The Total Synthesis of (3S,15S,20R)-Corynantheine[1,2]

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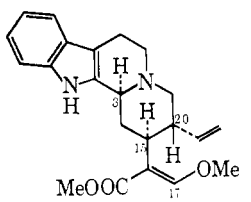
Abstract: Yohimban-17-one (**5**) is converted into 18-formylyohimban-17-one (**6**), the carbanion of which displaces at sulfur in methyl thiotosylate to give 18(*S*)-methioxyyohimban-17-one (**7**). On reaction with thionyl chloride in ether, the *anti*-oxime **9** of this ketone undergoes a Beckmann fragmentation to *trans*-18-methioxycorynanthenitrile (**10**). Desulfurization of the vinyl thioether by a specially prepared Raney nickel is not accompanied by reduction of the double bond; the corynanthenitrile **11** so obtained is converted into methyl corynantheate (**12**), desmethylcorynantheine (**14**), and corynantheine (**1**).

Corynantheine (**1**) is an alkaloid with a curious history. It occurs in admixture with dihydrocorynantheine (**2**) in *Pseudocinchona africana* (A. Chev.)



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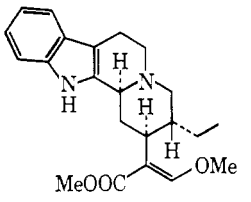

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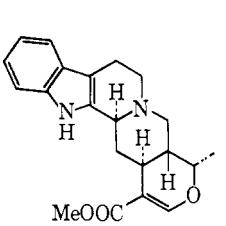
and in *Corynanthe yohimbé;* the two alkaloids cocrystallize as the free base and as a number of salts, and it is owing to this phenomenon that one cannot date its discovery as a pure substance. Its history may be traced to alkaloidal extracts by Perrot[4] slightly characterized by Fourneau.[5,6] It was independently discovered and named by Karrer in 1926.[7] Much of the evidence for its structure must be sifted from conflicting reports,[8,9] the origin for the conflict being in most if not all samples, the presence of both compounds, one with a vinyl side chain, the other with an ethyl group. For the most part, this history is satisfactorily reviewed.[10-12] The final characterization of the pure substance was made in 1953.[13,14]

The stereochemical assignment, with principal contributions by van Tamelen[15] and Wenkert,[16] is documented in the reviews. The most recently resolved controversy has centered about the stereochemical assignment at C-17 on the trisubstituted double bond. Wenkert's original assignment[17] that the double bond was *cis* was based on a faulty model. He compared the position of the nmr resonance of the C-17 hydrogen of corynantheine and dihydrocorynantheine with that of the C-17 hydrogen of several ring E heterocyclic indole alkaloids, *e.g.*, ajmalicine (**3**). This comparison suffers from the fact that, in the heterocyclic alkaloids



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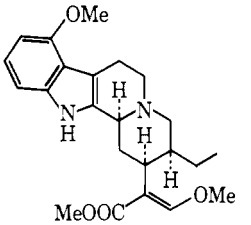

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the C-17 hydrogen is approximately in the plane of the molecule as a whole, whereas in the tetracyclic alkaloids the methoxyacrylate side chain bearing the C-17 is orthogonal to the plane defined by the ring system (see the X-ray determination[18] of the structure of mitragynine (**4**)). The reversal of the stereochemical assignment at C-17, to *trans*, was made by Weisbach[19] after the structure of mitragynine had been determined.

With the synthetic goal defined, we may proceed to the consideration of a synthesis. The two barriers to a total synthesis of corynantheine are the stereochemical problem inherent in the preparation of a compound with four centers of dissymmetry (carbons 3, 15, 17, and 20) and the problem posed by the presence of a vinyl side chain. The stereochemical problem is not serious—the configurations at carbons 3, 15, and 20 are all the most stable, and that at 17 is probably so. The vinyl group is more of an obstacle, as is attested by the existence of several syntheses of racemic dihydrocory-

(1) We gratefully acknowledge the partial support of this research by the William F. Milton Fund of Harvard University.

(2) A preliminary account of this work has appeared: R. L. Autrey and P. W. Scullard, *Chem. Commun.*, 841 (1966). It has also been presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Abstract S76. It is taken in part from the Ph.D. Dissertation (1967) of P. W. S. presented to the University of Rochester.

(3) To whom correspondence should be addressed at the Oregon Graduate Center, Portland, Oregon 97225.

(4) É. Perrot, *Compt. Rend.*, **148**, 1465 (1909).

(5) E. Fourneau, *ibid.*, **148**, 1770 (1909).

(6) M. Raymond-Hamet, *ibid.*, **197**, 860 (1933).

(7) P. Karrer and H. Salomon, *Helv. Chim. Acta*, **9**, 1059 (1926).

(8) V. Prelog, M.-M. Janot, and R. Goutarel, *Compt. Rend.*, **232**, 1305 (1951); P. Karrer, R. Schwyzer, and A. Flam, *Helv. Chim. Acta*, **34**, 993 (1951).

