# Total Synthesis of *dl*-Dihydrocorynantheine

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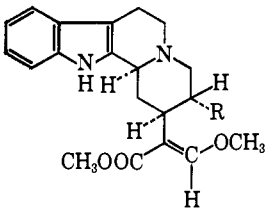
*Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin.* *Received January 30, 1969*

**Abstract:** The first synthesis (in the racemic form) of the naturally occurring indole alkaloid, dihydrocorynantheine, is described. Individual steps involved in the synthesis are II → III → IV → VII → XVIII → I.

Dihydrocorynantheine (I, R = $C_2H_5$) is one of three closely related, tetracyclic yohimbé alkaloids which enjoy considerable importance as uncovered "missing links" in the biogenetic sequence involving the yohimbine alkaloids, the structurally similar hetero-

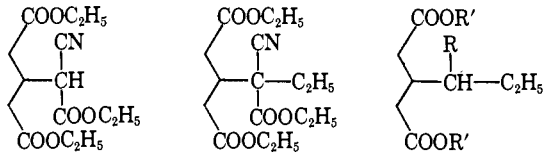


I

cyclic ring E bases of this series (*e.g.*, ajmalicine and serpentine), and the relatively dissimilar cinchonamine, cinchonine, and curaré bases (*e.g.*, mavacurine and fluorocurine). A crystalline mixture of dihydrocorynantheine and corynantheine (I, R = CH=$CH_2$) was first isolated from the bark of *Pseudocinchona africana* A. Chev. by Janot and Goutarel.[2] Catalytic hydrogenation of the mixture yielded the pure dihydro component, while separation into pure alkaloidal materials could be achieved by Craig countercurrent distribution and by paper chromatography. Subsequent investigation by several groups of workers established the correct gross structure of the corynantheine alkaloids,[3] and results secured in this laboratory defined the stereochemical relationship of the three asymmetric centers.[4,5]

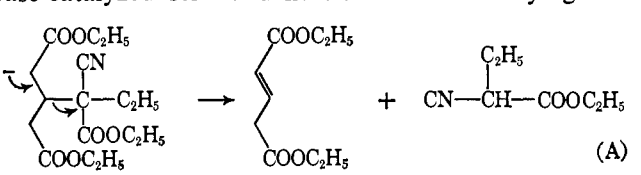
The synthesis described herein[6,7] parallels the approach used for the elucidation of its stereochemistry and is also related to certain sequences which were being investigated concurrently in connection with the chemistry of emetine.[8] The route pursued was selected and reduced to practice for these reasons, and also because certain of the new operations featured would serve as model experiments for more complicated indole alkaloid synthesis.[9]

Our approach to the synthesis of dihydrocorynantheine is based on the condensation of tryptamine with an acyclic compound suitable for the elaboration of the basic ring system of the natural product. Although initial experiments were directed toward a synthesis of a bromo diester (IV, R = $CH_2Br$; R′ = $C_2H_5$), which could be used to alkylate tryptamine in a fashion similar to that used for the dihydrocorynantheane synthesis,[8] preparative difficulties prompted a deviation from the original course. A relatively straightforward synthesis of the corresponding cyano diester (IV, R = CN; R′ = $C_2H_5$) had been described by Preobrazhenskii and coworkers,[10] and the projected reductive alkylation of this compound with tryptamine was well precedented by a similar reaction in the Russian emetine synthesis. Diethyl β-(1-cyano-1-propyl)glutarate (IV, R = CN; R′ = $C_2H_5$) was thus selected as the starting material and was prepared by the method of Preobrazhenskii and coworkers. A Michael condensation of diethyl glutaconate with ethyl cyanoacetate in the presence of a catalytic amount of sodium ethoxide produced II in good yield. This product was alkylated with ethyl iodide and sodium ethoxide to yield the cyano triester (III). Ini-



II III IV

tial experiments, patterned after the procedure of Preobrazhenskii, *et al.*, were designed to produce IV (R = CN; R′ = $C_2H_5$) by a selective saponification of the cyanoacetic ester followed by pyrolytic decomposition of the resulting acid. However, these experiments were erratic, and the yields of IV (R = CN; R′ = $C_2H_5$) were very low. Further investigation of the intermediate III demonstrated that this molecule undergoes sodium ethoxide induced elimination of ethyl ethylcyanoacetate, regenerating diethyl glutaconate (A); base-catalyzed self-condensation of the diethyl glutaconate then yielded the observed product, ethyl 2,6-dicarboethoxy-$\Delta^{2,5}$-cyclohexadien-5-ol-1-acetate (V).[11]



(A)

(1) Address correspondence to the author at the Department of Chemistry, Stanford University, Stanford, Calif. 94305.

(2) M.-M. Janot and R. Goutarel, *Compt. Rend.*, **206**, 1183 (1938).

(3) For a review with references, see J. E. Saxton, *Quart. Rev.* (London), 10, 108 (1956).

(4) E. E. van Tamelen, P. E. Aldrich, and T. J. Katz, *Chem. Ind.* (London), 793 (1956); *J. Am. Chem. Soc.*, 79, 6428 (1957).

(5) Assignment of geometry in the methoxymethylene moiety has been made by X-ray and nmr methods. For a discussion of this matter see footnotes in ref 7b.

(6) First reported in a Communication to the Editor, *J. Am. Chem. Soc.*, **81**, 3805 (1959).

(7) Other total syntheses have been disclosed more recently by (a) C. Szantay and L. Töke, *Acta Chim. Hung. Tomus*, **39**, 249 (1963), and (b) J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Letters*, 3457 (1965).

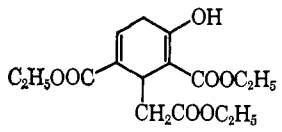
(8) E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, Jr., *J. Am. Chem. Soc.*, 79, 4817 (1957).

(9) E. E. van Tamelen and C. Placeway, *ibid.*, **83**, 2594 (1961); E. E. van Tamelen and I. G. Wright, *Tetrahedron Letters*, 295 (1964).

(10) R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. T. Zakharkin, and N. A. Preobrazhenskii, *J. Gen. Chem.*, 22, 1467 (1952).

(11) H. v. Pechman, W. Bauer, and J. Obermiller, *Chem. Ber.*, 37, 2117 (1904).

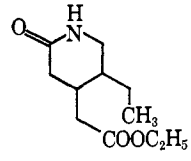
Thus, when cyano triester III was allowed to react for 30 min with anhydrous sodium ethoxide, a 64% yield of V was produced. Since in the early Russian experi-



V

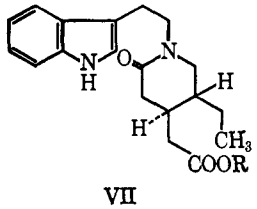
ments sodium hydroxide was formed *in situ* by adding 1 equiv of water to an ethanolic solution of the triester and sodium ethoxide, the erratic results were probably due to variation in the length of time between the addition of triester III to the sodium ethoxide solution and the addition of water to the resulting mixture. A 23.5% yield of IV (R = CN; R′ = $C_2H_5$) was obtained by the method of Preobrazhenskii when precautions were taken to minimize the contact of III with anhydrous base.

