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.

Acknowledgments. The authors wish to express their appreciation to the National Institutes of Health (G3892) and the National Science Foundation (G1240 and G3506) for financial support; to Merck and Co. for generous cooperation in supplying osmium tetroxide; to Gordon Knapp and Frank Lornitzo for invaluable experimental assistance; and to Dr. E. J. Eisenbraun and Professor C. Djerassi for supplying the optical rotatory dispersion curves.

Total Synthesis of Rhyncophyllol and *dl*-Isorhyncophyllol

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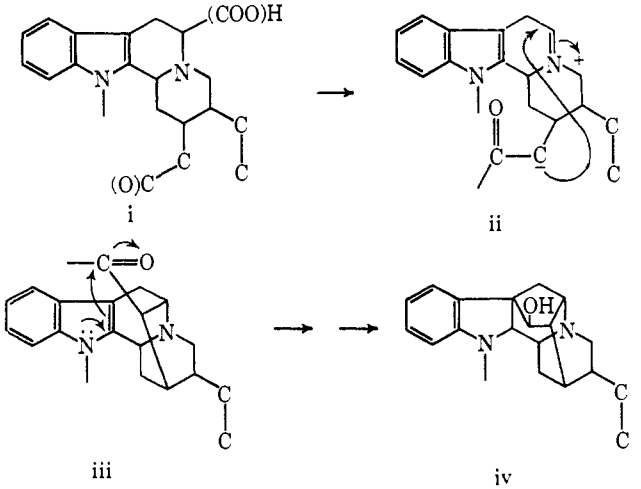
Abstract: A simple synthesis of rhyncophyllol (**14**), involving in its last stage a biogenetic-type cyclization reaction, has been completed. The scheme embraces the following intermediates: **7**, **9** (X = H), **11**, **12**, **13**, **3**, and **4**. In addition, an independent synthesis of the 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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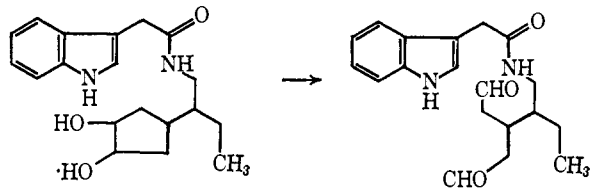
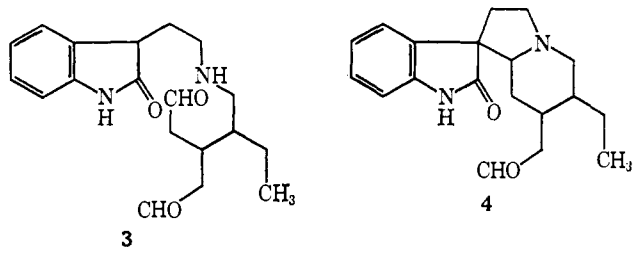
(2) For example, alkaloids in the sarpagine (iii)–ajmaline (iv) class very probably arise by cyclization of an intermediate type (ii) resulting from oxidation of precursor i at C-5. For a discussion of certain aspects of this case, see E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, **24**, 687 (1968).

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



1 2

dehyde **2** produced by oxidative cleavage of the substituted cyclopentanediol **1**, readily preparable by amide formation between indoleacetic acid and 2-(Δ^3-cyclopentenyl)-*n*-butylamine, followed by hydroxylation with osmium tetroxide.[4] With the indoleacetamide moiety intact, cyclization can be induced at either the α or β position of the indole nucleus, depending on the severity of the acid conditions employed.[5] In the modification, the indoleacetamide portion would be replaced by 3-(β-aminoethyl)oxindole (**3**), and by means of an intramolecular Mannich cyclization, generation of a tetracycle (**4**) would be anticipated. The resulting oxindole aldehyde corresponds to rhyncophyllol, an alcohol falling in the rhyncophylline (**5**)–corynoxeine (**6**) series. Presented below is the method used to reduce this scheme to practice.[6]



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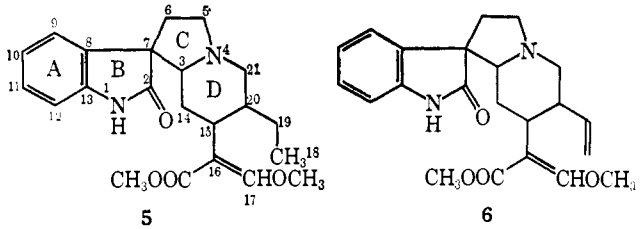
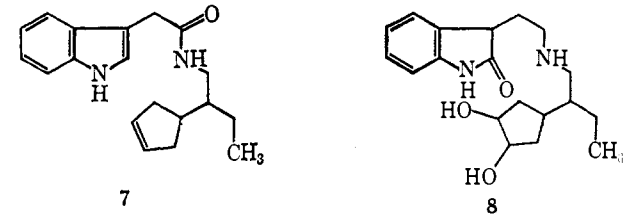


5 6

Given the previously described and readily available amide **7** of indole-β-acetic acid and 2-(cyclopenten-3-yl)butylamine,[4] one is obliged to make suitable adjustments in the oxidation levels at various sites in order to produce a heterocycle (**8**) suitable for oxidation–cyclization to rhyncophyllol. In view of the sensitivity of certain functions that must be preserved while the over-all change **7** → **8** is brought about (indole, olefinic, 1,2-diol, *sec*-amine), said change amounts to a subtle, sequential exercise in chemical selectivity. Of the methods available for oxidation of indole to oxindole, the direct, single-step process employing N-bromosuccinimide (NBS) oxidation was selected for use in this case, and this choice in turn dictated the order of the other chemical operations. In view of the presence of a highly reactive olefinic bond in the starting material (**7**) the NBS reaction could not be used as the initial reaction. Also, the reduction of the amide function in starting material to *sec*-amine would best be carried out by means of lithium aluminum hydride, meaning that both oxindole and cyclopentanediol moieties should not have been generated by that time. Thus, for various reasons, hydride reduction as the lead-off reaction was called for, and was accomplished readily in good yield under traditional conditions, *viz.*, refluxing in tetrahydrofuran solution. The amine product (**9**, X = H) was not characterized *per se* but was converted directly to



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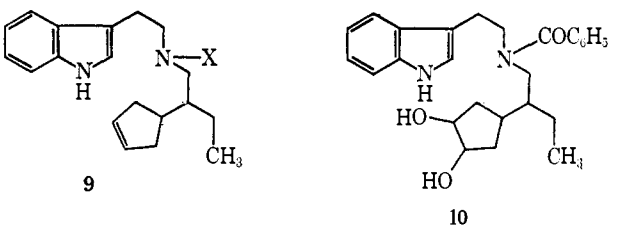
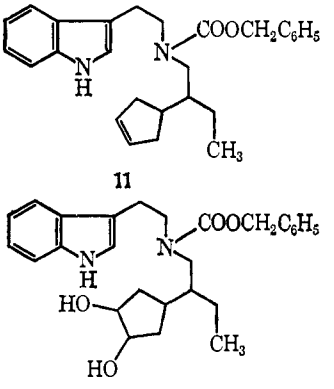


9 10

N-acyl derivatives. The benzamide (**9**, X = C_6H_5CO–) melted at 145–147.5° and could be converted by means of osmium tetroxide to the cyclopentanediol **10**, characterized as the trinitrobenzene (TNB) complex, mp 98.5–100°. Preliminary hydrolysis studies showed that the benzoyl unit could not be removed without considerable general destruction of the molecule, either with the indole unit intact or substituted by oxindole.

