removal, yielded well-defined imine **21**, mp 111.5–113.5°.



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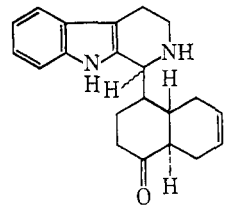

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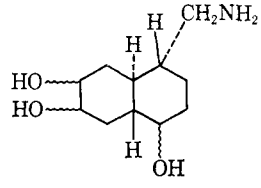
On being heated for 1 hr with 2 *N* hydrochloric acid in ethanol, the imine was converted to product the properties of which were consistent with cyclization structure **22**. However, osmylation or borohydride reduction of the imine led to no usable products.

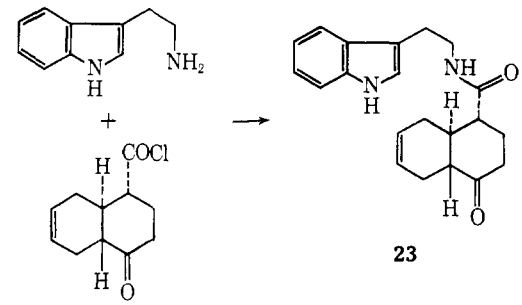
(11) It was possible, however, to convert, by treatment with ammonia in dioxane, the primary tosylate **19** to a basic product which analysis indicated to be the expected primary amine (i). Although amorphous,



i

the amine formed a crystalline (mp 224–225°) *p*-nitrobenzamide. Under similar conditions (55° overnight), the secondary tosylate **20** failed to react.

As it turned out, the only convenient means for incorporating the tryptamine unit was by means of amide bonding. After conversion of unsaturated keto acid **15** to (nonisolated) acid chloride with oxalyl chloride, tryptamine was introduced in the presence of pyridine, and tryptamide **23** was produced in good yield. Dimorphic forms (mp 150–151 and 161–162°) of the amide could be isolated (and interconverted), both of which

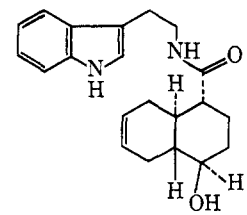


23

were useful for succeeding transformations (see below). Other devices for amide formation seemed to be less satisfactory.

IV. Oxidation–Reduction Adjustments in the α Unit

Synthesis of Triol Amide 27. Since the net result of our endeavors at this point was availability of only one tryptamine derivative (**23**) that might serve as a precursor for yohimbine, the flexibility in later stages of the synthesis was limited by whatever selective reactions could be carried out successfully on **23** and substances derived therefrom. Furthermore the *sequence* of operations had an important bearing on whether the requisite individual reactions could be realized and, where pertinent, made subject to stereochemical control. As a case in point, it was observed that various reducing devices (including electrolysis and lithium aluminum hydride in various solvents) did not affect the amide unit in intermediate **23**, but served only to convert the ketonic carbonyl group to secondary alcohol, presumably of configuration which does not correspond to that at



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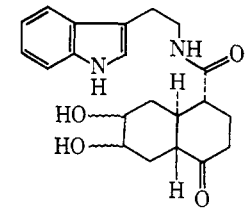

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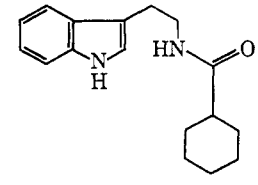
C-17 in yohimbine (**24**).[12] Furthermore, lithium aluminum hydride was without action on the ethylenedioxyl ketal corresponding to **23**. Obviously the required amide reduction had to be postponed until a later, more

(12) Clearly, solubility factors, in part determined by the centers bearing active hydrogen, play a determining role in these reduction attempts on **23**. By contrast, lithium aluminum hydride reduction of tryptamide (ii) proceeded to secondary amine without difficulty.

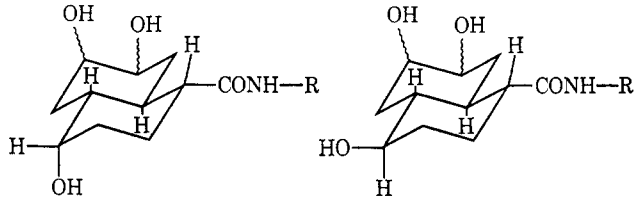


ii

propitious, stage, presumably when the number of active hydrogens was diminished. Moreover, reduction of the ketone group by noncatalytic means could not be tolerated; rather, generation of the required axial hydroxyl group (C-17) should wait upon an opportunity which would allow catalytic hydrogenation.

In view of the above constrictions, olefin hydroxylation—preparatory to cleavage—on amide **23** was demanded as the first step forward. Although 1,2-bis-hydroxylation of olefins is normally a commonplace reaction, execution in the presence of the sensitive indole moiety is a more problematical case which required serious consideration at an early point in this program of synthesis. Of the many available hydroxylation reactions, osmylation enjoys a reputation for selectivity and was favored *a priori* in the present connection. Encouraged by the report that β-allylindole can be hydroxylated by osmium tetroxide in 85% yield,[13] we attempted the reaction type on unsaturated keto amide **23**. Under the best conditions, a solution of reagent in tetrahydrofuran was added to a solution of amide in pyridine–tetrahydrofuran cooled at Dry Ice–acetone temperatures; after a hydrogen sulfide work-up, there was secured a 55% yield of major *cis*-diol **25**, mp 212–214°, accompanied by 5–15% of an isomer, mp 323–324°, regarded as the second possible *cis*-diol. Since the two new asymmetric centers in these keto diols were destined to be destroyed in succeeding operations, no effort was expended to obtain evidence for relative stereochemistry; indeed, predictions on this score seem insecure. All other hydroxylation experiments (*e.g.*, cold permanganate in acetone, perphthalic acid), either with unsaturated keto amide **23** or unsaturated keto acid **15**, led to products of little utility.

With the susceptible olefin link gone, conversion of the ketone unit to the axial substituent ultimately required at C-17 in yohimbine could now be realized by catalytic reduction means. In the experiment, hydrogenation of keto diol **25** over Adams catalyst in ethanol gave a good yield of the desired triol **26**, mp 227–228°, presumably formed by the characteristic, well-known approach of hydrogen-bearing catalyst from the less



26 **27**

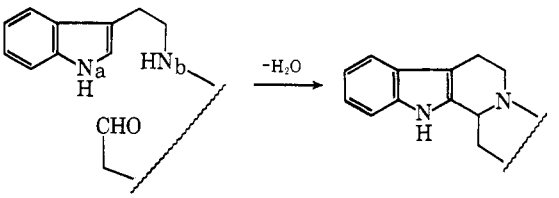
R = β-indCH$_2$CH$_2$–

hindered side of the decalone system. In order to establish the stereochemistry embodied in triol **26**, reduction of keto diol to an isomeric triol, mp 224–226°, was carried out through the agency of sodium–ethanol, a reagent combination noted for production of the stereochemically more stable alcohol from a given ketone. On the basis of the foregoing, stereochemistry **27** is assigned to the second triol.

(13) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952).

V. Formation of the Yohimbine Skeleton

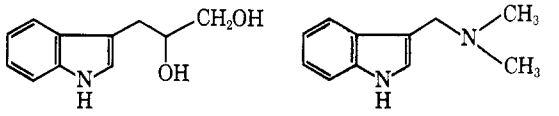
From the beginning, the over-all synthetic plan had featured construction of the yohimbine skeleton by means of a key cyclization (**28**) operation involving the indole ring, the N_b nitrogen, and an aldehyde unit generated by oxidative cleavage of the 1,2-glycol moiety. Despite the key role of this single reaction, the exact



28

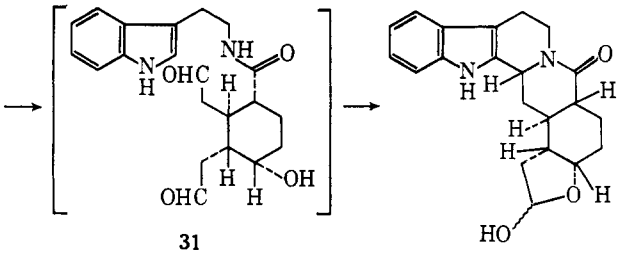
point at which it could be accomplished was not self-evident. In the hypothetical case where N_b is a secondary amine function, the cyclization would conform to the Pictet–Spengler type; however, generation of the required precursor by hydride reduction of the amide unit did not, because of the multiplicity of active hydrogens present, appear feasible. It was therefore decided to attempt a cyclization on aldehydo amide formed by periodate cleavage of triol amide. Although this reaction had no precedent in indole chemistry,[14] it appeared mechanistically attractive and highly appropriate for the synthesis planned—assuming that the lactam function generated thereby could be reduced to tertiary amine at a later stage.

In preparation for the ring closure process, periodate cleavage of the 1,2-glycol unit was required. That this oxidation could be achieved without concurrent attack on the indole ring could hardly be doubted, since (1) the glycol **29** was convertible by means of periodate to β-indolylacetaldehyde,[13] and (2) gramine (**30**) was recovered substantially after exposure to the reagent at room temperature.



29 **30**

On the other hand, no attempt was made to isolate the dialdehyde (**31**) (or corresponding N-acylalkanolamine) resulting from cleavage of triol amide in aqueous



31 **32**

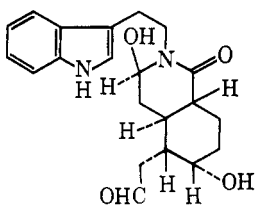
acetone; but instead cyclization was carried out *in situ* by addition of phosphoric acid and brief heating at 60–70°. By such means, a colorless, crystalline product, 215–217° (**32**), was obtained in 60% yield. That

(14) For a precedent in the benzenoid series, see B. Belleau, *J. Am. Chem. Soc.*, 75, 5765 (1953).

the reaction had indeed taken the desired course was indicated by (1) the elemental analysis, (2) preservation of the typical ultraviolet chromophore of an intact indole, (3) a negative response to the Erhlich test (indole unsubstituted in the α position), which was positive with the starting triol amide (**26**), and (4) disappearance of the 6.10-μ amide band in the infrared, and appearance of a new peak at 6.18 μ, ascribable to an N-alkyltetrahydropyridone carbonyl group.

Three aspects of the cyclization merit further comment: stereochemistry, mechanism, and over-all cyclization pattern.[15] In the reaction, the final asymmetric center in the alkaloidal pentacyclic framework is generated, and its stereochemistry relative to the other points of asymmetry demands inspection. Since the cyclization had not been employed previously in the indole series, predictions on this score were uncertain; and a definite answer emerged only at the completion of the formal synthesis. However, as a preliminary observation, the absence of 3.5–3.6-μ absorption in the infrared spectrum strongly implied that the C_3-hydrogen was β, and therefore that the D/E stereochemistry fell in the pseudoyohimbine category. This prediction was borne out, as described later in this publication.

Accepting for the moment this stereochemical result as fact, we can inquire into the matter of mechanism. Almost certainly, the closure of the C ring is preceded by formation of a cyclic N-acylalkanolamine (**33**) by interaction of the secondary amide function with one of two equivalent, newly generated aldehyde functions. In this presumed, but very probable, intermediate, the hydroxylic function of the alkanolamine moiety is likely to be oriented equatorial. Should the mechanisms of the cyclization involve an SN2-like displacement of the labilized (probably protonated) alcoholic function by the nucleophilic indole ring (**34**), the new center would be axial, *i.e.*, *trans* to C_{15}, as required. Alternatively, formation of the C ring may depend on prior dehydration of the N-acylalkanolamine to an N-acylenamine, which could undergo conjugate addition. By analogy with the stereochemical character of additions to olefinic type bonds, the attack of the indole center should be perpendicular to the plane of the π system; and, by reason of steric factors, this attack should take place on the face opposite the closer alkyl substituent (C_4) (**35**). Again, the less stable arrangement at the new asymmetric center would result.



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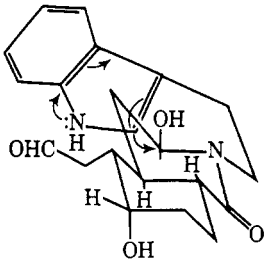

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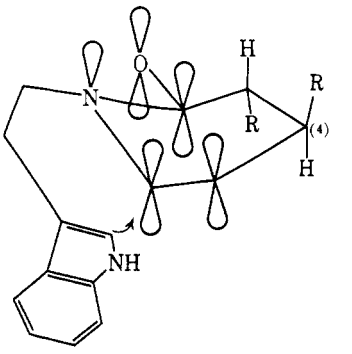
That the matter of product formation in this case reflects a delicate energy balance is indicated by the fact that a very similar reaction in the benzene series, namely the cyclization of β-phenethylamide (**36**) to tetrahydroisoquinoline (**37**), involves the opposite stereochemical result, *viz.* generation of the more stable relationship at the newly formed center.[16] Whether this more recent, related cyclization involves kinetic or thermodynamic control is not known.



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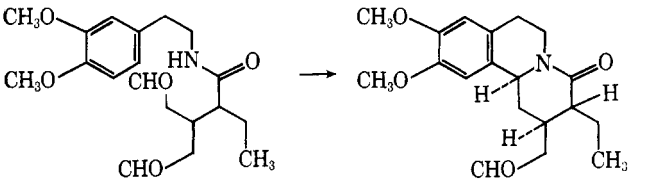
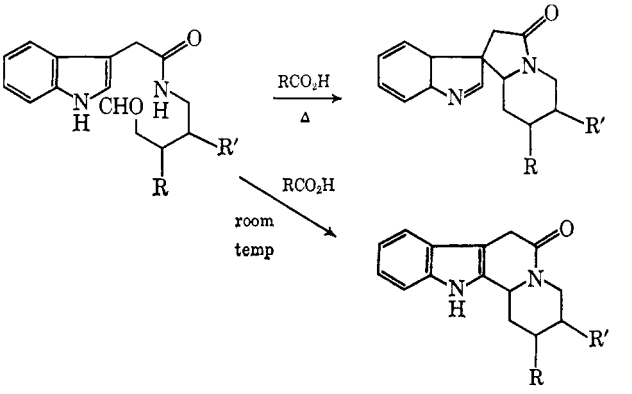


36 37

Both the α and β positions of the indole ring represent sites for carbon–carbon bond formation in ring closures of the type under consideration. In the case of substituted β-indoleacetamides, apparently the β cyclization is thermodynamically preferred, in that ring closure



under conditions milder than those employed for the β cyclizations led in the single case studied to α product. The indoleacetamide result is understandable in the sense that a five-membered lactam is ordinarily more stable than the six-membered type. Accepting the above, we conclude that appearance of the yohimbine synthesis intermediate under comparatively drastic conditions of acidity and temperature is a consequence of both thermodynamic and kinetic control. However, isomerization studies were not undertaken.[15]

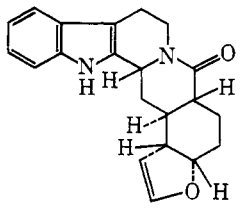
VI. Degradation of Intermediate 32 to Yohimbine

Returning to the main stream of the synthesis, we face (1) reduction of lactam moiety to tertiary amine, and (2) degradation of the 2-hydroxytetrahydrofuran ring to the 16,17-β-hydroxy ester moiety of yohimbine. Because of the pair of active hydrogens in the lactol (**32**), protection of the hydroxyl function was deemed advis-

(15) For related studies of indole cyclizations, see A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 403 (1968).

