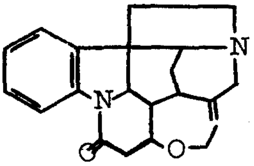
Tetrahedron Letters No. 19, pp. 30-35, 1960. Pergamon Press Ltd. Printed in Great Britain.

A BIOGENETICALLY-PATTERNED LABORATORY SYNTHESIS IN THE STRYCHNINE - CURARE ALKALOID SERIES

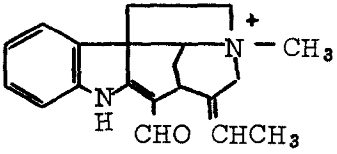
E. E. van Tamelen, L. J. Dolby and R. G. Lawton
Department of Chemistry, University of Wisconsin,
Madison, Wisconsin

(Received 15 July 1960)

Although the method by which Nature constructs the complex polycyclic structures characteristic of strychnine (I) and related bases (including the curare alkaloid group e.g. C-fluorocurarine, II[1,2]) has been the subject of detailed discussion,[3,4] no synthesis



I



II

---

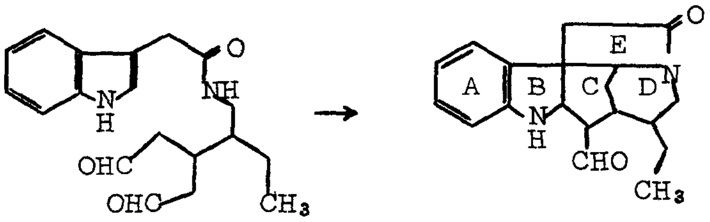
[1] W. von Philipsborn, H. Meyer, H. Schmid and P. Karrer, *Helv. Chim. Acta* **41**, 1257 (1958).

[2] H. Fritz, E. Besch and T. Wieland, *Angew. Chem.* **71**, 126 (1959).

[3] R. B. Woodward, *Nature* **162**, 155 (1948).

[4] E. Wenkert and N. V. Bringi, *J. Am. Chem. Soc.* **81**, 1474 (1959).

simulating a reasonable biogenetic route has been realized in the laboratory. We have discovered that the simple indole derivative III under mild conditions directly generates the fused system IV



III IV

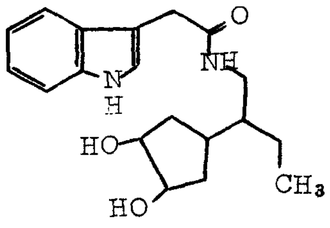
containing five rings and six asymmetric centers, and duplicating the essential framework of the strychnine-type natural products.[5]

The intermediary, unisolated dialdehyde was produced by periodate cleavage of the diol V, obtained by the following series of operations. The p-toluenesulfonate of Δ^3-cyclopentenol (prepared by hydroboration-oxidation of cyclopentadiene)[6] was used to alkylate ethylcyanoacetic ester, and the resulting product (b.p. 138-140°/ 13 mm.) was saponified and decarboxylated to give the unsaturated nitrile

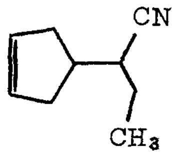
---

[5] For the total synthesis of strychnine, see R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, ibid. 76, 4749 (1954).

[6] E. L. Allred, J. Sonneberg and S. Winstein, ibid. 81, 5833 (1959).

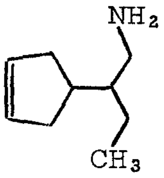


V

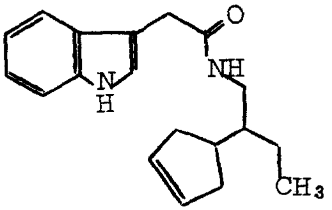


VI

(VI) (b.p. 115°/30 mm.). The primary amine (VII) (b.p. 97-100°/30 mm.) obtained by lithium aluminum hydride reduction of VI was heated with methyl indole-3-acetate, providing the oily amide VIII.

