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TOTAL SYNTHESIS OF dl-CORYNANTHEINE

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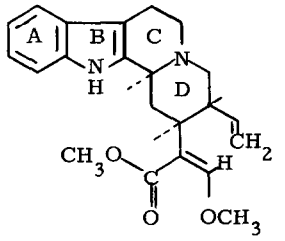
IN this Letter we summarize chemical operations which constitute the total synthesis (in the racemic form) of the alkaloid corynantheine (Ia),



Ia

best known of the tetracyclic ring-E seco yohimbine bases (1).

The synthetic route comprises eight steps and features as a key intermediate the keto ester IV, secured by methods (A-D) already employed in another connection (2), starting with the biogenetic-type interaction of tryptamine, formaldehyde and the keto triester II. As

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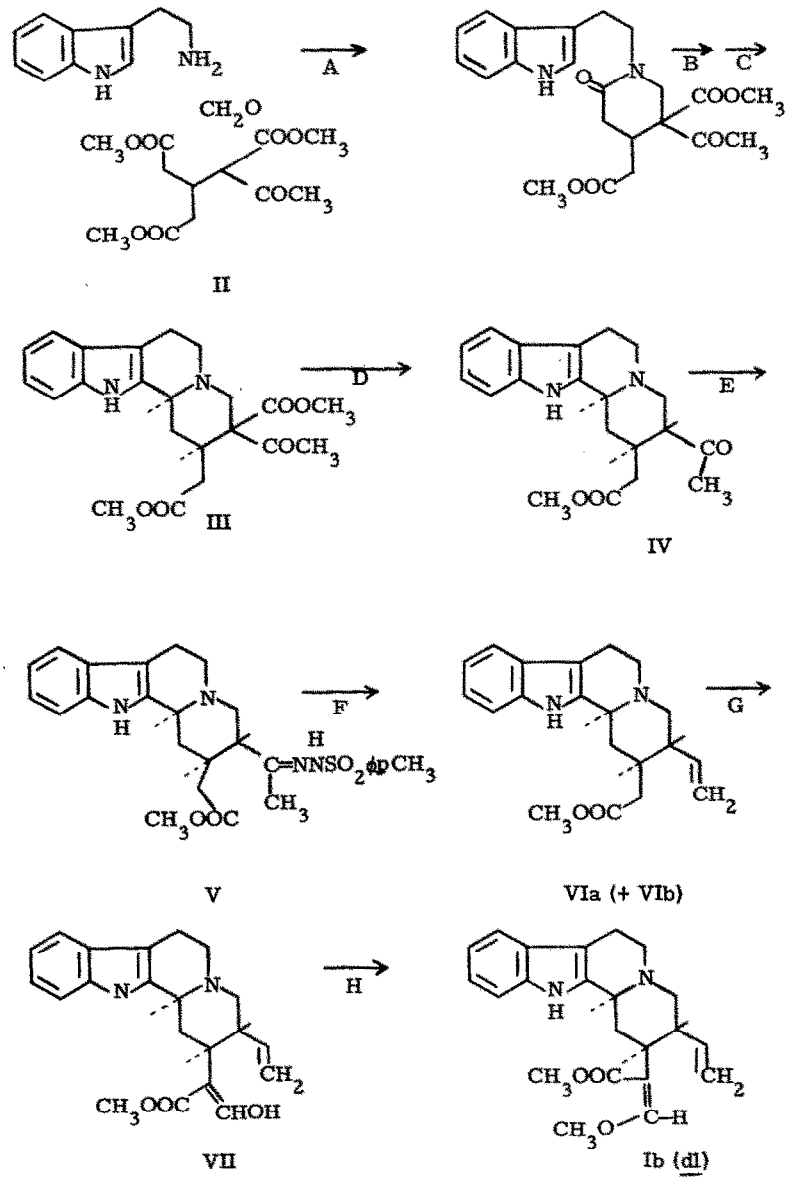
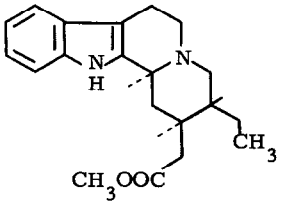