The condensation of the cyano diester (IV) (R = CN; R′ = $C_2H_5$) with tryptamine was achieved by reductive alkylation. This reaction, with 3,4-dimethoxyphenethylamine instead of tryptamine, had been investigated in this laboratory in connection with studies on the stereochemistry of emetine.[8] When an ethanolic solution of the cyano diester (IV) (R = CN; R′ = $C_2H_5$) and excess tryptamine in the presence of freshly prepared W-2 Raney nickel was subjected to carefully controlled high pressure catalytic hydrogenation conditions, a complex mixture of products was obtained. This mixture was fractionated by chromatography on alumina. The major product of the reaction, ethyl 5-ethyl-2-piperidone-4-acetate (VI), resulted from simple reduction of IV (R = CN; R′ = $C_2H_5$) to the primary amine

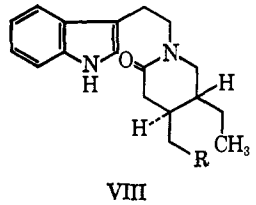


VI

followed by elimination of ethanol to give the δ-lactam. Reductive alkylation of tryptamine with the cyano diester occurred to the extent of about 13% with the formation of the desired lactam (VII, R = $C_2H_5$), contaminated by a small amount of lactam formed by reductive alkylation of tryptamine with unethylated cyano triester (II) which had been carried through the several succeeding steps.[12] Saponification of this mixture with 1 equiv of ethanolic potassium hydroxide yielded the corresponding acids, which were separated



VII



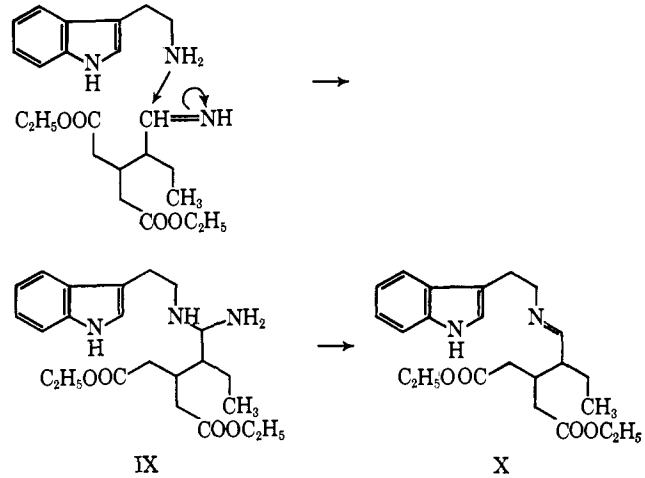
VIII

by silicic acid chromatography. Fisher esterification of the predominant acid, obtained in 12% over-all yield, provided without difficulty the pure ethyl ester VII (R = $C_2H_5$).

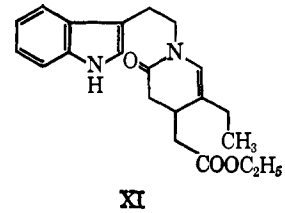
The structure and stereochemistry of piperidone VII were established by conversion to *dl-trans*-N-(3′-β-indolylethyl)-4,5-diethyl-2-piperidone (VIII, R = $CH_3$), accomplished by means of a reliable and proven degradative sequence.[8] Thus selective lithium borohydride reduction of VII (R = $C_2H_5$) yielded the alcohol (VIII, R = $CH_2OH$), which was converted to the tosylate (VIII, R = $CH_2OSO_2C_7H_7$) by reaction with *p*-toluenesulfonyl chloride in pyridine. A facile displacement on the tosylate with thiourea produced the isothiouronium tosylate salt (VIII, R = $CH_2SCN_2H_4^+$, $SO_3^-C_7H_7$), and the latter was hydrogenolyzed to VIII (R = $CH_3$) by Raney nickel desulfurization.

Mild alkaline hydrolysis of the *trans* ester (VII, R = $C_2H_5$) resulted in a 94% yield of the original acid (VII, R = H), mp 203–205°, and thus excluded the possibility of an acid-catalyzed epimerization during the esterification.[13]

The reductive alkylation of a nitrile with a primary amine probably proceeds by a condensation of the amine with the imine formed by partial reduction of the nitrile. Further reduction of the intermediate thus formed would lead to the observed condensation product, a secondary amine. Applied to the alkylation under discussion, this mechanism would lead to the intermediate IX, which, on elimination of ammonia, would produce the imine (X) or the tautomeric enamine. Lactamization would yield the dihydropyridone (XI), which could undergo further reduction to yield the piperidone (VII, R = $C_2H_5$). Alternatively the reduction of intermediates IX and X to the secondary amine diester XII followed by cyclization would yield a saturated lactam. In this case the product would be expected to have the more stable, *trans* geometry since in



IX X

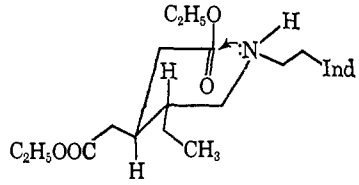


XI

(12) Although originally thought to be the *cis*-lactam, isomeric with VII, subsequent investigations by I. G. Wright (unpublished results, University of Wisconsin) revealed the true nature of this troublesome substance. Not the least important of the newer data was the absence of a C-ethyl substituent, as evidenced by the nmr spectrum.

(13) The less stable *cis* acid might have epimerized under the esterification conditions by an acid-catalyzed solvolysis of the lactam ring followed by a rapid cyclization to produce the more stable *trans* ester.

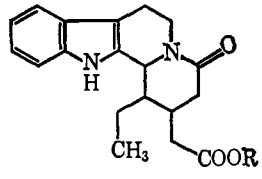
the intermediate XII both ester functions are equivalent; but in the transition state in which condensation of the ester with the amine has already begun the situation should resemble that of a six-membered ring with the



XII

expected steric interaction of axial and equatorial substituents. It is therefore evident that condensation of an ester to yield the *cis* geometry of the ring substituents would involve a less likely transition state and should be of minor consequence.

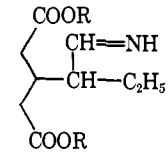
Some support for the second interpretation of the reduction sequence to VII was found in the isolation of the crystalline dihydropyridone (XI) from the reductive alkylation mixture and the demonstration that this dihydropyridone was not reduced sufficiently effectively to account for the yield in the original reductive alkylation. The survival of this compound at first seemed unusual in view of the conditions employed for the reaction. It became evident, however, that some component of the reaction poisoned the catalyst, since from all reductive alkylations some unreduced cyano diester was obtained. Further confirmation of this concept was derived from an attempt to reduce XI with W-2 Raney nickel under conditions similar to those employed for the reductive alkylation. This reduction resulted in a partial hydrogenation of the indole system (as evidenced by uv data), a reaction which was not observed during the reductive alkylation to VII. Catalytic hydrogenation of XI at atmospheric pressure with 10% palladium on carbon, followed by mild alkaline hydrolysis, yielded 47–51% of the *trans*-lactam acid (VII, R = H), the only identifiable product. This result establishes the basic ring system of XI, leaving in doubt only the position of the double bond. That the lactam XI was an N-acylenamine was determined by means of its acid-catalyzed cyclization to XIII (R = $C_2H_5$) carried out with phosphorus oxychloride under mild conditions and giving a 67% yield of a colorless oil with the expected infrared bands at 5.80 and 6.15 $\mu$. Hydrolysis of this oil with dilute alkali yielded a mixture of crystalline stereoisomeric acids (XIII, R = H) which was partially sepa-



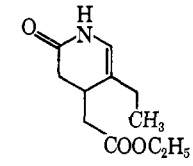
XIII

rated into three components. An analysis of the lower melting (192°) component was consistent with the assigned structure.