(9) M.-M. Janot, R. Goutarel, and V. Prelog, *ibid.*, **34**, 1207 (1951); P. Karrer and J. Kebrle, *ibid.*, **35**, 862 (1952).

(10) M.-M. Janot and R. Goutarel, *Bull. Soc. Chim. Fr.*, **18**, 588 (1951).

(11) J. E. Saxton, "The Alkaloids," Vol. 7, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 37–42.

(12) H.-G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, 1961, pp 541–546.

(13) R. Goutarel, M.-M. Janot, R. Mirza, and V. Prelog, *Helv. Chim. Acta*, **36**, 337 (1953).

(14) A. Blumenthal, C. H. Eugster, and P. Karrer, *ibid.*, **37**, 787 (1954).

(15) E. E. van Tamelen, P. E. Aldrich, and T. J. Katz, *J. Amer. Chem. Soc.*, **79**, 6426 (1957).

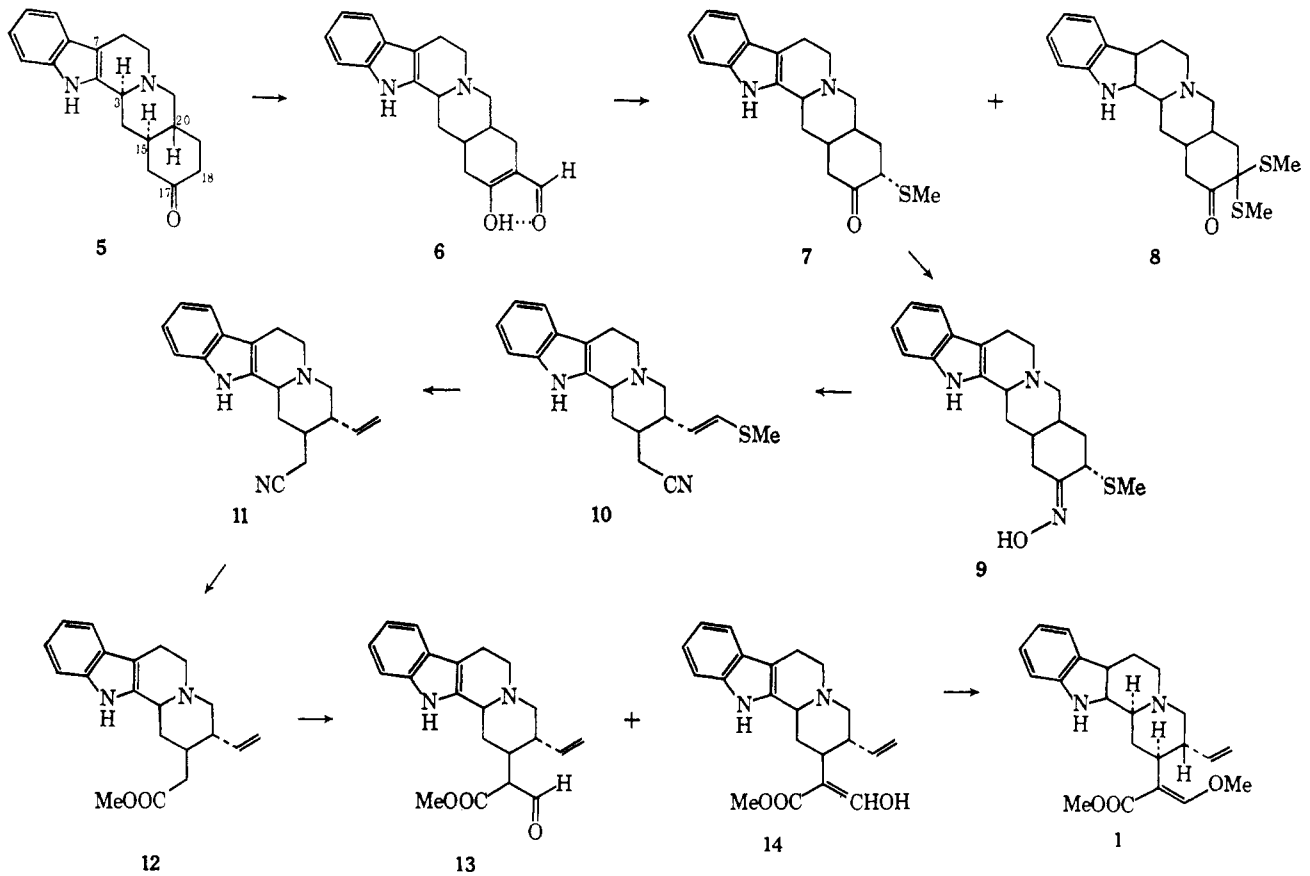
(16) E. Wenkert and D. K. Roychaudhuri, *ibid.*, **78**, 6417 (1956); E. Wenkert and N. V. Bringi, *ibid.*, **81**, 1474 (1959).

(17) E. Wenkert, B. Wickberg, and C. L. Leicht, *Tetrahedron Lett.*, 822 (1961).

