[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

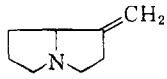
The Total Synthesis of (+)-Retronecine

T. A. GEISSMAN AND ANTHONY C. WAISS, JR.

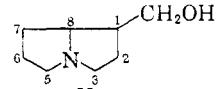
Received August 14, 1961

The total synthesis of (+)-retronecine has been accomplished.

Of the naturally occurring pyrrolizidine bases, which occur in the form of esters in alkaloids of *Senecio*, *Crotalaria*, and a number of genera of the Boraginaceae,[1] only those natural bases lacking the 7-hydroxy group (see II) have been prepared by synthetic means. For example, anagyroidine (I)[2] and isoretronecanol, trachelanthramidine, and laburnine (II)[3] have been synthesized, but the methods



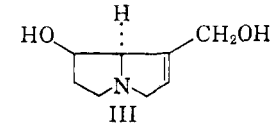
I



II

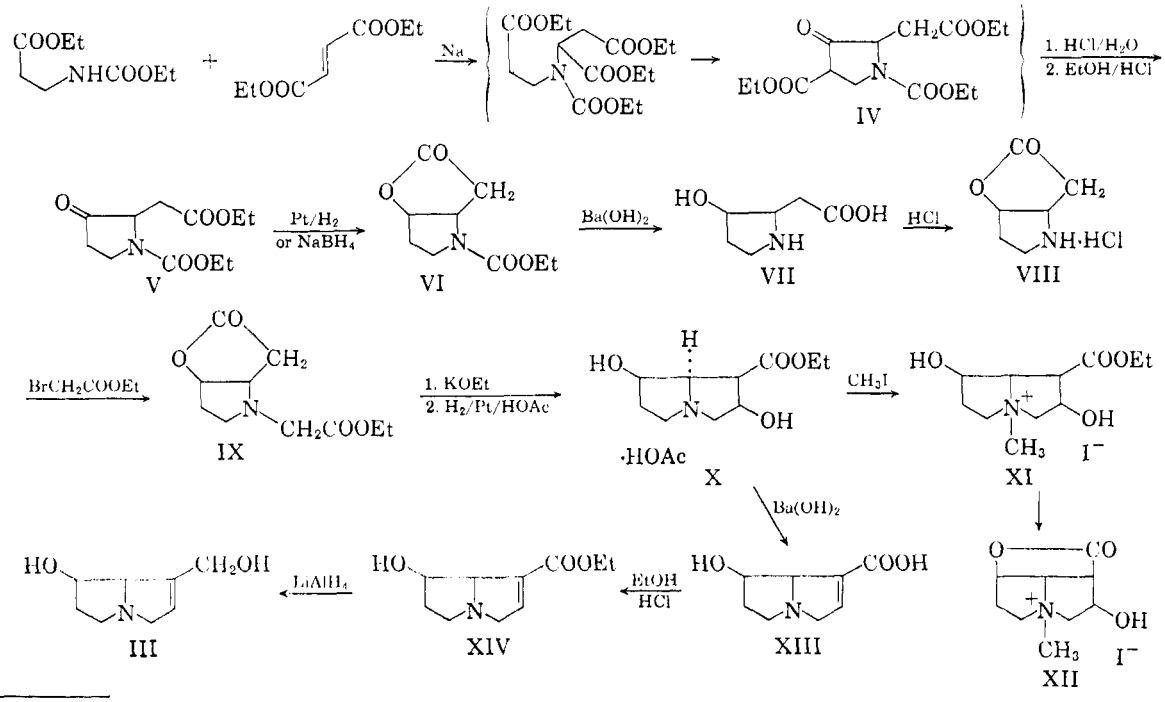
that were used are not readily applicable to the preparation of the bases that bear a 7-hydroxyl group.

Of these bases, retronecine (III) and heliotridine (III, but with the opposite configuration at C-7) are the most common, retronecine being the constituent base of the widely distributed senecionine, seneciphylline, retrorsine, and of numerous other alkaloids.



