Tetrahedron Letters No. 25, pp. 1757-1760, 1963. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF (±)-FOLICANTHINE

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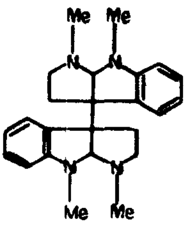
(Received 12 July 1963; in revised form 5 August 1963)

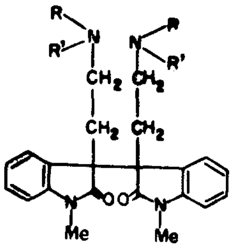
Folicanthine, one of the Calycanthus alkaloids, was isolated by Eiter (1) from Calycanthus floridus in 1951, and its structure was assigned as I by chemical (2) and X-ray method (3). Hendrickson et al. recently reported the synthesis of chimonanthine (4), another Calycanthus alkaloid, and this prompts us to report our results of the total synthesis of (±)-folicanthine.

One of the present authors (T.H.) published the synthesis of numbers of 3,3'-disubstituted 3,3'-bioxindoles, among which IIa was also included (5). After the method of synthesis of eserine type of compounds, IIa was treated with metallic sodium and butanol, but contrary to our expectation a fission of the molecule took place, affording N-methyltryptamine as the only isolable substance.

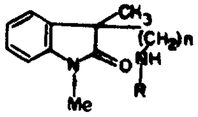
Prior to the lithium aluminum hydride reduction of IIa, a model experiment was carried out with III (R: H or CH_3, n: 2 or 3) and the cyclized products (IV, R: H or CH_3, n: 2 or 3) were obtained in acceptable yield (6). This procedure was now extended to IIb with success, furnishing (±)-folicanthine (I).



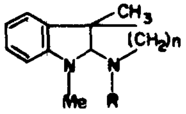
I



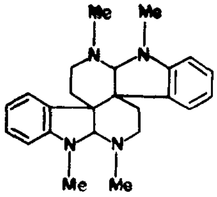
II



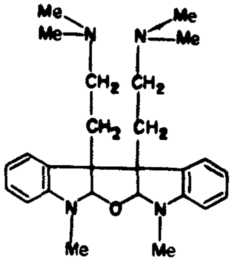
III



IV



V



VI

a: R,R' = H
b: R = H, R' = CH_3
c: R,R' = PhCH =
d: R,R' = CH_3

The Schiff's base (IIc), m.p. 188-189° (Found C, 78.15; H, 6.39; N, 10.36 %, $C_{36}H_{34}O_2N_4$ requires C, 77.95; H, 6.18; N, 10.10 %), was heated with an excess of methyl iodide at 100° in a sealed tube to afford dimethiodide, which was directly treated with diluted hydrochloric acid to give IIb, m.p. 184-186° (Found C, 70.40; H, 7.40; N, 14.20 %, $C_{24}H_{30}O_2N_4$ requires C, 70.91; H, 7.44; N, 13.78 %).

IIb was heated with an excess of lithium aluminum hydride in dioxane for 8-12 hrs. to afford (±)-folicanthine, m.p. 168-169° (Found C, 77.03; H, 8.05; N, 14.69 %, $C_{24}H_{30}N_4$ requires

C, 76.96; H, 8.07; N, 14.96 %), together with other oily products, and was purified through chromatographic separation over alumina. The infrared spectrum in carbon tetrachloride solution was superimposable with that of natural folicanthine, kindly supplied by Dr. Smith. The mass spectra of the both samples, taken by the direct inlet system through the courtesy of Dr. Djerassi, were identical in regard to main peaks, m/e 374,273,188,187,186(base peak),185,172,145, and 144, and in other peaks with abundance over 5 %. These data were also in conformity with those reported by Clayton et al. (7), thus clearly excluding the alternate cyclization to form V. The possibility of the meso type can not be excluded, since the stereochemistry of II has not been established. However, identity in the infrared spectrum of both natural and synthetic alkaloid, and of the Hofmann degradation product (VI) of the former (8), and the reduction product of IId(5), respectively, suggests that the synthetic product is the racemate of the alkaloid.

Acknowledgements We express our deep gratitude to Prof. Emeritus S.Sugasawa for his interest and encouragement throughout this work. We are indebted also to Dr. G.F.Smith for the gift of folicanthine, to Dr. C.Djerassi and Dr. M. Suzuki for the measurement of mass spectra.

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(8) The infrared spectrum of the Hofmann degradation product in carbon tetrachloride was kindly supplied by Dr.Smith.