(18) D. E. Zacharias, R. D. Rosenstein, and G. A. Jeffrey, *Acta Cryst.*, **18**, 1039 (1965).

(19) J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim, and B. Douglas, *Tetrahedron Lett.*, 3457 (1965). See also W. F. Trager, C. M. Lee, J. D. Phillipson, and A.H. Beckett, *Tetrahedron*, **23**, 1043 (1967).

Scheme I



nantheine or related compounds,[19,20] but only one synthesis of racemic corynantheine.[21] Weisbach concisely summarized some of the cogent reasons for the interest in the syntheses of these compounds.

Since the problems of stereospecific synthesis in the various tetracyclic and pentacyclic indole alkaloids had been surmounted in many ways, to give as desired either stable or unstable configurations at carbons 3 and 20 relative to 15, we chose to focus on the problem of the vinyl group, and accepted yohimbone (**5**) as a starting material. Its appositeness is clear—it has the correct relative and absolute configuration[22] to lead to the natural enantiomorph of corynantheine; it is commercially available; it has been totally synthesized and resolved by Swan.[23]

The conversion of yohimbone to corynantheine requires a cleavage of the bond between the C-17 carbonyl and the C-18 methylene. Traditionally a cleavage between carbonyl and methylene is oxidative (*e.g.*, the Baeyer–Villiger reaction). But because cleavage of that link leaves two two-carbon chains pendant from ring D, it must be one which preserves the distinction in oxidation level between the bond termini to permit their selective modification. Furthermore, tetrahydro-β-carboline derivatives are particularly susceptible to oxidative attack at C-7 (see **5**), and while elegant synthetic use[24] has been made of this susceptibility, it represents a hazard in our approach.

To circumvent this hazard we developed the use of methyl thiotosylate as an oxidizing agent which permits application of the Beckmann fragmentation to bring about the desired cleavage.[25,26] The reaction of moderately stable carbanions with thiolsulfonates was employed by Smiles[27] in his structure proofs of these esters, thought to be disulfoxides before his work. The reaction was reinvestigated by Woodward and Pachter with the development of trimethylenedithiol ditosylate as a methylene group blocking agent.[28,29] Neither of these research groups was specifically considering the thiolsulfonate as an oxidant, though of course their reactions were oxidations.

Our employment of the reaction is illustrated in Scheme I, which presents the whole synthesis. Smiles' studies indicated the need for a relatively acidic carbon acid, hence activation of the yohimbone was required. This, the condensation of yohimbone with methyl or ethyl formate, was first accomplished by Pächt[29] under homogeneous conditions, later under the classical conditions of the heterogeneous Claisen ester condensation.[30] We have used both procedures to prepare 18-formylyohimban-17-one (**6**) in almost quantitative yield;

(20) (a) E. E. van Tamelen and J. B. Hester, Jr., *J. Amer. Chem. Soc.*, **81**, 3805 (1959); (b) E. Wenkert, K. G. Dave, and F. Haglid, *ibid.*, **87**, 5461 (1965). See also the citations in Weisbach, *et al.*[19]

(21) E. E. van Tamelen and I. G. Wright, *Tetrahedron Lett.*, 295 (1964).

(22) Y. Ban and O. Yonemitsu, *Tetrahedron*, **20**, 2877 (1964).

(23) G. A. Swan, *J. Chem. Soc.*, 1534 (1950).

(24) (a) N. Finch, C. W. Gemenden, I. H.-C. Hsu, and W. I. Taylor, *J. Amer. Chem. Soc.*, **85**, 1520 (1963); (b) N. Finch and W. I. Taylor, *ibid.*, **84**, 3871 (1962), give an excellent bibliography of relevant transformations.

(25) R. L. Autrey and P. W. Scullard, *ibid.*, **87**, 3284 (1965).

(26) R. L. Autrey and P. W. Scullard, *ibid.*, **90**, 4924 (1968).

(27) (a) L. G. S. Brooker and S. Smiles, *J. Chem. Soc.*, 1723 (1926); (b) J. C. A. Chivers and S. Smiles, *ibid.*, 697 (1928).

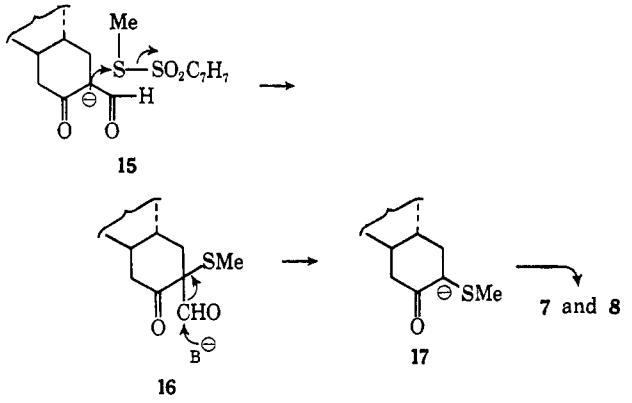
(28) See R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *ibid.*, 1131 (1957).