(16) A. W. Burgstahler and Z. J. Bithos, *J. Am. Chem. Soc.*, **82**, 5466 (1960).

able. In that connection, two devices were investigated. First, if it were possible to dehydrate to the enol ether **38**, protection in this sphere and setting the stage for later oxidative degradation would be simultaneously



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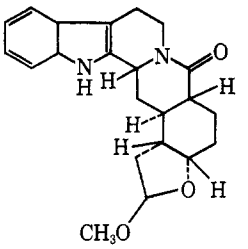
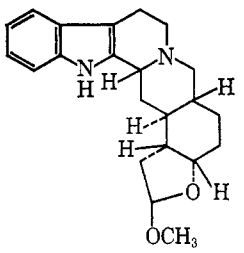


39

accomplished. Unfortunately, attempts to dehydrate with acid and then reduce with lithium aluminum hydride did not result in formation of the desired product. Thus compromise in the form of mere alternative protection of the lactol unit was in order; and by means of *p*-toluenesulfonic acid catalyzed methanolysis, the lactol was smoothly transformed into the lactol lactam methyl ether (**39**), mp 269–270°. Lithium aluminum hydride



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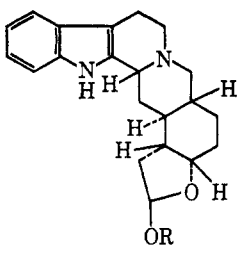
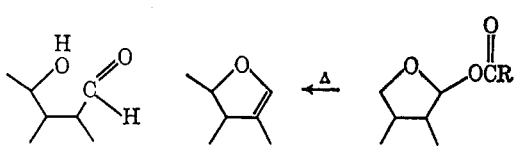


41

reduction in tetrahydrofuran afforded without difficulty the lactol ether base (**40**). Melting at 133–137°, this tertiary amine was, without deliberate purification, hydrolyzed by means of aqueous hydrochloric acid to the lactol base (**41**, R = H). The latter was then employed in an extensive series of attempts to form the enol ether base **42**, an investigation which required expenditure of considerable time and effort by comparison to other operations in the synthesis.

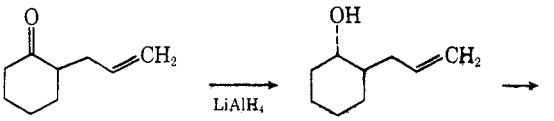
After a large number of unrewarding attempts in this direction, carried out with the hexacyclic lactol base itself, resort was taken in the form of an extensive investigation of Δ^2-dihydrofuran synthesis, using model compounds. The consequence of this program was emergence of ester pyrolysis as the only attractive means for achieving synthesis of the enol ether base from corresponding lactol.[17] Accordingly, the lactol base was converted by treatment with acetic anhydride–pyridine to the lactol acetate (**41**, R = Ac) (as acetate salt), which without purification was subjected to pyrolysis conditions. More specifically, a limited amount of acetate

(17) In connection with the degradation of cyclization product **32** to the yohimbine system, it became eivdent that generation of cyclic enol ether (**50**) from the corresponding γ-hydroxy aldehyde (**49**) would be a useful transformation. Unfortunately, preliminary experiments demonstrated that the desired change could not be effected in the particular case at hand as easily as might have been anticipated on the basis of other simple and complex precedents. Accordingly, a systematic attempt was made to develop a general and reliable method for carrying out the desired, over-all dehydration. As revealed earlier in this paper, the lactol ester pyrolysis (**51** → **50**) was just such a method.



49 50 51

In preparation for the cyclization studies, several model γ-hydroxy aldehydes were prepared by unambiguous methods, in particular the *trans*- and *cis*-2-hydroxy-4,5-tetramethylenetetrahydrofurans, **52** and **53**. The *trans* isomer was obtained by means of a straightforward synthesis starting from 2-allylcyclohexanone (**54**). Stereochemistry is



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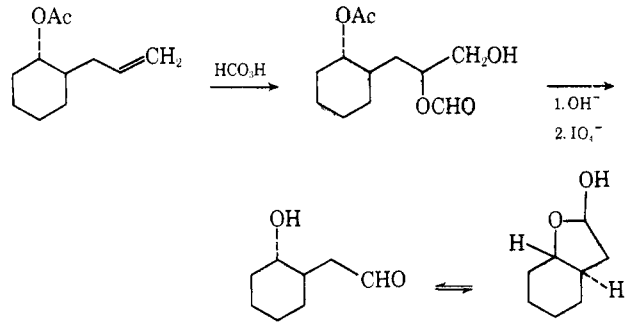
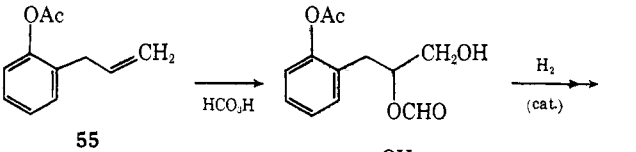


52

assigned on the basis of (1) prior results in related cases, and (2) its conversion to bicyclic lactol isomeric with but not identical with lactol **53**, the stereochemistry of which was designed to be *cis*. The lactol, a colorless liquid which possessed absorption in the infrared at 2.90 and 5.82 μ, was convertible to O-acetate; however, pyrolysis of the ester failed to yield the desired enol ether. Other agents for the dehydration which were examined, unsuccessfully, include phenol, salicylic acid, calcium chloride, boric anhydride, copper sulfate, phosphorus oxychloride, boron trifluoride, stannic chloride, acetic acid, thionyl chloride–pyridine.

More success attended similar chemical investigations in the *cis*-bicyclic series. Entry into this stereochemical category was afforded by the route indicated, starting with oxidation of 2-allyl phenylacetate (**55**).



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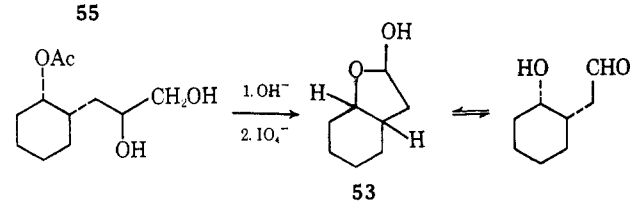
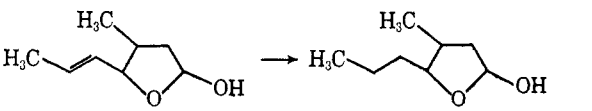


53

Distillation of lactol acetate at 200–220° under slight vacuum provided the considerably more volatile cyclic ether, the infrared spectrum of which showed sharp, well-defined bands at 3.30 and 6.28 μ, characteristic of the enol ether part structure,[18] as well as a peak at 14.0 μ due to *cis*-disubstituted double bond.

Similar results were experienced in a monocyclic series centering around 2-hydroxy-4-methyl-5-*n*-propyltetrahydrofuran (**57**), readily secured by Raney nickel hydrogenation of the lactol with unsaturated side chain (**56**). Glacet and Wiemann had reported in 1947 that two

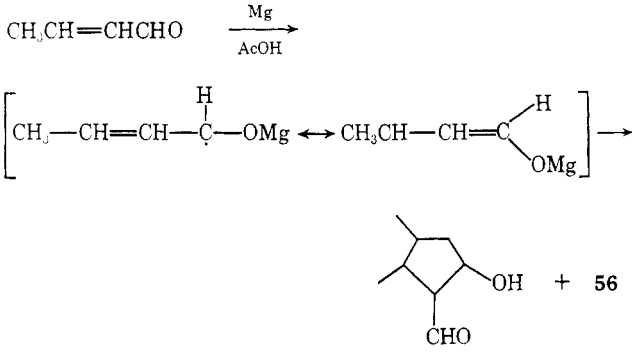


56 57

stereoisomeric forms of lactol **56** were formed when crotonaldehyde was reduced by means of magnesium–acetic acid.[19] Although one of the isomers indeed did turn out to be an unsaturated lactol of the assigned structure, the second substance appeared, on the basis of (1) its very ready dehydration to 4,5-dimethyl-1-cyclopentenecarboxaldehyde and (2) ir absorption at 5.8 μ, to be 2-hydroxy-4,5-dimethylcyclopentanecarboxaldehyde (**58**). Thus, the over-all reduction process in-

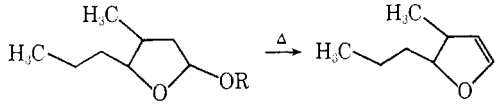
salt under 0.01 mm pressure in a sublimer was exposed to a metal bath previously heated to 285–295°. Within minutes, the reaction was essentially complete, the enol ether **42** having been formed and safely sublimed, as the

volves β,β coupling as well as direct interaction of a β site of one molecule with the carbonyl group of a second. After reduction of



58

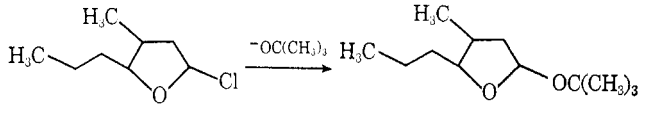
lactol **56**, a liquid saturated lactol was secured by distillation and characterized as a dinitrophenylhydrazone, mp 88.5–90.5°. Either pyrolysis of lactol acetate (**59**, R = Ac) at 180–190° or of lactol cathylate (**59**, R = COOEt) at 130–140° resulted in smooth formation of



59 60

cyclic enol ether **60**, a colorless liquid possessing infrared spectral properties in keeping with expected structure.

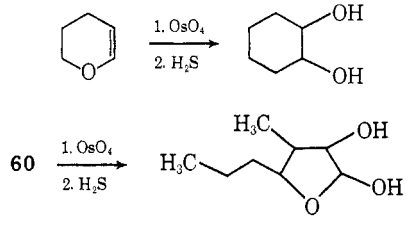
Although mechanistically reasonable and attractive, the *t*-butoxide-promoted elimination of hydrogen chloride from the α-chloro ether **61** failed. In an unexpected result, either potassium *t*-butoxide in dry *t*-butyl alcohol or in benzene displaced halogen, giving rise to the *t*-butyl ether (**62**), a liquid boiling at 83–84° (9 mm). As a base, triethylamine



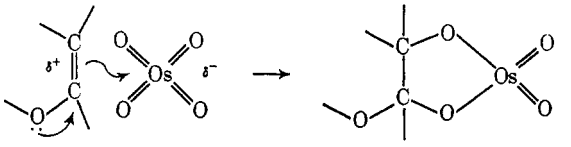
61 62

was, however, satisfactory in that its reaction in dry ether with chloro ether **61** resulted in formation of cyclic enol ether **60**. Toluenesulfonyl chloride in pyridine or triethylamine gave much less satisfactory results, as did methanesulfonyl chloride in pyridine.

Preparatory to the hydroxylation and metaperiodate cleavage of hexacyclic enol ether **42**, the osmium textroxide reaction was tested on two model cyclic enol ethers, dihydropyran and the dialkyl dihydrofuran **60**. Because of the presence of ethereal oxygen conjugated

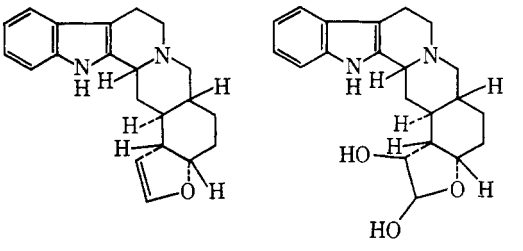


with the π bond, stabilization of carbonium ion character in the transition state might be anticipated, thereby possibly increasing the over-all reaction rate relative to a simple olefin. In such a case, the prognostication for the oxidation operation in the actual hexacyclic intermediate would be favorable, since undesired side attack on the A–B–C ring



system would be then comparatively slow. In fact, osmylation of both model enol ethers in tetrahydrofuran proceeded smoothly within 2 hr at Dry Ice temperatures, giving diol which was characterized as osazone by treatment with Brady's reagent, while yohimbine itself was recovered in amounts greater than 50% after being subjected to similar conditions. acetate salt, away from the seat of thermal activity. The product was converted by action of aqueous carbonate to the free enol ether base, a noncrystalline material which exhibited the infrared absorption at 6.28 μ characteristic of Δ^2-dihydrofurans. The enol ether was reconverted to the lactol acetate on exposure to acetic acid at room temperature.

The olefinic bond in the cyclic enol ether system served as an admirable site for well-precedented oxidative degradation, and, again, the sequence osmium

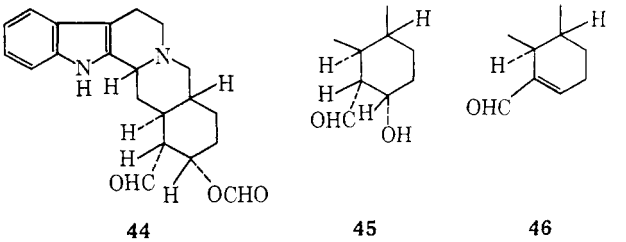


42 43

tetroxide–periodate oxidation was employed to advantage. Osmylation was carried out on the enol ether at −78° in tetrahydrofuran–pyridine. After the traditional treatment with hydrogen sulfide in ethanol–methylene chloride, the light tan osmate ester was converted to the diol **43**, the infrared spectrum of which was in keeping with the assigned structure.

Although up until this point the heterocyclic appendage on ring E possessed ample stability, the further oxidation degradation planned would involve β-hydroxycarbonyl intermediates, types prone to either elimination to undesired α,β-unsaturated carbonyl compounds or reverse aldol-type opening of the E ring. These potential difficulties were compounded by the need for generation at some point of a C_{16}-carbomethoxy function, the generation of which requires, again, a selective oxidation in the presence of the sensitive indole region. The successful confrontation of these problems is recounted in the final portion of the synthesis description.

Metaperiodate cleavage of the 1,2-glycol **43** proceeded along formal lines, affording the O-formate of pseudoyohimbaldehyde (**44**). Careful extraction of a solution



44 45 46

basic with aqueous sodium carbonate permitted isolation of this β-acyloxy aldehyde, whereas treatment under more drastically basic conditions led to loss of formate ester with apparent formation of β-hydroxyaldehyde **45** and α,β-unsaturated aldehyde **46**. Infrared spectral analysis of aldehyde **44** revealed the presence of indole N–H (2.90 μ), aldehyde C–H (3.65 μ), aldehyde

Thus, success of the osmylation step in the actual synthesis seemed assured.

(18) G. D. Meakins, *J. Chem. Soc.*, 4170 (1953); D. A. Barr and J. B. Rose, *ibid.*, 3766 (1954); R. Nahum, *Compt. Rend.*, **240**, 1898 (1955).

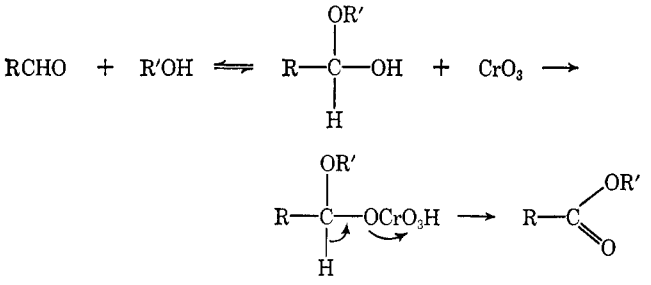
(19) C. Glacet, *Ann. Chim.*, [12] **2**, 293 (1947).

and formate carbonyl (~5.8 μ, strong), and formate ester (8.58 μ).

With the lithium aluminum hydride reduction of pentacyclic aldehyde **44–45**, a definitive point in the synthesis was reached: there was obtained *dl*-pseudoyohimbyl alcohol, identical by infrared spectral comparison with authentic material prepared by similar reduction of natural pseudoyohimbine.[20] Thus, at this stage, the gross structure and stereochemistry of the synthetic material were established, and completion of the program could be approached with confidence.