In order to effect the desired reductive alkylation of an amine with a nitrile it may be necessary to reduce the nitrile selectively to the *imine*. This imine must be sufficiently stable to allow its condensation with the amine which is to be alkylated. In our system a possible side reaction is the elimination of ethanol from the imine intermediate (XIV, R = $C_2H_5$) to form an unsaturated lactam (XV), analogous to the postulated formation of XI. If the intramolecular reaction were to occur



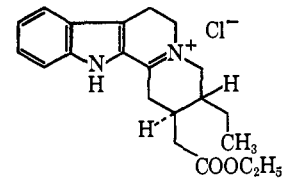
XIV



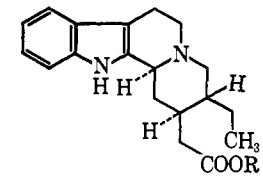
XV

readily it would compete with the alkylation and thus lower the yield of the desired product. In order to avoid cyclization of presumed intermediate imine XIV (R = $C_2H_5$) to lactam XV, proceeding at the expense of reductive alkylation of XIV with tryptamine, the reductive alkylation was carried out on the acid corresponding to IV (R = CN; R′ = $C_2H_5$). In this case, one would expect to obtain XIV (R = H), an intermediate less prone to lactamization than the amino diester.[14] Experimentally, tryptamine was alkylated with the cyano diacid to yield an amorphous mixture which, without purification, was esterified with sulfuric acid and ethanol. After chromatography and mild potassium hydroxide hydrolysis of the neutral ester fraction, an 18.4% yield of the pure *trans*-lactam acid (VII, R = H) was obtained. Although the yield of *trans*-lactam acid had been raised in this reductive alkylation, the improvement was not impressive and not sufficient to allow any conclusion regarding the postulated intramolecular condensation of the imino diester XIV.

Phosphorus oxychloride cyclization of the *trans*-lactam ester (VII, R = $C_2H_5$) proceeded under mild conditions[4] to form the crystalline quaternary ammonium chloride (XVI), which was not characterized but was catalytically reduced over platinum to yield the hydrochloride of XVII (R = $C_2H_5$) in 84.5% over-all



XVI



XVII

yield. Since catalytic hydrogenation of similar systems affords the more stable stereomer, the hydrogen at C-3 was assigned the $\alpha$ configuration. Support for this assignment was derived from the infrared spectrum of XVII (R = $C_2H_5$), which exhibited peaks at 3.55 and 3.61 $\mu$, characteristic of this axial hydrogen.[15]

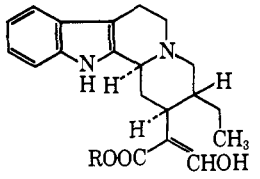
With the synthesis of the basic ring system accomplished, it remained to complete the synthesis of the natural product by incorporating the methoxymethylene function into the side chain. Attempts to formylate XVII (R = $C_2H_5$) by modifications of the method of Horning and Schock[16] with ethyl formate and sodium

(14) δ-Aminovaleric acid was converted to the corresponding piperidone by the elimination of water at its melting point, 157–158°. The corresponding methyl ester could not be isolated in pure form but was studied as a solution in benzene [C. Schotten, *Ber.*, 21, 2235 (1888)].

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

(16) E. C. Horning and R. U. Schock, Jr., *ibid.*, 70, 2945 (1948); 71, 1359 (1949).

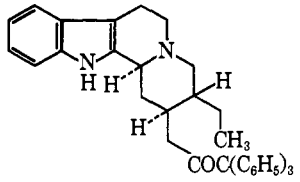
methoxide failed as did similar attempts with sodium hydride under forcing conditions. The formylation could be carried out, however, with triphenylmethylsodium and ethyl formate under conditions similar to those described for the formylation of ethyl isobutyrate.[17] The desired product (XVIII), which was readily purified by silicic acid chromatography, had infrared bands at 5.80 and 6.05 $\mu$, positions expected for the $\alpha$-hydroxymethylene ester system.[18] After a concentrated solution of the chromatographically pure formyl derivative in ethyl acetate had been allowed to



XVIII

stand for 12 hr, a crystalline solid was obtained. Although this material was only slightly soluble in chloroform, an infrared spectrum of this substance in this solvent could be obtained if some of the crystals were dissolved in a large volume of chloroform and the solution was concentrated. This spectrum was considerably different from that of the noncrystalline material, especially in the carbonyl region, where it had only one band at 6.05 $\mu$ with shoulders at 5.82 and 6.24 $\mu$. This behavior is probably due to the selective crystallization of one isomeric form of the hydroxymethylene ester derivative from the ethyl acetate solution.

The formylation reaction yielded, in addition to the acidic formyl derivative, unreacted tetracyclic ester and a third compound which formed a highly crystalline hydrochloride. The latter exhibited infrared absorptions at 5.86 $\mu$ attributed to a ketone carbonyl, and at 2.86, 3.55, and 3.61 $\mu$, characteristic of the substituted tetrahydro-$\beta$-carboline system. The ultraviolet spectrum, $\lambda_{max}$ 290 m$\mu$ ($\epsilon$ 5780), 283 (6870), and 224 (43,900), was characteristic of the indole chromophore; while strong end absorption indicated the presence of a second aromatic system. The compound has been tentatively assigned structure (XIX) and results from a condensa-



XIX

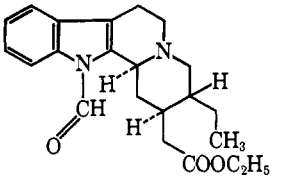
tion of the trityl anion with the tetracyclic ester. Although this is not the usual reaction of triphenylmethylsodium with an ester,[17] an example of the formation of a trityl ketone in this manner has been observed.[19] Structure XIX is supported by infrared absorption at 6.24 and 6.66 $\mu$, attributed to the aromatic trityl group.

(17) B. E. Hudson Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, 63, 3156 (1941).

(18) Model formylation experiments with ethyl $\delta$-phenylpropionate, carried out by the method of Horning and Schock, yielded a formyl derivative which had infrared maxima at 5.80 and 6.00 $\mu$. Methylation of this derivative with sodium methoxide and dimethyl sulfate proceeded to yield a methyl ether with infrared bands at 5.85 and 6.06 $\mu$. These compounds were not rigorously purified and were characterized only by their spectral properties.

(19) E. G. Lindstrom and W. D. McPhee, *J. Am. Chem. Soc.*, 65, 2387 (1943).

In an attempt to find an alternate base or the formylation reaction, the anion of XVII (R = $C_2H_5$) was made by means of excess ethereal mesitylmagnesium bromide.[20] The addition of ethyl formate to this anion yielded not XVIII (R = $C_2H_5$), but the N-formyl derivative (XX), which had an infrared maximum at 5.88 $\mu$,



XX

ascribable to the unresolved amide and ester carbony absorptions. The new product had ultraviolet maxima $\lambda_{max}$ 247 m$\mu$ ($\epsilon$ 17,000), 291 (4300), and 299 (3800), characteristic of N-acylindoles.[21] Solvolysis of this compound, carried out by refluxing its ethereal solution with dry sodium methoxide, produced a good yield of the original tetracyclic ester (XVII, R = $C_2H_5$), along with some methyl ester, formed by transesterification during the reaction. A possible explanation for the N formylation follows from the observed heterogeneity of the mesitylmagnesium bromide reaction. Thus, addition of the base to an ethereal solution of XVII (R = $C_2H_5$) resulted in the removal of the acidic indole hydrogen, forming an insoluble magnesium salt which failed to react further with an excess of the reagent. Addition of ethyl formate to this salt led to the formation of the N-formyl derivative and magnesium ethoxide, which, being insoluble, would not effect reversal of the reaction by cleavage of the amide function. Alternatively, removal of the indole proton may be due to preliminary complexing of the nitrogen with the Grignard reagent followed by rapid acid–base reaction at this site.