(29) P. D. Pächt, Dissertation, Harvard University, 1960.

(30) J. D. Albright, L. A. Mitscher, and L. Goldman, *J. Org. Chem.*, **28**, 38 (1963).

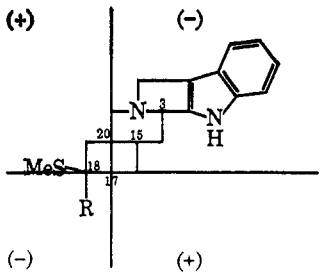
Pächt's procedure gave a slightly purer product, whereas Goldman's procedure was much easier to conduct on a 5-g scale. Both these groups have discussed the structure of the product **6**.[31]

The condensation of formylyohimbone with methyl thiotosylate was first tried under the conditions defined by Pachter: approximately 0.10 *M* in each reagent, 0.5 *M* in potassium acetate, in anhydrous ethanol. Two products were obtained: 18(*S*)-methioxyyohimban-17-one (**7**) in 27% and 18,18-bismethioxyyohimban-17-one (**8**) in 20%[32] yield. The disubstituted product was not unexpected, as the intermediate anion **17** may either take a proton from solvent to give **7**, or react with more methyl thiotosylate to give **8**. It was, however, unwanted, and to suppress its formation we increased the proton availability by adding water, and we



increased the concentration of the reaction solution. The monomethioxy compound was appreciably more insoluble than the bismethioxy derivative, and was much less soluble in 95% ethanol than in absolute ethanol. Thus, in 95% ethanol in concentrated solution, the desired product quickly separated in pure condition in yields of 57 to 63%. The structural assignment of **7** was based on the appearance of a methyl singlet in the nmr spectrum at 2.08 ppm[33] and on the concept of axial protonation of enolates. The bismethioxy compound **8** showed two methyl singlets, at 2.07 and 1.98 ppm.

The optical rotatory dispersion curves of these two ketones confirmed the absolute configurational assignment of yohimbone[22] and hence of corynantheine,[34] and confirmed the substitution of the second methioxy group in an axial configuration at C-18. The octant rule projection[35] of the two ketones (**18** and **19**) shows the substitution on the cyclohexanone ring in a negative octant, the monomethioxy substituent in a nodal plane, and the second, axial methioxy group near the ketone on a diagonal, also in a negative octant if it is at C-18. The ultraviolet absorption of the carbonyl was of course lost under the tetrahydro-β-carboline chromophore, but its optical rotatory dispersion was readily observable in both compounds as a Cotton effect



18, R = H; **19**, R = SMe

centered at 301 nm, negative (amplitude = 15,500°) for **18**, deeper trough (amplitude = 16,200°) for **19**.

The preparation of methioxyyohimbone oxime (**9**) posed a problem the solution of which was important in determining the later course of the synthesis. The standard conditions of acid catalysis proved of no avail, as did the harshest practicable conditions—hydroxylamine hydrochloride in boiling acetic acid; the ketone was recovered unchanged. Presumably, the cation resulting from protonation at the tertiary nitrogen repelled the catalytic proton under conditions of acid catalysis sufficiently mild that one may have free hydroxylamine present.

Oximation by hydroxylamine in aqueous ethanolic sodium hydroxide was successful; **9** was obtained as an amorphous solid in essentially quantitative yield. We did not succeed in crystallizing it, and its combustion analysis was not wholly satisfactory, so that its purity and stereochemical integrity were open to question. Nonetheless, we believe it to consist only of the *anti* isomer shown. It gave an intense green-brown color with dilute (colorless) cupric nitrate, indicating the formation of a chelate,[26] and therefore the presence of at least some *anti* oxime. The oxime of 2-methioxy-7-methoxytetralone-1 is also *anti*;[26] if the methioxy group is thus large enough to force the oxime hydroxyl away from itself toward a phenyl ring, its effect will apply *a fortiori* in the case where the steric hindrance on the side of the ketone away from methioxy is less. It is to be noted that apart from these arguments, the subsequent Beckmann fragmentation does not have to be taken as proof of the structure of the oxime. In meticulous, thorough work, Grob[36] has shown that the fragmentation, unlike the Beckmann rearrangement, is not stereospecific. In our view as detailed in the accompanying article,[26] the fragmentation governed by sulfur does not have the same mechanism, however, and does provide additional proof that the stereochemistry assigned the oxime is correct.

Recent interest in the mechanism[37] and synthetic applications[38] of the Beckmann fragmentation[39] is extensive. For our present application of it we tried many conditions, but found most satisfactory a simple modification of the conditions described for one of the oldest examples, that of the cleavage of dihydro-

(31) See also G. Stork and R. K. Hill, *J. Amer. Chem. Soc.*, **79**, 495 (1957).

(32) Based on methyl thiotosylate, the limiting reagent in its formation.

(33) Nmr spectra are reported in parts per million on the δ scale.

(34) See also C. M. Lee, W. F. Trager, and A. H. Beckett, *Tetrahedron*, **23**, 375 (1967).