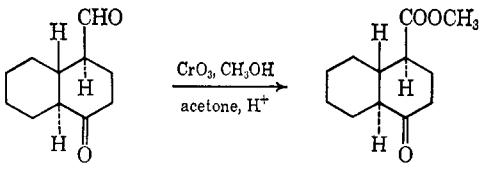
With a pseudoyohimbaldehyde derivative in hand, the need for a dependable, selective method for aldehyde oxidation became crucial. This requirement had been anticipated and model oxidation studies had already been initiated at the time the total synthesis had reached this point. In various cases, the behavior of a given oxidizing agent was tested by subjecting a mixture of yohimbine and a representative aldehyde, such as saturated keto aldehyde (**11b**), to its action. In such experiments, the following reagents were shown to be unsuitable: manganous acetate–air; trimethylamine oxide, with and without ferric oxide; 30% hydrogen peroxide; mercuric acetate; and silver oxide. In all except the last two cases, yohimbine was recoverable, but oxidation of aldehyde to acid did not occur. With silver oxide, aldehyde oxidation did proceed but yohimbine or yohimbic acid could not be recovered.

Ideally, the oxidation sought should lead directly from starting aldehyde to final natural product, *i.e.*, the methyl ester of the carboxylic acid. A device for accomplishing just this change was conceived, based on the anticipated susceptibility to oxidation of *hemiacetal* existing when an aldehyde is dissolved in an alcohol.



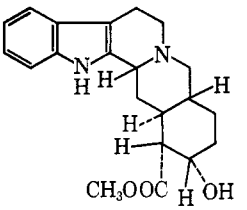
47

With chromic anhydride, the hemiacetal should be convertible to a chromate ester (**47**) which, by reason of the electron-contributing ether linkage, should undergo, with exceptional ease, loss of the inorganic entity in the usual fashion to generate a carbonyl function, in this case part of an ester group. The concept was tested in a model case, Jones oxidation of keto aldehyde **11b** in



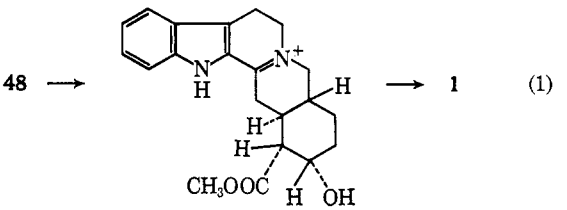
11b 16

acetone–methanol solution; keto ester **16**, as hoped, was formed. Moreover, since yohimbine could be isolated after subjection to Jones oxidation conditions, the new oxidation procedure seemed suitable for the alkaloidal case at hand. In this final operation, the crude periodate product dissolved in methanol–acetone was treated at 0° with chromic anhydride (2.0–3.5 equiv) in sulfuric acid for 30 min. The neutral product, after being heated in methanol for 2 hr to remove the formyl group, was subjected to alumina chromatography with chloroform, chloroform–methanol, and methanol. By such means, yields of 5–15% crude *dl*-pseudoyohimbine **48** were obtained. After crystallization from methanol the racemate melted at 252–256° and exhibited in solution an infrared spectrum identical



48

with that of authentic pseudoyohimbine.[21] Resolution of the synthetic base was accomplished by means of *l*-camphorsulfonic acid, which gave a salt (mp 274–278°) identical with the *l*-camphorsulfonate (mp 276–278°) of natural *d*-pseudoyohimbine (mixture melting point undepressed and infrared spectra identical). The regenerated, optically active synthetic base was identical with natural *d*-pseudoyohimbine, on the basis of melting point, optical rotation, and infrared spectral compar-



(1)

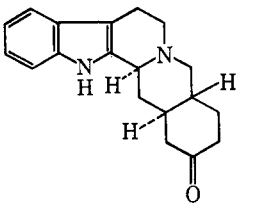
ison. Since pseudoyohimbine already had been epimerized to yohimbine (eq 1),[22] the steps described constitute the total synthesis of the latter alkaloid.[23]

(20) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958).

(21) (a) P. Karrer and H. Salomon, *Helv. Chim. Acta*, **9**, 1059 (1926); (b) P. Karrer and P. Enslin, *ibid.*, **32**, 1390 (1949); (c) M.-M. Janot, R. Goutarel, and M. Amin, *Compt. Rend.*, **230**, 2041 (1950).

(22) W. O. Godtfredsen and S. Vandegal, *Acta Chim. Scand.*, **10**, 1414 (1956).

(23) In view of the continuing, occasionally articulated,[24] doubt regarding the veracity of the yohimbine synthesis reported in 1957 by Preobrazhenskii and coworkers,[25a] we wish to place on record results



63

gathered in this laboratory while studying the essential, critical step reported by the Russian group, namely, the carboalkoxylation of yohimbone (**63**).[25b]

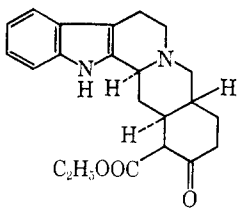
Preobrazhenskii, *et al.*, stated[25a] in their 1957 communication that the carboethoxylation reaction generated keto ester **64** ("in 60% yield"). Since yohimbone had been previously synthesized by Swan,[26] reduction of the keto carbonyl group in **64** to axial hydroxyl group and transesterification had only to be accomplished in order to complete the total synthesis of the alkaloid. This latter sequence was in fact also claimed by the Preobrazhenskii group. The key step, *i.e.*, conversion of yo-

Experimental Section

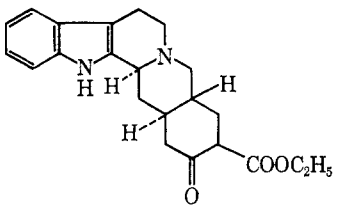
Melting points and boiling points are uncorrected. Ir spectra were measured on Perkin-Elmer Infracord spectrophotometers, and uv curves were recorded on a Cary spectrophotometer. Elemental analyses were carried out by Spang and Huffman analytical laboratories and in the microanalytical laboratories of the University of Wisconsin. All compounds are racemic unless otherwise indicated.

p-**Benzoquinone–Butadiene Adduct.** This substance was conveniently prepared in a larger scale preparation as follows: 500 g

himbone to material of structure **64**, was, however, in the minds of many, suspect, in that both steric considerations as well as expected (based on



64



65

the *trans*-β-decalone system) direction of enolization in the *trans*-fused D–E ring system are factors that would direct entry of the carboethoxyl group into the 18 rather than the 16 position and thus lead to formation of the isomeric keto ester (**65**). In our experience, it is the 18-keto ester (**65**) that is formed as the only detectable product under conditions which duplicate as closely as possible those described by the Russian school.

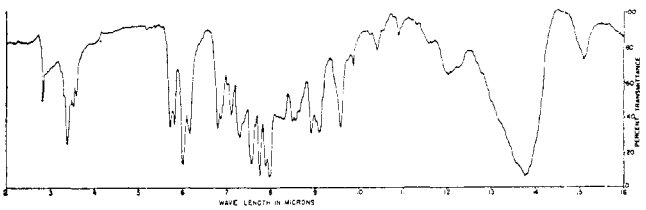


Figure 1. Ethyl ester of yohimbone-18-carboxylic acid (**65**) ($CHCl_3$ solution).

According to the Russian report functionalization was achieved "by treating yohimbone with a large excess of diethyl carbonate while stirring for 3–4 days at room temperature. After this time no more yohimbone remained; the solvent was removed *in vacuo;* the condensation product was worked up, and the sodium salt of the enol was decomposed by acetic acid. The precipitate was extracted with chloroform. The ethyl ester of yohimbone carboxylic acid (**64**) was secured as a yellowish crystalline material, mp of crude base of 98–105°, in 60% yield. Hydrochloride, mp 241–243° (from 70% ethanol).

"The ethyl ester of yohimbone carboxylic acid (**64**) was catalytically hydrogenated in anhydrous methanol with platinum oxide at 35–40° and 80 atmospheres. The reduction product gave no color with ferric chloride solution. The yield of ethyl ester of yohimbic acid was 93%, mp 178–184° (dec) (from 60% ethanol). Hydrochloride, mp 275–280° (dec) (recrystallized many times from 70% ethanol). This hydrochloride is identical with the hydrochloride of the ethyl ester of yohimbic acid obtained by saponification of the natural alkaloid yohimbine with potassium carbonate in 70% methanol, with subsequent esterification with ethanol. Mp of hydrochloride 279–281° (dec) (from 70% ethanol). The mixed mp of the hydrochlorides of the ethyl esters of natural and synthetic yohimbic acids did not depress, mmp 277–280° (dec).

"The natural alkaloid yohimbine appears as the methyl ester of 16α-carboxy-17α-hydroxyyohimbane. Therefore we carried out the conversion of the ethyl ester of 16-carboxy-17-hydroxyyohimbane to the methyl ester. With this objective in mind, the ethyl ester of the synthetic β-hydroxy acid was completely dissolved in a solution of potassium carbonate in 60% methanol, and the acid was isolated, mp 245–249° (dec) (recrystallized from water). Subsequently esterification of the β-hydroxy acid was carried out in methanol by saturation with hydrogen chloride, and we thus obtained the hydrochloride of the methyl ester of yohimbic acid. This compound was purified by neutralization with base (aqueous ammonia), converted to the tartrate (alcoholic solution of (+)-tartaric acid) and again neutralized (aqueous ammonia), followed by crystallization from 70% ethanol. The methyl ester of yohimbic acid existed as needles, mp 234–236.5° (dec) (sinters 226°). The hydrochloride, mp 299–302° (dec) (sinters 294°). The mixed mp with natural hydrochloride was 298–300°."

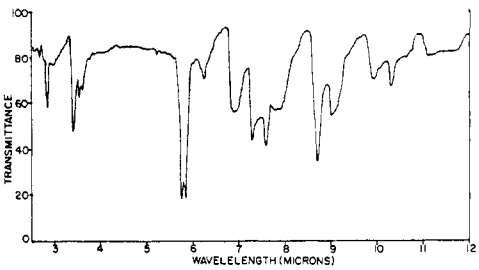
Although the reaction conditions employed by the Russian workers were sketchily described, we endeavored to parallel their experiences as closely as possible. Toward that end, the following series of experiments was carried out.

A successful reaction was run with yohimbone, sodium hydride, and a large excess of diethyl carbonate in tetrahydrofuran. Chromatography of this reaction product yielded one crystalline product (A) in 30% yield. Compound A analyzed as a carboethoxylated yohimbone ($C_{22}H_{26}O_3N_2$), and had mp 182.5–184° dec. Unlike yohimbinone and an authentic sample of the ethyl ester of 16-carboxy-17-ketoyohimbine,[27] compound I showed considerable concentration-dependent enolization in its infrared spectrum in chloroform.

Further carboalkoxylation experiments, in which the reaction conditions were changed to duplicate more nearly the conditions implied in the Russian paper, were carried out. Unless a large ratio of base to yohimbone was used, starting material was recovered with no indication of ester carbonyl or enolized β-diketone absorption in the infrared spectrum of the reaction product. Although yohimbine has limited solubility in dimethyl carbonate and diethyl carbonate, the reaction of yohimbone in diethyl carbonate with sodium hydride as a base did give one crystalline compound after chromatography. This product proved to be identical with the keto ester obtained by carboethoxylation of yohimbone with diethyl carbonate and sodium hydride using tetrahydrofuran as a solvent. In the same manner, chromatography of the product from a carboalkoxylation reaction using yohimbone, diethyl carbonate, and sodium ethoxide again yielded only compound A as a pure, crystalline substance.

In every case, attempts to crystallize or identify the tarry dark brown fractions coming off the column after the crystalline fractions failed. Every attempt to find either starting material or another crystalline carboethoxylated product was unsuccessful.

An *authentic* sample of the ethyl ester of 16-carboxy-17-ketoyohimbane (**64**) was prepared by oxidation of ethyl yohimbate. Compound **64** had mp 248–250° dec, and its infrared spectrum was clearly different from that of synthetic compound A. The most striking difference between compound A and keto ester **64** was noted in the carbonyl and double bond (enolic) region of the infrared spectrum. The synthetic compound A had bands at 5.75, 5.84 (β-keto ester ketonic absorption), 6.03, and 6.18 μ (enolic β-diketone absorption). The relative strength of these bands could be varied by changing from a 1% to a 7% (saturated) solution in chloroform at room temperature. On the other hand, yohimbinone and an authentic ethyl ester of 16-carboxy-17-ketoyohimbine (**64**) showed no change in their spectra with dilution—both samples (yohimbinone and compound **64**) have strong absorption bands at only 5.73 and 5.82 μ, regardless of concentration in chloroform. The "fingerprint regions" of compound A and of compound **64** in the infrared differed greatly. Compound A has what would be considered a normal indole ultraviolet spectrum. Inasmuch as compound A showed marked enolization and neither yohimbinone nor the corresponding ethyl ester showed any enolization at all, the former would appear to be the ethyl ester of 18-carboxy-17-ketoyohimbine (**65**).



The second step of the Russian synthesis involved reduction of the carboethoxylation product by high-pressure hydrogenation. Reduction of compound A, using the method employed by the Russian workers, yielded a product displaying a single carbonyl absorption in the infrared region. The substance behaved on chromatography as a pure material. Since recrystallization of the peak fractions proved difficult, the hydrochloride salt of the reduction product was prepared and recrystallized from ethanol–water to give material of mp 302–303° dec. An authentic sample of ethyl yohimbate,[27] mp 190–191.5° dec, was converted to the corresponding hydrochloride salt which had mp 301–303° dec. The mixture melting point of the hydrochloride salts was *depressed* to 292–297° dec. Infrared spectra of the two hydrochloride salts (taken as KBr pellets) proved the compounds *to be different*, in that they showed similar absorptions for all the major functional groups, but very different fingerprint regions.

In further attempts to find a true yohimbine derivative arising from the carboalkoxylation of yohimbone followed by reduction, one sample of starting material was carried through the carboethoxylation process without purification of product (the material could not be crystallized from ethanol–water), and was subjected as such to reduction. Chromatography of the product again revealed only one peak in fractions which were crystalline, tailing into resinous tars. The infrared spectrum of each of these fractions (totaling a 7.8% yield from yohimbone) was *not* identical with the infrared spectrum of ethyl yohimbate.

of *p*-benzoquinone (Practical) was placed in a 5-l. round-bottomed flask, 3500 ml of benzene added, and the mixture cooled to 0° in an ice bath. A 500-ml charge of freshly distilled and condensed (acetone–Dry Ice) butadiene was then rapidly introduced (best in two equal portions), and the flask tightly closed with a rubber stopper securely wired in place. After warming to room temperature (22–28°) the reaction mixture was set aside for 2–3 weeks with occasional shaking during the first week to facilitate solution and reaction of the partially soluble quinone. At the end of the specified period the dark mixture was treated with Norite, filtered through Filter Cel, the solvent removed under reduced pressure on the steam bath and the product crystallized from petroleum ether (bp 60–68°) and a small quantity of benzene as pale yellow (sometimes green) clusters of needles: mp 52–54°; yield 650–700 g (87–93%).

Dihydro Adduct (7). By a modification of the original method[8] for the reduction of the above adduct to the dihydro adduct (**7**), satisfactory and reproducible results were obtained. To a very rapidly and efficiently stirred solution of 300 g of quinone–butadiene adduct in 1000 ml of 95% acetic acid contained in a 5-l. three-necked flask fitted with a thermometer and immersed in a good water–ice bath, 5-g portions of zinc dust were slowly added, with care being taken to keep the reaction temperature in the range 30–50°. The addition was discontinued when the temperature ceased to rise as further quantities of zinc were added (30–40 min required using *ca.* 125–150 g of zinc dust). Further small quantities of acetic acid (100–300 ml) occasionally were required during the reduction to keep the product in solution and the reaction mixture sufficiently fluid. After completion of the reduction 1000 ml of acetone was added, and stirring was continued at room temperature for an additional 5 min. The reaction mixture was then filtered under vacuum with the aid of Filter Cel, the filter cake of zinc salts and excess zinc being washed carefully with two 300-ml portions of acetone. The nearly colorless (or slightly yellow) filtrate was then concentrated rapidly under reduced pressure on the steam bath, and the product (**7**) recovered from the residue by either of the following alternative procedures.

