Tetrahedron Letters No. 16, pp. 1011-1016, 1963. Pergamon Press Ltd.
Printed in Great Britain.

BIOGENETIC-TYPE SYNTHESIS IN THE OXINDOLE ALKALOID SERIES

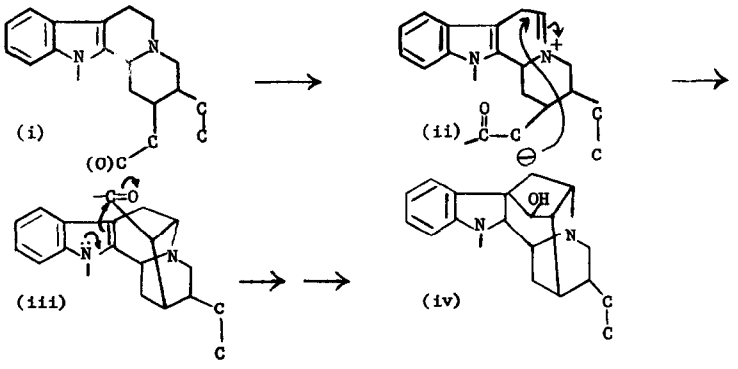
E. E. van Tamelen[a], J. P. Yardley and M. Miyano
Department of Chemistry, University of Wisconsin, Madison, Wisconsin
(Received 11 April 1963)

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[b]. 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 reasonable

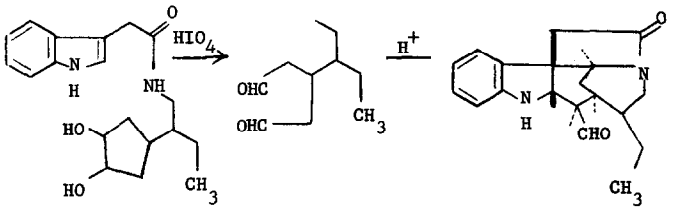
---

[a] Present address: Stanford University, Department of Chemistry, Stanford California.

[b] 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 (at least):

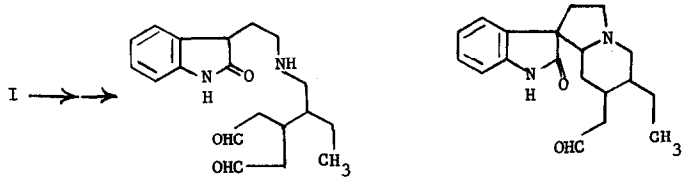


that relatively direct, simply executed laboratory construction of intricate natural organic systems might be possible if the required types of oxidation were performed on suitable substrates with ordinary chemical reagents, in lieu of enzymes; while the desired annulation processes, being normal chemical changes, would be expected to follow, as in the natural systems (1). As an example of this principle, the in vitro conversion of the simple indole derivative I, via II, to the strychninoid system III, accomplished recently



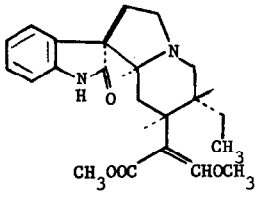
I II III

in this Laboratory, may be cited (2). In order to provide further support for the principle and to develope a new synthetic approach to yet another natural product system, efforts were made to modify slightly the case reproduced above by setting up the oxindole aldehyde IV, which would be

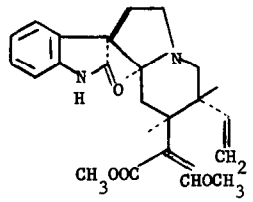


IV V

expected to ring close to the tetracyclic oxindole V, of obvious relation to the rhyncophylline-corynoxeine (3) cases (4) (VIa-b). Summarized



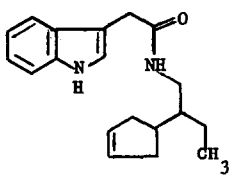
VIa



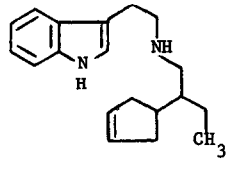
VIb

below is the method used to reduce this scheme to practice.

Lithium aluminum hydride reduction of the amide VII, prepared as previously outlined (2), afforded the corresponding secondary amine (VIII), which was converted without purification to derivatives (benzamide, m.p. 145-147.5°, after crystallization from ethyl acetate-petroleum ether; glycol

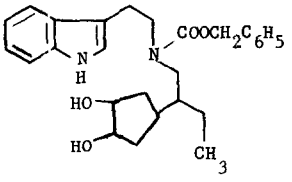


VII

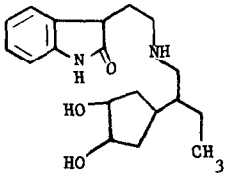


VIII

secured by osmylation of cyclopentene double bond, characterized as the trinitrobenzene (TNB) complex, m.p. 98.5-100°, after crystallization from aqueous methanol). Through the use of benzyl chloroformate, amine VIII was converted to the carbobenzoxy derivative (TNB complex, m.p. 98.5-100°), non-crystalline material which was hydroxylated by means of osmium tetroxide at -70° in tetrahydrofuran-pyridine followed by hydrogen sulfide in EtOH-CH_2Cl_2. The diol was not crystalline, but did form a well-defined TNB



