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THE BIOGENETIC-TYPE SYNTHESIS OF EMETINE

E. E. van Tamelen,[a] G. P. Schiemenz and H. L. Arons[b]
Department of Chemistry, University of Wisconsin, Madison, Wisconsin
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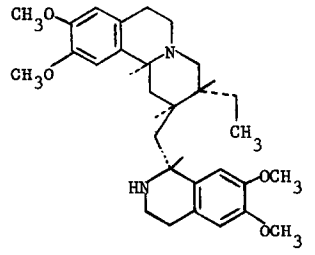
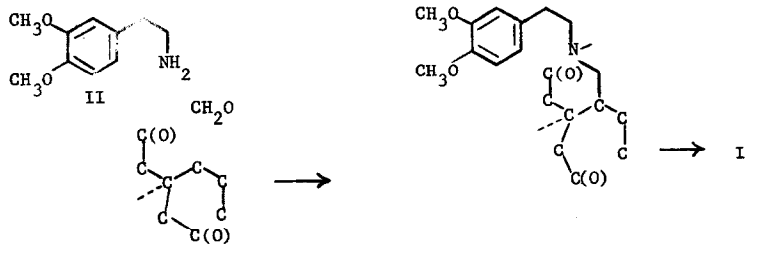
ALTHOUGH crucial experiments on the biosynthesis of the well-known medicinal agent emetine (I) (1) have not been reported, the present state of biogenesis



I

science (2) permits the proposal that the alkaloid originates _in vivo_ from 3,4-dimethoxyphenethylamine (II) (or a related species), formaldehyde (or its equivalent) and a third, as yet poorly defined, component which may be

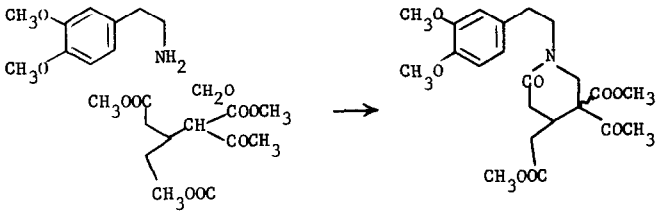


II III IV

[a]Present address: Stanford University, Department of Chemistry
[b]National Science Foundation Fellow.

represented at the present time only as III. Along with the key biochemical operations, viz., condensation to an intermediate of type IV, a second 3,4-dimethoxyphenethylamine unit is introduced; and, subsequent to any necessary adjustments in the oxidation state, the emetine system evolves. A rather similar pathway undoubtedly is followed in the biosynthesis of ajmalicine (formally, from tryptamine, formaldehyde and III); and recently an economical, biogenetically-patterned total synthesis of that indole alkaloid was accomplished in this Laboratory (3). It seemed that modification to the emetine case would be feasible and worthwhile, and in this disclosure we report laboratory operations which constitute a practical, stereoselective synthesis of that naturally-occurring base (4).

By means of a Mannich reaction involving 3,4-dimethoxyphenethylamine, formaldehyde and the keto triester V (4) and carried out in t-butanol,

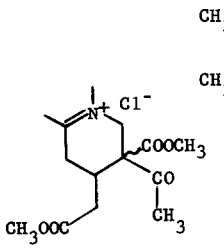


V VI

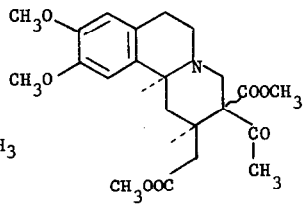
the integral part of the emetine molecule can be constructed in a single operation. Spontaneous lactamization of the initially produced Mannich base is involved in formation (approximately quantitative yield[c]) of the isolated product VI, an oil, distillable under high vacuum, which exhibited

[c] A small amount of 6,7-dimethoxytetrahydroisoquinoline, formed by simple interaction of the starting amine with formaldehyde, was also isolated.

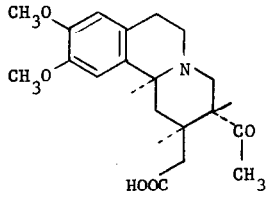
infrared absorption bands, inter alia, at 5.75 μ (ester), shoulder 5.8 μ (ketone) and 6.10 μ (lactam), and maxima in the ultraviolet (methanol solvent) at 230 mμ (log ε = 3.93) and 280 mμ (log ε = 3.47). Bischler-Napieralski cyclization (phosphorus oxychloride-benzene) of lactam VI afforded directly, crystalline tricyclic iminium chloride (VII).