(35) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(36) H. P. Fischer, C. A. Grob, and E. Renk, *Helv. Chim. Acta*, **45**, 2539 (1962).

(37) C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, *ibid.*, **47**, 1003 (1964); see also the extensive bibliography of this reference.

(38) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Amer. Chem. Soc.*, **89**, 2748 (1967); M. Ohno, N. Naruse, S. Torimitsu, and I. Terasawa, *ibid.*, **88**, 3168; (1966); M. Ohno and I. Terasawa, *ibid.*, **88**, 5683; Y. L. Chow, *ibid.*, **87**, 4642 (1965).

(39) The use of this name rather than the old and uninformative designation "Second Order Beckmann Rearrangement" has been suggested in ref 36.

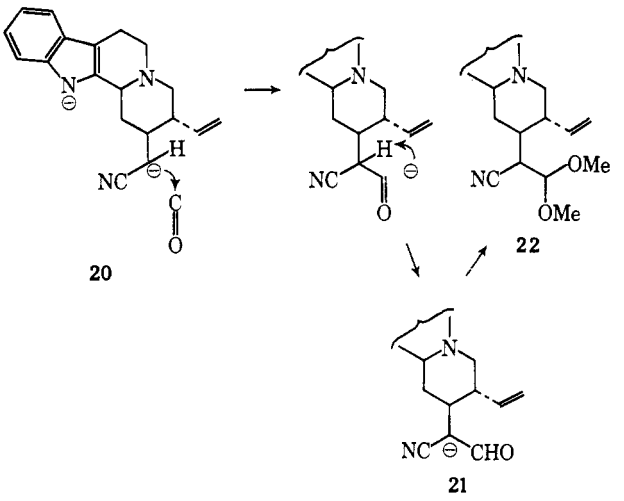
codeinone oxime.[40] Addition of thionyl chloride to an ether slurry of the oxime caused a change in the appearance of the solid, converting it probably to the hydrochloride of the oxime chlorosulfite ester. Shaking the new solid with ice water and dichloromethane caused no apparent change, but addition of dilute ammonia caused dissolution, and the organic phase yielded the enol thioether **10** (18-*trans*-methioxycorynanthenitrile). The structure of **10** was clear from its spectral properties. The infrared spectrum showed a sharp nitrile band at 4.44 μm. The nmr spectrum displayed the methyl singlet shifted downfield to 2.31 ppm, a doublet at 6.20 (J = 14.0 cps) for the vinyl hydrogen on the carbon bearing sulfur, and a quartet at 5.15 with J = 13.9 and 6.1 cps for the other vinyl hydrogen.

In the vinyl thioether **10** we had in hand a potential aldehyde, application to which of the Bamford–Stevens reaction should have led to the vinyl group. This possibility was closely similar to the scheme of van Tamelen and Wright,[21] but had the advantage that the carbonyl group, being at the chain terminus, would lead only to a vinyl group and not to a mixture of olefins. However, the hydrolysis of enol thioethers requires far more vigorous conditions[26] than does the hydrolysis of enol ethers; and the consideration of that fact together with our failure to obtain the acid-catalyzed oximation caused us to abandon that approach untried.

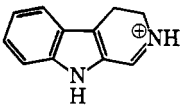
We turned instead to the possibility of desulfurization without reduction of the vinyl group, a possibility which seems to be without precedent. Most desulfurizations of enol thioethers in which the olefin is not reduced have been conducted on tetrasubstituted olefins[41] or on trisubstituted olefins in which the product disubstituted double bond is conjugated.[42] In their review of desulfurizations, Pettit and van Tamelen[43] report very few examples of disubstituted olefins which are not saturated, and none of monosubstituted olefins. Our study of the desulfurization was complicated as much by reactions in which the nitrile function was lost as it was by reduction of the vinyl group. After many experiments we discovered conditions under which the desired reaction proceeded reproducibly, smoothly, and in good yield. The over-all yield of recrystallized corynanthenitrile (**11**) from yohimbone was 23%. That the stable, finely crystalline product had the correct structure was evident from its infrared spectrum, which displayed the nitrile band at 4.44 μm and the characteristic bands of the vinyl group at 6.08, 10.03, and 10.80 μm. Melting at 283°, it was too insoluble for us to measure its nmr spectrum directly, but its N-acetyl derivative clearly showed, in the vinyl region of the nmr, a second-order spectrum integrating for three hydrogens.

Experiments designed to accomplish the direct formylation of corynanthenitrile were not successfully developed, though one is deserving of comment. A solution of the nitrile **11** and potassium *t*-butoxide in anhydrous *t*-butyl alcohol was heated and shaken at 90° under 1400 psi of carbon monoxide[44] and the supposed product (**21**) from that reaction was treated with methanolic hydrogen chloride in an attempt to convert it directly to corynantheine. The mass spectrum of the

Scheme II



crude product showed only an insignificant blip at *m/e* 366 (though correct, probably not corynantheine) but the peak at 365 was the most intense peak (relative intensity 0.55) in the spectrum other than the base peak at 171 due to dihydrocarbazolium **23**. We later learned



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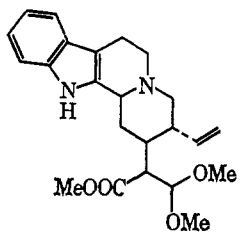
that the methanolysis of corynanthenitrile was very slow, and it seems entirely possible that the peak at 365 is to be ascribed to the nitrile acetal **22** (Scheme II).