In view of the impending oxidation of indole to oxindole, the secondary amine function nevertheless required protection, but by a group more easily detached than benzoyl. The carbobenzoxy blocking group was selected and attached, as usual, by use of benzyl chloroformate. Although not in itself crystalline, the carbamate (**11**) formed a well-defined TNB complex, mp 98.5–100°. Osmylation at −70° in THF–pyridine of the new amide provided the expected diol (**12**), a non-

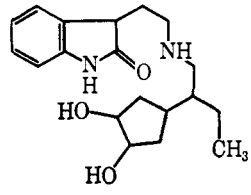


11 12

crystalline material which was characterized as a TNB complex (mp 73–74°) and which could be purified by silicic acid chromatography. In an analytical determination, the diol consumed 1 mole of sodium metaperiodate.

(4) E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Lett.*, No. 19, 30 (1960).
(5) E. E. van Tamelen, J. A. Webber, G. Schiemenz, and W. Barker, unpublished results.
(6) For a preliminary report of part of this work, see E. E. van Tamelen, J. P. Yardley, and M. Miyano, *Tetrahedron Lett.*, 1011 (1963).

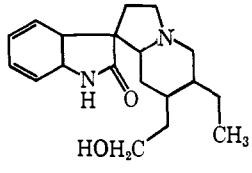
Attempts to generate oxindole from indole by means of peracid were unsuccessful. Transformation of diol **12** to oxindole was accomplished through a modification of the Lawson and Witkop method, involving use of N-bromosuccinimide in aqueous acetic acid. The product of the initial reaction was *ar*-bromoxindole, which was simultaneously reductively debrominated and debenzylated by addition of palladium on carbon directly to the original reaction mixture followed by catalyzed hydrogenation at atmospheric pressure. Neither the free oxindole glycol **13** nor any of the salts



13

prepared from it was crystalline,[7] and therefore amorphous hydrobromide having suitable ultraviolet spectral characteristics ($\lambda_{max}^{ethanol}$ 250 mμ (ε 7000)) was used for the cleavage and cyclization experiments, described next.

Oxidation to the dialdehyde (or cyclic alkanolamine) **3** was brought about by reaction with sodium metaperiodate, carried out in aqueous solution at 0° for 15 min. Aldehyde material was isolated by extraction and immediately heated under reflux in 8% aqueous hydrochloric acid for 3 hr. Subsequent to borohydride reduction of total nonacidic material, a chromatographic separation using Woelm neutral alumina (12% water, activity grade IV–V) was carried out. The 100%



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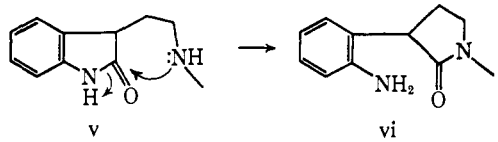
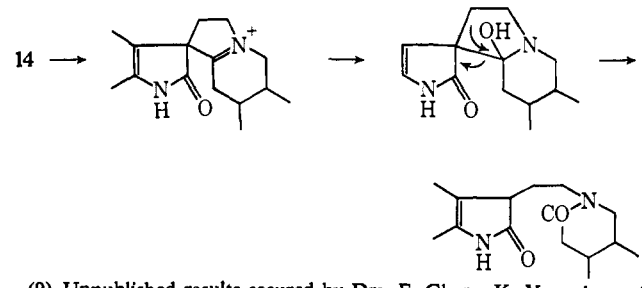
chloroform fractions provided crystalline material (mp 106–112° after recrystallization from chloroform–petroleum ether, bp 30–60°) which was shown by analysis to be the 1:1 chloroform solvate of material with the desired composition (material freed from solvent by sublimation was, again, not crystalline).[8] The substance

(7) Under various conditions (standing for several days in methanol solution, or chromatography over silicic acid with chloroform–methanol elution), the normal ultraviolet spectrum of the oxindole gradually shifted to one indicative of an *o*-toluidine system, *i.e.*, λ_{max}^{MeOH} 236 mμ (ε 7000); λ_{min} 227 mμ (ε 6750); λ_{infl} 248, 280 mμ (ε 5300, 1100). This observation may be interpreted as indicating the rearrangement v → vi.



v vi

(8) Initial evidence that the anticipated change had indeed occurred was secured by mercuric acetate oxidation of this material, which process gave rise to product with an infrared band at 6.1 μ (six-membered lactam). As suggested by earlier observations [J. C. Seaton, M. D. Nair, O. E. Edward, and L. Marion, *Can. J. Chem.*, **38**, 1035 (1960)], this result may be viewed in terms of the process



(9) Unpublished results secured by Drs. E. Ghera, K. Yamada, and R. Coates.

was identified as the rhyncophylline-derived degradation product, rhyncophyllol (**14**) (*dl*), by (1) comparison of its infrared spectrum with that of authentic rhyncophyllol, both measured on chloroform solutions, and (2) optical resolution as the di-*p*-toluoyl D-tartrate, mp

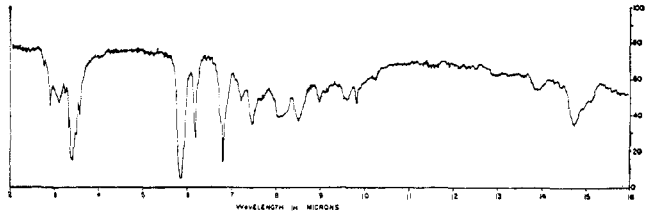


Figure 1. Ir spectrum of synthetic rhyncophyllol.

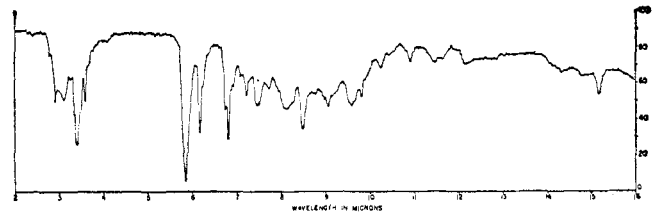
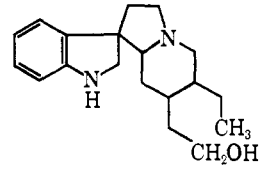


Figure 2. Ir spectrum of natural rhyncophyllol.

189–190.5° dec, and comparison with the di-*p*-toluoyl D-tartrate of authentic rhyncophyllol, mp 188–189.5° dec, mmp 189.0–190.5° dec (see Figures 1 and 2).

As a consequence of the earlier study concerned with the direct cyclization of the indole dialdehyde **2**,[4] tetracyclic indolines assigned the general constitution **15** were available in this laboratory.[9] In the hope of verifying the structural proposal and also establishing stereochemistry, correlation with the rhyncophylline series



15

was carried out. More precisely, the synthetic "amine alcohol **2**" of structural type **15** was converted by appropriate means to *dl*-isorhyncophyllol. In a corroborative exercise, the direct comparison of base "**2**" with the dihydrodesoxyisorhyncophyllol secured by lithium aluminum hydride reduction of isorhyncophyllol was also accomplished.

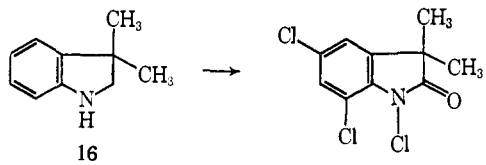
Reduction of rhyncophyllol by lithium aluminum hydride in tetrahydrofuran according to the procedure outlined by Marion[10a] led to a 48% yield of a chromatographically homogeneous oil whose spectrometric characteristics indicated that it was the expected dihydro desoxyrhyncophyllol. This oil could not be induced to crystallize. Thin layer chromatographic comparison of the product of the above sequence with each of the synthetic tetracyclic amines indicated nonidentity of any synthetic product with material derived from the natural source.