A. By Chloroform Extraction. The residue was taken up in 1 l. of chloroform which was extracted successively with two 500-ml portions of water and two 300-ml portions of 5% sodium bicarbonate solution (color partially removed), and finally dried over magnesium sulfate and Norit. After filtration and removal of the solvent *in vacuo* on the steam bath, the dihydro adduct was obtained as a white crystalline mass on slowly stirring the hot residue into excess ether; the yield of collected and air-dried product was 230–250 g (76–83%), mp 100–104°.

B. By Direct Crystallization. The still hot residue was poured slowly into 800 ml of distilled water with vigorous stirring to yield the dihydro adduct directly as a pale cream colored crystalline deposit, which, after cooling, collecting by filtration, washing, and drying, weighed *ca.* 280 g (93%), mp 95–102°. These crude preparations of dihydro adduct were found to be suitable for the glycidic ester condensation described below.

Diastereomeric Ethyl β-(4-Keto-1,2,3,4,5,8,9,10-octahydronaphthyl-1)-glycidates (9). A solution of 98.4 g (0.6 mole) of diketone **7** and 86.4 g (0.7 mole) of ethyl chloroacetate in 2.5 l. of dry benzene was placed in a 5-l. three-necked round-bottomed flask equipped with a dropping funnel and an efficient stirrer. The solution was cooled in an ice bath while a solution of 0.62 mole of potassium *t*-butoxide in 700 cc of dry *t*-butyl alcohol was slowly added over a period of 4 hr with constant stirring. After the addition was completed, the solution was stirred for 1 additional hr and then allowed to stand overnight at room temperature. The reaction mixture was then filtered and the precipitate discarded. The benzene and *t*-butyl alcohol were distilled off under reduced pressure, and the remaining dark oil was taken up in 350 cc of ether and 350 cc of water. The ether layer was separated and evaporated down on a steam bath, and the remaining oil distilled between 150 (0.25 mm) and 180° (1.8 mm) to give 121 g (81%) of a yellow oil, $n^{25}D$ 1.5090.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.56; H, 7.56.

In distilling the product, a *crystalline* forerun (bp 105–120° (0.05 mm) or 10–130° (0.1 mm)) could be collected separately from the main fraction (bp 120–140° (0.03 mm) or 135–155° (0.1 mm)), which crystallized much more slowly and only on standing. In a typical run commencing from 164 g (1.0 mole) of the above crude dihydro adduct, the forerun fraction weighed 10–15 g, and on recrystallization from benzene–petroleum ether furnished a recovery of 5–8 g of the *trans*-dihydro adduct (mp 92–94°). The weight of the main fraction weighed 165–180 g, which, if assumed to be entirely the desired glycidic ester, corresponds to a yield of 71–77% from **7** consumed in the condensation reaction.

Glycidic Acid Mixture 10a–b. To 100 g (0.40 mole) of glycidic ester **9** in a 1-l. erlenmeyer flask a freshly prepared, hot solution of 30 g of sodium hydroxide in 160 ml of hot water was added all at once, with stirring, and with a slow stream of nitrogen blowing over the neck of the flask during the hydrolysis (oxygen exclusion is critical). The two-phase reaction was then allowed to proceed on the steam bath for 0.5 hr, with occasional stirring. After 15 min the oily upper layer of unreacted ester had completely disappeared, leaving a homogeneous light yellow or tan solution. After completion of the reaction the mixture was cooled to 5° in an ice bath; with the nitrogen stream continuing, 250 ml of ether was added, finally the aqueous phase was slowly neutralized to pH 2 with ice cold 6 *N* hydrochloric acid. The liberated acid largely dissolved in the ether layer to produce a light yellow solution and then slowly deposited as a white crystalline product at the interface while the lower aqueous phase became almost colorless. After standing overnight at 0° the copious mass of product was collected in a Büchner funnel and washed three times with cold water and twice with 150-ml portions of ether cooled to −30°. After drying at 60° for 2 hr and then overnight in a vacuum desiccator, the nearly colorless glycidic acid product (**10**) weighed 70–75 g, corresponding to yields of 79–87% in the hydrolysis. The melting point of the acid prepared in this manner (mixture of isomers) was 140–148°.

Separation of the Diastereomeric Ethyl β-(4-Keto-1,2,3,4,5,8,9,10-octahydronaphthyl-1)-glycidates 9a–b and the Glycidic Acids 10a–b. To a solution of 20 g (0.08 mole) of glycidic esters in 20 cc of acetone was added enough water to make the solution just cloudy. The mixture was then cooled in ice, scratched, and allowed to stand in the refrigerator overnight. On the next day, 6.5 g of colorless crystals, mp 72–85°, was filtered off; the mother liquor was set aside. The crystals were recrystallized five times from light petroleum ether to give 4.45 g of colorless crystals, mp 91.5–91.7° (glycidic ester **9a**).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.50; H, 7.11.

The hydrolysis of the pure glycidic ester **9a** was accomplished by dissolving 4.1 g (0.0164 mole) of the ester in a little over an equivalent amount of 0.5 *N* aqueous sodium hydroxide and heating over a steam bath for 15 min under nitrogen. The solution was then cooled and made definitely acidic with hydrochloric acid. The oily acid soon crystallized; it was collected by filtration and then washed with ether and petroleum ether. The colorless crystals (glycidic acid **10a**) obtained weighed 2.85 g (78%), mp 138–140° dec.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.06; H, 6.56.

To the mother liquor from crystallization of glycidic ester **9a** there was added excess 0.1 *N* sodium hydroxide. The mixture was heated for 15 min, then cooled and acidified with dilute hydrochloric acid. The oil thus obtained solidified on cooling. The

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An authentic sample of the ethyl ester of 16-carboxy-17-ketoyohimbine (**64**) was subjected to carboethoxylation conditions with sodium ethoxide and diethyl carbonate. More than 75% starting material was recovered by recrystallization of the reaction product, thereby demonstrating that the desired carboalkoxylation product, if formed, should survive the reaction conditions. This material is eluted from alumina with 20% benzene–80% chloroform, and is eluted from a silicic acid column with chloroform. If compound **64** were present in the carboethoxylation product in any reasonable amount, it should have been eluted many fractions before the point at which tarry material starts to come off the column. However, no evidence was ever obtained for the presence of such a product in the chromatography fractions from the carboalkoxylation of yohimbone.[28,29]

(24) (a) J. E. Saxton, *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **55**, 306 (1958); (b) P. D. Pacht, Ph.D. Thesis, Harvard University, 1960.

(25) (a) L. A. Aksanova and N. A. Preobrazhenskii, *Dokl. Akad. Nauk SSSR*, **117**, 81 (1957). (b) All translations from the Russian in this section were made by Dr. Marvin Melcher.

(26) G. A. Swan, *J. Chem. Soc.*, 1534 (1950).

(27) Prepared by Jones oxidation of the ethyl ester of yohimbine, which was made by Fischer esterification of yohimbic acid [E. Field, *ibid.*, **123**, 3003 (1923)]. *Cf.* E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959).

(28) After the completion of this carboalkoxylation study, J. D. Albright, L. A. Mitscher, and L. Goldman [*J. Org. Chem.*, **28**, 38 (1963)] reported like conclusions on the basis of related condensations of alkyl magnesium carbonate, dialkyl formate, and oxalate with yohimbone.

(29) This portion is taken in part from the M.S. Thesis (University of Wisconsin, 1960) of R. R. Shaffer.

solid material was filtered off and was repeatedly washed with acetone and finally recrystallized from methanol to give 2.6 g of colorless crystals of glycidic acid **10b**, mp 210–211° dec (softening at 206°).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.51; H, 6.27.

Decarboxylation of Pure β-(4-Keto-1,2,3,4,5,8,9,10-octahydronaphthyl-1)-glycidic Acid 9a. A 2.8-g (0.0126 mole) fraction of glycidic acid **9a**, mp 138–140° dec, was ground into a very fine powder and mixed intimately with 0.28 g of copper powder. The sample was then heated at 150° for 0.5 hr, care being taken to pass a current of nitrogen over the reaction mixture while heating. The mixture was then distilled to give 1.10 g (49%) of oily keto aldehyde **11**: bp 118–121° (0.2–0.4 mm); $n^{25}D$ 1.5183.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.08; H, 7.69.

Decarboxylation of Pure β-(4-Keto-1,2,3,4,5,8,9,10-octahydronaphthyl-1)-glycidic Acid 9b. A 1.9-g (0.0086 mole) fraction of glycidic acid **9b**, mp 210–211° dec, was ground into a very fine powder and mixed intimately with 0.19 g of copper powder. The sample was then heated at 220° for 0.5 hr, again while nitrogen was passed over the reaction mixture. Distillation gave 0.56 g (37%) of a yellow, oily keto aldehyde **11**: bp 124–134° (0.2–0.4 mm); $n^{25}D$ 1.5230.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.35; H, 7.55.

The ir spectra of the aldehyde samples from **10a** and **10b** were indistinguishable.

Unsaturated Keto Aldehyde (11). The thermal decarboxylation of glycidic acid (**10**) to the unsaturated keto aldehyde (**11**) was found to proceed most smoothly and cleanly in hot diethylene glycol. To a 100-ml round-bottomed flask containing 22.2 g (0.10 mole) of starting acid and 2 g of copper powder as a catalyst, 40 ml of commercial diethylene glycol (Dow Chemical Co.) was added, an air condenser attached, and the contents were heated in a bath at 155–160°. The acid dissolved rapidly on warming, and a copious evolution of carbon dioxide commenced when the temperature approached 155°. After 1.5–2 hr gas evolution became very slow and the reaction mixture was cooled to room temperature, poured into 100 ml of water, and the product recovered by thorough extraction with three 100-ml portions of chloroform. The combined chloroform extracts were washed twice with 100-ml portions of water and then concentrated under reduced pressure on the steam bath. The residue was taken up in 30 ml of hot alcohol, and 3 *N* hydrochloric acid was added until the solution became slightly opaque. Heating on the steam bath under reflux was continued for 1 hr, after which the product was recovered by chloroform extraction as before. (Omission of this acid treatment resulted in greatly diminished yields of pure product, apparently as a result of the presence of hemiacetals or acetals from the diethylene glycol.) After drying the final combined chloroform extracts over magnesium sulfate, the solvent (after filtration) was removed under reduced pressure on the steam bath and the residue distilled under high vacuum to yield as a single major fraction 12.5–13.5 g (70–76%) of the pale yellow unsaturated keto aldehyde **11**: bp 107–109° (0.01 mm): $n^{25}D$ 1.5223.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.16; H, 8.14.

The bisphenylhydrazone of **11**, mp 171–173°, formed ivory colored needles from ethanol, but it decomposed too rapidly on standing to be suitable as a good derivative. The bisoxime, secured in 80–85% yields, crystallized from alcohol as stable white needles, mp 171–173°. After recrystallization from ethanol–ethyl acetate, the dioxime was obtained pure, melting at 175.0–175.5°.

Anal. Calcd for $C_{11}H_{16}O_2N_2$: C, 63.44; H, 7.75. Found: C, 63.62; H, 7.45.

With keto aldehyde prepared by the copper-catalyzed pyrolysis of glycidic acid mixture, the isomerization and dioxime formation observations given in Table I were made.

Table I

Keto aldehyde 11	Aldehyde, mg	Dioxime, mg	Yield, %	Mp, °C
Acid epimerized	540	511	81	171–173
Base epimerized	536	448	71	165.5–170.5
Unepimerized	770	493	55	145–155

Unsaturated Keto Acetal (12). From the decarboxylation of 20 g (0.090 mole) of the glycidic acid mixture **10** with 2 g of copper powder in redistilled trimethylene glycol under the same conditions as above, there was obtained by chloroform extraction, but without use of acid, a viscous product which on distillation at reduced pressure (0.05 mm) furnished fractions boiling at 90–120° (A), 120–130° (B), and 130–155° (C). A and B, weighing 5.5 g combined, appeared to be mixtures of the glycol and the desired keto aldehyde (V); C, weighing 9.5 g, afforded 6.5 g of the crystalline unsaturated keto acetal **12**, mp 114–116°, raised to 115.5–116.5° on recrystallization from benzene–petroleum ether. Vigorous acid hydrolysis of this material under conditions described above resulted in 90% yields of the unsaturated keto aldehyde.

Hydroxylation of this unsaturated keto acetal by aqueous potassium permanganate in acetone solution at low temperatures under a wide variety of reaction conditions furnished the corresponding ketol (**13**), mp 168–170°, in maximum yields of about 25%. In a typical experiment, 1.2 g (5 mmoles) of acetal **12** was dissolved in 125 ml of acetone, and the solution cooled to −10°, 10 ml of 20% aqueous magnesium sulfate (buffer) was added, and 0.8 g (5 mmoles) of potassium permanganate, dissolved in a minimum volume of water, slowly mixed in with efficient stirring. The reaction was then allowed to proceed until the permanganate color was completely discharged. Usually a period of 4–6 hr was required for this change, at the end of which time the precipitated manganese dioxide was removed by filtration and the filtrate concentrated under reduced pressure on the steam bath. During this operation varying amounts of the starting material (**12**) crystallized out; and, after its removal by filtration, the concentrated aqueous residues were extracted with chloroform to recover the hydroxylation product **13**. The yield was 0.40 g; on recrystallization from ethyl acetate the yield dropped to 0.25 g of material, mp 165–169°. Recrystallized for analysis this material deposited from the same solvent as fine needles, mp 168–170°. Product crystallized from ethyl acetate melted at 174–175°.

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.57; H, 7.52.

The oxidation product was shown to be a ketol by (i) its utilization of 2 equiv of hydrogen in ethanol under platinum catalysis, (ii) a positive Tollens test (when heated), and the presence of intense carbonyl absorption at 5.83–5.90 μ (two carbonyl groups).

Reduction of the ketone carbonyl function in **12** through the agency of lithium aluminum hydride or sodium in alcohol afforded the liquid, unsaturated hydroxy acetal, which was purified by chromatography on alumina and then converted to a solid 3,5-dinitrobenzoate, crystallized as fine needle clusters, mp 176–177°, from benzene–petroleum ether.

Anal. Calcd for $C_{21}H_{24}O_8N_2$: C, 58.83; H, 5.59. Found: C, 58.08; H, 5.59.

***trans*-1,4-Diketo-1,2,3,4,5,8,9,10-octahydronaphthalene.** A 1-g sample (0.0062 mole) of the pure *cis* isomer **7** (mp 100–102°) was dissolved in 50 ml of ether and added to a solution of 2 g of sodium hydroxide (0.087 mole) in 50 ml of water, all under an atmosphere of nitrogen in a stoppered flask. The two phase system was stirred magnetically for 1 hr at room temperature. The ether layer was then separated and dried; and solvent was removed to yield 0.90 g of diketone, mp ~80°. Ir analysis indicated at least 95% of the *trans* isomer.

Three recrystallizations from petroleum ether (100–140°) yielded pure *trans* diketone, mp 94–94.5° (lit.[8] mp 95°).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.22; H, 7.26.

***trans*-1,4-Diketodecahydronaphthalene.** A 29-mg sample (0.000123 mole) of the above *trans*-diketone was dissolved in 10 ml of absolute ethanol and hydrogenated in the presence of 50 mg of 2% palladium on carbon, uptake 4.40 ml (calcd 3.96 ml). Filtration of the catalyst and removal of ethanol *in vacuo* yielded 22 mg of diketone, mp 116°. After one recrystallization from petroleum ether (60–68°), the melting point was raised to 119° (lit.[8] mp 122°).

***cis*-1,4-Diketodecahydronaphthalene.** A 3-g sample of *cis*-diketone **7** (mp 102°) was hydrogenated over palladium on carbon in methanol. Filtration and evaporation of the methanol gave 2.9 g of yellow oil, crystallization of which from petroleum ether (60–68°) provided 2.4 g of pure *cis*-diketone, mp 48–49° (lit.[8] mp 49–50°).