IX



X

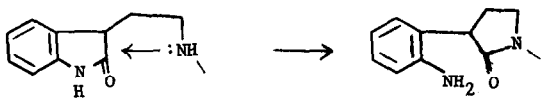
complex (m.p. 73-74°) and could be purified by silicic acid column chromatography. Transformation to the oxindole was accomplished through a modification of the Lawson and Witkop method (5)[c]: N-bromosuccinimide oxidation to ar-bromoxindole, silicic acid chromatography of the latter, followed by catalytic (Pd) hydrogenolysis of aromatic halogen and carbobenzoxy group. Neither the free oxindole glycol nor any of the salts prepared from it was crystalline, 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[d].

Oxidation to the dialdehyde (or cyclic alkanolamine) IV was brought about by reaction with sodium metaperiodate, carried out in aqueous solution

---

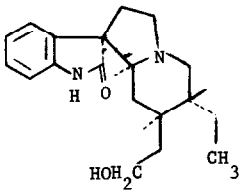
[c] For conversion of 3-alkyl indoles to oxindoles by NBS/t-butanol, see R. L. Hinman and C. P. Bauman, Abs. of Papers, Division of Organic Chemistry, 18M, 144th American Chemical Society Meeting, April 1-5, 1963.

[d] Under various conditions (standing for several days in methanol solution, or chromatography over silicic acid with chloroform-methanol elution), the normal U.V. 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) $\lambda_{infl.}$ 248, 280 mμ (ϵ = 5300, 1100). This observation may be interpreted as indicating the rearrangement v ⟶ vi:



(v) (vi)

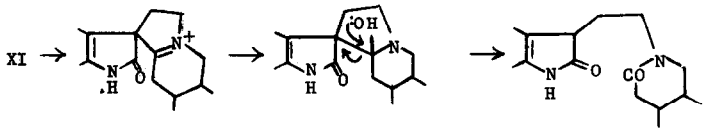
at 0° for fifteen minutes. Aldehyde material was isolated by extraction and immediately heated under reflux in 8% aqueous hydrochloric acid for three hours. Subsequent to borohydride reduction of total non-acidic material, a chromatographic separation using Woelm neutral alumina (19% water, activity grade IV-V) was carried out. The 100% chloroform fractions provided



XI

crystalline material (m.p. 106-112° after recrystallization from chloroform-petroleum ether) which was shown by analysis to be the 1:1 chloroform solvate or material with the desired composition (material freed from solvent by sublimation was, again, not crystalline)[e]. The substance was identified as the rhyncophylline-derived degradation product, rhyncophyllol (XI) (dl), by 1/ comparison of its infrared spectrum with that of authentic rhyncophyllol (3), both measured on chloroform solutions, and 2/ optical resolution as the di-p-toluoyl-D-tartrate, m.p. 189-190.5° (dec.); di-p-toluoyl-D-tartrate

[e]Initial evidence that the anticipated change has indeed occurred was secured by mercuric acetate oxidation of this material, which process gave rise to product with an I.R. band at 6.1 μ (6-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:



of authentic rhyncophyllol, m.p. 188-189.5° (dec.); mixed m.p. 189-190.5° [f-i]

ACKNOWLEDGMENT

The authors are indebted to the National Science Foundation (G19-515) and the National Institutes of Health (RG-3892) for financial support. Rhyncophylline used in this investigation was provided by Professor T. Nozoye, Itsuu Laboratory, Tokyo; and a sample of rhyncophyllal was supplied by Dr. L. Marion (National Research Council, Ottawa).

REFERENCES

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

(2) E. E. van Tamelen, L. J. Dolby and R. G. Lawton, Tetrahedron Letters No. 19, 30 (1960).

(3) J. C. Seaton and L. Marion, Can. J. Chem. 35, 1102 (1957); N. A. Cu, R. Goutarel and M. M. Janot, Bull Soc. chim. France, 1292 (1957).

(4) For stereochemistry, see N. Finch and W. I. Taylor, J. Amer. Chem. Soc. 84, 3871 (1962) and references therein.

(5) W. B. Lawson and B. Witkop, J. Org. Chem. 26, 263 (1961).

[f] The mechanistic and stereochemical aspects of this synthesis will be considered in detail later.

[g] The elemental analyses, U.V. and I.R. spectra of all crystalline intermediary materials were satisfactory; substances described as non-crystalline were not subjected to C-H analyses.

[h] Routes by which a rhyncophyllol might be converted to the parent alkaloidal system can be visualized. However, in principle the problem of a rhyncophylline total synthesis has been solved, in that dihydrocorynantheine has been converted to the aforementioned base (footnote d), and dl-dihydrocorynantheine has been secured by total synthesis [E. E. van Tamelen and J. B. Hester, Jr., J. Amer. Chem. Soc. 81, 3805 (1959)].

[i] Since epimerization during the conversion of rhyncophylline to rhyncophyllol has not been ruled out, the stereochemistry designated herein for the latter base should be regarded as tentative.