Although preliminary experiments[18] had indicated that dimethyl sulfate was a suitable reagent for methylating hydroxymethylene derivatives, this reagent proved to be unsatisfactory for methylating XVIII (R = $C_2H_5$), probably due to preferential attack on the tertiary nitrogen. The adition of dimethyl sulfate to a refluxing methanolic solution of XVIII (R = $C_2H_5$) and sodium methoxide did, however, yield a small amount of an O-methylated product which had an infrared spectrum with bands expected for the ethyl ester of the natural product.

The reaction of diazomethane with an ether solution of hydroxymethylene ester corresponding to I, obtained from the natural product by mild treatment with anhydrous hydrogen chloride in acetone, had been reported to yield none of the natural product but only unidentified crystalline material.[22] However, when a solution of crystalline XVIII (R = $CH_3$)[23] in ethyl acetate was allowed to react with an excess of diazomethane, *dl*-dihydrocorynantheine (27%) was formed, and was purified as its crystalline hydrochloride. The *dl* base gave correct elemental analyses, and an infrared spectrum of a

(20) M. A. Spielman and M. T. Schmidt, *ibid.*, 59, 2009 (1937).

(21) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3172 (1952).

(22) A. Chatterjee and P. Karrer, *Helv. Chim. Acta*, 33, 802 (1950).

(23) Obtained by formylation of the methyl ester XVII (R = $CH_3$), which itself was made by transesterification of tetracyclic ethyl ester XVII (R = $C_2H_5$).

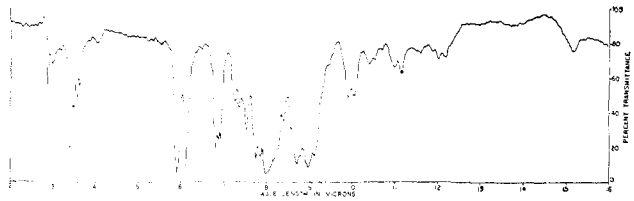


Figure 1. Ir spectrum of *dl*-dihydrocorynantheine.

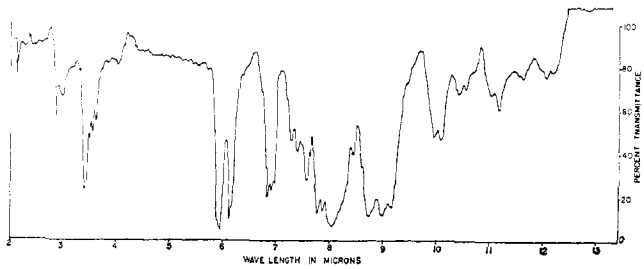



Figure 2. Ir spectrum of natural dihydrocorynantheine.

chloroform solution was identical with that of the natural product.[24]

## Experimental Section

**Diethyl 2-Cyano-3-(carboethoxymethyl)glutarate (II).** A solution of 10 g (0.0527 mole) of diethyl glutaconate and 14.1 g (0.124 mole) of ethyl cyanoacetate in 10 ml of absolute ethanol was allowed to reflux gently under nitrogen for 12 hr. During this period at 2-hr intervals a total of 50 drops of a 3.6 *N* ethanolic solution of sodium ethoxide was added to the reaction mixture by means of a dropping funnel. The cooled reaction mixture was poured into 5 g of ice water and concentrated *in vacuo* to remove the ethanol. The organic material was extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. Distillation of the residue at reduced pressure yielded 13.09 g (83%) or X, bp 150–154° (0.7 mm) [lit.[10] bp 167–169° (3 mm)].

**Ethyl 3-Cyano-3-carboethoxy-4-(carboethoxymethyl)hexanoate (III).** To an ice cold solution of 32.5 g (1.42 g-atoms) of sodium in 650 ml of absolute ethanol was added 364 g (1.22 moles) of the triester (II) and 404 g (2.59 moles) of ethyl iodide. The resulting solution was refluxed gently for 3 hr and concentrated at reduced pressure to remove the ethanol and excess ethyl iodide. The residue was taken up in ether, washed successively with water and saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. Distillation of the product at reduced pressure yielded 387.6 g (97.5%) of XI: bp 145–157° (0.5 mm); $n^{25}$D 1.4502 [lit.[10] bp 169–171° (3 mm), $n^{20}$D 1.4521].

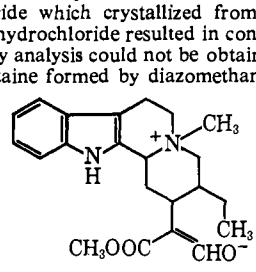
**Diethyl β-(1-Cyano-1-propyl)glutarate (IV, R = CN; R′ = $C_2H_5$).** To an ice-cold solution of 7.04 g (0.306 g-atom) of sodium in 125 ml of absolute ethanol was added 100 g (0.306 mole) of the triester (III), 5.50 g (0.306 mole) of water, and 25 ml of absolute ethanol. After the reaction mixture had been allowed to stand at room temperature for 12 hr the alcohol was removed under reduced pressure, and the residue was dissolved in water and extracted with ether. The ether extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated to yield 27.5 g of crude XI as a neutral oil. The aqueous solution from the ether extraction was acidified with 32 g of concentrated hydrochloric acid, saturated with sodium chloride, and extracted with chloroform. The chloroform extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated to yield 68.37 g of a crude acid. This was pyrolyzed at 170° (20 mm) for 1.5 hr and distilled at reduced pressure to yield 18.3 g (23.5%) of the cyano diester (IV, R = CN; R′ = $C_2H_5$), bp 111–118° (0.2 mm). A sample of IV (R = CN; R′ = $C_2H_5$) was redistilled two times for analysis, bp 107–108° (0.1 mm), $n^{25}$D 1.4441 [lit.[9] bp 139–140° (2.4 mm), $n^{20}$D 1.4519]. Diester IV had infrared bands at 4.44 and 5.80 μ, corresponding to the nitrile and ester groups, respectively.

*Anal.* Calcd for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29. Found: C, 61.23; H, 8.16.

**Reaction of IV (R = CN; R′ = $C_2H_5$) with Sodium Ethoxide.** An ice-cold solution of sodium ethoxide, prepared under nitrogen from 1.76 g (0.0765 g-atom) of sodium and 35 ml of absolute ethanol, was treated with 25 g (76.5 mmoles) of the cyano triester. The thick yellow mixture was allowed to warm up to room temperature and to stand for 0.5 hr before it was again cooled in an ice bath and treated with 1.38 ml of water. After this solution had been allowed to stand for 12 hr at room temperature it was refluxed for 1 hr and concentrated at reduced pressure. The residue was dissolved in 20 ml of water and extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated to yield 7.92 g of a neutral oil. Acidification of the aqueous solution, which contained the sodium salt of any acid formed during the saponification, with concentrated hydrochloric acid yielded 7.98 g (64%) of a white crystalline solid, mp 67.5–74.2°. Several crystallizations of this compound from cold absolute ethanol yielded needles, mp 79.6–80.9°, which had infrared maxima at 5.81, 5.95, 6.09, and 6.35 μ. It had ultraviolet absorption at $\lambda_{max}$ 323 mμ (ε 7570), 300 (7350), and 263 (12,700). It formed a dark brown copper complex when it was treated with an aqueous solution of cupric acetate. This complex could be extracted with chloroform and crystallized from ethanol, mp 144.5–146.5°. This compound, mp 81°[10] (copper complex mp 145°), has been obtained from the reaction of diethyl glutaconate with sodium ethoxide and has been shown to be ethyl 2,6-dicarbethoxy-$\Delta^{2,5}$-cyclohexadien-5-ol-1-acetate (V).