Epimerization of *cis*-1,4-Diketodecahydronaphthalene. The above *cis*-decalindione (0.3 g, 0.0185 mole) was warmed in excess acetic anhydride for 1 hr. The acetic anhydride was removed *in vacuo* and the residue taken up in petroleum ether (bp 100–104°). After cooling of the solution there was obtained 0.2 g of *trans*-

diketone, mp 116°. Recrystallization from petroleum ether raised the melting point to 118–119°. The mixture melting point of this product with the *trans* isomer prepared from reduction of *trans*-1,4-diketo-1,2,3,4,5,8,9,10-octahydronaphthalene was 118–119°.

1-Hydroxymethyl-4-hydroxyl-1,2,3,4,5,8,9,10-octahydronaphthalene. A solution of 5 g (0.0281 mole) of keto aldehyde **11** in 25 cc of dry ether was slowly added with efficient stirring into a suspension of 2 g (0.053 mole) of lithium aluminum hydride in 50 cc of ether. After the addition was completed, the stirring was continued for another 2 hr. At the end of this time, 5 cc of water was slowly and carefully added with slow stirring. When the effervescence had completely subsided, the precipitate was filtered off and washed with ether. The combined ether wash and filtrate were evaporated to leave a yellow, oily residue which was dissolved in three times its volume of acetone. The solution was then cooled in ice and scratched to give a colorless, crystalline precipitate which after repeated recrystallizations from acetone melted at 125–126°: yield 1.20 g (24%) of pure, crystalline enediol.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.14; H, 9.93.

The remaining oily material in the acetone mother liquors also analyzed approximately correctly for an enediol (C, 71.68; H, 9.83). However, it did not crystallize even after chromatography on silicic acid using chloroform as solvent and eluting with increasing proportions of methanol.

4-Ketodecahydronaphthalene-1-carboxaldehyde (11b). A 7.2-g sample (0.041 mole) of oily keto aldehyde **11a** dissolved in 95 cc of ethanol was hydrogenated at room temperature and pressure over 0.5 g of 10% palladium on carbon. Hydrogen (1 mole) was rapidly absorbed within the first half-hour. The catalyst was then filtered off, and the ethanol was removed by evaporation over a steam bath and under a current of nitrogen. The residue consisted of an oily keto aldehyde **11b**, $n^{25}D$ 1.5028, which was used in the subsequent steps in this series. For analytical purposes, a small sample of the material was sublimed at 150° (0.09 mm) to give an oil, $n^{25}D$ 1.5020.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 8.76.

Catalytic Reduction of 1-Hydroxymethyl-4-hydroxy-1,2,3,4,5,-8,9,10-octahydronaphthalene to 1-Hydroxymethyl-4-hydroxydecahydronaphthalene. A 0.182-g (0.001 mole) fraction of enediol, mp 125–126°, dissolved in 15 cc of ethanol was hydrogenated at room temperature and pressure over 0.03 g of 10% palladium on carbon. Hydrogen (1 mole) was rapidly absorbed within the first 20 min of the hydrogenation. The catalyst was then filtered off, and the ethanol removed by evaporation over a steam bath and under a current of nitrogen. A colorless oil was obtained which readily dissolved in 1 cc of acetone. Evaporation of the acetone by passing a current of nitrogen over the mixture gave a colorless, crystalline residue which was recrystallized from acetone to give 0.15 g (83%) of crystals, mp 111.5–112.5°.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.92. Found: C, 71.82; H, 11.07.

Unsaturated Keto Acid (15). Oxidation of the unsaturated keto aldehyde **11** to the corresponding acid **15** was achieved in *ca.* 35% yield by the action of silver oxide, using the following procedure. To a solution containing 18 g (0.10 mole) of **11** in 200 ml of ethanol and 40 g of silver nitrate previously dissolved in 80 ml of distilled water, 10% aqueous potassium hydroxide was added dropwise at room temperature with stirring, while a slow stream of nitrogen was passed through the system. The addition of the alkali was continued over 3–4 hr until the reaction mixture reached a pH of 11–12. Stirring under nitrogen was continued for an additional 6–8 hr with care being taken to maintain the pH as specified. The precipitated silver and unreduced silver oxide were then removed by vacuum filtration through Filter Cel, the filter cake was washed several times with hot 5% sodium carbonate solution, and the combined filtrates extracted several times with 200-ml portions of ether to remove unoxidized keto aldehyde (1.5–2 g, recoverable by distillation). Careful acidification of the aqueous phase with ice and 6 *N* hydrochloric acid, followed by thorough chloroform extraction, washing with water, drying, and removal of the solvent under reduced pressure, afforded the crude unsaturated keto acid (**15**) as a tan crystalline mass weighing 12–14 g. Direct purification by decolorization–crystallization procedures was unsuccessful. Distillation gave 10–12 g of a nearly colorless glass, bp 155–165° (0.05 mm), which on being dissolved in a minimum amount of hot benzene and petroleum ether (bp 60–68°) furnished, on standing, a copious deposit of fine, white crystals: mp 141–144°; yield 7–8 g (36–41%). Recrystallized from benzene–petroleum ether, these crystals melted at 146–147° and weighed 6.5–7.5 g, corresponding to an over-all yield of 33–38% of the pure acid **15** from the aldehyde.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.33; H, 7.23.

Isomeric crystalline acidic material was obtained from the mother liquors of **15** by esterification with methanol and distillation of the resulting ester, bp 120–125° (0.05 mm), followed by hydrolysis with 10% aqueous alcoholic sodium hydroxide. Crystallized from benzene–petroleum ether, this acid sample melted over the range 105–103° and showed little improvement on recrystallization, yield 2–2.5 g (10–13%).

By the action of ethereal diazomethane on acid **15** the corresponding crystalline methyl ester was obtained in 95% yield as rectangular prisms, mp 72.5–73°, when recrystallized from petroleum ether (bp 60–68°).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.94. The yellow *2,4-dinitrophenylhydrazone* of this keto ester formed small prisms, mp 174–175°, on recrystallization from benzene–petroleum ether.

Anal. Calcd for $C_{18}H_{20}N_4O_6$: C, 55.66; H, 5.19. Found: C, 56.00; H, 5.05.

Mild hydrolysis of the above unsaturated keto methyl ester by warming with 10% aqueous alcoholic potassium hydroxide under nitrogen afforded the original unsaturated keto acid **15**, mp 145–146°, in 80% yield. Attempted epimerization of the ester with hot sodium methoxide or ethoxide under nitrogen, followed by hydrolysis, led only to amorphous, ill-defined acidic products.

By means of lithium aluminum hydride in ether at room temperature a small sample (0.50 g) of the above unsaturated keto ester was reduced in fair yield (0.25 g, 55%) to the corresponding unsaturated diol, which crystallized from a small volume of acetone as fine needles, mp 123–125°, undepressed with the enediol prepared by reduction of the parent unsaturated keto aldehyde **11**.

Our methods for the oxidation of the unsaturated keto aldehyde to acid **15** were examined, but without much promise. Chromic acid in pyridine at room temperature afforded the desired product in less than 10% yield, while sodium dichromate in acetic acid furnished only a trace of the acid. Aerial oxidation in acetic acid at room temperature with manganous acetate as a catalyst provided the acid in 20% yield, but the procedure was developed only after the silver oxide method had been applied satisfactorily and was therefore not employed in the preparative sequence.

Saturated Keto Acid (16, R = H). Catalytic hydrogenation of 1.0 g of unsaturated acid **15**, using a 10% palladium-on-carbon catalyst in benzene solution, resulted in the uptake of 1 mole of hydrogen and the formation of 0.90 g of crystalline product (**16**, R = H), mp 14–150°, which recrystallized from benzene–petroleum ether as fine prism clusters, mp 154–156°.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.51; H, 8.28.

This same acid was obtained in 40% yield by the manganese acetate catalyzed air oxidation of the corresponding saturated keto aldehyde (similarly prepared from **11** by catalytic hydrogenation in benzene solution with 10% palladium-on-carbon catalyst).

The corresponding methyl ester (made by the action of diazomethane) crystallized from petroleum ether (bp 60–68°) as large, rectangular prisms, mp 66–67°.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.88.

When subjected to epimerizing conditions of sodium methoxide in absolute methanol, followed by hydrolysis, this ester reverted to the parent acid **16** (R = H), crude mp 153–155°, as the only isolable acidic product. On reesterification with diazomethane the same ester, mp and mmp 66–67°, was obtained.

Unsaturated Keto Amide (23). To a suspension of 9.70 g (0.05 mole) of the recrystallized unsaturated keto acid **15** (mp 145–146°) in 200 ml of anhydrous ether containing 1 drop of pyridine, 10 ml of oxalyl chloride (Kodak White Label grade) was added at 18–20° (hood), with swirling to facilitate reaction of the suspended acid. The reaction was protected from moisture and allowed to proceed (slow gas evolution) at room temperature for 6–8 hr with occasional shaking. The ether and excess oxalyl chloride were then removed *in vacuo* on the steam bath and the residue of crude acid chloride treated three times successively with 20-ml portions of dry benzene distilled off on the steam bath under partial pressure. After cooling to 10°, 20 ml of alcohol-free chloroform (prepared by shaking stock grade chloroform with concentrated sulfuric acid, followed by washing with sodium carbonate solution, and drying over magnesium sulfate) was added to the light tan residue; and the resulting solution of acid chloride added dropwise with efficient

stirring, over a 10-min period, to a solution of 9.0 g (0.055 mole) of tryptamine (mp 115–116°) in 50 ml of purified dry pyridine (distilled from calcium hydride) and 50 ml of the same chloroform, cooled to 5–10° in a water–ice bath. A fine light tan precipitate (presumably pyridine hydrochloride) appeared after the first few minutes of the addition, and then generally subsequently dissolved. After completion of this operation the flask was stoppered and placed in the refrigerator for 8–10 hr. The product was recovered by repeated chloroform extraction after the addition of 100 ml of water, followed by washing the chloroform layer with cold dilute (3 *N*) hydrochloric acid until the odor of pyridine was no longer detected (usually two or three times), then with dilute (10%) sodium carbonate solution, and water, and finally drying with magnesium sulfate and Norit. After filtration and removal of the solvent the unsaturated keto amide (**23**) crystallized readily and rapidly on the addition of hot ethyl acetate (40–50 ml) to the light yellow residue. The amide appeared as colorless, fine needle clusters, mp 159–162°, yield 12.5 g (75%). Recrystallized from alcohol–ethyl acetate, the product melted at 161–162° and weighed 11.5 g (69%). The ir spectrum showed carbonyl absorption at 5.85 and 6.10 μ.

Anal. Calcd for $C_{21}H_{24}O_2N_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.56; H, 6.82; N, 8.64.

When the amide preparation reaction was allowed to proceed for longer periods the product appeared to be somewhat altered in its physical properties and behavior on crystallization, although the ir spectra of the two preparations were indistinguishable. This isomeric product was somewhat more readily soluble in ethyl acetate and crystallized more slowly than the above material. It melted at 150–151°, and when mixed with the 161° material, melted at 153–158°. Recrystallization of the lower melting polymorph from ethanol–water gave the higher melting form. Conversely, recrystallization of the higher melting polymorph from pyridine–ether gave the lower melting form. The hydroxylation of 150–151° material by the procedure described below for the preparation of **25** gave a glycol product which did not recrystallize well and appeared to be impure *25*.

Anal. Calcd for $C_{21}H_{24}O_2N_2$: C, 74.97; H, 7.19. Found: C, 75.34; H, 7.45.

Other attempts to prepare the amide **23** from acid chloride generated by the action of thionyl chloride failed to produce any crystalline product. Efforts to condense tryptamine and the free acid directly by means of dicyclohexylcarbodiimide afforded inseparable mixtures of dicyclohexylurea and the desired amide product.

1-Hydroxymethyl-4,6,7-trihydroxydecahydronaphthalene (18). To a solution of 1.02 g (0.059 mole) of enediol **17** in 18 cc of formic acid was added 0.9 cc (0.008 mole) of 30% hydrogen peroxide solution ("Superoxol"). The mixture slowly warmed up on being shaken manually, but was kept at room temperature by cooling in an ice bath. After 0.5 hr the mixture was placed in an erlenmeyer flask equipped with a short neck and heated at 40° for 30–35 hr, at which point no more oxidizing agent was left in the reaction mixture (potassium iodide test).

The formic acid was then distilled off under reduced pressure, and to the remaining oil was added excess 3 *N* ethanolic potassium hydroxide solution. A colorless precipitate was obtained which was filtered out and discarded. The filtrate was refluxed for 1 hr and then cooled in an ice bath. Concentrated hydrochloric acid was then slowly added with cooling and shaking until the reaction mixture was definitely acidic. The solution was then cooled in ice and filtered, and the solvent in the filtrate was evaporated under reduced pressure. The oily residue remaining solidified on thorough drying under reduced pressure to an amorphous, off-white solid, which was powdered with a glass rod and taken up in acetone. After being repeatedly heated and cooled in acetone (with manual pulverization of any large solid mass formed) the product appeared as 1 g (83%) of a white, powdery tetrol (mp 170–175°), soluble in water, ethanol, and methanol, but insoluble in most other organic solvents.

To a solution of 0.4 g (0.00185 mole) of tetrol **18** in 5 cc of dry pyridine was added 5 cc of benzoyl chloride. The mixture was allowed to stand at room temperature for 0.5 hr. A 100-cc portion of 5% sodium bicarbonate solution was then added, and the mixture was stirred thoroughly and extracted with ether. If a precipitate formed in the ether layer at this point, it was filtered out and retained. The ether in the ether layer was evaporated over a steam bath and replaced with ethanol. On standing in the refrigerator, the solution deposited most of the tetrabenzoate. The precipitates from the ether and ethanol layers were combined and washed with ethanol to give 0.72 g (62%) of colorless crystalline tetrabenzoate, mp 184–184.5°.

Anal. Calcd for $C_{39}H_{36}O_4$: C, 74.03; H, 5.74. Found: C, 73.93; H, 5.71.

1-*p*-Tosyloxymethyl-4,6,7-trihydroxydecahydronaphthalene (19) and 1-Hydroxymethyl-4-*p*-tosyloxy-6,7-dihydroxydecahydronaphthalene (20). To a solution of 2.38 g (0.011 mole) of tetrol **18** in 35 cc of dry pyridine at room temperature was slowly added over a period of 45–60 min, with vigorous stirring, a solution of 2.15 g (0.011 mole) of *p*-toluenesulfonyl chloride in 15 cc of dry pyridine. After the addition was complete, the solution was allowed to stand at room temperature overnight. The pyridine was then distilled off under reduced pressure at a temperature no higher than 35°. When most of the solvent had been stripped off, 15 cc of chloroform and 15 cc of water were added. The mixture was cooled in an ice bath, and 6 *N* hydrochloric acid was added until the mixture became definitely acidic. The mixture was shaken manually for 5 min and then allowed to stand in the refrigerator for 2–3 days. At the end of this time, the colorless, crystalline precipitate was filtered off, and the 2.1 g of crude material was taken up in about 15 cc of boiling ethanol. After cooling of the solution to ice, the colorless crystals were filtered off; and this "washing procedure" was repeated until colorless crystals of the monotosylate **19**, mp 184–185°, were obtained (0.5 g, 14%).

Anal. Calcd for $C_{18}H_{26}SO_6$: C, 58.38; H, 7.08. Found: C, 58.55; H, 6.94.

When the ethanolic mother liquors were evaporated and the colorless crystalline residue was repeatedly recrystallized from ethanol, 0.14 g (4%) of tetrol tosylate **20**, mp 151–153°, was obtained.

Anal. Calcd for $C_{18}H_{26}SO_6$: C, 58.37; H, 7.08. Found: C, 58.05; H, 7.19.