VII



VIII

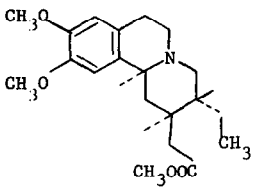


IX

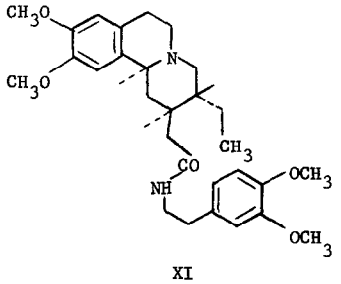
Recrystallized from nitrobenzene-petroleum ether, the salt so produced melted at 148.5-150° and exhibited U.V. maxima (methanol solvent) at 246 mμ (log ε = 4.12), 307 mμ (log ε = 3.91) and 359 mμ (log ε = 3.94)[d]. Catalytic reduction of the crude Bischler-Napieralski product was carried out in methanol over platinum; the hydrochloride secured was best converted to the free base VIII and purified in that state (m.p. 119-120°, after crystallization from ether). Hydrolysis and decarboxylation of the β-keto ester unit was managed by heating of the keto diester VIII in refluxing 2% hydrochloric acid for several days. After chromatography on silicic acid, the keto acid IX hydrochloride (m.p. 196-198°; mol. wt. by titration, 393) was recrystallized for analysis from chloroform-carbon tetrachloride.

[d] Carbon analyses on the slightly unstable salt were 1.5-2% low.

Removal of the ketonic carbonyl group remained, and this was accomplished by conversion of the methyl ester of keto acid IX to dithioketal, followed by Raney nickel desulfurization. The former reaction was carried out by treatment of keto ester hydrochloride with ethylenedithiol in the presence of boron trifluoride-etherate; the intermediate dithioketal was not ordinarily purified, but reductively desulfurated in boiling methanol directly to tricyclic ester X hydrochloride. Since this intermediate had



X



XI

already been transformed, via amide XI, to emetine (5), obtention of that substance by the route outlined constitutes a new total synthesis of the alkaloid. Identification of the key intermediate X was made by comparison of the hydrochloride (m.p. 199-199.5°) with equivalent dl-material (m.p. 198.5-199°) produced by an alternative route (1a, 5) (mixed m.p. 199-199.3°). Similarly, melting point and mixed melting point comparison of the amide XI (m.p. 148-150°), prepared from ester secured as described herein, with authentic amide (1a, 5) (m.p. as observed in parallel determination, 151.5-153°) were satisfactory, as were infrared spectral comparisons made on free base X, amide XI and corresponding authentic specimens[e,f].

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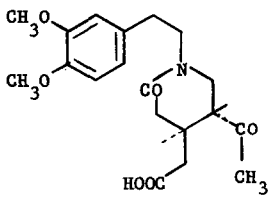
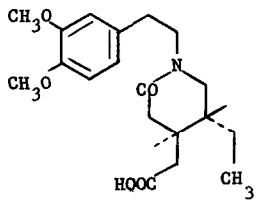
[e] The melting point behavior of ester X was not satisfactory for comparison purposes (see Reference 1a).

[f] Except where indicated, satisfactory elemental analyses on all new substances were obtained.

Although the route described above is direct and easily executed, even more efficient pathways to emetine from the starting lactam VI can be imagined. For example, hydrolysis-decarboxylation to XII, followed by deoxygenation of the acetyl group would mean ready acquisition of trans-lactam acid XIII, which substance has already been converted (6) to emetine



XII



XIII

by means of a double Bischler-Napieralski reaction followed by reduction, executed on lactam amide derived from XII. The hydrolysis and decarboxylation procedure as applied to starting keto lactam diester VI was, however, troublesome, and the expected product would not be secured. Furthermore, attempts to abbreviate the sequence XII $\longrightarrow$ X by carrying out a Clemmensen reduction concurrently with the hydrolysis-decarboxylation of VI, were unsuccessful.

ACKNOWLEDGMENT

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