In view of this result, attention was turned to the iso series (C-7 epimer). Rhyncophyllol was refluxed overnight in pyridine, and the resultant mixture was separated by careful continuous thin layer chromatography. Recovery from the plates was quantitative, the mixture consisting of 83% isorhynchophyllol, 12% rhyncophyllol, and 5% of a hitherto unreported third isomer. Unfortunately, the third isomer, which fell between rhyncophyllol and isorhyncophyllol in polarity on silica gel, was obtained in too minute a yield to allow more than simple ir and uv spectrometric determinations. However, the similarity of the spectra of all three compounds indicated that the third was undoubtedly another C_3/C_7 isomer.

A solution of isorhyncophyllol in tetrahydrofuran was added to a refluxing slurry of lithium aluminum hydride in the same solvent. This reduction led to a 76% yield of a chromatographically homogeneous oil whose spectra were consistent with its formulation as dihydrodesoxyisorhyncophyllol. This material was less polar on silica gel tlc than dihydrodesoxyrhyncophyllol, and corresponded exactly in R_f value to cyclization product "amine alcohol **2**." The infrared, ultraviolet, and pmr spectra of this oil also were identical with those of the "amine alcohol **2**" and similar to, but clearly not identical with, the spectra of the other two amine alcohol products of the cyclization sequence **2** → **15**.

Although a convincing correlation had been made between the tetracyclic "amine alcohol **2**" and naturally derived dihydrodesoxyisorhyncophyllol, a final proof of this identity was lacking in that no crystalline derivatives were available for mixture melting point comparison. Rather than attempt preparation of some simple derivative, it was decided that conversion of the synthetic amine alcohol to the oxindole derived from the natural product would be a more profitable undertaking.

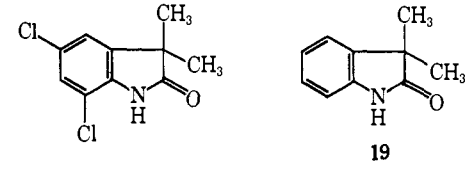
In a model experiment, 3,3-dimethylindoline (**16**) was treated with an excess (6 equiv) of *t*-butyl hypochlorite in chloroform in the presence of a large amount of sodium acetate. The product, a dark oil which showed no NH absorption in its infrared spectrum but did exhibit a new carbonyl band at 5.71 μ, was homogeneous on tlc and much less polar than the indoline starting material.



16 17

These data, and the subsequent reactions, allow its structural assignment as 1,5,7-trichloro-3,3-dimethyloxindole (**17**). Treatment with hydrogen over W-2 Raney nickel resulted in rapid uptake of 1 equiv of hydrogen to yield a crystalline compound, mp 182–184°. The infrared spectrum in chloroform of this compound showed the extremely characteristic oxindole pattern in the NH region, a sharp free NH absorption at 2.9 μ, and a broad hydrogen-bonded absorption at 3.1 μ. In carbon disulfide, the carbon–chlorine absorption at 13.2 μ was visible. The pmr spectrum of this compound was diagnostic for 5,7-dichloro-3,3-dimethyloxindole (**18**). The aromatic protons were represented by a pair of doublets (J = 2 cps) between δ 7.02 and 7.25 and the methyl groups by a sharp singlet at δ 1.41. The very broad one-proton singlet centered at δ 8.55, representing the proton on nitrogen, vanished on mixing the sample with deuterium oxide.

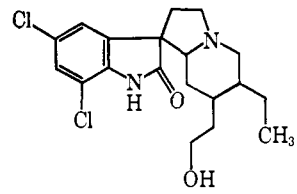
The hydrogenolysis of aromatic chlorine was sluggish over Raney nickel. However, the hydrogenolysis was complete in 3 hr over 30% palladium on carbon and provided 3,3-dimethyloxindole (**19**), which exhibited a melting point and mixture melting point indicating identity with an authentic sample.[11]



18 19

Attempts to extend this oxidation *per se* to the natural series met with repeated failure. Treatment of authentic dihydrodesoxyisorhyncophyllol with *t*-butyl hypochlorite in a chloroform–sodium acetate slurry gave complex mixtures of products from which a variety of carbonyl-containing compounds could be isolated in extremely poor yield. Since undesired oxidation might be occurring in the vicinity of H_b, that nitrogen was protected by protonation with naphthalene-2-sulfonic acid.

Although the naphthalenesulfonate salt of dihydrodesoxyisorhyncophyllol was soluble neither in chloroform nor water, treatment on a small scale of a three-phase system consisting of chloroform, water, and alkaloid salt with 4 equiv of *t*-butyl hypochlorite overnight at 25° led to a quantitative yield of a chlorine-containing compound with infrared and ultraviolet spectra diagnostic of oxindole. On the basis of the model experiments, this oxindole was assigned structure **20**. Reduction of this chlorinated product with palladium on carbon led to an 87% crude yield of an oil that was homogeneous on tlc and of R_f value identical with isorhyncophyllol. Tlc analysis indicated no trace of the more polar rhyncophyllol in the crude product.



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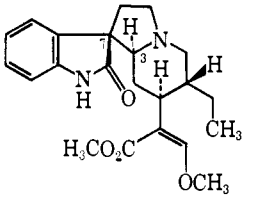
(10) (a) J. C. Seaton and L. Marion, *Can. J. Chem.*, **35**, 1102 (1957); (b) N. A. Cu, R. Goutarel, and M.-M. Janot, *Bull. Soc. Chim. France*, 1292 (1957).

(11) K. Brunner, *Monatsh.*, **18**, 95 (1897).

Purification by preparative tlc provided a colorless oil whose infrared and ultraviolet spectra were identical with those of an authentic sample of isorhyncophyllol prepared from rhyncophyllol by the equilibration technique of Marion.[12] A picrate prepared in 75% yield from the oily reduction product showed no depression of melting point on admixture with a sample of authentic picrate.

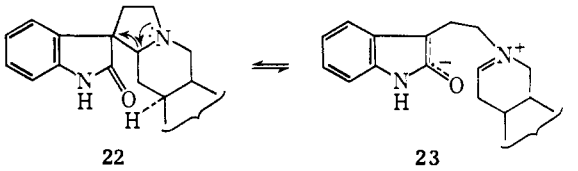
This result provided the means for conformation of the identity of the tetracyclic "amine alcohol **2**" with dihydrodesoxyisorhyncophyllol. Oxidation–chlorination of the former compound followed by hydrogenolysis of aromatic chlorine gave a good yield of a chromatographically homogeneous oil whose solution spectra were identical with those of isorhyncophyllol. This oil formed a nicely crystalline picrate which was compared with picrate of authentic *dl*-isorhyncophyllol. *dl*-Rhynocophyllol was isomerized in pyridine using Marion's procedure,[12] and *dl*-isorhyncophyllol was isolated by preparative thin layer chromatography. This base also readily formed a picrate which crystallized spontaneously. The melting points of the picrates of the isorhyncophyllols prepared by these two routes were identical and showed no depression upon mixing. This result confirms the identity of "tetracyclic amine alcohol **2**" and dihydrodesoxyisorhyncophyllol, and relates the synthetic amine alcohol derived by cleavage–cyclization–reduction of diol amide **1** directly to natural, optically active material.