III

As part of the plan for the study of the biogenesis of *Senecio* alkaloids (in particular, the formation of the final esters) it was necessary to have specifically labeled, radioactive retronecine, and in order to secure this, a total synthesis of the natural (+) base was desirable. This synthesis has been accomplished by the route shown in the following chart:



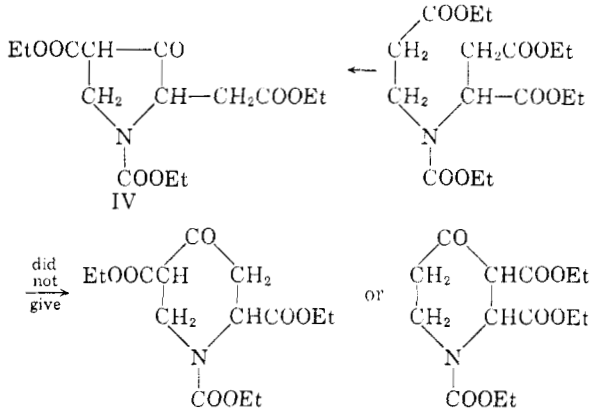
Certain features of the synthetic sequence are worth comment. The key intermediate, V, had been prepared earlier by Clark-Lewis and Mortimer[4] in a reaction that it was originally hoped would proceed to yield the 4-pyridone, but which took the alternative course to the pyrrolidone IV, hydrolysis, decarboxylation, and reesterification of which led to V. Catalytic reduction of the keto

(1) (a) N. J. Leonard, in *The Alkaloids* (R. H. F. Manske and H. L. Holmes, Eds.), vol. I, vol. VI; Academic Press, New York, 1950; 1960; (b) F. L. Warren, *Fortschr. Chem. Org. Naturstoff*, **12**, 198 (1955).

(2) N. K. Kochetkov, A. M. Likhosherstov, and A. M. Kritsyn, *Tetrahedron Letters*, No. **3**, 92 (1961).

(3) (a) K. Babor, I. Ježo, V. Kalac, and M. Karvač, *Chem. Zyesti*, **13**, 163 (1959); (b) N. J. Leonard and S. W. Blum, *J. Am. Chem. Soc.*, **82**, 503 (1960); (c) N. K. Kochetkov and A. M. Likhosherstov, *Zhur. Vsesoyuz. Khim. Obsh.* in *D. I. Mendeleeva*, **5**, 477 (1960); (d) N. K. Kochetkov, A. M. Likhosherstov, and E. I. Budovskii, *Khim. Nauka i Prom.*, **4**, 678 (1959).

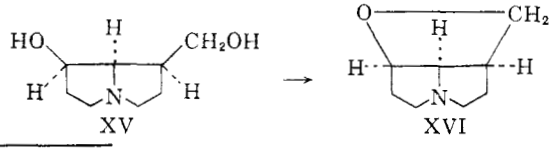
(4) J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1960).



ester (V) gave VI, by way of what was presumably the corresponding hydroxypyrrolidine, which on distillation lactonized. Sodium borohydride reduction of V gave what appeared to be a mixture of the lactone (VI) and the (presumably epimeric) hydroxy ester. Clark-Lewis and Mortimer[4] obtained 3-pyrrolidinol-2-acetic acid by sodium borohydride reduction of V, followed by saponification of the ethoxycarbonyl groupings. That their hydroxy acid was the *cis* isomer is indicated by the fact that it was prepared in the present work by saponification of VI, and by the fact that Clark-Lewis and Mortimer obtained a phenylcarbamoyl derivative of the lactone when the amino hydroxy acid was treated with phenylisocyanate.

The lactone (VIII) formed from V (by way of the amino acid VII) was alkylated with ethyl bromoacetate and the resulting *N*-carboethoxymethyl lactone (IX) cyclized with potassium ethoxide in benzene. The immediate product of this reaction, the ester of the 2-ketopyrrolidizidine-1-carboxylic acid corresponding to the 2-hydroxy compound X, was not characterized, but the crude material gave the purple ferric chloride color characteristic of a compound of the expected structure. It was found convenient to submit the crude β-keto ester to hydrogenation to form ethyl 2,7-dihydroxypyrrolizidine-1-carboxylate (X).

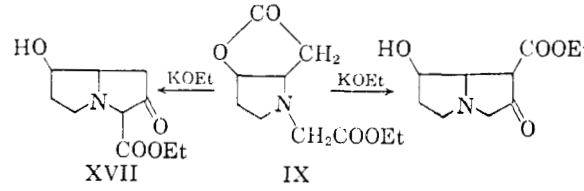
The sterochemical result of this hydrogenation was expected to be favorable for two reasons: The carboxyl group should assume a position *cis* to the 7-hydroxyl group, and the 2-hydroxyl group should be *trans* to the hydrogen atom in the 1-position. This stereochemical course was anticipated from the fact that retronecine is converted by catalytic reduction into platynecine (XV),[5] the *cis*-(7-OH)—(1-CH_2OH) relationship of which is known from its ready dehydration to anhydroplatynecine (XVI):



(5) R. Adams and E. F. Rogers, *J. Am. Chem. Soc.*, **63**, 537 (1941).