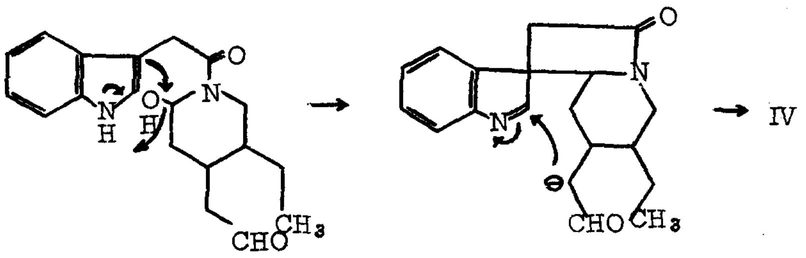


VII



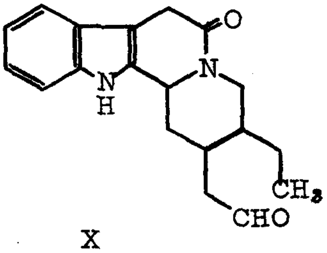
VIII

Hydroxylation of crude VIII by means of osmium tetraoxide led to the required diol V, characterized as the trinitrobenzene complex, m.p. 145.5-146.5°. When generated, intermediate III cyclizes spontaneously to the alkanol amide IXa, detected by its infrared spectrum (peaks at 5.79 and 6.03 μ). On being heated briefly in aqueous acetic acid-sodium acetate or formic acid-sodium formate, III-IXa, by-passing

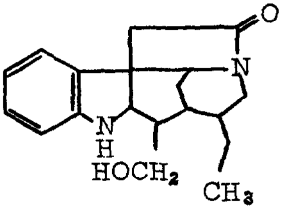


IXa IXb

normal α-cyclization to X, forms directly the indoline IV, presumably by way of sequence IXa → IXb → IV.[7] The unstable aldehyde lactam (not analyzed), appearing in part as the N-formyl derivative,



X



XI

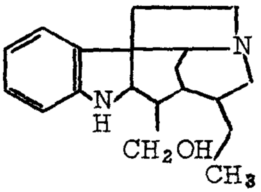
was reduced with sodium borohydride to the lactam alcohol XI (m.p. 53-56°, sublimed at 145°/ca. 10^{-4} mm.; picrate, m.p. 152-154°), which in turn was converted with lithium aluminum hydride to

---

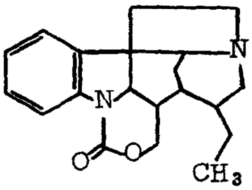
[7] The factors controlling the course of cyclization in this and related cases are under investigation in this Laboratory.

the amino alcohol XII (sublimed at 110°/ca. 10^{-4} mm.).

Assignment of structure to product IV depends upon the following observations. The ultraviolet spectrum of, e.g., XI (λ^{alc}_{max} 243, 295 mu, ϵ = 9600, 3400) is virtually identical with that of the Wieland-Gumlich aldehyde (λ^{alc}_{max} 243, 295 mu, ϵ = 9100, 3000)[8] thus revealing the presence of the indoline ring system (ring A and saturated ring B). Substance IV or XI possesses a lactam carbonyl band in the infrared at 5.97 μ, indicating a five-membered E-ring.[9] The presence of the second new carbon-carbon bond, incorporated into a β-aminoaldehyde system and requiring the presence of a six-membered C-ring, was proved by conversion of alcohol XII to a tetrahydrooxazinone (XIII), m.p. 123-126° (infrared



XII



XIII

---

[8] F. E. Bader, E. Schlittler, and H. Schwarz, Helv. Chim. Acta 36, 1258 (1953).

[9] P. J. Scheuer, J. Am. Chem. Soc. 82, 193 (1960).

peak at 5.97 μ). This heterocyclic derivative was secured by reaction with phenylchlorocarbonate, followed by cyclization of the intermediary urethane (carbonyl peak at 5.90 μ) with sodium hydride in benzene.[10] Finally, elemental analyses demonstrate that complete cyclization of III is accompanied by dehydration. These findings allow no reasonable structure other than that proposed for the cyclization product IV.

Where possible and except as indicated, elemental analyses have been obtained on all substances described.

This research was supported by a National Science Foundation postdoctoral fellowship (to L. J. D.).

---

[10] In a model series, N-phenyl-3-aminopropanol was converted similarly to the phenyl carbamate (5.90 μ), and thence to the cyclic urethane (5.97 μ).