The stereochemistry of the synthetic amine alcohols remains to be considered. Using conformational analysis and some of the physical properties of rhyncophylline and isorhyncophylline and several other interconvertible pairs of *Mitragyna* alkaloids, Hendrickson[13] has deduced the stereochemistry shown in **21** for isorhyncophylline, assigning the structure of the C_3 epimer to rhyncophylline. However, Finch and Taylor[14] have suggested on the basis of other physical properties that structure **21** represents rhyncophylline and that its C_7 epimer is isorhyncophylline. Circular dichroism measurements[15] have been used to support the assignment of Finch and Taylor, as have X-ray studies on



21

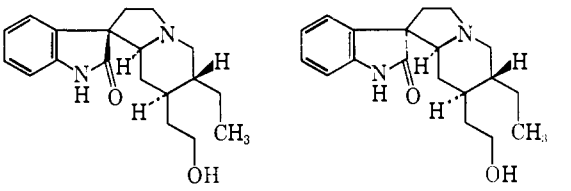
rauvoxinine.[16] For the purposes of the present discussion, the assignments of Finch and Taylor are accepted. However, it should be emphasized that establishment of the stereochemistry of rhyncophylline and isorhyncophylline does not rigorously connote the stereostructures of the degradation products considered here, since epimerization *via* process **22** ⇌ **23** during the conversion of the natural alkaloids to rhyncophyllol



22 23

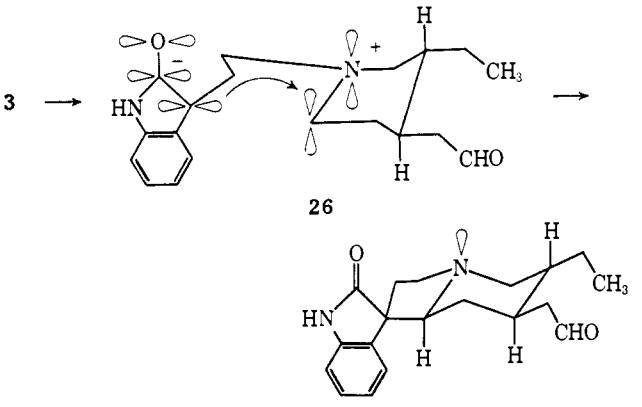
and isorhyncophyllol has not been ruled out.

If it is assumed that the rhyncophylline–isorhyncophylline stereostructures correspond to the rhyncophyllol–isorhyncophyllol pair, then the assignments **24** and **25**, respectively, follow for the two amine alcohols. In regard to the cyclization of the oxindole dialdehyde



24 25

3 to rhyncophyllal, it is evident that formation of the C ring involves the same type of intermediate (**23**) involved in the rhyncophylline–isorhyncophylline interconversion. Further, if cyclization of the piperidinoid D ring involves fixation of the two side chain units in the more stable *trans* relationship, as expected, then the direct generation of *dl*-rhyncophyllal can be interpreted as **3** → **26** → **27**. Whether this cyclization process is



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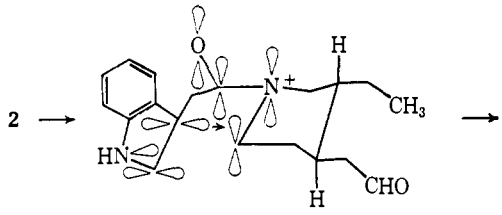
stereoselective cannot be judged, since (1) the presence of isorhyncophyllal in the cyclization product has not by any means been excluded, and (2) concurrent rhyncophyllol–isorhyncophyllol isomerization cannot be ruled out.

Cyclization of the indole dialdehyde to tetracyclic products apparently does not involve this stereochemical mode of ring formation, since not one of these products possesses the rhyncophylline stereochemistry. Formation of the isorhyncophyllal framework can be interpreted as involving the process **2** → **28** → **29**. In this as well as the **3** → **26** → **25** sequence, presumably attack of the indole or oxindole anion moiety takes place perpendicular to the plane of the imine–enamine acceptor, and on the face which will lead to the more stable stereochemical arrangement at C-3. The factors which control stereochemistry at C-7 are not obvious; and since other isomers are produced—not only in the indole dialdehyde case, but probably also in the oxindole case—the energy differences involved may be small.

(12) See reference 8.
(13) J. B. Hendrickson, *J. Am. Chem. Soc.*, **84**, 650 (1962).
(14) N. Finch and W. I. Taylor, *ibid.*, **84**, 3871 (1962), and references therein.
(15) J.-L. Pousset, J. Poisson, and M. Legrand, *Tetrahedron Lett.*, 6283 (1966).
(16) C. Pascard-Billy, *Bull. Soc. Chim. France*, 3289 (1968).



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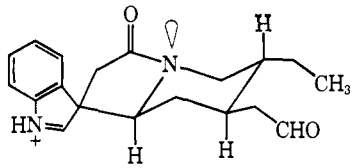

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It is worthy of note that, in the C-15,20 *trans* series, *only* tetracycle possessing the rhyncophylline stereochemistry is sterically capable of further ring closure to members of the pentacyclic strychnine–curare class, and that (as noted above) none of the tetracycles formed by cyclization of the indole aldehyde does in fact possess such stereochemistry. It is possible that these tetracycles are isolable because they are not convertible to these more highly fused systems.

Experimental Section

Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are uncorrected. Infrared spectra were recorded on an Infracord spectrophotometer. The following abbreviations are used for the relative intensities of infrared spectral bands: s, strong; vs, very strong; w, weak.

N_b-2-Cyclopent-3-enylbutyltryptamine (9, X = H). A solution of N_b-2-cyclopent-3-enylbutylindole-3-acetamide (7)[4] (24.9 g, 0.083 mole) in anhydrous tetrahydrofuran (200 ml) was added dropwise under nitrogen, during 30 min, to a stirred slurry of lithium aluminum hydride (14 g, 0.368 mole) in 800 ml of tetrahydrofuran. The mixture was heated under reflux for 48 hr. The ice-cooled reaction mixture was treated successively with 15 ml of water, 11 ml of 20% sodium hydroxide solution, and 50 ml of water. The precipitated solid was removed with the aid of a diatomite filter, washed with ether, and discarded. The combined tetrahydrofuran–ether filtrates were concentrated on the steam bath, and the dark oily residue was taken up in chloroform. The chloroform solution was shaken with five 200-ml portions of 25% aqueous phosphoric acid, followed by two 100-ml portions of water. The combined aqueous extracts were filtered, cooled in an ice bath, and made strongly basic with 20% sodium hydroxide solution. The precipitated amine was extracted into chloroform. Evaporation of the dried (Na_2SO_4) chloroform extracts at *ca.* 30° under reduced pressure (nitrogen bleed) afforded 18.45 g (78%) of the amine 9. The infrared spectrum showed no absorption in the carbonyl region.

Benzamide (9, X = C_6H_5CO–). A stirred solution of N_b-2-cyclopent-3-enylbutyltryptamine (9, 13.5 g, 4.8×10^{-2} mole) in ether (500 ml) containing 20 g of suspended K_2CO_3 was heated under reflux while benzoyl chloride (6.95 g, 4.9×10^{-2} mole) in ether (100 ml) was added over a period of 20 min. The reaction mixture was heated under reflux for a further 3 hr and the ether evaporated. Chloroform (300 ml) and water (300 ml) were then added to the reaction flask and stirred vigorously for 1 hr. The chloroform layer was separated and washed successively with dilute hydrochloric acid (two 100-ml portions), 10% K_2CO_3 solution, water, and dried (Na_2SO_4). After removal of the solvent the residue crystallized from aqueous methanol as prisms (15.05 g, 81% yield), mp 144°. The analytical sample, recrystallized from ethyl acetate–petroleum ether (bp 40–60°), mp 145–147.5°.

Anal. Calcd for $C_{26}H_{30}ON_2$: C, 80.79; H, 7.82; N, 7.25. Found: C, 80.86; H, 7.79; N, 7.27.

The uv spectrum showed λ_{max} 291 mμ (ε 4950), 282 (5700), 274 (5550), 221 (37,800); ir absorption 6.17 s μ.

Osmylation of the Benzamide 9 (X = C_6H_5CO). A magnetically stirred solution of the benzamide (3.25 g, 8.4×10^{-3} mole) in pyridine (8 ml)–anhydrous tetrahydrofuran (10 ml) contained in a 1-l. round-bottomed flask was cooled to −70° and treated dropwise, during 20 min, with a solution of osmium tetroxide (2 g, 7.8×10^{-3} mole) in tetrahydrofuran (60 ml). The resulting mixture was stirred with continued cooling for a further 2 hr before dilution with 500 ml of dry ether. After a further 30 min the precipitated osmate ester–pyridine adduct was filtered using a diatomite filter aid, washed with ether, and then rapidly transferred together with the filter aid back to the reaction flask, dissolved in 200 ml of ethanol–dichloromethane (1:1), and saturated with hydrogen sulfide (*ca.* 20 min) at room temperature. The mixture was allowed to stand overnight. After filtration from precipitated osmium sulfide the filtrate was evaporated leaving an oily residue of the diolamide (**10**) (3 g, 91% yield).