Indeed, a comparable reaction was observed in the case of the pyrrolizidine X: the methiodide (XI) of this compound readily lost the elements of ethanol to yield a lactone (XII).

This lactonization reaction served also to establish the course of the ring closure of IX, which it can be seen could have taken an alternative course, in which condensation on the $N—CH_2—$ group could have occurred to yield the isomeric pyrrolizidine-3-carboxylic acid derivative (XVII):



The ready formation of the lactone XII shows that the cyclization did process in the desired direction; models show that the formation of a lactone (from XVII) between a carboxyl group at position 3 and a 7-hydroxyl group would involve considerable strain. In addition, the infrared spectrum of the lactone XII (band at 1780 $cm.^{-1}$) is in perfect accord with the presence of a γ-lactone.[6]

The facile dehydration of the dihydroxy ester X during alkaline saponification to the amino acid XIII is not without precedent.[7] The formation of ethyl 1,2-dehydro-7-hydroxypyrrolizidine-1-carboxylate (XIV) and reduction with lithium aluminum hydride gave (±) retronecine (III). The racemic base and natural (+)-retronecine showed identical R_f values when run side by side on paper with butanol–5% acetic acid (1:1, organic phase) as the irrigating solvent. The infrared spectra of the natural and racemic bases were similar but not identical when taken in KBr discs, probably because of different orientations in the crystalline state, but the infrared spectra in chloroform were identical in all respects.

Resolution of the synthetic (±)-retronecine was accomplished by means of the salt with *d*-camphoric acid, which preliminary experiments with the natural base proved to yield a readily crystallizable salt. The crystalline *d*-camphorate formed from the racemic base was identical in melting point and rotation with that of natural (+)-retronecine. Decomposition of the salt of the synthetic base yielded retronecine with melting point and infrared spectrum identical with those of the natural material.

The synthetic route employed in this work appears to be adaptable to the insertion of isotopic carbon by the use of ethyl 2-C^{14}-bromoacetate in the step VIII → IX.

(6) It should be pointed out, however, that some δ-lactones show abnormally high carbonyl frequencies in the infrared. See T. A. Geissman, *Austral. J. Chem.*, **12**, 247 (1959).

(7) R. L. Shriner, *The Reformatsky Reaction, Org. Reactions*, **I**, 11 (1942).

EXPERIMENTAL

Ethyl N-ethoxycarbonyl-3-pyrrolidinone-2-acetate (V). (a) To an ice-cooled solution of 356 g. of β-alanine and 160 g. of sodium hydroxide in 1 l. of water were gradually added, with stirring, 466 g. of ethyl chloroformate, and a solution of 172 g. of sodium hydroxide in 1.5 l. of water. The additions were made simultaneously over 4 hours. The reaction mixture was acidified and extracted with five 200-ml. portions of chloroform. The dried (sodium sulfate) chloroform solution was taken to dryness and the product recrystallized from benzene to yield 592 g. (92%) of *N*-ethoxycarbonyl-β-aminopropionic acid. (b) A solution of 200 g. of *N*-ethoxycarbonyl-β-aminopropionic acid in 500 ml. of absolute ethanol was saturated with dry hydrogen chloride. After 16 hours the ethanol was evaporated, the residual oil dissolved in 500 ml. of ethanol, and the resulting solution again evaporated. The oily residue was distilled to yield 196 g. (84%) of the ester, b.p. 89–93/0.3 mm. (c) A mixture of 350 ml. of dry benzene, 4.6 g. of powdered sodium, 34.4 g. of diethyl fumarate, and 38.1 g. of ethyl *N*-ethoxycarbonyl-β-aminopropionate was stirred for one hour and then heated on the steam bath for an additional hour. The cooled mixture was shaken with 300, 75, and 75 ml. of ice-water and the combined aqueous extracts washed with ether, acidified with sulfuric acid, saturated with sodium chloride, and extracted with ethyl acetate. Removal of the ethyl acetate left 56 g. of an oil that gave a purple color with ferric chloride.