While exploring the formylation of corynanthenitrile, we investigated also the formylation of methyl corynantheate (**12**), since this had been accomplished, albeit in poor yield, on racemic methyl corynantheate by Wright,[21,45] and on racemic methyl dihydrocorynantheate in good yield by Weisbach, *et al.*[19] The methyl ester could be prepared directly from the nitrile by boiling for 48–60 hr with anhydrous methanolic hydrogen chloride, but was more quickly made by acid- or base-catalyzed hydrolysis of the nitrile, followed by Fischer esterification. The optically active ester, unlike the racemic ester,[45] was a crystalline solid. Its formylation, like that of the nitrile, was made difficult by the fact that one had to steer between Scylla and Charybdis. On the one hand lay the need for generation of a dianion like **20**; on the other was the fact that very strong bases bring about a rapid α elimination from formate esters, with essentially instantaneous loss of all the strong base and formation of alkoxide. All the base and solvent combinations that we tried were either too weak or too strong[46] except the one which Wright reported successful, sodium triphenylmethyl. His yield of 18% in pure ether solution was bettered by Weisbach, *et al.*, in the dihydro series in diglyme–ether to 53%, and by us in tetrahydrofuran–ether to 73%. Our

(40) C. Schöpf, *Ann.*, **452**, 211 (1927).
(41) *E.g.*, R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).
(42) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).
(43) G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, **12**, 356 (1962); see especially p 391.
(44) J. Kollonitsch, U. S. Patent 3,211,778 (1965); *Chem. Abstr.*, **63**, 1811z (1965); we thank Dr. Kollonitsch for discussing some of his experiments with P. W. S.
(45) I. G. Wright, Dissertation, University of Wisconsin, 1965.
(46) In dimethyl sulfoxide solution, even ethoxide is strong enough to decompose ethyl formate at an appreciable rate.

use of tetrahydrofuran as cosolvent was suggested by the success of Pächt in formylating yohimbone therein in homogeneous medium. The formylation product, desmethylcorynantheine, was clearly shown by infrared and nmr spectroscopy to be a variable mixture of the two tautomers **13** and **14**. Desmethyldihydrocorynantheine showed the same phenomenon.

The conversion of desmethylcorynantheine to corynantheine is an old reaction. Karrer observed that the reaction of desmethylcorynantheine with diazomethane led apparently to some N-methylation.[47] We found more suitable the procedure of Weisbach, employing anhydrous methanolic hydrogen chloride. The product corynantheine was difficult to free completely from accompanying acetal **24**, but was eventually obtained identical with natural material. It is interesting that product arising from loss of methanol from the acetal to give 17-isocorynantheine (**25**) does not seem to be present in the crude product. The C-17 hydrogen may be expected to appear upfield[17] from that



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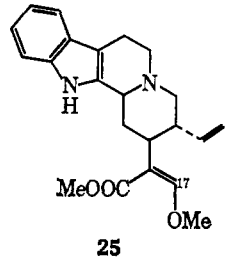

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of corynantheine perhaps as much as 0.53–0.94 ppm.[48] This portion of the nmr spectrum is just upfield of the aromatic hydrogens and is void of absorption. It is tempting, but probably not proven by our experiments, to conclude that the *trans* disposition of the methoxyacrylate chain is the stable configuration.

Inasmuch as a number of alkaloids has been partially synthesized from corynantheine or from dihydrocorynantheine, our total synthesis of corynantheine completes syntheses of the natural enantiomorphs of the following alkaloids: dihydrocorynantheine,[49] corynoxeine,[24b] rhyncophylline,[24b] dihydrocorynantheol,[50] dihydrocorynantheol methochloride,[50] and dihydrositsirikine.[51]

Experimental Section

General. Melting points, unless otherwise stated, were determined in soft glass capillaries evacuated to a few micrometers and sealed; Anschütz thermometers totally immersed in a modified Hershberg melting point apparatus were used. Infrared spectra were taken on Perkin-Elmer Model 137, 237, and 21 spectrophotometers; nmr spectra were observed in deuteriochloroform solution, unless otherwise stated, on a Varian A-60 instrument; rotations were measured on a Perkin-Elmer Model 141 polarimeter. The mass spectra were measured on an Associated Electrical Industries MS9 spectrometer through the valued assistance of Dr. G. Dudek and his assistants. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

Dry solvents were prepared as follows: benzene was dried over calcium hydride; tetrahydrofuran (THF) was distilled from lithium aluminum hydride directly into the dried flask to be used; methyl and ethyl formate were distilled from phosphorus pentoxide; methanol was distilled from magnesium methoxide. Alumina for chromatography was Woelm neutral alumina, activity I, unless otherwise specified.