1-Thiophenylmethyl-4,6,7-trihydroxydecahydronaphthalene. A 0.025-g (0.011 mole) sample of sodium was dissolved in 8 cc of ethanol and 0.16 g (0.0015 mole) of distilled thiophenol added. To this mixture was added a solution of 0.370 g (0.001 mole) of tetrol tosylate **19** in 5 cc of benzene and 3 cc of ethanol. After being refluxed for 2 hr, the reaction mixture was allowed to stand at room temperature overnight, and then poured into 30 cc of water and extracted three times with ether. The combined ether extracts were evaporated over a steam bath, leaving 0.320 g of colorless crystals, mp 154–159°. This material was washed carefully with ether and petroleum ether and then recrystallized from an ethanol and benzene mixture to give 0.235 g (76%) of colorless crystals of the thiophenyl ether of **18**, mp 163–164°.

Anal. Calcd for $C_{17}H_{24}SO_3$: C, 66.21; H, 7.85. Found: C, 65.14; H, 7.61.

A solution of 0.2 g (0.00065 mole) of the above thiophenyl ether in 30 cc of ethanol was refluxed over nitrogen with 2.5 g of Raney nickel for 1 hr. The reaction mixture was then cooled; the catalyst filtered off; and the ethanol evaporated over a steam bath. The residue was an oil which was soluble in ethanol, but insoluble in ether. On addition of 2 cc of ether and 2 drops of ethanol, and on letting the mixture stand overnight in the refrigerator, a colorless, amorphous solid, the crude triol, was obtained. This material was dissolved in methanol and the solution filtered; the filtrate was evaporated over a steam bath and the remaining oil dried under a vacuum overnight to give 0.065 g (50%) of a colorless, amorphous solid. A C-methyl determination gave a value of 3.76%, while the calculated value for one methyl group is 7.5%.

1-Aminomethyl-4,6,7-trihydroxydecahydronaphthalene. A mixture of 1 g (0.0027 mole) of tetrol tosylate **19**, 15 cc of pure dioxane, and 10 cc of liquid ammonia was heated in a sealed tube at 55° overnight. The tube was then cooled in Dry Ice and opened; the excess ammonia was allowed slowly to evaporate at room temperature. The precipitate was filtered off and repeatedly extracted (about six times) with dioxane saturated with ammonia; the combined dioxane washings were mixed with the original dioxane filtrate. Evaporation of this solution over a steam bath and under a current of nitrogen afforded a colorless, amorphous precipitate of trihydroxyamine, which was further purified by dissolving it in ethanol, filtering, and reevaporating the solvent. The colorless, solid residue still proved to be amorphous (0.485 g, 84%).

Anal. Calcd for $C_{11}H_{21}N$: C, 60.86; H, 9.73; N, 6.51. Found: C, 61.37; H, 9.83; N, 5.96.

The *p*-nitrobenzamide could be crystallized from ethanol as nearly colorless material, mp 224–225°.

Anal. Calcd for $C_{18}H_{25}N_2O_3$: C, 59.33; H, 6.64. Found: C, 59.58; H, 6.82.

Imine (21) of Keto Aldehyde 11a and Tryptamine. A benzene solution of 2.53 g of keto aldehyde **11a** and 2.27 g of tryptamine was

refluxed for 15 min with removal of water. Addition of petroleum ether brought down a dark tan oil. After the solvent was decanted and treated with Norit, the imine crystallized slowly from solution on standing in the refrigerator. Recrystallization from benzene–petroleum ether gave 1.05 g of imine **21**, mp 111.5–113.5°, displaying bands at 2.90 (indole NH), 5.90 (C=O), and 6.05 (C=N) in the ir and λ_{max} 291, 282, and 275 mμ (ε 5080, 5800, and 5500) in the uv.

Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.54. Found: C, 78.35; H, 7.36.

The imine was recovered from 10% phosphoric acid in methanol or water. Heating for 1 hr with 2 *N* hydrochloric acid in ethanol and cooling induced formation of a white solid, mp *ca.* 240°. The ir spectrum of this salt showed bands at 4.10, 5.9, and 6.4 μ, while the free base (mp 219–222°) lacked the imine band at 6.05 μ.

Attempted Reductions of Keto Amide 23. Prior to the direct hydroxylation of keto amide **23** to the keto glycol amide **25,** considerable effort was expended to reduce the amide function to the substituted tryptamine system as a model for subsequent work, but all attempts in this direction were unsuccessful. Excess lithium aluminum hydride in refluxing ether, tetrahydrofuran, dioxane, dioxymethylene, N-methylpiperidine, and dibutyl ether reduced the ketone carbonyl function but not the amide grouping. A somewhat impure sample of the resulting unsaturated *hydroxy* amide, crystallizing from ethanol–ethyl acetate as fine clusters, mp 195–197°, could be isolated in low yield.

Keto Diol Amide 25. To a magnetically stirred and Dry Ice cooled solution of 10.4 g (0.309 mole) of unsaturated keto amide **23** in 32 ml of dry pyridine and 40 ml of freshly dried and distilled tetrahydrofuran was added rapidly a solution of 8.0 g (0.315 mole) of osmium tetraoxide in 250 ml of freshly distilled tetrahydrofuran. After 2 hr, 1.5 l. of dry ether was added and the mixture was kept at −78° for 30 min to ensure complete precipitation of the osmium complex. The light brown solid was separated by filtration and washed thoroughly with ether. The complex was dissolved immediately in 700 ml of 1:1 ethanol–methylene chloride and hydrogen sulfide was passed vigorously into the solution for 90 sec. The resulting black solid was removed by filtration through Filter Cel. The light yellow to deep red-brown filtrate was treated briefly with hydrogen sulfide in order to ensure the complete destruction of the complex, and then the solvents were removed. The residue was boiled with 200–300 ml of ethanol, after which an insoluble grey powder was removed by filtration. Norit and 2–3 teaspoons of Raney nickel were added to the filtrate; after stirring for 1 hr, these materials were removed by filtration. The filtrate was concentrated rapidly, diol partly crystallizing on cooling. Ethyl acetate (50–75 ml) was added, and the mixture was kept overnight at 0° to give 5–6 g of diol, mp 218–220°. An additional 0.5–1.0 g was obtained by concentrating the mother liquors. It was convenient to add second crops to the crude product from another experiment and use only the first crop for the next stage of the synthesis. A series of seven experiments involving 59.8 g of keto amide gave 36.4 g (55.8%) of keto diol amide **25** and 7.46 g (11.3%) of insoluble isomer.

The keto diol amide crystallized from ethyl acetate–ethanol as fine clusters, mp 212–214°. The ir spectrum (KBr pellet) displayed pronounced associated hydroxyl absorption at 3.0 μ and carbonyl peaks at 5.85 and 6.1 μ.

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07. Found: C, 68.10; H, 7.15.

The insoluble isomer was dissolved in boiling dimethyl formamide; the solution was cooled, and ethyl acetate was added to give a solid showing mp 323–324° (chars 320°) and typical indole absorption at 222, 282, and 290 mμ in the uv. The ir spectrum (KBr pellet) exhibited associated hydroxyl absorption at 3.0 μ and carbonyl peaks at 5.85, 6.08, and 6.51 μ.

Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07. Found: C, 68.02; H, 6.98.

Triol Amide 26. Low-pressure catalytic hydrogenation of diol amide **25** at room temperature in ethanol solution, using Adams catalyst, resulted in the uptake of 1 mole of hydrogen in about 1 hr, with no further absorption. From the reduction of 2.0 g of the keto diol amide, 170 g (85%) of the triol amide (**26**), crystallizing as fine clusters from ethanol–ethyl acetate, resulted. On recrystallization these melted sharply at 227–228°; the ir spectrum had the intense associated hydroxyl absorption noted above for *25*, but had only a single carbonyl band, corresponding to the amide function, which appeared at 6.10 μ. The uv spectrum was typical for β-substituted indole derivatives, λ_{max}^{EtOH} 181, 189 mμ (ϵ_{max} 3900 and 3100, respectively).

Anal. Calcd for $C_{21}H_{28}O_4N_2$: C, 67.72; H, 7.58. Found: C, 67.76; H, 7.70.

When the reduction was conducted in the presence of acetic acid or with traces of mineral acid the neutral reduction product crystallized far less readily and appeared to contain difficultly removed impurities. Only small quantities (10–15%) of triol **26** were obtained pure.

Epimeric Triol Amide 27. To a solution of 305 mg of amide **25** in 100 ml of absolute ethanol, small pieces of sodium (2.0 g) were gradually added. At the end of this operation the reaction was cooled to 10° and carefully neutralized with 15 ml of 1:1 hydrochloric acid to pH 7–8. The inorganic salts were separated and the solvents removed. The residue was dissolved in ethanol and the solution was treated with Norit, filtered and concentrated to *ca.* 10 ml. Ethyl acetate (5 ml) was added, and the solution was kept at room temperature overnight. The sodium chloride which crystallized was removed; the solution was concentrated to 10 ml, and 5 ml of ethyl acetate was added. The fractional crystallization was continued; the fourth crop (130.5 mg) contained the desired triol amide. The triol was repeatedly recrystallized from ethanol–chloroform–petroleum ether and finally washed carefully with cold water to remove the last trace of sodium chloride. Another recrystallization from ethanol–chloroform–petroleum ether gave well-defined crystals, mp 224–226°. When mixed with a sample of triol amide **26** (mp 229–232°) a mp of 215–217° was observed. The ir spectra (KBr pellets) of the two triols displayed distinctly different patterns in the fingerprint region.

Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58. Found: C, 67.34; H, 7.65.

Lactol Lactam 32. To a solution of 1.60 g of triol amide **26** in 30 ml of 1:1 acetone–water heated to 60–70° was added in one lot a solution of 959 mg of sodium metaperiodate in 20 ml of water. After 20 sec, 9 drops of phosphoric acid was added and heating was continued for 20 min. The lactol lactam **32** generally began to crystallize within 2–3 min. Water (25 ml) was added, and the product was allowed to crystallize completely by standing at 0° overnight. Recrystallization from aqueous acetone afforded 1.0 g (60%) of colorless plates, mp 215–217° (capillary, rapid heat), λ_{max} 224, 283, 290 (ε 45,000; 7500, 6500, respectively). The ir spectrum displayed strong absorption at 3.0 μ and a single carbonyl peak at 6.18 μ. A negative response to the Ehrlich test was observed, in contrast to the strongly positive test produced with triol amide **26.**

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86. Found: C, 71.41; H, 7.04.

Lactol Lactam Methyl Ether 39. A solution of 1.0 g of lactol lactam **32** and 500 mg of *p*-toluenesulfonic acid in 150 ml of dry methanol was kept at room temperature for 3 days. The acid was neutralized with 25 ml of saturated sodium carbonate, and 200 ml of water was added to redissolve the inorganic salts which had precipitated. Standing at 0° for 3 hr resulted in precipitation of 0.8 g of fine needles, mp 160°, resolidifying and remelting at *ca.* 270°. Recrystallization from methanol–tetrahydrofuran gave fine needles, mp 269–270°, showing a single carbonyl peak at 6.18 μ, but lacking associated hydroxyl absorption at 3.0 μ.

Anal. Calcd for $C_{22}H_{28}O_3N_2$: C, 72.10; H, 7.15. Found: C, 72.18; H, 7.19.

Lactol Base 40 (R = H). To a magnetically stirred and refluxing solution of 3.0 g of lithium aluminum hydride in 50 ml of freshly dried and distilled tetrahydrofuran was added rapidly a solution of 2.5 g of lactol lactam methyl ether **39** in 150 ml of dry tetrahydrofuran. After being heated for 2–4 hr the mixture was cooled, and water was added carefully until a heavy gel formed. Additional water (1–4 ml) was added until the inorganic salts coagulated, and the mixture was stirred freely. The salts were removed by filtration and washed thoroughly with methylene chloride. The solvents were removed *in vacuo* to afford a colorless white foam which possessed no carbonyl absorption in the ir, and was therefore normally used directly in the next step. In order to purify the amine, it was evaporated down several times with methanol in order to remove traces of tetrahydrofuran, and then dissolved in methanol. On standing at 5°, the solution deposited large crystals, which after filtration and washing with methanol weighed 2.19 g. After fourfold recrystallization from methanol and drying at 80°, the amine melted at 133–137°.

Anal. Calcd for $C_{22}H_{28}O_2N_2$: C, 74.96; H, 8.01. Found: C, 74.17; H, 8.21.

Hydrochloric acid (160 ml, 1 *N*) was added to the product isolated above, and the mixture was heated on a steam bath for 3 hr under a vigorous stream of nitrogen. Filtration gave 1.2 g of hydrochloride

salt displaying absorption at 3.10 and 3.9 μ. The acidic solution was neutralized with aqueous sodium carbonate and extracted thoroughly with methylene chloride. Evaporation of the solvent afforded 617 mg of crude lactol base **41** (R = H).

The insoluble salt isolated as described above was dissolved under a vigorous stream of nitrogen in 30 ml of boiling methanol, and 7 ml of concentrated hydrochloric acid and 100 ml of water were immediately added. The methanol was removed and the solution was heated for 2 hr. Work-up as described above gave an additional 1.1 g of colorless lactol base (**41**, R = H).

These results were extremely difficult to reproduce, and the total amount of lactol base finally isolated varied from 1.0 to 1.8 g. The remainder of the organic material was accounted for as an intractable yellow solid, insoluble in all solvents. Attempts to recover lactol base from this yellow solid were unrewarding.

Enol Ether Base 42. A solution of 1.1 g of lactol base in 6 ml of acetic anhydride and 1 ml of pyridine was kept at room temperature overnight, and then the volatile materials were removed *in vacuo* below room temperature. The resulting acetic acid salt of the lactol base acetate was used without further purification.

The acetate was dissolved in 80–110 ml of methylene chloride; an aliquot (8–11 ml) was charged to a sublimer, and the solvent was removed. The sublimer was evacuated to a pressure of *ca.* 0.01 mm, and after 30 min it was plunged into a Woods metal bath maintained at 285–295°. Within 5–10 sec a white sublimate appeared on the sides of the cold finger and the pressure rose to 0.2–0.5 mm. The sublimer was removed from the Woods metal bath after 5 min and the sublimate was scraped from the sides of the cold finger. This process was repeated until the entire batch of acetate had been pyrolyzed. The total yield of sublimate varied from 220 to 740 mg. The ir spectrum of the sublimate displayed peaks at 2.93, 3.20, 5.80, 6.27, and 8.0–8.10 μ. The absorption at 3.20 μ disappeared, and the intensity of the 6.27-μ peak diminished when the product was washed with aqueous sodium carbonate, indicating that the enol ether was present as its acetic acid salt. The persistence of the band at 5.80 μ suggested the presence of an appreciable amount of unreacted acetate.

The enol ether was reconverted to the lactol base acetate on standing in acetic acid at room temperature, as evidenced by the reappearance of a strong band at 5.80 μ. Owing to the instability of the enol ether it was used immediately in the next step of the synthesis.

Pseudoyohimbaldehyde O-Formate 44. To a Dry Ice cooled solution of 780 mg of enol ether base **42** in 2.5 ml of dry pyridine and 25 ml of freshly distilled tetrahydrofuran was added 489 mg of osmium tetraoxide in 5 ml of tetrahydrofuran. The dark red solution was kept at −78° for 7 hr, and then dry ether was added. The light tan complex was recovered by filtration, washed thoroughly with ether, and dissolved in 200 ml of 1:1 ethanol–methylene chloride. Hydrogen sulfide was bubbled vigorously into the solution for 1 min and the black precipitate was removed by filtration. The solvents were evaporated, and the residue was taken up in methanol. The solution was filtered and the methanol removed to give 320 mg of crude diol.