The crude β-keto ester (IV) was dissolved in 150 ml. of 12*N* hydrochloric acid and the solution left overnight. The solution was taken to dryness under reduced pressure and the residue dissolved in 100 ml. of ethanol and the solution again evaporated. This was repeated. Finally, 150 ml. of ethanol, saturated with dry hydrogen chloride, was added and the solution refluxed for 3 hours. Removal of the solvent and distillation of the residual oil yielded 22 g. (45%) of ethyl *N*-ethoxycarbonyl-3-pyrrolidinone-2-acetate (II), b.p. 135–140°/2 mm. The semicarbazone had m.p. 124–124.5 (reported,[4] 123–124°).

Lactone of N-ethoxycarbonyl-3-pyrrolidinol-2-acetic acid (VI). A solution of 20 g. of ethyl N-ethoxycarbonyl-3-pyrrolidinone-2-acetate (IV) in 200 ml. of ethanol was cooled in ice and, while stirring, 1.86 g. of sodium borohydride was added in portions. After 30 min. the ice bath was removed and stirring continued for 2 hours at room temperature. After the addition of 2 ml. of acetone and 1 l. of water the solution was saturated with sodium chloride and extracted with ten 20 ml. portions of chloroform. After removal of the chloroform the residue was distilled to yield 11.5 g. (70%) of a colorless oil. The compound has strong absorption peaks at 1690 cm.$^{-1}$ (*N*-COOEt) and 1785 cm.$^{-1}$ (γ-lactone).

3-Pyrrolidinol-acetic acid lactone (VIII). Five g. of the lactone (VI) of *N*-ethoxycarbonyl-3-pyrrolidinol-2-acetic acid, 25 g. of barium hydroxide octahydrate, and 150 ml. of water were heated under reflux for 16 hrs. The reaction mixture was saturated with carbon dioxide, the barium carbonate removed, and the aqueous solution concentrated under reduced pressure. The amino acid (3 g.) crystallized when ethanol and ether were added. Five recrystallizations from ethanol-water gave the amino acid monohydrate (IV), melting at 217–218° (reported,[4] 215–216°).

Two grams of the amino acid hydrate (VII) was dissolved in 20 ml. of *N* hydrochloric acid and the solution heated on the steam bath for 1 hour. Removal of the solvent under reduced pressure and recrystallization of the residue from ethanol-ether afforded 1.4 g. (70%) of the lactone (VIII), m.p. 175–177°. The strong carbonyl absorption at 1780 cm.$^{-1}$ was that of the γ-lactone.

Anal. Calcd. for $C_6H_{10}O_2NCl$: C, 44.04; H, 6.11; N, 8.55. Found: C, 44.18; H, 6.35; N, 8.32.

Lactone of N-carboethoxymethyl-3-pyrrolidinol-2-acetic acid (IX). A mixture of 20 g. of lactone (VIII), 16 g. of sodium carbonate, 25 g. of ethyl bromoacetate, and 500 ml. of ethanol was refluxed on a steam bath overnight. The solvent was removed, 200 ml. of ether was added to the residue, and inorganic salts were removed. When hydrogen chloride gas was passed into the ether solution a viscous oil precipitated. This crystallized when cooled and scratched. It was recrystallized from ethanol-ether to give 21 g. (70%) of colorless crystals of IX, m.p. 150–152°. Carbonyl absorption bands were observed at 1750 and 1780 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{16}O_4NCl$: C, 48.09; H, 6.44; N, 5.61. Found: C, 48.27; H, 6.66; N, 5.74.

Ethyl 2,7-dihydroxypyrrolizidine-1-carboxylate (X). An aqueous solution of 25 g. of the hydrochloride of lactone VI was neutralized with aqueous sodium carbonate and extracted with five 100-ml. portions of benzene. The benzene extract was dried over sodium sulfate, filtered, and concentrated to 250 ml. by distillation. A suspension of potassium ethoxide in benzene was prepared from 10 g. of potassium and 25 ml. of ethanol in 500 ml. of benzene, excess ethanol being removed by distillation of some of the solvent. The benzene solution of the lactone was added and the resulting mixture heated under reflux for 5 hours in a nitrogen atmosphere.

