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STEREOSPECIFIC TOTAL SYNTHESIS OF *dl*-CORYNANTHEIDINE AND *dl*-DIHYDROCORYNANTHEINE

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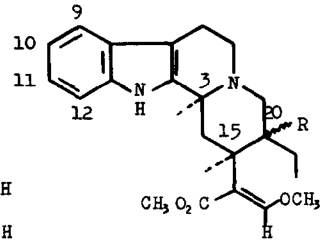
CORYNANTHEIDINE and dihydrocorynantheine are isomeric, tetracyclic indole alkaloids which can be graphically represented by structures I and II^{1,2}. If the presumption that these molecules or their direct transformation products represent potential links between the yohimbinoid and cinchona types is taken together with the



I R=α-H

II R=β-H

suggestion "that all alkaloids of the tryptamine +C$_{10}$ structure type may be derived from corynantheinoid or closely related precursors"^{7,8}, the development of practical methods for their synthesis assumes added significance. Prior to the start of this investigation a low-yielding, apparently non-stereospecific synthesis of II had been reported.[10,12] To date[13], there have been no publications devoted to the synthesis of the more elusive $C_{3,15,20}$-α,α,α isomer I. We now describe a stereospecific sequence utilizing a common intermediate which leads to the total syntheses of I and II[14].

Compound III, m.p. 206-208° (lit.[15] 205-207°), obtained from tryptamine in 38% over-all yield was converted to IVa (88%, yield), m.p. 252-255° dec. (HCl) $\lambda_{max.}^{CHCl_3}$ 5.88, 6.09 μ (base) and IVb (93%), m.p. 122-124° $\lambda_{max.}^{CHCl_3}$ 5.89, 6.10 μ N.M.R. peak at δ 5.70 (s) (vinyl-H) by reaction with trimethyl and triethylphosphonoacetate, respectively. Catalytic reduction (10% palladium on carbon/absolute ethanol) yield Va, m.p. 142-143° and Vb, m.p. 126-128° (85-95%). In both instances the infrared spectra ($CHCl_3$) exhibited saturated carbonyl absorption at 5.76 μ as well as Bohlmann bands[16-18] in the 3.5 μ region characteristic of a $C_{3,15}$-α,α configuration. These data, taken together with the agreement of melting points with reported figures,[10] allowed a tentative assignment of stereochemistry as $C_{3,15,20}$-α,α,β. Compound Va was converted to VI in a substantially improved yield of 53% (lit.[11] 18.5%) by using methyl formate and triphenylmethylsodium in a mixture of diglyme and ether. A revised methylation procedure for the preparation of β-methoxyvinyl esters through acetal-forming conditions (HCl/methanol) rather than the use of diazomethane[10,11] provided <u>dl</u>- dihydrocorynantheine in 55% yield (lit.[11] 27%) shown to be identical with an authentic specimen by infrared spectral ($CHCl_3$) and thin layer comparison (several systems).

As it appeared most advantageous to use this general sequence or a modification thereof for preparation of both I and II, a determination was made as to (a) the stage at which the relative stereochemistry at incipient C_3-C_{20} became oriented trans and (b) how these centers could be converted to C_3-C_{20} cis. It appeared certain that the trans orientation is present in III; further, equilibration experiments indicate that this is in fact the stable isomer. Attempts at epimerization of C_3 or C_{20} in IV (alkoxide/alcohol) provided the corresponding β,γ-unsaturated esters VIIa, m.p. 126-127°, $\lambda_{max.}^{CHCl_3}$ 5.78 μ (26% yield) and VIIb, m.p. 100-102°, $\lambda_{max.}^{CHCl_3}$ 5.79 μ (86% yield), N.M.R. spectrum contains no peak attributable to vinyl hydrogen, molecular weight (mass spec.[19]) 338, rather than the corresponding $C_{3,20}$-cis molecules. Compound VII provides another opportunity to obtain $C_{3,15,20}$-α,α,α by direct reduction of the $C_{15,20}$ unsaturation. In spite of a report of reduction in somewhat analogous species[20], no material corresponding to VIII could be isolated. In order to provide a system more amenable to reduction, yet retaining potential for conversion to $C_{3,15,20}$ cis stereochemistry, all optical centers in VIIb[21] were eliminated by oxidation (I_2/NaOAc[22]) to IXb, isolated as an insoluble, high melting mixture of perchlorate and iodide, $\lambda_{max.}^{Nujol}$ 5.76, 6.13, 6.42 μ. The crude, vacuum dried mixture was reduced directly (10% palladium on carbon/ethanol/sodium ethoxide) to VIIIb, m.p. 272-274° dec. (HCl), $\lambda_{max.}^{Nujol}$ 5.79 μ, which was converted to VIIIa, m.p. 257-258° dec. (HCl), $\lambda_{max.}^{Nujol}$ 5.79 μ, molecular weight (mass spec.[19]) 326, on treatment with sodium methoxide in methanol (over-all yield from IV, 39.6%).