A
B
C
D
E
F
G
H
II
III
IV
V
VIa (+ VIb)
VII
Ib (dl)

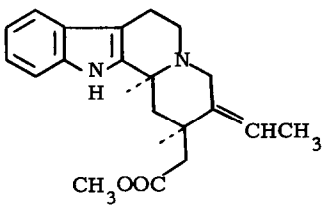
produced by hydrolysis-decarboxylation of tetracyclic intermediate III, followed by esterification, the crude keto ester IV appears to consist of a 15, 20-trans/cis mixture, with the trans isomer predominating (ratio 61:39 by n-m-r). The stereochemical assignments are based upon conversion of the keto ester mixture to isomeric ethylene dithioketals, which were separated by chromatography over silicic acid, characterized as crystalline hydrochlorides (major isomer m. p. 259. 5-260° with dec., and minor isomer m. p. 296-298° with dec.) and reductively desulfurized. Dithioketal corresponding to the lower-melting hydrochloride gave rise to the tetracyclic ester VIII, identical with an authentic specimen (3). In



VIII

keeping with the above finding, the stereoisomeric keto ester (IV) mixture was found to give rise to, on treatment with p-toluenesulfonyl hydrazine in glacial acetic acid-methanol, isomeric tosyl hydrazones, separable by chromatography and fractional crystallization from methanol into major (trans) (m. p. 226-227° with dec.) and minor (cis) (m. p. 202° with dec. after sintering at ca. 150° and resolidifying) components.

With the pure tosylhydrazone (IV) of trans keto ester IV in hand, means were now available (4) for generation of the distinguishing mark of corynantheine, the vinyl substituent. Sodium methoxide in hot diglyme served to convert V to a mixture of several products, the major components of which were found to be the vinyl (VIa) and ethylidene (VIb) elimination products. Through a combination of thin layer chromatographic



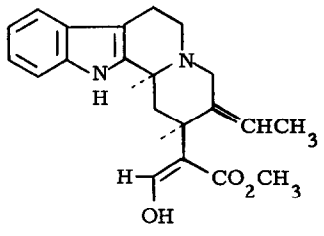
VIb

and direct crystallization techniques, hydrochlorides of the two unsaturated isomers were secured. The terminal olefinic isomer VIa (hydrochloride, m. p. 276-278°) was identified unequivocally by: 1) catalytic reduction to the saturated tetracyclic ester VIII, and 2) the presence of three olefinic hydrogens (4. 3-5. 1 τ), but no C-methyl hydrogens, in the n-m-r spectrum.

Completion of the synthesis was achieved by unexceptional means. By treatment of the olefinic ester VIa with methyl formate in the presence of sodium triphenyl methyl, the desired hydroxymethylene ester (VII) was secured; and this intermediate in turn was O-methylated by means of diazomethane in ether-ethyl acetate. The O-methylated product was isolated by

means of extractions which depended upon the known solubility of corynantheine hydrochloride in chloroform; and after application of chromatographic methods, a crystalline hydrochloride (m.p. 176-179°) was obtained. The corresponding base was identified as dl-corynantheine by the identity of its infrared spectrum with that of an authentic sample of corynantheine.[b]

When the formylation procedure was applied to the ethylidene ester VIb (hydrochloride, m.p. 264-265° with dec.) there was produced a substance, the properties of which required its formulation as the



IX

expected hydroxymethylene derivative (IX). However, a variety of comparisons (infrared and n-m-r spectral, m.p. of (-)dibenzoyltartrate) left no doubt that the hydroxymethylene ester was not identical with the base of same gross structure, geissoschizine, a molecular bisection product of the complex indole alkaloid geissospermine (5). Apparently the natural and synthetic materials differ with respect to the geometry of the olefinic link.

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[b]Spectral and analytical data on all crystalline intermediates are in agreement with the assigned structures.

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