The mixture was cooled and extracted with 50, 25, and 25 ml. of water and the aqueous extract added to 100 ml. of acetic acid. The resulting solution was hydrogenated, after the addition of 500 mg. of platinum oxide, at 40 p.s.i. for 24 hours. The solution was filtered (Celite) and evaporated to dryness under reduced pressure. The powdered residue was extracted with dry tetrahydrofuran in a Soxhlet apparatus. From the solution was obtained 15 g. of crude product. Recrystallized from tetrahydrofuran, this afforded 11.5 g. (42%) of the acetic acid salt of ethyl 2,4-dihydroxy-1-pyrrolizidinecarboxylate (VII), m.p. 120–121°. The infrared spectrum showed bands at 3400 (OH), 1227 (ester) and 1600, 1400 (carboxylate anion) cm.$^{-1}$ The compound was characterized as the methiodide (see below), but the presence of acetic acid in the salt of m.p. 120–121° was demonstrated by distilling a solution of 1.0 g. in 10 ml. of 3*N* sulfuric acid and converting the acetic acid in the distillate into the *p*-bromophenacyl ester, m.p. 84–85°.

The *methiodide* (XI) of the dihydroxy ester was prepared in the usual way. It had m.p. 155–156°, and showed infrared absorption peaks at 3320 and 1720 cm.$^{-1}$

Anal. Calcd. for $C_{11}H_{20}O_4NI$: C, 36.98; H, 5.64; I, 35.53. Found: C, 36.81; H, 5.61; I, 35.81.

When the methiodide was recrystallized from aqueous ethanol, its properties changed, and it was at length converted into the lactone (XII), m.p. 245°, as shown by the appearance of a strong infrared absorption band at 1780 cm.$^{-1}$

Anal. Calcd. for $C_9H_{14}O_3NI$: C, 34.75; H, 4.53; I, 40.80. Found: C, 34.95; H, 4.71; I, 41.14.

Ethyl 1,2-dehydro-7-hydroxypyrrolizidine-1-carboxylate (XIV). A solution of 10 g. of the dihydroxy ester (X) and 100 g. of barium hydroxide octahydrate in 250 ml. of water was heated under reflux for 2 hours. Removal of the barium with carbon dioxide and evaporation of the filtrate to dryness was followed by treatment of the residue with 200 ml. of ethanol saturated with hydrogen chloride. After 24 hrs. at room temperature the solvent was removed under reduced pressure and 50 ml. of ice water was added. The solution was neutralized with sodium bicarbonate and extracted with ten 25-ml. portions of chloroform. Removal of the chloroform and distillation of the residue *in vacuo* (bulb tube, bath at 150°) afforded 2.2 g. (28%) of a colorless oily product. The compound showed infrared absorption bands at 1700 (α,β-unsaturated ester) and 1630 cm.$^{-1}$ (conjugated double bond). It had an ultraviolet absorption maximum at 206 mμ (ε 11,700). The ester was converted into the picrate, m.p. 137–138°.

Anal. Calcd. for $C_{16}H_{18}O_{10}N_4$: C, 45.08; H, 4.25; N, 13.14. Found: C, 45.15; H, 4.08; N, 13.24.

Attempts to crystallize the crude α-β-unsaturated amino acid (XIII) before esterification (above) were unsuccessful.

The glassy material showed an ultraviolet absorption maximum at 206 mμ (ε 6800).

(±)-*Retronecine* (III). A solution of 2.0 g. of the ester XIV in 50 ml. of anhydrous tetrahydrofuran (THF) was dropped slowly into a solution of 1.0 g. of lithium aluminum hydride in 100 ml. of THF. When the addition was complete, the solution was refluxed overnight and the excess reagent decomposed by the addition of 10 ml. of ethyl acetate and 20 ml. of water. The mixture was filtered through Celite and the filtrate evaporated to dryness. The residue was dried by the addition of benzene and distillation to dryness.

The dried residue was transferred to a Soxhlet thimble and extracted with chloroform. Removal of the chloroform left a brown oil which, when dissolved in a mixture of ethanol and acetone and cooled overnight, yielded 0.8 g. and 0.4 g. (second crop) of brownish crystals. The crude material was recrystallized twice from acetone, affording 0.95 g. of (±)-retronecine, m.p. 130–131°. The compound could also be purified by sublimation at 80°/0.01 mm.

The infrared spectrum of the (±)-base was similar, but not identical to that of natural (+)-retronecine when taken taken in KBr discs, but the infrared spectra in chloroform solution were identical.

Anal. Calcd. for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.00; H, 8.35; N, 9.21.