In any reaction requiring the treatment of indolic substances with base, even so mild a base as potassium acetate, rigorous exclusion of air by nitrogen was mandatory to obtain the yields stated.

Yohimban-17-one (5). On a 30–35-g scale, Witkop's procedure[52] for the Oppenauer oxidation of yohimbine gave, even with the use of recrystallized aluminum phenoxide, no more than 45–50% of recrystallized yohimbone:[53] mp 313.6–316.0° no dec (vacuum); lit. mp 307° dec,[52] 298–303° dec;[54] $\lambda_{C=O}^{CHCl_3}$ 5.83 μm. Consequently most of our yohimbone was obtained from S. B. Penick & Co. It was recrystallized by Soxhlet extraction with methanol prior to use.

18-Formylyohimban-17-one (6). Method A. Yohimbone (5.00 g) was triturated with hot methanol, pressed to give a firm cake, then placed in a flask with 5.0 g of sodium methoxide, 100 ml of benzene, and 10 ml of ethyl formate. The thick yellow mixture was stirred for 24 hr at room temperature, then mixed thoroughly with 150 ml of ice water, then centrifuged. The aqueous layer was neutralized with dilute acetic acid and chilled thoroughly; the formylyohimbone was collected by filtration, pressed with a rubber dam, and used directly in the subsequent reaction (*vide infra*).

Method B.[30] In dry apparatus there were mixed 3.00 g of yohimbone, 90 ml of benzene, 6 ml of ethyl formate, 3 ml of methanol, and 2.46 g of sodium hydride dispersion in mineral oil. The mixture was stirred in the dark for 18 hr at room temperature, then cooled and poured into 200 g of ice and water. The benzene layer was extracted thrice with 80-ml portions of aqueous potassium carbonate. The combined extract was acidified to pH 6.5 with dilute hydrochloric acid and extracted with dichloromethane in many portions to yield 3.22 g (98%) of formylyohimbone suitable for use in the next step.

Method C.[55] In dry apparatus the following were mixed: 1.50 g of yohimbone, 180 ml of THF, 12 ml of ethyl formate, 1.0 g of sodium hydride, and 0.15 ml of methanol. The mixture was stirred in the dark for 8 hr at room temperature; it became red-brown and homogeneous. Distillation of the solvent *in vacuo* left a dark syrup which dissolved readily and endothermically in 200 g of ice; the temperature dropped below −10°. Addition of 0.5 *N* hydrochloric acid (73 ml, then dropwise to pH 7) caused precipitation of a gel, extracted with 1.5 kg of dichloromethane in many portions. The dried dichloromethane solution afforded 1.67 g (100%) of virtually colorless, amorphous formylyohimbone, suitable for use directly in the next step.

Trituration of the amorphous material with methanol caused it all to crystallize; recrystallization from methanol gave fine needles: mp 193–194° dec (vacuum), $[\alpha]_D$ −231° (*c* 1.00, DMF); lit.[54] hemihydrate mp 207–211° dec, $[\alpha]_D$ −232° (*c* 1.3, DMF); $\lambda\lambda^{CHCl_3}$ 6.01 (C=O) and 6.28 μm (more intense, enolic C=C).

Anal. Calcd for $C_{20}H_{22}N_2O_2 \cdot CH_4O$: C, 71.16; H, 7.39; N, 7.90. Found:[55] C, 70.94; H, 7.03; N, 8.16.

18(*S*)-Methioxyyohimban-17-one (7). Method A. In 35 ml of hot absolute ethanol, 3.346 g of formylyohimbone and 2.140 g of methyl thiotosylate were almost completely dissolved. To the hot mixture was added 3.40 g of freshly fused potassium acetate in hot ethanol; the whole was then boiled gently under nitrogen for 6 hr. Some product began to separate almost immediately. After 6 hr the mixture was cooled in ice and filtered to give 958 mg (27.1%) of almost colorless product. Five recrystallizations from chloroform–methanol gave the analytical sample as small prisms: mp 264.7–265.5° dec (vacuum); $[\alpha]^{24}D$ −126° (*c* 1.00, DMF); ORD in 95% ethanol (*c* 0.00524); $[\phi]_{313}$ −4800°, $[\phi]_{285}$ +8700°, $[\phi]_{255}$ −3500°, $[\phi]_{238}$ +2900°.

Anal. Calcd for $C_{20}H_{24}N_2OS$: C, 70.55; H, 7.11; N, 8.23; S, 9.42. Found: C, 70.63; H, 7.32; N, 8.38; S, 9.22.