**Reductive Alkylation of Tryptamine with IV (R = CN; R′ = $C_2H_5$).** A solution of 34.2 g (0.214 mole) of tryptamine in ethanol was stirred with 15 g of W-2 Raney nickel for 2 hr. The resulting mixture was filtered through Filtercel, and the filtrate was concentrated to about 80 ml and added to a 270-ml steel bomb along with 9.0 g (35.6 mmoles) of IV (R = CN; R′ = $C_2H_5$), 9 g of W-2 Raney nickel, and 10 ml of absolute ethanol. This mixture was hydrogenated at 80° for 6 hr at an initial hydrogen pressure of 1390 psi. The total hydrogen uptake was 210 psi (112% of theory). After the cooled reaction mixture had been filtered through Filtercel it was concentrated under reduced pressure. Water was added to the dark residue and the mixture was acidified with dilute hydrochloric acid and extracted with chloroform. (Excess tryptamine was recovered from the aqueous solution by extracting its free base with chloroform.) The chloroform extracts, containing the neutral product, were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield 9.36 g of a dark gum. This gum was dissolved in benzene and chromatographed on 600 g of alumina. The first component of the mixture, ethyl *dl*-N-(β-3′-indolylethyl)-3,4-dihydro-5-ethyl-2-pyridone-4-acetate (XI), was eluted from the column with ether and was crystallized from ethyl acetate–petroleum ether to yield 361.6 mg (2.87%), mp 73–75°. An analytical sample of XI, mp 72.5–74°, had infrared maxima at 2.85, 5.80, and 6.05 μ, corresponding to the indole NH, the ester carbonyl, and the lactam carbonyl absorption, respectively. The ultraviolet spectrum exhibited maxima at $\lambda_{max}$ 221 mμ (ε 38,000), 266 (9200) and 289 (6000).

(24) During the diazomethane methylation of XVIII (R = $CH_3$) a by-product crystallized from the reaction mixture. When a chloroform solution of the concentrated reaction mixture was chromatographed on silicic acid XVIII (R = $CH_3$) was eluted from the column with 0.5% ethanol–chloroform, while the crystalline by-product was eluted with methanol. This substance crystallized from ethanol–ethyl acetate and yielded a hydrochloride which crystallized from ethanol. Repeated crystallization of the hydrochloride resulted in considerable decomposition, and a satisfactory analysis could not be obtained. The compound was probably i, a betaine formed by diazomethane methylation of the



i

zwitterionic hydroxy methylene derivative. A similar result has been reported with several amino acids, in that diazomethane gave mixtures of the corresponding betaines and amino acid esters.[25-27] In support of proposal XXI are infrared bands at 5.91 and 6.05 μ and ultraviolet maxima at $\lambda_{max}$ 289 mμ (ε 14,000), 272 (23,000), and 220 (58,400).

(25) H. Biltz and H. Paetzold, *Ber.*, **55**, 1066 (1922).
(26) R. Kuhn and W. Brydowna, *ibid.*, **70**, 1333 (1937).
(27) R. Kuhn and H. W. Ruelius, *ibid.*, **85**, 38 (1952).

*Anal.* Calcd for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.39; $OC_2H_5$, 12.71. Found: C, 71.04; H, 7.44; $OC_2H_5$, 10.02.

Lactam component was eluted from the column with chloroform. Lactam VII crystallized from the mixture to yield 1.266 g (9.97%), mp 98–107°. The mother liquor from this crystallization (1.478 g, 4.15 mmoles) was dissolved in ethanol and refluxed under nitrogen for 6 hr with 7.1 ml of 0.587 *M* potassium hydroxide. The resulting solution was concentrated under reduced pressure and the residual salts were dissolved in water and treated with 1 equiv of hydrochloric acid to precipitate the lactam acids. Sodium acetate was added to this mixture to neutralize any excess mineral acid, and the resulting mixture was concentrated to dryness. The residue was dissolved in ethanol and the ethanol was replaced with chloroform by an azeotropic distillation at reduced pressure. This chloroform solution was filtered, washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate, and chromatographed on silicic acid. *dl-trans*-N-(β, 3′-Indolylethyl)-5-ethyl-2-piperidone-4-acetic acid (VII, R = H) was eluted from the column with a 0.5% ethanol–chloroform solution and was crystallized from ethanol to yield 221.5 mg (1.89%), mp 195–202°. It was insoluble in chloroform and slightly soluble in ethanol. An analytical sample, mp 203–205° uncor, was prepared by subliming the crude acid at 195–200° (20 μ) and crystallizing the sublimate from ethanol. It had infrared bands at 2.95, 5.90, 6.25, and 6.62 μ (KBr disk).

*Anal.* Calcd for $C_{19}H_{24}O_3N_2$: C, 69.49; H, 7.37. Found: C, 69.78; H, 7.63.

Another component, ethyl *dl*-5-ethyl-2-piperidone-4-acetate (VI), of the reductive alkylation product was also eluted from the alumina column with chloroform. It was crystallized from benzene to yield 2.036 g (26.8%), mp 94–95°. It has infrared bands at 2.90, 5.80, 6.03, and 6.64 μ.

*Anal.* Calcd for $C_{11}H_{19}O_3N$: C, 61.94; H, 8.98. Found: C, 61.81; H, 8.88.

***dl-trans*-N-(β-3′-Indolyl)-5-ethyl-2-piperidone-4-acetic Acid (VII, R = H).** A solution of 200.3 mg (0.563 mmole) of VII (R = $C_2H_5$), mp 103–106°, in ethanol was refluxed for 6 hr with 0.96 ml of 0.587 *N* potassium hydroxide and then allowed to stand for 12 hr at room temperature. The resulting solution was concentrated at reduced pressure, and the residue was dissolved in water and washed with chloroform. The aqueous solution was acidified with dilute hydrochloric acid, and the flocculent white solid which precipitated was collected by filtration and washed with water. Crystallization of this solid from ethanol yielded 174.5 mg (94.3%) of the *trans* acid, mp 203–205°.

**Ethyl *dl-trans*-N-(β-3′-Indolylethyl)-5-ethyl-2-piperidone-4-acetate (VII, R = $C_2H_5$).** A solution of 914.5 mg (2.79 mmoles) of VIII (R = COOH) and 38.0 mg of concentrated sulfuric acid in 30 ml of absolute ethanol was refluxed under nitrogen for 7 hr. The cooled reaction mixture was then neutralized with dilute ammonium hydroxide and concentrated *in vacuo*. The residue was dissolved in ether, washed with dilute ammonium hydroxide and saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated. Crystallization of the residue from ethyl acetate yielded 874.0 mg (88%) of the lactam ester (VII, R = $C_2H_5$), mp 105–110°. Unesterified acid was recovered by acidifying the aqueous washes. Crystallization of this material yielded 70.9 mg (7.75%) of the *trans* acid, mp 204–206°.

The ester was crystallized from ethyl acetate–diisopropyl ether for analysis, mp 108–110° uncor. It has infrared bands at 2.85, 5.80, 6.15, and 6.64 μ. The absorption at 6.15 μ is attributed to the carbonyl of N-alkyl-α-piperidones; the band at 6.64 μ is characteristic of α-piperidones which have an unsubstituted methylene adjacent to the lactam nitrogen.

*Anal.* Calcd for $C_{21}H_{28}O_3N_2$: C, 70.76; H, 7.92. Found: C, 70.61; H, 7.99.