The uv spectrum showed λ_{max} 290 mμ (ε 5200), 281 (6200), 274 (6350), 221 (38,000); ir absorption 6.17 s μ.

The diol could, with difficulty, be obtained as colorless prisms, mp 110–118°, on slow evaporation of its solution in methanol–ether. Analysis of diol was unsatisfactory; but the diol was fully characterized by analysis of its **trinitrobenzene complex,** mp 98.5–100°, crystallizing from aqueous methanol in deep red prisms.

Anal. Calcd for $C_{26}H_{32}N_2O_3$: $C_6H_3N_3O_6$: C, 60.55; H, 5.57; N, 11.05. Found: C, 61.01; H, 5.72; N, 10.92.

The diolamide (188 mg) in methanol was treated with aqueous 0.1 *N* sodium metaperiodate (10 cc) at 0° and the volume was adjusted to 50 cc with methanol. The mixture was kept at room temperature in the dark and the excess of periodate estimated in the usual way (10-cc portions) at various times, together with appropriate blank determinations. Results are expressed as the percentage oxidation of one *vic*-glycol unit at the stated time: 45 min (97%), 1.5 hr (99%), 2 hr (92%), 4 hr (93%). No oxidation of the benzamide 9 (X = C_6H_5CO) was observed under these conditions.

Oxidation of the Indole Diolamide 10 to the Oxindole Analog. Under the conditions used by Dagleish and Kelly[17] for the oxidation of skatole with monopersulfuric acid (28% yield, 2 hr at room temperature) no reaction was observed. The most severe conditions tried, *viz.*, overnight reflux in aqueous *t*-butyl alcohol with the reagent led only to tar together with some chloroform-soluble material which showed only the typical indole ultraviolet absorption. More success was obtained using a method recently reported by Lawson and Witkop.[18]

N-Bromosuccinimide (1.95 g, 1.09×10^{-2} mole) was added over a period of 5 min to a stirred and ice-cooled solution of the diolamide **10** (2.296 g, 5.46×10^{-3} mole) in aqueous (40%) acetic acid (60%). After 25 min at room temperature 1 g of 10% Pd on carbon was added and the mixture hydrogenated overnight at atmospheric pressure. After filtration from catalyst the pale yellow solution was evaporated and the oily residue taken into chloroform (200 cc). The chloroform layer was washed repeatedly with water to remove succinimide and evaporated to give the oxindole diolamide as a pale, amber, viscous oil which could not be crystallized. No crystalline derivative of this compound has been obtained.

The uv spectrum showed λ_{max} 244 mμ (ε 9500); inflection 280 (1550); λ_{min} 238 (3300); *cf.* rhyncophyllal[10a] λ_{max} 252 mμ (ε 7760), shoulder 280 (1500), λ_{min} 228 (3300); ir absorption 1618 (6.18 μ) s; 1711 cm^{-1} (5.85 μ) s.

The product gave a positive color test for oxindoles.[19] The oxindole (2–3 mg) in ethanol containing 2 drops of 5 *N* hydroxide was warmed on the steam bath for 10 min, then acidified, diazotized with 2 drops of 2 *N* sodium nitrite solution, and coupled to a red dye with β-naphthol in 5 *N* sodium hydroxide. The test was negative without previous base treatment.

Attempts to remove the amide protective grouping by prolonged acid hydrolysis afforded only methanol-soluble tars together with a little chloroform-soluble material which still showed both amide peaks in the infrared.

The carbamate (**11**) was obtained as a straw-colored gum (90% yield) by treatment of N_b-2-cyclopent-3-enylbutyltryptamine (9, X = H) with benzyl chloroformate exactly as described for the benzamide (9, X = C_6H_5CO) preparation. The product was purified by filtration of its solution in chloroform through a short silicic acid column.

The uv spectrum showed λ_{max} 222 mμ (ε 28,000), 275 (4000), 282 (4850), 291 (4200); ir carbonyl absorption 5.95 s μ.

The carbamate was convertible to a crystalline orange-red **trinitrobenzene complex,** mp 98.5–100°.

(17) C. E. Dagleish and W. Kelly, *J. Chem. Soc.*, 3726 (1958).
(18) W. B. Lawson and B. Witkop, *J. Org. Chem.*, 26, 263 (1961).
(19) K. Freter, M. Weissbach, B. Redfield, S. Udenfriends, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 983 (1958).

Anal. Calcd for $C_{27}H_{32}N_2O_2 \cdot C_6H_3N_3O_6$: N, 11.21. Found: N, 11.12.

Osmylation of the carbamate **11** at −70° in tetrahydrofuran–pyridine exactly as described above afforded the diol **12** in 83% yield as a pale straw-colored gum after chromatography on silicic acid (chloroform–2% methanol fraction).

A deep red **trinitrobenzene complex,** mp 73–74°, was obtained by warming the diol **12** (200 mg) with trinitrobenzene (100 mg) in benzene (10 cc), evaporation of the solvent, and crystallization of the residue from aqueous methanol.

Anal. Calcd for $C_{27}H_{34}N_2O_4 \cdot C_6H_3N_3O_6$: C, 59.72; H, 5.62; N, 10.55. Found: C, 59.73; H, 5.66; N, 10.61.

The uv spectrum showed λ_{max} 220 mμ (ε 32,000), 274 (4900), 281 (5300), 290 (4500); ir absorption 5.95 s μ.

Oxindole Diolamine 13. N-Bromosuccinimide oxidation of the diolcarbamate (**12**) by the method of Lawson and Witkop,[18] carried out exactly as described above, gave, after filtration from the Pd hydrogenation catalyst and evaporation of the filtrate under reduced pressure, a viscous solution of the **oxindole diolamine 13** in a small volume of acetic acid. The oxindole content of the acetic acid solution was determined by ultraviolet analysis using the 252-mμ (ε 7760) band of rhyncophyllol as the standard. Reaction yields of 60–70% were indicated. Many of the early periodate oxidation–cyclization attempts were made directly on the concentrate of oxindole diolamine **13** in acetic acid, in view of the observed instability of the free amine (see below).

Attempted Isolation of the Oxindole Diolamine 13.[7] The oxindole diolamine concentrate from the oxidation of 773 mg of diol (12) was treated with excess saturated $NaHCO_3$ solution and extracted with five 50-ml portions of chloroform. Evaporation of the combined extract at room temperature under reduced pressure afforded 438 mg of residue.

Ir absorption showed 1710 s μ (5.85); uv λ_{max} 250 mμ (ε 6250); inflection 280 (1170); min 228 (3960).

A solution of the oxindole diolamine **13** (8.8 mg) in methanol (100 cc) was prepared and left to stand at room temperature; the ultraviolet absorption spectrum was determined periodically as indicated: 1 day—λ_{max} 236 mμ (ε 6700), 250 (5300), min 225 (66,300), 244 (5250), inflection 280 (1050); 3 days—λ_{max} 236 mμ (ε 7000), min 227 (6750), inflection 248 (5300), 280 (1100); 8 days—identical with "3-day" spectrum.

The same change is observed on attempted chromatography of the oxindole on a silicic acid column with chloroform–methanol. No apparent change in the infrared spectrum was observed.

The following experimental procedure was used to prepare oxindole diolamine **13** of sufficient purity for fission with sodium metaperiodate and ensuing cyclization.