Subsequently it was discovered that IVa and b were oxidized by mercuric acetate[23] to IXa, m.p. 209-211° dec. (ClO_4^-), $\lambda_{max.}^{Nujol}$ 5.73, 6.10, 6.42 µ, and IXb, m.p. 227-229° dec. (ClO_4^-) in 52 and 60% yields, respectively. Reduction as previously described gave VIIIa[24] and b (69 and 72%). It thus appears that the sequence IV→IX→VIII, although simpler and more direct, is nevertheless only competitive with regard to yield in this series. However, experimentation to date with corresponding methoxyindole compounds shows promise for potential practical advantage in those series. Thus, a sequence is now at hand where a single intermediate (IV), by direct reduction or alternately oxidation followed by reduction, provides $C_{3,15,20}$-α,α,β and $C_{3,15,20}$-α,α,α substituted moieties[25] stereospecifically.

Formylation as previously described gave X (<u>ca.</u> 25% yield), isolated as the hydrochloride, which was directly methylated (CH_2N_2) to yield <u>dl</u>-corynantheidine, II, m.p. 240-242° ($HClO_4$), whose infrared spectrum (free base in $CHCl_3$) and thin layer behavior (several systems) was identical with a specimen of the natural alkaloid.

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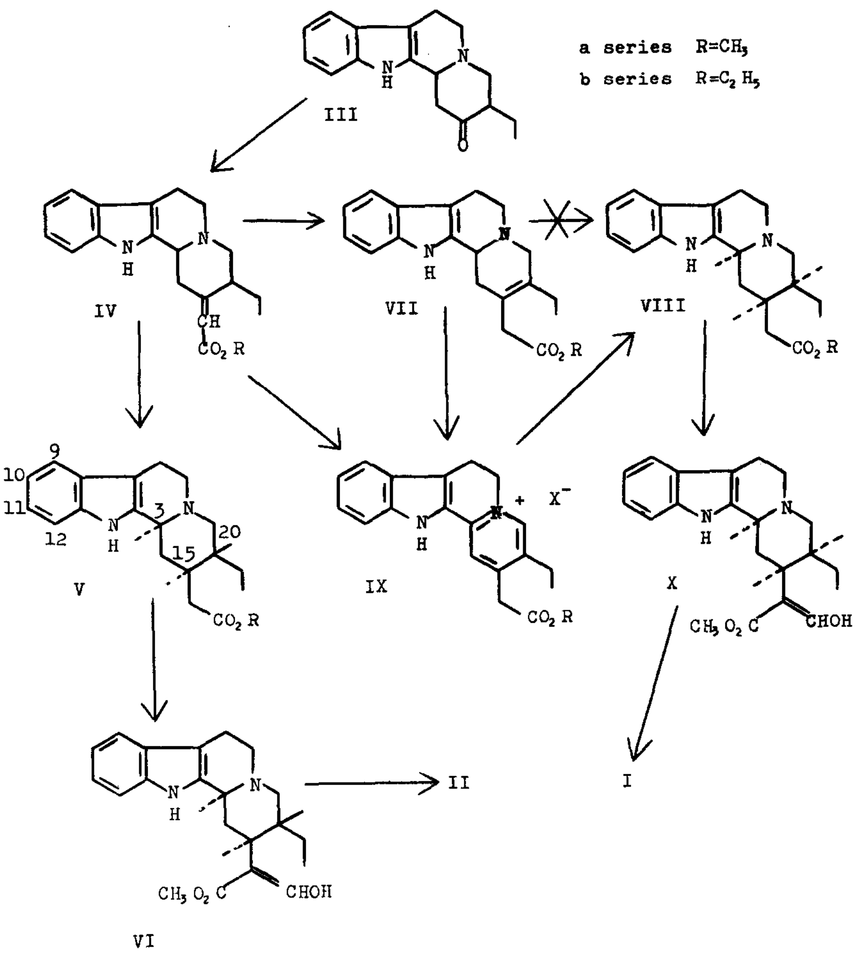

a series R=CH₃
b series R=C₂H₅
III
IV
VII
VIII
V
IX
X
VI
II
I
CO₂R
CH₃O₂C
CHOH
X⁻
9
10
11
12
3
15
20

REFERENCES

1. For a review of the chemistry of this area see J. E. Saxton in R. H. F. Manske "The Alkaloids", Volume VII, p. 37, Academic Press Inc., New York (1960).