***dl-trans*-N-(β-3′-Indolylethyl)-5-ethyl-4-(ω-hydroxyethyl-2-piperidone (VIII, R = $CH_2OH$).** A solution of 334.8 mg (0.940 mmole) of the *trans*-lactam ester (VII, R = $C_2H_5$), mp 106.5–109.5°, in 6 ml of a 1 *M* solution of lithium borohydride in tetrahydrofuran was refluxed with mechanical stirring. The progress of the reaction was followed by measuring the carbonyl absorption at 5.8 μ of aliquots of the reaction mixture at intervals during the course of the reaction. After 325 min the ester was completely reduced, and the mixture was cooled and diluted with *n*-butyl alcohol. The resulting solution was washed successively with saturated sodium chloride, a dilute hydrochloric acid solution saturated with sodium chloride, saturated sodium chloride, a dilute potassium hydroxide solution saturated with sodium chloride, and finally with saturated sodium chloride. The butanol solution was then concentrated to dryness and the residue was azeotroped successively with toluene, ethanol, and chloroform. A chloroform solution of the residue was filtered and concentrated to yield 403.3 mg of a light yellow chloroform and crystallized from ethyl acetate to yield 225.6 mg (76.4%) of the alcohol (VIII, R = $CH_2OH$), mp 144–147°. An analytical sample, mp 145.0–145.8° cor, had infrared maxima at 2.85, 3.05, 6.15, and 6.63 μ.

*Anal.* Calcd for $C_{19}H_{26}O_2N_2$: C, 72.58; H, 8.34. Found: C, 72.55; H, 8.28.

***dl-trans*-N-(β-3′-Indolylethyl)-5-ethyl-4-(ω-tosyloxyethyl)-2-piperidone (VIII, R = $CH_2OSO_2C_7H_7$).** An ice-cold solution of 102.7 mg (0.237 mmole) of the *trans* alcohol (VIII, R = $CH_2OH$), mp 145–146.5°, in 358.1 mg of dry pyridine was treated with 81.1 mg (0.425 mmole) of *p*-toluenesulfonyl chloride and allowed to stand in the refrigerator for 15 hr. A drop of water was then added to the mixture which was replaced in the refrigerator for 20 min. It was then diluted with water and extracted with chloroform. The chloroform extracts were washed rapidly with dilute sulfuric acid, water, dilute sodium bicarbonate, water, and finally saturated sodium chloride. The combined chloroform extracts were dried over anhydrous sodium sulfate and concentrated to yield an oil which was chromatographed on silicic acid. An oil (143.6 mg) which failed to crystallize was eluted with 1% ethanol–chloroform. It had infrared bands at 7.35, 7.70, 8.51, and 9.11 μ, characteristic of tosylate esters.

***dl-trans*-N-(β-3′-Indolylethyl)-4,5-diethyl-2-piperidone (VIII, R = $CH_3$).** A solution of 143.6 mg (0.306 mmole) of the tosylate (VIII, R = $CH_2OSO_2C_7H_7$) and 24.8 mg (0.326 mmole) of thiourea in a little ethanol was heated on the steam bath for 7 min. This solution was then refluxed for 40 min with 0.5 g of W-2 Raney nickel. The cooled mixture was filtered and concentrated to yield 153.5 mg of an oil which was chromatographed on silicic acid with 1% ethanol–chloroform to yield 70.8 mg of crude VIII (R = $CH_3$). Crystallization of this material from ethyl acetate–petroleum ether yielded 33.4 mg, mp 120–125°, which could not be purified further by crystallization. Silicic acid chromatography of this crystalline material followed by one crystallization from ethyl acetate–petroleum ether yielded pure VIII (R = $CH_3$), mp 127–128°, which had an infrared spectrum, bands at 2.85, 6.15 and 6.65 μ, identical with that of an authentic sample of *dl-trans*-N-(β-3′-indolylethyl)-,45-diethyl-2-piperidone,[3] mp 125.5–128°. A mixture melting point of VIII (R = $CH_3$) with the authentic sample was undepressed.

**Catalytic Reduction of Ethyl *dl*-N-(β-3′-Indolylethyl)-3,4-dihydro-5-ethyl-2-pyridone-4-acetate (XI).** An ethanolic solution of 141.0 mg (0.398 mmole) of XI was treated with 26.9 mg of 10% palladium on carbon and hydrogenated at atmospheric pressure. After 4 hr 9.70 ml (98.4%) of hydrogen had been consumed. The resulting mixture was filtered, and the filtrate was concentrated slightly *in vacuo* and refluxed under nitrogen with 0.7 ml of 0.58 *N* potassium hydroxide for 18 hr. This solution was concentrated and the residue was dissolved in water and acidified with dilute hydrochloric acid. The acidic material was extracted with chloroform, and the chloroform extracts were washed with water, concentrated *in vacuo*, and chromatographed on silicic acid. Crystallization of the resulting acid from ethanol yielded 66.3 mg (51%) of the *trans*-lactam acid (VII, R = H), mp 202.0–206.5°.

**Reaction of XI with Phosphorus Oxychloride.** A solution of 122.7 mg (0.348 mmoles) of XI and 0.2 ml of freshly distilled phosphorus oxychloride in 2 ml of dry benzene was heated under nitrogen at 75–85° for 1 hr. The heterogeneous reaction mixture was concentrated *in vacuo*, and the residue was dissolved in chloroform, washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Chromatography of the product on silicic acid with 0.5% ethanol–chloroform yielded 82.1 mg (67.0%) of a colorless oil (XIII, R = $C_2H_5$), infrared bands at 2.85, 5.80, and 6.15 μ, which failed to crystallize. A solution of 74.6 mg (0.211 mmole) of this oil in ethanol was refluxed under nitrogen with 0.40 ml of aqueous 0.587 *N* potassium hydroxide for 7 hr. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in water and washed with ether. The aqueous solution was acidified with dilute hydrochloric acid and extracted with chloroform; the chloroform extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 60.8 mg of a mixture of crystalline acids (XIII, R = H). Fractional crystallization aided by silicic acid chromatography resulted in a partial separation of these acids. A low melting isomer, mp 192–198°, was crystallized from ethyl acetate for analysis.

*Anal.* Calcd for $C_{19}H_{22}O_3N_2$: C, 69.92; H, 6.79. Found: C, 69.84; H, 6.99.

Other components of the mixture, mp 262–273 and 245–249°, were not characterized.

*dl*-β-(1-Cyano-1-propyl)glutaric Acid (IV, R = CN; R′ = H). A mixture of 2.0 g (7.85 mmoles) of the cyano diester (IV, R = CN; R′ = $C_2H_5$) and 30 ml of aqueous 0.587 *N* potassium hydroxide was refluxed for 17 hr. The cooled, homogeneous reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated. Crystallization of the product from ethyl acetate–petroleum ether yielded 1.194 g (76.5%) of the diacid (IV, R = CN; R′ = H), mp 107.5–110°. It was crystallized from ethyl acetate–petroleum ether for analysis, mp 110–111.5°.

*Anal.* Calcd for $C_9H_{13}O_4N$: C, 54.26; H, 6.58. Found: C, 54.50; H, 6.48.