The total chromatographed product (**12**) (5.30 g, 1.175×10^{-2} mole) resulting from osmylation of 4 g of carbamate **11** was treated in 200 cc of 50% aqueous tetrahydrofuran at 0–5° with N-bromosuccinimide (4.2 g, 2.36×10^{-2} mole) over a period of 10 min. The reaction mixture was allowed to stand for 20 min at room temperature before concentration under reduced pressure to remove the bulk of the tetrahydrofuran. The orange-yellow oil which separated was extracted into chloroform (three 100-cc portions). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated down; the residue was immediately chromatographed on a silicic acid (80 g) column. The product (4.6 g), eluted with chloroform–2% methanol as a pale yellow oil, was hydrogenolyzed in absolute ethanol (50 cc) with 10% Pd on carbon (1.5 g), affording 3.41 g of **oxindole diolamine (13) hydrobromide.** The presumed hydrobromide is a white, extremely hygroscopic solid which dissolves easily in water, methanol, or ethanol, but is insoluble in chloroform and less polar solvents. No crystalline derivative has been obtained—chloroplatinate, perchlorate, hydrochloride, hydrobromide, and picrate are amorphous.

The uv spectrum showed λ_{max} 250 mμ (ε 7000), min 226 (3100), inflection 280 (1220).

Cleavage and Cyclization of Oxindole Diolamine 13. A solution of the oxindole diolamine hydrobromide (3.41 g, 8.25×10^{-3} mole) in water (50 cc) was clarified by filtration through a diatomite filter aid, cooled to 0°, and treated dropwise with sodium metaperiodate (1.76 g 8.25×10^{-3} mole) in 30 cc of water. Slow, dropwise addition of the sodium metaperiodate to the stirred reaction mixture at first caused a faint purplish coloration possibly indicating iodine formation. The remaining oxidant was added rapidly, and the resulting solution allowed to stand at 0° for 15 min. Solid $NaHCO_3$ (4 g) was then added, followed immediately by rapid chloroform (four 40-cc portions) extraction. The chloroform extract was washed with water (20 cc back-extracted), dried (Na_2SO_4), and evaporated under reduced pressure (nitrogen bleed). The total cleavage product was heated with stirring under reflux in 8% aqueous hydrochloric acid (180 cc) under a nitrogen atmosphere. Some acid-insoluble red tar was formed at this stage, but the majority of material dissolved. After 3 hr the reaction mixture was cooled in an ice bath and treated cautiously with solid NaHCO (30 g) followed by excess saturated $NaHCO_3$ solution (*ca.* 200 cc) and the product isolated exactly as described for the periodate cleavage product. The cyclized material (1.8 g) in methanol (50 cc) was treated with sodium borohydride (1 g) in water (20 cc) overnight at 0°. The reaction mixture was concentrated under reduced pressure (nitrogen bleed) to remove the bulk of the methanol, and the product (1.4 g), isolated as described above, obtained as a pale brown foam. A small amount of chloroform-insoluble material was also obtained at this stage but was not further investigated. Chromatography of the borohydride reduction product on Woelm neutral alumina afforded partially crystalline product[13] upon elution with chloroform.

The borohydride reduction product (1.4 g) absorbed from methanol onto Woelm alumina (5 g) was added as a slurry in benzene to a 40-g sample of Woelm neutral alumina column (activity grade IV–V, 12% water) and chromatographed. Rechromatography of the 100% $CHCl_3$ fractions containing crystalline material (313.8-mg fractions 5, 6, and 7) on a 10-g Woelm neutral alumina (12% water) column resulted in moderate separation but indicated that the chromatographic properties of the material had altered appreciably, 90% of the material being eluted with benzene containing 50% and 75% $CHCl_3$ (see Table I). A 250-mg sample was recovered by

Table I[a]

Fraction	Eluent (cc)	Product (mg)
1	Benzene (300)	Yellow brown oil (451)
2	Benzene–10% $CHCl_3$ (100)	Yellow brown oil (7)
3	Benzene–30% $CHCl_3$ (100)	Yellow brown oil (23)
4	Benzene–50% $CHCl_3$ (100)	Yellow brown oil (88)
5	$CHCl_3$ (100)	Pale yellow gum containing traces of crystalline material (178)
6	$CHCl_3$ (100)	Partially crystalline (78.8)
7	$CHCl_3$ (300)	Crystalline with only traces of oily material (67)
8	$CHCl_3$ (600)	Dark brown glass (35)
9	$CHCl_3$–1% MeOH (250)	Dark brown glass (62)
10	$CHCl_3$–2% MeOH (250)	Dark brown glass (94)
11	MeOH (500)	Dark brown glass (210)

[a] Total recovery 1.304 g.

Table II

Fraction	Eluent (cc)	Product (mg)
1	Benzene (100)	Dark brown oil (8)
2	Benzene (100)	Almost colorless glass (4)
3	Benzene (150)	Almost colorless glass (14)
4	Benzene–25% $CHCl_3$ (100)	Almost colorless glass (40)
5	Benzene–50% $CHCl_3$ (60)	Almost colorless glass (30)
6	Benzene–50% $CHCl_3$ (60)	Almost colorless glass (31)
7	Benzene–50% $CHCl_3$ (60)	Crystalline (10.5)
8	Benzene–50% $CHCl_3$ (60)	Crystalline (21)
9	Benzene–65% $CHCl_3$ (50)	Crystalline (4)
10	Benzene–75% $CHCl_3$ (50)	Crystalline (10)
11	$CHCl_3$ (100)	Crystalline (21)
12	$CHCl_3$ (100)	Crystalline (20)
13	$CHCl_3$ (350)	Traces of crystalline material (13)
14	$CHCl_3$–5% MeOH (250)	Dark brown glass (47)

elution with benzene–chloroform and 100% $CHCl_3$. A 28-mg sample of material eluted with chloroform–5% methanol was rejected. Recrystallization from chloroform–petroleum ether (bp 60–80°) of crystalline material from the chromatographic procedure gave the chloroform solvate of *dl*-rhyncophyllol, mp 106–112°. For analysis, the sample was dried at room temperature over solid potassium hydroxide.

Anal. Calcd for $C_{19}H_{26}N_2O_2 \cdot CHCl_3$: C, 55.25; H, 6.26; N, 6.44; Cl, 24.46. Found: C, 55.34; H, 6.37; Cl, 24.45.

Sublimation of *dl*-rhyncophyllol solvate provided noncrystalline, chloroform-free product. A 33.7-mg sample of sublimate (1.07×10^{-4} mole) and mercuric acetate (200 mg, 6.27×10^{-4} mole) dissolved in 1.5 ml of 90% aqueous acetic acid were heated on the steam bath. A crystalline precipitate of mercurous acetate began to separate almost immediately. The mixture was heated for 4 hr, cooled, and filtered. The filtrate was made basic with $NaHCO_3$ and extracted into chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to a yellow brown glass (12.3 mg) which could not be induced to crystallize. The infrared spectrum of the product showed, in addition to the oxindole carbonyl at 5.85 μ, a strong band at 6.1 μ indicative of a six-membered lactam ring formed by hydrolytic ring cleavage of the initial immonium ion.

Preparation of Di-*p*-toluoyl D-tartrates of *d*- and *dl*-Rhyncophyllols. Rhyncophyllol (3.3 mg), derived as described from the alkaloid rhyncophylline,[10] and 4.05 mg of di-*p*-toluoyl D-tartaric acid were dissolved in acetone. Slow evaporation of the solvent provided crystalline salt, mp 188–189.5° dec. Similarly, *dl*-rhyncophyllol was dissolved with 1 molar equiv of the tartaric acid in hot acetone. On cooling, the acetone solution deposited colorless crystalline salt, mp 189–190.5° dec. The mixture melting point of the two samples was 189–190.5°.