(+)-*Retronecine* (III). A solution of 174 mg. of (±) retronecine and 220 mg. of *d*-camphoric acid in 1.5 ml. of ethanol was warmed and diluted dropwise with ethyl acetate until it became cloudy. The solution was cleared with a few drops of ethanol and allowed to cool. The 210 mg. of crude crystalline product was recrystallized five times from ethanol–ethyl acetate, after which 46 mg. of material was obtained, m.p. 146–148°, $[\alpha]_D^{27}$ 35.5 (*c* 2, EtOH). Further recrystallization finally afforded 21 mg. with m.p. 151–152°, $[\alpha]_D^{27}$ 35.8° (*c* 1.37, EtOH). Natural (+)-retronecine gave a *d*-camphorate, m.p. 151–152°, $[\alpha]_D^{27}$ 35.4° (*c* 1.61, EtOH). A mixture of the natural and synthetic salts melted at 151–152°.

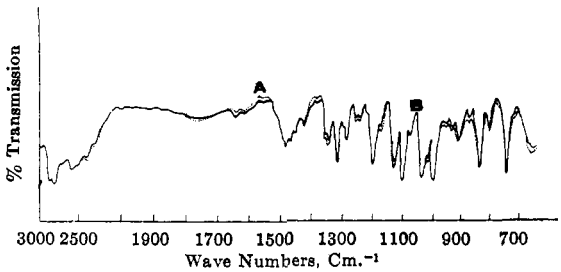


Fig. 1. Infrared absorption spectra of A) natural; B) synthetic (+)-retronecine. In KBr

The synthetic *d*-camphorate (13.7 mg.) was neutralized with aqueous sodium carbonate. A small amount of Celite was added and the slurry was dried on a steam bath in a current of air. The dry residue was extracted (Soxhlet) with chloroform for 24 hours. Removal of the chloroform left crude (+)-retronecine as a thick paste; this was dried in a vacuum desiccator, sublimed at 70°/0.1 mm., and the sublimate recrystallized from acetone. The 4.6 mg. of (+) retronecine that was obtained had m.p. 119–120° and did not depress the m.p. of natural (+)-retronecine (m.p. 120–121°). The infrared absorption spectra of the natural and synthetic materials (in KBr) were identical in every detail (Fig. 1).

In another preparation the (+)-retronecine had m.p. 119–20° and $[\alpha]_D^{26}$ +4.95° (*c* 0.58, ethanol); a sample of natural (+)-retronecine had $[\alpha]_D^{26}$ +50.2°.

Acknowledgment. The authors gratefully acknowledge the support of U.S. Public Health Service research grant RG-6457.

LOS ANGELES, CALIF.

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE]

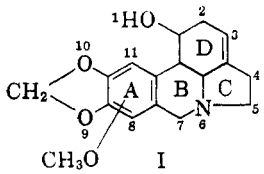
Contribution to the Structure of Falcatine. Synthesis of Isoanhydrofalcatine Lactam

F. BENINGTON AND R. D. MORIN

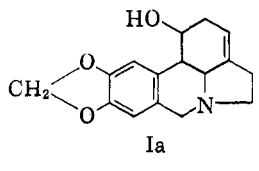
Received November 4, 1960

Previous investigations by others have shown that the methoxyl group in falcatine (I) is located at either C-8 or C-11. Oxidation of I gives anhydrofalcatine lactam which may possess either structure Ic or Id. An unambiguous synthesis of isoanhydrofalcatine lactam (Id), which has properties differing from anhydrofalcatine lactam, shows that the latter compound possesses structure Id and, accordingly, the methoxyl group in falcatine is located at C-11.

Fales and Wildman[1] have shown that the amaryllidacae alkaloid falcatine (I) undergoes ar-demethoxylation with sodium and *n*-amyl alcohol to produce caranine, whose structure has been established[2] as Ia. Thus, the only remaining problem concerning the structure of falcatine was whether the methoxyl group occupies the 8- or the 11-position in the A-ring. Oxidation of I with selenium dioxide followed by treatment with nitric acid afforded the intermediate quaternary salt, anhydrofalcatinium nitrate (Ib), which on further oxidation with potassium ferricyanide gave anhydrofalcatine lactam[1] (Ic or Id). Fales and Wildman have suggested that the synthesis of either 8- or 11-methoxy-4,5-



I



Ia

(1) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 4395 (1958).

(2) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **79**, 2192 (1957).