To an ice-cold solution of 164 mg of the crude diol in 25 ml of methanol and 10 ml of water was added a solution of 99 mg of solution metaperiodate in 15 ml of water. The solution, protected from light, was kept at 0° for 2 hr, and then was extracted with carbon tetrachloride. The aqueous solution was carefully neutralized with aqueous sodium carbonate and extracted with methylene chloride. The solvent was removed to give 132 mg of crude aldehyde displaying typical indole absorption in the uv and ir peaks at 2.90 (indole NH), 3.65 (aldehyde CH), 5.8 (carbonyl), and 8.58 μ (formate ester deformation).

***dl*-Pseudoyohimbine 48.** A solution of 132 mg of freshly isolated *dl*-pseudoyohimbaldehyde O-formate in 5 ml of methanol and 30 ml of pure acetone was cooled to 0° and stirred while 0.3 ml of 8.0 *N* chromium trioxide in sulfuric acid–water was added. The mixture was kept at 0° for 30 min; the precipitate was filtered and washed with chloroform. The filtrate was washed with aqueous sodium carbonate solution and then water, after which the solvents were removed to leave 108 mg of neutral product. This material was dissolved in 5 ml of chloroform and placed on a column containing 6 g of alumina. Elution with 0.5–1.0% methanol–chloroform gave 10 mg of what appeared to be apopseudoyohimbaldehyde (λ_{max} 6.0 μ), whereas 2.0–5.0% methanol–chloroform afforded 20.7 mg of amorphous solid, the ir spectrum of which was identical with that of authentic pseudoyohimbine.

The pseudoyohimbine fractions isolated from a total of seven oxidation experiments (involving ≤100 mg of pseudoyohimbaldehyde O-formate) were combined and allowed to recrystallize from methanol to afford 6.2 mg of crystalline alkaloid which was used in the resolution experiments. The alkaloidal material present in the mother liquor (80 mg) was chromatographed on 6 g of alumina. Elution with 1.0–3.0% methanol–chloroform gave 41.7 mg of crude pseudoyohimbine. Crystallization from methanol gave a first crop of 12 mg. Four recrystallizations of this sample gave a crystalline solid, mp 252–256° (chars at 250°).

Anal. Calcd for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.40; N, 7.91. Found: C, 70.81, 71.17; H, 7.39, 7.59; N, 8.30, 8.42.

***d*-Pseudoyohimbine *l*-Camphor-10-sulfonate.** As pseudoyohimbine (102 mg) and *l*-camphor-10-sulfonic acid (75 mg) were dissolved in 1–2 ml of acetone, the expected salt crystallized as colorless needles (79% yield). Recrystallization was effected by dissolving the salt in warm methanol and slowly replacing the alcoholic solvent with acetone at the steam bath until crystallization started. The product obtained after cooling and filtration was a colorless crystalline solid, which after three such crystallizations softened at 273° and melted at 276–278° (evacuated capillary).

Anal. Calcd for $C_{31}H_{42}SO_7N_2$: C, 63.48; H, 7.17. Found: C, 63.48; H, 7.20.

Rotation was $[\alpha]^{25}_{Hg}$ −3.59 ± 2.01° (*c* 4.18, 50% methanol–water).

l-Camphor-10-sulfonic acid and pseudoyohimbine were regenerable from the salt.

Resolution of *dl*-Pseudoyohimbine. *dl*-Pseudoyohimbine (6.2 mg) and *l*-camphor-10-sulfonic acid (4.1 mg) were dissolved in a few drops of acetone. After standing, the solution deposited 3.6 mg of salt. Recrystallization from acetone provided 2.0 mg of colorless crystals, mp 274–278°. The ir spectrum of the salt, measured on a 5% solution in chloroform, was identical with that of authentic *d*-pseudoyohimbine *l*-camphor-10-sulfonate, taken under similar circumstances. The mixture melting point of the two salts was not observably lower than that of either pure specimen. By treatment of the salt of resolved alkaloid with dilute ammonia and extraction with chloroform, the free synthetic base (mp 284–287° dec) was recovered. Again, ir spectra of synthetic and authentic pseudoyohimbines were identical. The nature of the synthetic materials was further confirmed by its optical rotatory dispersion, measured on a methanol solution. The virtual identity of curves exhibited by natural and synthetic bases in the range 300–700 mμ established the dextrorotatory nature of the latter.

***cis*-4,5-Tetramethylene-4,5-dihydrofuran.** To a solution of 23 ml of 33% hydrogen peroxide in 175 ml of formic acid was added 35 g of *o*-allylphenyl acetate, bp 120–122° (20 mm), $n^{22}D$ 1.5088, at a rate such that the temperature was maintained at 40–45°. After standing at room temperature overnight, the product, on distillation under diminished pressure, gave 36 g of a viscous, yellow liquid, bp 153–174° (0.35 mm), $n^{22}D$ 1.5184. Redistillation gave approximately equal amounts of two fractions: (a) bp 80–83° (0.02 mm), $n^{25}D$ 1.5262; and (b) bp 118–136° (0.03–0.1 mm), $n^{25}D$ 1.5147.

The ir spectrum of fraction a indicated the presence of a formate ester, 5.77 and 8.18 μ, and the absence of hydroxyl groups. Fraction *a* was assigned a furan or pyran structure.

Anal. Calcd for $C_{11}H_{22}O_3$: C, 68.73; H, 6.30. Found: C, 68.66; H, 6.32.

Fraction b showed strong hydroxyl absorption at 2.90 and a formate carbonyl bands at 5.7–5.9 and 8.0–8.7 μ.

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 59.86; H, 5.57.

A sample of fraction b was hydrogenated in the presence of Raney nickel at 135° to give a viscous, colorless liquid, bp 142–155° (0.25 mm), the ir spectrum of which demonstrated the absence of an aromatic ring.

An ethanol–water solution of 12 g of the hydrogenated product was kept with 4.4 g of sodium hydroxide for 5 hr, after which water was added and the alcohol removed. The pH was adjusted to 5, and 12 g of sodium metaperiodate in 100 ml of water was added; the mixture was kept at 0° for 2 hr. Extraction with ether and distillation afforded 3.75 g of a lactol, bp 126–127° (1.7 mm), which displayed a strong hydroxyl band at 2.97 μ and weak carbonyl absorption at 5.83 μ.

A solution of 2.3 g of the lactol, 5 g of acetic anhydride, and 0.31 ml of pyridine was kept at room temperature overnight, and then the volatile reactants were removed at room temperature by distillation under diminished pressure. The residue was distilled under slightly diminished pressure using a bath temperature of 200–220°. The distillate was collected over aqueous sodium carbonate and extracted with ether. Redistillation gave 0.25 g of enol ether (bp 83–93° (95–120 mm), $n^{25}D$ 1.4746) and 0.50 g of enol ether

contaminated with lactol acetate, bp 74° (65 mm). The ir spectrum of *cis*-4,5-tetramethylene-4,5-dihydrofuran exhibited a sharp peak at 3.30 μ, a strong band at 6.28 μ characteristic of the enol ether double bond, and broad absorption at 14.0 μ typical of a *cis*-disubstituted double bond. The enol ether gave the same 2,4-DNP derivative, mp 73–76°, as obtained directly from the lactol.

2-Hydroxy-4-methyl-5-propyltetrahydrofuran. Acetic acid (340 g) was added over a 10-hr period to a cooled and stirred mixture of 250 g of crotonaldehyde, 85 g-atoms of magnesium dust, and 3.5 l. of water. Sodium chloride (300 g) was added, and the mixture was extracted with ether. Distillation gave 108 g of yellow liquid, bp 83–90° (2.0 mm), n^{18}D 1.4675–1.4694, which showed ir peaks at 2.9, 3.62, 5.83, and 6.0 μ.

The unsaturated lactol obtained as above was hydrogenated in a Parr apparatus using Raney nickel as a catalyst and methanol as a solvent. The reduction proceeded exothermically and 150% of 1 equiv of hydrogen was absorbed in 4.5 hr. The catalyst and solvent were removed, and the residue was fractionally distilled to give 46 g of the lactol, bp 91–98° (11 mm), n^{25}D 1.4430.

The 2,4-DNP derivative of the lactol was recrystallized several times from ethanol–water and then showed mp 88.5–90.5°.

Anal. Calcd for $C_{14}H_{20}N_4O_5$: C, 51.84; H, 6.22. Found: C, 51.21; H, 6.00.

Dehydration of 2-Hydroxy-4-methyl-5-propyltetrahydrofuran. A. Acetate Pyrolysis. A solution of 6.6 g of 2-hydroxy-4-methyl-5-propyltetrahydrofuran in 9 g of acetic anhydride and 2 ml of pyridine was kept at room temperature overnight. The volatile reactants were removed at room temperature under diminished pressure, and the residue was distilled at *ca.* 400 mm using a bath temperature of 180–190°, the distillate being collected over aqueous sodium carbonate. The organic phase was separated and distilled to give 3.5 g of enol ether, bp 127–133°; 0.6 g of a mixture of enol ether and lactol acetate, bp 137–145°; and 1.2 g of residue which was composed of unaltered lactol acetate. 4-Methyl-5-propyl-Δ-4,5-dihydrofuran (**64**) exhibited ir bands at 3.30, 6.18, and 14.0 μ.

B. Cathylate Pyrolysis. Ethyl chloroformate (8 ml) was added slowly to a cooled and stirred solution of 5 g of 2-hydroxy-4-methyl-5-propyltetrahydrofuran in 10 ml of dry pyridine. The mixture was allowed to stand at 0° overnight and was then extracted with petroleum ether. The combined extracts were washed with water, dried, and distilled to give the cathylate, bp 50–55° (*ca.* 1 mm). The cathylate began to evolve carbon dioxide on being heated to 130–140° at atmospheric pressure. The resulting liquid was kept at 150° for 30 min; then the bath temperature was raised to 200°, resulting in the distillation of 0.8 g of ethanol containing a small amount of enol ether, and 2.0 g of crude enol ether, bp 120–140°.

C. Dehydrochlorination of 2-Chloro-4-methyl-5-propyltetrahydrofuran. Dry hydrogen chloride was bubbled for 2 hr into a cooled ether solution of 3 g of 2-hydroxy-4-methyl-5-propyltetrahydrofuran over Drierite. The dark brown solution was decanted from the drying agent, and the ether was distilled. Fresh ether was added and removed in order to ensure the complete removal of hydrogen chloride.

An exothermic reaction took place when the crude chloride obtained above was added to a dry benzene solution of potassium *t*-butoxide. The insoluble salts were removed; and, after being washed with water, the solution was distilled to give 2.0 g of a colorless liquid, bp 100–140° (*ca.* 120 mm). A redistilled portion of the *t*-butyl lactol ether (**66**) exhibited bp 83–84° (9 mm), n^{25}D 1.4260.

Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.32; H, 11.80.

Dehydrochlorination of the chloro ether was effected by treatment for 1 day with triethylamine. From 3.0 g of lactol there was obtained 1.2 g of enol ether, bp 55–90° (50–100 mm), contaminated with triethylamine.

Hydroxylation and Periodate Cleavage of 2-Allyl-1-cyclohexanol. To a solution of 14 ml of 30% hydrogen peroxide in 100 ml of formic acid was added slowly 15 g of 2-allyl-1-cyclohexanol (obtained by lithium aluminum hydride reduction of 2-allylcyclohexanone). During the addition the temperature was maintained at 40° using an ice bath, after which the reaction mixture was allowed to stand overnight. Distillation afforded 8.5 g of a colorless, mobile liquid, bp 130–145° (*ca.* 10 mm), and 5.5 g of viscous, colorless oil, bp 150–160° (1 mm).

The ir spectrum of the lower boiling fraction showed bands at 5.8 and 8.6 μ characteristic of a formate ester. A weak band was present at 2.90 μ which was probably an overtone of the formate ester and not a hydroxyl band. On this basis the liquid may be assigned structure **56**, **57**, and/or **58**.

Strong absorption at 2.90 μ, as well as the presence of formate ester maxima at 5.80 and 8.4 μ, suggest that the higher boiling fraction be represented as triol monoformate.

The latter ester (5.5 g) was treated at room temperature with 2.0 g of sodium hydroxide in methanol. Water was added and the methanol removed. The solution was neutralized with dilute hydrochloric acid, and 6.0 g of sodium metaperiodate added. The mixture was kept overnight and extracted with ether. Distillation afforded 0.7 g of viscous liquid, bp 105–119° (*ca.* 10 mm). This liquid displayed bands at 2.90, 5.66, and 5.83 μ in the ir. Heating with potassium hydrogen sulfate gave a polymer. On treatment with Brady's reagent, an orange solid precipitated, mp 80–83°, the melting point of which was raised to 86.5–87.5° by recrystallization from ethanol–water.

Anal. Calcd for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63. Found: C, 51.69; H, 5.96.

Hydroxylation and Cleavage of 2-Allyl-1-cyclohexanol Acetate. A solution of 8.95 g of 2-allyl-1-cyclohexanol, 15 ml of acetic anhydride, and 0.7 ml of dry pyridine was kept for 24 hr, and the volatile reactants were removed *in vacuo*. The residue was dissolved in 100 ml of formic acid and 7.2 ml of 30% hydrogen peroxide added, after which a mild exothermic reaction resulted. The solution was heated at 40° for 1 additional hr and was left at room temperature overnight. Distillation afforded 13 g of viscous liquid: bp 145–150° (0.3 mm); n^{21}D 1.4686; ir 2.93, 5.8–5.9, and 8.0–8.9 μ.

The hydroxylation product was hydrolyzed with 6.0 g of sodium hydroxide in ethanol–water. The ethanol was removed and the pH adjusted to 5. A solution of 11.4 g of sodium metaperiodate in 100 ml of water was added; and after standing of the solution for 2 days, the product was extracted with ether. Distillation gave 4.6 g of colorless liquid, bp 85–93° (0.9 mm). The ir spectrum of this substance exhibited a strong hydroxyl band at 2.90 μ and a relatively strong carbonyl band at 5.82 μ. On standing the viscosity increased, the 5.82 μ becoming stronger and a new band at 5.65 μ appearing.

Treatment with Brady's reagent slowly afforded a precipitate. Recrystallization from ethanol–water gave a first crop, mp 64–66°, and a second crop, mp 77–78°. The ir spectra of these two crops were identical. Two or three minor differences were noted between these spectra and that of the 2,4-DNP, mp 86–87°, described above.

The lactol was converted to the corresponding acetate with acetic anhydride/pyridine. The acetate showed bp 98–100° (3.5 mm) and ir bands at 5.80 and 8.10 μ. Pyrolysis of this material failed to yield the desired enol ether.

Model Hydroxylation Experiments. A. Dihydropyran. To a Dry Ice cooled solution of 81 mg of dihydropyran in 15 drops of pyridine and 1 ml of tetrahydrofuran was added 213 mg of osmium tetraoxide in 1 ml of tetrahydrofuran. After 2 hr ether was added and the solid product collected by filtration. The solid was dissolved in methylene chloride–ethanol and hydrogen sulfide was bubbled into the solution. The black precipitate was removed with the aid of Celite and the solvents were distilled. The residue was treated with 2,4-DNP reagent and after heating for 30 min a precipitate appeared. On cooling 208 mg of oxazone, mp 203–209°, was isolated. Recrystallization from ethanol–ethyl acetate gave a sample which showed mp 235–237° (lit.[30] mp 242°).

B. 4-Methyl-5-propyl-Δ^{4,5}-dihydrofuran. Enol ether (445 mg) was osmated as described above. Treatment with 2,4-DNP reagent at room temperature gave 204 mg of osazone derivative (extensive decomposition was observed if heat was applied during the osazone formation). The osazone derivative was recrystallized from ethanol–ethyl acetate and showed mp 211–212°.

Anal. Calcd for $C_{20}H_{22}N_8O_9$: C, 46.33; H, 4.28. Found: C, 46.62; H, 4.49.