Isorhyncophyllol (25).[8] A solution of crystalline rhyncophyllol (34 mg, 0.108 mmole) in 9.0 ml of pyridine was refluxed overnight in a 25-ml round-bottomed flask equipped with a water-cooled condenser. After 16 hr, the solution was cooled to 25° and the pyridine removed by coevaporation with six 10-ml portions of petroleum ether (bp 60–68°). The yellow oil remaining was chromatographed on 2 cm × 20 cm × 1 mm silica gel GF_{254} plates, eluting with 3% methanol in chloroform saturated with concentrated ammonia and employing a technique of continuous evaporation of solvent from the top edge of the plate for 2 hr. Three bands were visible on the plate under uv light. The lowest band provided 4.1 mg (12%) of rhyncophyllol; the middle band provided 1.7 mg (5%) of an unknown compound whose infrared and ultraviolet spectra were similar to those of rhyncophyllol; the upper band provided 28.2 mg (83%) of a colorless glassy foam identical with the isorhyncophyllol described by Marion, *et al.*[8] A crystalline picrate was prepared from this foam by mixing 7 mg of the foam with 5.6 mg of picric acid (twice recrystallized from chloroform) in 3 drops of methanol. Cooling the solution overnight at −10° precipitated 10 mg (80%) of crystalline picrate that was recovered by centrifugation, mp 165–168° (lit.[8] mp 168–169°).

In an alternate procedure, 157 mg of the oily mixture obtained by the pyridine thermolysis of rhyncophyllol were mixed with 1 equiv (115 mg) of picric acid in methanol and cooled overnight to provide 142 mg of crude picrate (mp 155–169°). The free amine regenerated from this picrate was chromatographically homogeneous isorhyncophyllol. The low yield afforded by this separation technique could be avoided since the picrate crystallization liquors could be reconverted to a mixture of the free amines and purified by preparative tlc as described above.

Dihydrodesoxyisorhyncophyllol. A slurry of 35 mg of reagent lithium aluminum hydride in 6 ml of tetrahydrofuran was prepared in a 25-ml, three-necked conical flask equipped with a water-cooled condenser, 25-ml pressure-equalized addition funnel, nitrogen inlet, and magnetic stirring bar. To this refluxing slurry was slowly added isorhyncophyllol (16.5 mg, 0.052 mmole) in 4 ml of tetrahydrofuran over a period of 20 min. The solution was allowed to reflux for 2.5 hr, then cooled to 0°. The excess lithium aluminum hydride was decomposed by addition of 3 drops of water and the slurry was filtered through a sintered glass funnel. The filter cake was mixed with 0.5 g of sodium sulfate and washed with six 10-ml portions of chloroform. The combined filtrate and wash solutions were evaporated at a reduced pressure to provide 15 mg of a colorless oil that rapidly darkened on standing. This oil was chromatographically homogeneous and much less polar on silica gel tlc (elution with 7.5% methanol–1% concentrated ammonia, in chloroform) than isorhyncophyllol. It was also considerably less polar than a similar reduction product obtained from rhyncophyllol and reported by Marion[10a] to be dihydrodesoxyrhyncophyllol.

The crude reduction product was chromatographed on a 20 cm × 20 cm × 1 mm silica gel GF_{254} tlc plate, eluting with 10% methanol in chloroform saturated with concentrated ammonia. The single band visible under uv light provided 12 mg (76%) of a light yellow oil which was assigned the structure of dihydrodeoxyisorhyncophyllol in analogy with Marion's work.[10a] This oil had tlc behavior identical with the tetracyclic amines **2** and **3** obtained by cleavage–cyclization–reduction of diol amide **1**.[4,9] Chromatography of each of these three samples was carried out simultaneously on three 10 cm × 20 cm × 0.5 mm silica gel GF_{254} tlc plates and the colorless oils obtained were compared. The synthetic tetracyclic amine **2** had infrared and ultraviolet spectra identical in every respect with the spectra of dihydrodesoxyisorhyncophyllol. This result, combined with the conversions described below, allows the unequivocal assignment of the ring structure of dihydrodeoxyisorhyncophyllol to synthetic tetracyclic amine **2**.

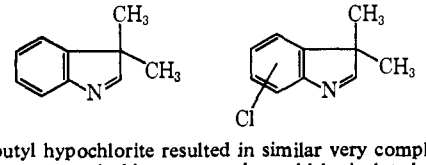
3,3-Dimethylindoline (16). A solution of twice recrystallized bis(3,3-dimethylindolenine)zinc chloride complex (200 mg, 0.471 mmole) in 35 ml of absolute ethanol in a 50-ml round-bottomed flask was treated with a solution of 200 mg of potassium borohydride in 5 ml of 50% aqueous ethanol at 25° for 19 hr. The mixture was then filtered to remove a white precipitate and the solid washed with three 10-ml portions of chloroform. The combined filtrate and wash solutions were concentrated at a reduced pressure to provide 117 mg of a pungent red oil.

Sublimation of this oil at 70° and 0.02 mm provided 80 mg (59%) of a white solid that melted at about 30° (lit.[11] mp 31–32°). The ultraviolet spectrum was characteristic of an indoline: λ_{max}^{MeOH} 242, 290 mμ $\lambda_{max}^{MeOH,\ H^+}$ 260, 266 mμ. The infrared spectrum was consonant with the expected structure. These data allowed a structural assignment of 3,3-dimethylindoline (**16**) to the sublimate. The material was further purified by preparative tlc before use in the succeeding experiments.

1,5,7-Trichloro-3,3-dimethyloxindole (17). A mixture of 3,3-dimethylindoline (26.5 mg, 0.178 mmole) and 60 mg of anhydrous sodium acetate in 30 drops of chloroform was cooled to −10° in a 13 × 100 mm test tube. While the cold solution was stirred rapidly with a small magnetic bar, a similarly cooled solution of *t*-butyl hypochlorite (117 mg, 6 equiv, 1.07 mmoles) in 30 drops of carbon tetrachloride was slowly added from a pipet. The solution became first intensely blue, then green, and finally maroon. It was allowed to warm to 25° and stirred under nitrogen. After 24 hr, the solution was mixed with an equal volume of water and extracted with three 2-ml portions of chloroform. The combined extracts were washed with 3 ml of water, dried over sodium sulfate, filtered, and concentrated to provide 49 mg of a dark oil. The infrared spectrum of this oil possessed a strong carbonyl absorption at 5.71 μ and no bands in the N–H stretching region. On the basis of this spectrum and further conversions outlined below, it was assigned the structure of 1,5,7-trichloro-3,3-dimethyloxindole (17). The oil was not stained on silica gel H tlc plates by iodine or acidic ceric sulfate. The crude yield represents an essentially quantitative conversion to the trichlorooxindole derivative.[20]

5,7-Dichloro-3,3-dimethyloxindole (18). A solution of oily 1,5,7-trichloro-3,3-dimethyloxindole (48 mg, 0.183 mmole) was dissolved in methanol and the solvent evaporated to remove traces of residual chloroform. The oil was then dissolved in 10 ml of 1 *N* methanolic potassium hydroxide; this solution was mixed with 30 mg of W-2 Raney nickel in a 50-ml hydrogenation flask and treated with hydrogen at atmospheric pressure. After 19 hr, the solution was filtered and the filtrate was mixed with 10 ml of water and extracted with three 10-ml portions of chloroform. The combined

(20) Attempts to oxidize 3,3-dimethylindoline (**16**) using limited amounts of *t*-butyl hypochlorite were not very successful. Although treatment with 4 equiv of the reagent provided good yields of the dichloro derivative **18**, smaller amounts of oxidant gave complex mixtures of products. Treatment with 1 equiv of *t*-butyl hypochlorite resulted in an extremely low yield (4% based on assumed product) of an oil (shown to contain chlorine by Beilstein's test) with an ultraviolet spectrum similar to that of 3,3-dimethylindolenine. This product was presumably a ring-chlorinated indolenine. Treatment of **16** with **2** or **3**



equiv of *t*-butyl hypochlorite resulted in similar very complex mixtures from which no recognizable compounds could be isolated.