**Reductive Alkylation of Tryptamine with *dl*-β-(1-Cyano-1-propyl)-glutaric Acid (IV, R = CN; R′ = H).** An ethanolic solution of 2.8 g (17.57 mmoles) of tryptamine was allowed to stir at room temperature with 1 g of W-2 Raney nickel for 2 hr. It was then filtered, concentrated *in vacuo* to about 8 ml, and added to a 42-ml steel hydrogenation bomb. To this solution was added 378.4 mg (1.89 mmoles) of the cyano diacid (IV, R = CN; R′ = H), 2 ml of ethanol, and 1 g of W-2 Raney nickel; the resulting mixture was hydrogenated at 80° for 8 hr at an initial hydrogen pressure of 1500 psi. The cooled reaction mixture was filtered through Filtercel and the filtrate was concentrated *in vacuo* to yield a dark oil which was mixed with water, cooled in an ice bath, and treated with 0.65 ml of aqueous 5.81 *N* potassium hydroxide. Extraction of the resulting mixture with ether removed the excess tryptamine. The aqueous solution which contained the potassium salt of any carboxylic acid formed during the reaction was acidified with 0.559 g of concentrated hydrochloric acid[28] and extracted with ether. The ether extract was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated to yield 58.0 mg of a crude acidic material. Purification of this material by silicic acid chromatography followed by crystallization from ethyl acetate yielded 8.2 mg of the *trans*-lactam acid (VII, R = H), mp 198–201°.

The aqueous solution was concentrated to dryness under reduced pressure; last traces of water were removed by adding several portions of absolute ethanol to the residue and concentrating the resulting solution to dryness after each addition. A solution of the product in absolute ethanol was treated with a few drops of concentrated sulfuric acid and allowed to reflux under nitrogen for 4 hr. The resulting solution was neutralized with dilute ammonium hydroxide and concentrated under reduced pressure. The residue was treated with water and extracted with chloroform, the chloroform extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated to yield 526.5 mg of an oil which was chromatographed on alumina. An oil (247.4 mg) which had the infrared bands expected for the desired lactam ester was eluted from the column with chloroform. This material was dissolved in ethanol and refluxed for 6 hr with 1.18 ml of aqueous 0.587 *N* potassium hydroxide. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water. Acidification of this solution with 69.5 mg of concentrated hydrochloric acid yielded a white precipitate which was collected by filtration, washed with water, and crystallized from ethanol–ethyl acetate to yield 114.3 mg (18.4%) of the *trans* lactam acid (VII, R = H), mp 200–205°.

***trans*-3-Ethyl-2-carboethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine.** A solution of 2.060 g of VII (R = $C_2H_5$) and 5 ml of freshly distilled phosphorus oxychloride in 50 ml of dry toluene was heated under nitrogen at 95–115° for 2 hr. The product (XVI) separated from the solution as a red oil which crystallized on cooling. Concentration of the reaction mixture under nitrogen and reduced pressure yielded a semisolid residue which was dissolved in chloroform. The chloroform solution was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. An ethanolic solution of the residue was hydrogenated at atmospheric pressure over a prereduced platinum oxide catalyst. After 3.25 hr the reduction was complete with a hydrogen uptake of 144 ml (100.8%). This solution was filtered through Filtercel, concentrated to about 40 ml, diluted with ethyl acetate, and allowed to crystallize. Several crystallizations of the product from ethanol–ethyl acetate yielded 1.835 g (84.5%) of the hydrochloride of XVII (R = $C_2H_5$), mp 274.6–277.0° dec (sealed tube). An analytical sample of this hydrochloride, mp 271.6–272.6° dec (sealed tube), was prepared by crystallizing it several times from ethanol–ethyl acetate.

*Anal.* Calcd for $C_{21}H_{29}O_2N_2Cl$: C, 66.91; H, 7.76. Found: C, 66.84; H, 7.85.

The free base (XVII, R = $C_2H_5$), prepared from the hydrochloride in the usual manner, crystallized from ethyl acetate–petroleum ether as fine, wooly needles, mp 128–129°, and had infrared bands at 2.85, 3.41, 3.55, 3.61, and 5.80 μ. Repeated crystallization of this compound was not desirable since it had some tendency to decompose when heated or allowed to stand in a crystallizing solvent.

**Reaction of XVII (R = $C_2H_5$) with Mesitylmagnesium Bromide.** A solution of mesitylmagnesium bromide in ether was prepared by refluxing 2.013 g (10.1 mmoles) of mesityl bromide in a little ether with about 300 mg-atoms of magnesium which had been washed with ether and dried. It was diluted to 5 ml with anhydrous ether and a 1.5-ml aliquot was added to a stirred solution of 233.3 mg (0.685 mmole) of the tetracyclic ester (XVII, R = $C_2H_5$) in 5 ml of ether. A gummy, white precipitate formed immediately. This mixture was treated with 1 ml of ethyl formate, which had been distilled twice from phosphorus pentoxide, and allowed to stand for 1.5 hr. The reaction mixture was then cooled in an ice bath and acidified with glacial acetic acid. Water was added to the resulting mixture and the aqueous solution was extracted with ether. The ether extract was washed with water, and the combined aqueous solution was neutralized with potassium carbonate and extracted with ether; these ether extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated to yield 249.1 mg of a solid. Crystallization of this solid from ethyl acetate–petroleum ether yielded 189.2 mg (75.0%) of XX as colorless needles, mp 117–141°. Repeated crystallization from ethyl acetate–diisopropyl ether or chromatography on silicic acid failed to change the melting point of this compound. An analytical sample [mp 120–137° uncor, $\lambda_{max}$ 247 mμ (ε 17,100), 291 (4300) 299 (3800)] was prepared by crystallizing XX several times from ethyl acetate–diisopropyl ether. It had a broad infrared band at 5.88 μ, corresponding to the unresolved carbonyl absorption of the two functional groups.

*Anal.* Calcd for $C_{22}H_{28}O_3N_2$: C, 71.71; H, 7.66. Found: C, 71.97; H, 7.73.

**Reaction of XX with Sodium Methoxide.** Dry sodium methoxide was prepared by concentrating 0.2 ml of a 1.07 *N* solution of sodium in absolute methanol and heating the residue at 90–100° (6 mm) for 30 min. To the powder thus obtained was added a solution of 80.2 mg (0.218 mmole) of XX in 10 ml of anhydrous ether, and the resulting mixture was allowed to reflux under nitrogen for 5 hr. It was then cooled and neutralized with glacial acetic acid. The acetic acid salt which crystallized from the solution was dissolved in water, and the resulting solution was washed with ether. It was then made ammoniacal and extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over sodium sulfate, and concentrated to yield 70.8 mg of a crude base which was shown to be a mixture of XVII (R = $C_2H_5$ and $CH_3$) by its infrared spectrum.

***trans*-3-Ethyl-2-carbomethoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine.** A solution of 1.125 g (3.31 mmoles) of the ethyl ester (XVII, R = $C_2H_5$) in 25 ml of absolute methanol was treated with 0.5 ml of 1.07 *N* sodium methoxide and refluxed under nitrogen for 8 hr. The cooled solution was neutralized with glacial acetic acid and concentrated under reduced pressure. The residue was dissolved in water, made ammoniacal, and extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated. Crystallization of the product from methyl acetate–petroleum ether yielded 891.0 mg (82.6%) of the methyl ester (XVII, R = $CH_3$), mp 143.5–145.5°, which had infrared maxima at 2.85, 3.55, 3.61, 5.80, and 6.94 μ. The mother liquor from the free base crystallization was dissolved in methanol, acidified with an ethereal solution of anhydrous hydrogen chloride, concentrated, and dried over potassium hydroxide in a vacuum desiccator. Crystallization of the resulting hydrochloride from methanol–methyl acetate yielded 190.0 mg (15.8%) of the crude hydrochloride of XVII (R = $CH_3$). An analytical sample of this hydrochloride, mp 274.6–275.2° cor (sealed tube), was prepared by crystallizing it several times from methanol–methyl acetate.