2. It has been concluded by N.M.R. spectral correlation[3] that the geometry about the C_{16}-C_{17} double bond in I and II was *cis* with respect to methoxy and carbomethoxy. In contrast, the recent X-ray crystallographic determination of structure for 9-methoxycorynantheidine[4,5] established the corresponding configuration in that molecule as *trans*. Re-examination of the N.M.R. data, with the latter compound instead of ajmalicine as the standard, for anticipated C_{17}-hydrogen chemical shift has shown that the spectra of I and II (vinyl proton at 7.45 and 7.42, respectively, vs. 9-methoxycorynantheidine at 7.456; spectra taken in deuteroacetone) are in complete accord with a *trans* formulation. On the basis of this correlation with the *single*, available exact model and the potential similarity of biogenetic origin of this moiety in all of these compounds, I and II are now formulated *trans* as shown.

3. E. Wenkert, B. Wickberg and C. Leicht, *Tetrahedron Letters*, 822 (1961).

4. D. E. Zacharias, R. D. Rosenstein and G. A. Jeffrey, Presented at the Annual Meeting of the American Crystallographic Association, Bozeman, Montana, July 1964; *Acta Crystallographica* in press (1965).

5. B. S. Joshi, Raymond-Hamet and W. I. Taylor, *Chem. and Ind.*, 573 (1963).

6. E. Ochiai and M. Ishikawa, *Chem. Pharm. Bull. Jap.*, **7**, 256 (1959).

7. E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965).

8. Another stereochemical series related to I and II can be derived from geissoschizine[9], which is differentiated by replacement of the C_{20} asymmetric center with a C_{19}-C_{20} double bond.

9. H. Rapport, R. J. Windgassen, Jr., N. A. Hughes and T. P. Onak, *J. Am. Chem. Soc.*, **82**, 4404 (1960).

10. E. E. Van Tamelen and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 3805 (1959).

11. J. B. Hester, Thesis, University of Wisconsin (1960). Additional work in this series[12] has shown that the sequence was in fact stereospecific.

12. I. G. Wright, Thesis, University of Wisconsin (1965).

13. Subsequent to completion of that phase of our work related to dihydrocorynantheine (II) an essentially equivalent route to V was reported - C. Szántay and L. Tőke, *Acta. Chim. Hung. Tomus*, **39**, [illegible] (1965).

14. Satisfactory analyses (combustion and spectral) were obtained for all compounds unless noted. Infrared spectra were taken in chloroform solution or Nujol and N.M.R. spectra were taken in deuterochloroform unless otherwise specified and are reported in δ units (internal TMS=0).

15. H. T. Openshaw and N. Whittaker, J. Chem. Soc., 1449 (1963).

16. F. Bohlmann, Chem. Ber., **91**, 2157 (1958).

17. E. Wenkert and D. K. Roychaudhuri, J. Am. Chem. Soc., **78**, 6417 (1956).

18. W. E. Rosen, Tetrahedron Letters, 481 (1961).

19. We are indebted to Dr. G. O. Dudek (Harvard University) for the mass spectral determinations.

20. P. G. Philpott and A. M. Parsons, J. Chem. Soc., 3018 (1958).

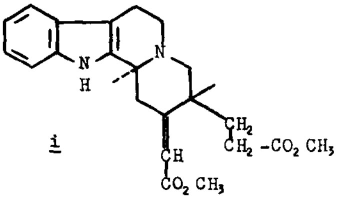
21. The ethyl, rather than methyl, ester was used even though this then requires a later transmethylation because of the advantageous yield in step IV→VII.

22. R. C. Elderfield and B. A. Fischer, J. Org. Chem., **23**, 949 (1958).

23. F. L. Weisenborn and P. A. Diassi, J. Am. Chem. Soc., **78**, 2022 (1956).

24. This compound has been obtained by a non-stereospecific and circuitous route during synthesis of corynantheine. E. E. Van Tamelen and I. G. Wright, Tetrahedron Letters, 295 (1964).

25. A recent synthesis of yohimbine and β-yohimbine, C. Szantay, L. Toke and K. Honti, Tetrahedron Letters, 1665 (1965) uses i as an intermediate. Mercuric acetate oxidation followed by catalytic reduction should provide ready access to the corresponding compounds in the alloyohimbane series.



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