extracts were washed with water, dried over sodium sulfate, filtered, and concentrated to provide 37 mg of a light yellow oil. This material was purified by chromatography on a 20 cm × 20 cm × 1 mm silica gel GF_{254} plate, eluting with 1% methanol in chloroform. Removal of the strongest band visible under uv light provided 32 mg (77%) of white crystals, mp 182–184°. This compound was homogeneous on tlc and considerably less polar than 3,3-dimethyloxindole.[11] Its infrared spectrum ($CHCl_3$) contained a 5.82-μ carbonyl band and 2.91- and 3.15-μ NH absorptions, characteristic of oxindoles. The ultraviolet spectrum, λ_{max}^{MeOH} 253 mμ, was also characteristic of the oxindole chromophore. An infrared spectrum in carbon disulfide indicated the presence of the carbon–chlorine bond (13.2 μ). The pmr spectrum, described in the Discussion, allowed structural assignment of 5,7-dichloro-3,3-dimethyloxindole (**18**) to the crystalline product, mp 182–184°.

3,3-Dimethyloxindole (19). A slurry of 200 mg of 30% palladium on carbon in 2.5 ml of triethylamine (distilled from potassium hydroxide) and 5.0 ml of ethanol was equilibrated with hydrogen gas at atmospheric pressure in a 50-ml hydrogenation flask. A solution of 1,5,7-trichloro-3,3-dimethyloxindole (86 mg, 0.326 mmole) in 1 ml of ethanol was added through the side arm and treated with hydrogen for 16 hr. The mixture was filtered through Celite and the solvent removed at a reduced pressure. The residue was taken up in 25 ml of chloroform and the solution was extracted with six 5-ml portions of water to remove triethylamine hydrochloride. Evaporation of the chloroform left 57 mg of a yellow oil. Chromatography of this oil on a 20 cm × 20 cm × 1 mm silica gel GF_{254} tlc plate, eluting with 1% methanol in chloroform, provided 41.0 mg (78%) of a tan solid when the major band was worked up in the usual fashion. This solid was recrystallized from benzene to give white crystals of mp 150–153°. This compound melted at 150–153° when mixed with an equal amount of authentic 3,3-dimethyloxindole (**19**) (mp 151–152.5°). The infrared and ultraviolet spectra of the synthetic and authentic compounds were identical in every respect.

Isorhyncophyllol from Dihydrodesoxyisorhyncophyllol. A dry mixture of dihydrodesoxyisorhyncophyllol (6.2 mg, 0.021 mmole) and 2-naphthalenesulfonic acid (4.4 mg, 0.021 mmole) was placed in a 13 × 100 mm test tube equipped with a small magnetic stirring bar. Addition of 25 drops of warm water led to formation of an oily red precipitate; subsequent addition of 40 drops of chloroform was followed by cooling to 0°. To this cooled and rapidly stirred three-phase solution was added *t*-butyl hypochlorite (9.0 mg, 0.083 mmole) in 30 drops of ice-cold chloroform. The test tube was flushed with nitrogen and allowed to stir at 25°. After 14 hr, 2 ml of saturated salt water and 0.25 ml of concentrated ammonia were added and the mixture was extracted with three 5-ml portions of chloroform. The combined extracts were washed with 3 ml of water, dried over sodium sulfate, filtered, and concentrated to give 9 mg of a dark purple foam.

This foam and 100 mg of 30% palladium on carbon were mixed with 4 ml of absolute ethanol and 2 ml of triethylamine and the slurry was treated with hydrogen gas at 1 atm pressure for 4 hr. Filtration to remove the catalyst (washed with three 10-ml portions of ethanol) followed by evaporation of the solvent from the filtrate gave 5.8 mg of a light gray oil which was chromatographically homogeneous and identical in tlc behavior with isorhyncophyllol. The crude yield was 87%.

This oil was chromatographed on a 10 cm × 20 cm × 1 mm silica gel GF_{254} tlc plate, eluting with 10% methanol in chloroform saturated with ammonia. Extraction of the major band visible under uv light led to 3.0 mg (46%, 0.0096 mmole) of a colorless oil whose infrared spectrum was absolutely identical with the spectrum of isorhyncopyllol.

The pure oil was mixed with picric acid (2.2 mg, 0.0096 mmole) in 1 drop of methanol and stored overnight at 0°. By centrifugation and repeated washing with cold methanol, it was possible to obtain 3.9 mg (75%) of yellow crystals melting at 166–169°. A sample of this picrate when mixed with a sample of authentic isorhyncophyllol picrate (mp 168–169°) showed no melting point depression, mp 167–169°.

***dl*-Isorhyncophyllol from Tetracyclic Amine Alcohol 2.** In a manner completely analogous to the preceding experiment, tetracyclic amine alcohol **2** (10.6 mg, 0.035 mmole)[9] and 2-naphthalenesulfonic acid (7.35 mg, 0.035 mmole) were treated in chloroform–water suspension with *t*-butyl hypochlorite (15.3 mg, 0.141 mmole). Work-up provided 12.0 mg of chlorinated oxindole which was treated at once with the previously described hydrogenolysis conditions to provide 6.3 mg of a tan foam for a 57% crude yield of *dl*-isorhyncophyllol. This material was chromatographed on a 10 cm × 20 cm × 1 mm silica gel GF_{254} tlc plate and the major band extracted to provide 3.5 mg (32%) of a colorless oil whose solution infrared and ultraviolet spectra were identical with the spectra of natural isorhyncophyllol.

This oil (3.5 mg, 0.011 mmole) was mixed with picric acid (2.6 mg, 0.011 mmole) in 1 drop of methanol. Crystals spontaneously formed and were collected by centrifugation and washed with methanol. The 2.4 mg (39%) of bright yellow needles melted at 195–197°.

Authentic *dl*-Isorhyncophyllol. A solution of *dl*-rhyncophyllol (17.2 mg, 0.055 mmole) in 7 ml of pyridine was heated at reflux in a 100-ml round-bottomed flask equipped with a water-cooled condenser. After 17 hr the solution was cooled and the pyridine removed at reduced pressure by coevaporation with petroleum ether (bp 60–68°). The dry, nonvolatile oil remaining was chromatographed on a 20 cm × 20 cm × 1 mm silica gel GF_{254} plate using 5% methanol in chloroform saturated with concentrated ammonia. Three bands were visible under uv light, perfectly analogous to the observation on the similarly equilibrated natural material. The lowest band provided 3.0 mg (17.4%) of oily material which was identical with rhyncophyllol in tlc and solution spectrometric behavior. The least polar band provided 8.9 mg (51.7%) of a light yellow glassy foam which was identical with natural isorhyncophyllol in tlc and solution spectrometric behavior. The middle band was discarded.

The *dl*-isorhyncophyllol was again chromatographed on a 10 cm × 20 cm × 1 mm silica gel GF_{254} plate, eluting with 10% methanol in chloroform saturated with concentrated ammonia. Extraction of the single band visible under uv light provided 5.7 mg of a colorless oil. This oil (5.7 mg, 0.0182 mmole) was mixed with picric acid (4.2 mg, 0.0184 mmole) in 1 drop of methanol. Bright yellow needles crystallized spontaneously and were isolated by centrifugation and washing with cold methanol. This provided 5.6 mg (56%) of crystals, mp 196–197°.

A mixture melting point of the *dl*-isorhyncophyllol picrate obtained above and the *dl*-isorhyncophyllol picrate prepared from tetracyclic amine alcohol **2** in the preceding experiment was undepressed (mp 195–197°).

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