Stability of Yohimbine to Oxidation. In order to assess the feasibility of oxidizing an aldehyde function in the presence of yohimbine, a number of experiments involving the oxidation of the saturated keto aldehyde **11b** to the saturated keto acid were conducted. In a preliminary run, 1.0 g of the aldehyde was dissolved in 20 ml of acetic acid and 20 ml of toluene, 0.2 g of manganous acetate in 3 ml of water was introduced, and a slow stream of air was bubbled through the solution for 12–15 hr at room temperature. The solvent was removed under reduced pressure on the steam bath, and the residue separated into acidic and neutral components by chloroform–sodium carbonate extraction. From the acid fraction

(30) C. D. Hurd and C. D. Kelso, *J. Am. Chem. Soc.*, 70, 1484 (1948).

0.4 g of crystalline **16** (R = H), mp 145–152°, separated. On recrystallization from benzene–petroleum ether this acid melted at 153–155°, undepressed with a sample prepared by the hydrogenation of **15** (*cf.* above). When the same experiment was conducted in the presence of 0.5 g of yohimbine only a trace of crystalline acidic material could be isolated. By chromatography on Alcoa alumina (20 mesh), the neutral–basic portion from the extraction was separated into 0.85 g of recovered keto aldehyde (benzene fraction), identified by ir and 2,4-DNP's and 0.30 g (60%) of crystalline yohimbine (chloroform–alcohol fraction), identified by melting point and mixture melting point (234–236°). In the absence of aldehyde, yohimbic acid was recovered from these same oxidation conditions in 70% yield by direct isolation. At higher temperatures yohimbine and yohimbic acid were rapidly attacked by air in the presence of manganese acetate. Without the catalyst the aldehyde was oxidized only slightly.

Yohimbine (194 mg) was treated using the exact conditions for osmation described above. A trace of solid was observed after standing of the mixture at Dry Ice temperatures for 6 hr and addition of ether. The solid was removed, and hydrogen sulfide bubbled into the filtrate; the mixture was filtered and the solvents were removed. Addition of water to an ethanol solution yielded 108 mg of yohimbine.

Basic silver oxide converted the saturated keto aldehyde to the corresponding keto acid. However, under these conditions yohimbic acid was not recovered. Washed silver oxide had no effect on the keto aldehyde in methanol or tetrahydrofuran. Silver oxide in aqueous ammoniacal solution had a similar effect, both yohimbine and keto aldehyde were unaltered.

A solution of 1.0 g of saturated keto aldehyde in 15 ml of methylene chloride was stirred overnight with 0.7 ml of 30% hydrogen peroxide in 10 ml of water. The organic layer was separated, washed with sodium carbonate solution and water, and evaporated leaving 150 mg of crude keto aldehyde. The basic solution was acidified and extracted with methylene chloride yielding 450 mg of crude acid. Recrystallization from benzene–petroleum ether afforded 215 mg of saturated keto acid, mp 153–155°. Yohimbine was recovered from these reaction conditions or from treatment with 2 equiv of hydrogen peroxide in ethanol.

Only a small amount of acidic material was isolated when a mixture of keto aldehyde and yohimbine were treated with hydrogen peroxide. The yield of acidic solid was slightly higher using dilute acetic acid as solvent. At least 50% of the yohimbine was recovered from these experiments.

To a cooled and stirred solution of 1.0 g of saturated keto aldehyde and 0.5 g of yohimbine in 50 ml of acetone (distilled from potassium permanganate) was added 1.5 ml of Jones reagent (8 *N* chromium trioxide in 1 *N* sulfuric acid). After standing 0.5 hr sodium carbonate solution was added, and the mixture was filtered and extracted with methylene chloride–chloroform. The basic aqueous layer was neutralized and extracted with methylene chloride, affording a crude acid from which 0.5 g of white solid, mp 155–157°, was obtained.

Yohimbine was isolated on working up the neutral extract. However, when the experiment was repeated using yohimbic acid, the keto acid was again obtained, but yohimbic acid could not be recovered.

Yohimbinone. To an ice-cooled and stirred solution of 6 g of yohimbine in 250 ml of pure acetone was slowly added 5.8 ml of 8 *N* CrO_3 solution. The resulting mixture was kept at room temperature overnight, and 50 ml of saturated sodium carbonate and 200 ml of chloroform were added. The mixture was filtered, and the aqueous phase was repeatedly extracted with methylene chloride. The organic layers were combined and the solvents removed under diminished pressure. The dark yellow residue was taken up in ethanol and the solution allowed to stand in a refrigerator overnight to yield 2.0 g of needles, mp 249–252° dec. Recrystallization from ethanol gave 0.5 g of long, white needles, mp 263–266°, which showed λ_{max} 227, 283, and 290 mμ (ε 35,500, 6950, and 5900, respectively) and ir maxim at 5.80 and 5.90 μ. Yohimbinone did not give a ferric chloride color test, lit. mp 265°.

Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86 or $C_{21}H_{24}N_2O_3 \cdot C_2H_5OH$: C, 69.32; H, 7.59. Found (sample dried at 55°): C, 69.84; H, 7.87. Found (sample dried at 105°): C, 71.02; H, 6.69.

A solution of 89 mg of yohimbinone and 100 mg of sodium hydroxide in 25 ml of 1:1 ethanol–water was heated for 2 hr, after which the alcohol was removed. On cooling of the resulting solution, a tan solid separated. Recrystallization from methanol afforded 44 mg of colorless needles, mp 315–318°, the ir spectrum (KBr disk) of which was identical with that of an authentic sample of yohimbone.

β-Yohimbine. Hydrogenation of 87 mg of yohimbinone in 95% ethanol using platinum oxide as a catalyst resulted in the uptake of 1 equiv of hydrogen in 90 min. The solvent and catalyst were removed and the residue was crystallized from methanol to afford 24.5 mg of a white solid, mp 236–238°, whose ir spectrum was identical with the spectrum of β-yohimbine.

Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39. Found: C, 70.52; H, 7.56.

Hydrogenation of yohimbinone in glacial acetic acid using platinum oxide as catalyst resulted in the uptake of 1 equiv of hydrogen in 8 hr. Work-up in the usual manner gave a crude product whose ir spectrum indicated it was predominantly yohimbine.

Carboethoxylation of Yohimbone in Tetrahydrofuran with Sodium Hydride. Dry tetrahydrofuran (50 ml) was distilled from lithium aluminum hydride into a well-dried flask under high purity, dry nitrogen. Diethylcarbonate (20 ml, bp 124–125°) was distilled from calcium hydride into the same reaction flask. Yohimbone (614 mg, 2.08 mmoles) which had been dried at 100° for 24 hr *in vacuo* was added quickly. After stirring of the heterogeneous mixture for 10 min, 648 mg of sodium hydride (27.0 mmoles) was added. The reaction mixture was stirred at room temperature under high purity, dry nitrogen for 87 hr. After cooling of the reaction mixture to ice temperature, 2.6 ml of glacial acetic acid was added, followed by 20 ml of water. The reaction mixture was stirred at 0° for 10 min. After adding additional water and chloroform, the aqueous layer was made pH 9 with ammonium hydroxide. The layers were separated and the aqueous layer was extracted three times with chloroform. The chloroform solution was washed with water, and the organic solution was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure giving a dark brown semisolid product. This material was chromatographed on 25 g of silicic acid. Crystalline material was eluted with chloroform. After recrystallization from ethanol–water, the material was rechromatographed on silicic acid to give only one peak, which was again combined and recrystallized from ethanol–water. This crystalline compound (A) weighed 216 mg (30%) and had mp 182.5–184° dec. The hydrochloride salt of the product possessed mp 280–282° dec.

The free base (7% solution in chloroform) showed bands in the ir at 2.85, 3.41, 3.54, 3.60, 5.75, 5.84, 6.03, and 6.18 μ; λ_{max}^{EtOH} 290 mμ (ε 6800), 226 (38,500).

Anal. Calcd for $C_{22}H_{26}O_3N_2$: C, 72.13; H, 7.10; N, 7.65. Found: C, 72.23; H, 7.15; N, 7.79.

Carboethoxylation of Yohimbone with Sodium Hydride. In dry glassware, 692 mg of dry yohimbone (2.34 mmoles) was suspended in 150 ml of dry diethyl carbonate (freshly distilled from calcium hydride) under dry, high purity nitrogen. Sodium hydride (700 mg, 29.2 mmoles) was added quickly. The system was evacuated and flushed with dry, high purity nitrogen three times. The reaction mixture was stirred at room temperature under dry, high purity nitrogen for 72 hr. Work-up was similar to that described above. The material was chromatographed on 30 g of silicic acid; the only crystalline material was eluted with chloroform. The crystalline material proved to be identical with the product A obtained from the carboethoxylation of yohimbone in tetrahydrofuran with sodium hydride. The product of this reaction was obtained in crude chromatographed form in 28% yield.

Carboethoxylation of Yohimbone with Sodium Ethoxide. Using precautions described above, 571 mg of dry yohimbone (1.94 mmoles) was suspended in 180 ml of dry diethyl carbonate which had just been freshly distilled from calcium hydride. The system was flushed with dry nitrogen, and 1.453 g of freshly prepared, dry, alcohol free sodium ethoxide (21.7 mmoles) was added quickly. The system was evacuated and flushed three times with dry, high purity nitrogen. The reaction was stirred at room temperature under dry, high purity nitrogen for 84 hr. After work-up as usual, the product was chromatographed on silicic acid, crystalline material being eluted with chloroform. After recrystallization from ethanol–water this product (mp 182–184°) (25% yield) proved to be identical with the product A obtained from the carboethoxylation of yohimbone in tetrahydrofuran with sodium hydride.

Ethyl Ester of 16-Carboxy-17-ketoyohimbane (64). Through the use of the Jones oxidation procedure described above, ethyl yohimbate (3.2 g, 8.7 mmoles) was converted to keto ester with 1.6 g of chromium trioxide in 3.2 ml of 1 *N* sulfuric acid. After work-up as described in the precedent, the product was chromatographed on 50 g of Merck acid washed alumina. The product was eluted with 20% benzene–80% chloroform with starting mate-

rial coming off the column directly behind the product. The product was recrystallized from ethanol–water giving 253 mg (8%) material, mp 248–250° dec. An ir spectrum of the material has bands at 2.85, 3.41, 3.55, 3.62, 5.73, and 5.82 μ (with no absorption bands in the region 6.0–6.5 μ); λ_{max}^{EtOH} 290 mμ (ε 7800), 225 (45,800).

Anal. Calcd for $C_{22}H_{26}O_3N_2$: C, 72.13; H, 7.10; N, 7.65. Found: C, 72.31; H, 7.15; N, 7.87.

Subjection of the Ethyl Ester of 16-Carboxy-17-ketoyohimbine to Carboethoxylation Conditions. In dry glassware, under a dry, high purity nitrogen atmosphere, the ethyl ester of 16-carboxy-17-ketoyohimbane (**64**) (212 mg, 0.58 mmole) was suspended in 50 ml of diethyl carbonate which had been freshly distilled from calcium hydride. Taking precautions to exclude moisture, 482 mg of freshly prepared dry, alcohol-free sodium ethoxide (7.08 mmoles) was added quickly. By proceeding in the usual way, as described, a light colored material was obtained, which was recrystallized from ethanol–water to give 165 mg (first crop) of material, mp 248–250° dec. The material proved to be starting material by ir spectrum, uv spectrum, and an undepressed mixture melting point with the ethyl ester of 16-carboxy-17-ketoyohimbine. The material was therefore recovered unchanged in 77% yield from one recrystallization of the reaction product.

High-Pressure Reduction of Compound A. Compound A (156 mg, 0.42 mmole) in 45 ml of anhydrous ethanol was hydrogenated at 1200 psi with 90 mg of PtO_2 at room temperature for 5 hr. Attempts to recrystallize the material from ethanol–water gave poor results, and therefore the material was chromatographed on 4 g of Merck acid washed alumina. The material was eluted with 1% ethanol in benzene giving only one peak with some tailing. The peak fractions still would not crystallize readily, so the hydrochloride salt of the product was prepared. After recrystallization from ethanol–water the hydrochloride salt of the reduced product had mp 302–303° dec.

Synthetic reduced carboethoxylation product hydrochloride as a KBr pellet has ir bands at 2.86, 3.11, 3.25, 3.86, 5.86, 7.01, 7.29, 7.59, 7.91, 8.02, 8.12, 8.22, 8.33, 8.44, 9.05, 9.60, 9.71, 10.40, 11.37, 13.35, 13.86, and 14.42 μ.

A mixture melting point with a known sample of ethyl yohimbate hydrochloride (mp 301–303° dec) gave a depressed melting point of 292–297° dec. Ir spectra show the two compounds to be distinctly different.

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Total Synthesis of Rhyncophyllol and *dl*-Isorhyncophyllol

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Abstract: A simple synthesis of rhyncophyllol (**14**), involving in its last stage a biogenetic-type cyclization reaction, has been completed. The scheme embraces the following intermediates: **7, 9** (X = H), **11, 12, 13, 3,** and **4.** In addition, an independent synthesis of the diastereoisomeric system, *dl*-isorhyncophyllol, was achieved by starting with a tetracyclic indole base (**15**) available by cyclization of the indolic dialdehyde **2.** The cyclization aspects are interpreted in terms of stereoformulas **24** and **25** for rhyncophyllol and isorhyncophyllol, respectively.

As the number and variety of established indole alkaloid structures increase, it becomes more and more apparent that many of the structural types derive by varying modes of cyclization of natural intermediates in which certain reactive sites have been brought to specific oxidation levels.[2] In such cases, these cyclizations, being eminently reasonable chemical events, may be spontaneous, for all practical purposes; on the other hand, the oxidation processes necessary to set the stage for these ring closures are almost certainly enzyme catalyzed. Assuming the foregoing, it seems that relatively direct, simply executed laboratory construction of intricate natural product systems might be possible if the required types of oxidation were performed on suitable substrates with ordinary chemical reagents, in lieu of enzymes; while the desired annulation processes, being normal chemical changes, would be expected to ensue, as in the biosynthesis route. At the present time, a number of such examples have appeared, and some of the early cases have been discussed in review.[3] In order to provide further support for the principle and to develop a new synthetic approach to yet another natural product system, efforts were made to modify slightly an earlier case studied in this laboratory and thereby to divert the synthesis stream in the direction of another natural polycyclic system. In preliminary form, we reported some years ago cyclization studies of the dial-

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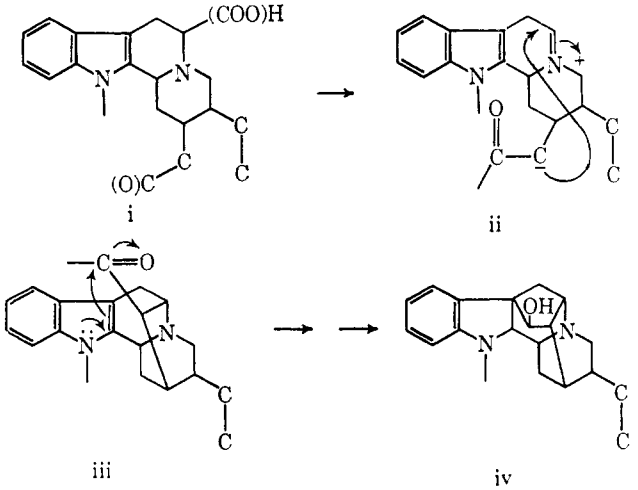
(2) For example, alkaloids in the sarpagine (iii)–ajmaline (iv) class very probably arise by cyclization of an intermediate type (ii) resulting from oxidation of precursor i at C-5. For a discussion of certain aspects of this case, see E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, **24**, 687 (1968).



(3) E. E. van Tamelen in Zechmeister's "Fortschritte der Chemie organischer Naturstoffe," Vol. XIX, Springer-Verlag, Vienna, 1961, p 242.