*Anal.* Calcd for $C_{20}H_{27}O_2N_2Cl$: C, 66.19; H, 7.50. Found: C, 66.29; H, 7.47.

(28) In a second experiment, carried out under the same conditions, acidification of this aqueous solution with concentrated hydrochloric acid yielded a crystalline precipitate. This was washed with water, dried, and crystallized from ethanol–ethyl acetate to yield 141.1 mg (17.3%) of the *trans*-lactam acid, mp 201–207°.

*dl*-**Desmethyldihydrocorynantheine (XVIII, R = $CH_3$).** To an ice-cold, stirred solution of 503.4 mg (1.54 mmoles) of XVII (R = $CH_3$) in 5 ml of dry ether, under pure nitrogen, was added 25 ml of a 0.165 *N* ethereal solution of triphenylmethylsodium. As the rapid addition proceeded the solution became cloudy and finally red as the last of the reagent was added. After 0.5 min 2 ml of methyl formate (freshly distilled from phosphorus pentoxide) was added to the reaction mixture and the resulting solution was allowed to stand in the ice bath for 3 hr. A small amount of glacial acetic acid was then added to the cloudy solution, and the resulting acetic acid salt was extracted with water. Acidification of the ether solution with concentrated hydrochloric acid yielded a crystalline hydrochloride of trityl ketone (XIX·HCl) which was collected by filtration and dried to yield 276.7 mg, mp 295.8–299.8°. An analytical sample, mp 304.5–305.2°, was prepared by crystallizing XIX (HCl) from ethanol–chloroform and drying the pure, finely ground crystals at 100° (0.01 mm) for 24 hr.

*Anal.* Calcd for $C_{38}H_{39}ON_2Cl$: C, 79.35; H, 6.83. Calcd for $C_{38}H_{39}ON_2Cl \cdot 0.5H_2O$: C, 78.12; H, 6.90. Calcd for $C_{38}H_{39}ON_2Cl \cdot 1H_2O$: C, 76.94; H, 6.97. Found: C, 77.79, 77.85; H, 7.04, 7.01.

The infrared spectrum of XIX has maxima at 2.86, 3.55, 3.61, 5.86, 6.24, and 6.66 $\mu$. In the ultraviolet XIX absorbs at $\lambda_{max}$ 290 m$\mu$ ($\epsilon$ 5780), 283 (6870), and 224 (43,900).

The aqueous solution, which contained the acetic acid salts of the formyl derivative and of the unreacted starting material, was made ammoniacal and extracted with ether; the ether extracts were washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield 410.3 mg of the crude free base which was purified by silicic acid chromatography. Unreacted starting material was eluted from the column with chloroform and was isolated as its hydrochloride to yield 184.2 mg (33.0%), mp 272.6–274.2°. The formyl derivative (XVIII, R = $CH_3$), which had infrared bands at 5.80 and 6.05 $\mu$, was eluted with 0.5% ethanol–chloroform and was crystallized from ethyl acetate to yield 100.6 mg (18.5%), mp 185.2–187.0°. An analytical sample of XVIII [R = $CH_3$], mp 185.0–186.2° dec (sealed tube), was prepared by rapidly chromatographing a sample of the crystalline formyl derivative on silicic acid and crystallizing the resulting material from ethyl acetate–petroleum ether. It had infrared bands 2.87, 3.55, 3.61, and 6.05 $\mu$.

*Anal.* Calcd for $C_{21}H_{26}O_3N_2$: C, 71.16; H, 7.40. Found: C, 70.68; H, 7.47.

The hydrochloride of XVIII (R = $CH_3$) crystallized from ethanol–ethyl acetate, mp 236.2–238.0° dec (sealed tube).

*dl*-**Dihydrocorynantheine.** An ice-cold solution of XVIII (R = $CH_3$) (88.3 mg, 0.248 mmole) in 15–20 ml of ethyl acetate was treated with 4 ml of a cold 0.49 *M* ethereal solution of diazomethane. Within a short time the reaction mixture became cloudy and a white solid began to form. After this mixture had been kept at 0° for 6 hr the solvent was removed under a stream of nitrogen; the residue was dissolved in chloroform and chromatographed on silicic acid. With 0.25% ethanol–chloroform 24.8 mg (27.2%) of the O-methylated product was obtained. *dl*-Dihydrocorynantheine was characterized as its hydrochloride, mp 242.2–243.3° dec (sealed tube), which crystallized from 95% ethanol–ethyl acetate.

*Anal.* Calcd for $C_{22}H_{28}O_3N_2 \cdot HCl$: C, 65.25; H, 7.22. Found: C, 64.90; H, 7.17.

The infrared spectrum of a solution of pure *dl*-dihydrocorynantheine in chloroform was identical in every respect with that of a solution of the natural product[29] in the same solvent.

Further elution of the silicic acid column with 0.5% ethanol–chloroform yielded 11.6 mg of the starting material. With methanol 30.0 mg of a compound was eluted which was crystallized from ethanol–ethyl acetate, mp 228.3–238.0° dec (sealed tube). Crystallization of the hydrochloride of this compound, mp 254.8–257.2° dec (sealed tube), from ethanol–ethyl acetate resulted in considerable decomposition.

*Anal.* Calcd for $C_{22}H_{29}O_3N_2Cl$: C, 65.25; H, 7.22. Found: C, 64.64; H, 7.06.

Although a satisfactory analysis was not obtained, this compound was considered to be i.

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(29) A mixture of *d*-corynantheine and *d*-dihydrocorynantheine was obtained by the method of Janot and Goutarel[30] from a crude alkaloidal extract. An ethanolic solution of this mixture was hydrogenated at atmospheric pressure over a 10% palladium-on-carbon catalyst, and the resulting alkaloid was crystallized several times from methanol–water and dried in a vacuum desiccator over anhydrous calcium chloride to yield pure *d*-dihydrocorynantheine, mp 103–106° after softening at 88°, $[\alpha]^{24.5}D$ +31.2 ± 1.4° (*c* 1.04, methanol) [lit. softens at 70°, resolidifies at 95°, mp 103–104°; $[\alpha]^{18}D$ +30° (*c* 0.93, methanol)].

(30) M. M. Janot and R. Goutarel, *Bull. Soc. Chim. France*, **18**, 588 (1951).

# Total Synthesis of *dl*-Corynantheine

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**Abstract:** By utilizing a key tetracyclic intermediate in the ajmalicine synthesis,[2] the first total synthesis of corynantheine (**3**) (racemic form) was achieved, along with a related base in the geissoschizine family. The corynantheine synthesis proceeds through the following sequence of intermediates: **5, 25b, 26,** and **31.**

In the biogenesis of indole alkaloids of the yohimbine family, appearance of many structural variants seems to depend on various oxidation, reduction, and cyclization options open to certain key biological intermediates. For example, it seems certain that such diverse structures as the corynantheine, ring-E heterocycle, ajmaline/sarpagine, and other types derive from a common—as yet unknown—elementary precursor. As one facet in our program of biogenetic-type synthesis, we have attempted to simulate this over-all behavior by carrying out a biogenetically patterned synthesis of a polycyclic indole derivative, which by suitably different chemical operations could be transformed to one or another alkaloidal type. As an example of this approach, we cite the simple, Mannich type condensation of tryptamine, formaldehyde, and keto triester **1** to the lactam **2**, which can be converted to ajmalicine,[2] or in-

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(2) E. E. van Tamelen and C. Placeway, *J. Am. Chem. Soc.*, **83**, 2594 (1961); E. E. van Tamelen, C. Placeway, I. G. Wright, and G. P. Schiemenz, *ibid.*, **91**, 7359 (1961).