Method B. Formylyohimbone (508 mg) and sodium methoxide (83 mg) were dissolved in 7 ml of boiling 95% ethanol; 312 mg of methyl thiotosylate in 4 ml of ethanol was added dropwise over 10 min. A precipitate of fine, white crystals formed quickly. After

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(52) B. Witkop, *Ann.*, **554**, 83 (1943).
(53) Reference 29 and our own results.
(54) For a substantial improvement in yield, but not, in our hands, in convenience of operation on a large scale for transforming yohimbine to yohimbone, see J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).
(55) This experiment was first performed by P. D. Pächt.[29]

15-min heating, the flask was cooled in ice and the precipitate collected by filtration, 335 mg (62.5%). One recrystallization from chloroform–methanol gave colorless prisms, mp 264.5–265.5° dec (vacuum).

Method C. The moist formylyohimbone (see method A above) was covered with 50 ml of 95% ethanol followed by 5.0 g of potassium acetate, then heated to reflux. To the resulting yellow solution there was quickly added 40 ml of hot ethanol containing 3.40 g of methyl thiotosylate. The solution was boiled 1 min, then seeded with product. A precipitate formed very quickly. Heating was continued for 0.5 hr; the mixture was cooled briefly and filtered. The solid was washed with cold ethanol and dried to give 3.22 g (57% based on yohimbone) of colorless, very fine crystals, $\lambda_{C=O}^{CHCl_3}$ 5.83 μm.

18,18-Bismethioxyyohimban-17-one (8). The absolute ethanol filtrate from the preparation of 18-methioxyyohimbone (method A, above) was distilled *in vacuo*, and the resulting solids were partitioned between dichloromethane and water. The dried organic phase yielded a bronze glass which afforded, on trituration with methanol, a mass of feathery needles and a dark syrup, separated by filtration. A single recrystallization from chloroform–methanol gave 173 mg of feathery needles, mp 199.9–201.0° dec (vacuum). An additional 210 mg (total yield, 9.9% based on yohimbone) was obtained by chromatography of the mother liquors and methanol triturate in 1:1 benzene–dichloromethane on activity II alumina. The analytical sample, mp 214.9–215.5° dec (vacuum), was recrystallized from chloroform–methanol.

Anal. Calcd for $C_{21}H_{26}N_2OS_2 \cdot 1.5CH_4O$: C, 62.18; H, 7.42; N, 6.45; S, 14.75. Found: C, 62.28; H, 7.32; N, 7.43; S, 14.55.

The exact mass was 386.1468 (calcd 386.1486); $\lambda_{C=O}^{CHCl_3}$ 5.87 μm; ORD (*c* 0.00494, 95% ethanol); $[\phi]_{314}$ −6800°, $[\phi]_{285}$ +9400°, $[\phi]_{254}$ −4100°, $[\phi]_{239}$ 0° (peak).

18(*S*)-Methioxyyohimban-17-one *anti*-Oxime (9). Methioxyyohimbone (850 mg), hydroxylamine hydrochloride (800 mg), and 95% ethanol (60 ml) were mixed and treated with 600 mg of sodium hydroxide dissolved in 25 ml of warm 75% ethanol. The mixture was boiled for 1 hr under reflux, cooled in ice, acidified to pH 5 with dilute hydrochloric acid, and concentrated *in vacuo* until solid began to form. The mixture was basified to pH 8 with cold dilute ammonia, cooled in ice for 1 hr, and filtered. The dried solid (870 mg, 98%) was an amorphous, off-white powder, apparent mp 249–53° dec (vacuum), used directly in the subsequent reaction. It was not successfuly crystallized. It could be purified by solution in ethanol and dilution with water.

The analytical sample was prepared as described above from analytically pure methioxyyohimbone. It showed $[\alpha]_D$ −52.5° (*c* 1.00, pyridine).

Anal. Calcd for $C_{20}H_{25}N_3OS$: C, 67.57; H, 7.09; N, 11.82; S, 9.02. Calcd for hemihydrate: C, 65.90; H, 7.19; N, 11.53; S, 8.80. Found: C, 65.14; H, 7.18; N, 11.87; S, 8.70.

The exact mass was 355.1714 (calcd 355.1718); ir spectrum, no carbonyl absorption, weak bands at 6.04 and 6.17 μm.

***trans*-18-Methioxycorynanthenitrile (2(*R*)-Cyanomethyl-3(*S*)-(*trans*-3-thiabut-1-enyl)-1,2,3,4,6,7,12,12b(*S*)-octahydroindolo[2,3-*a*]-quinolizine) (10).** Dry, finely powdered methioxyyohimbone oxime (1.195 g) was slurried under nitrogen in 50 ml of ether. The rapid addition of 3 ml of thionyl chloride caused the prompt formation of a heavy yellow precipitate which, on being stirred at room temperature for 4.5 hr, changed in texture and color to dark green. It was filtered, washed free of thionyl chloride with fresh ether, covered with ether, and slurried with ice water. The ether–water slurry was then treated with excess ice-cold dilute ammonia and methylene chloride. The mixture was shaken vigorously, whereupon the dark green solid slowly disappeared and the organic layer became dark red. The aqueous phase was washed with a second portion of dichloromethane and the combined dichloromethane extract was dried over magnesium sulfate, filtered, and distilled *in vacuo*. The brown residue (1.1 g) was dissolved in 9:1 dichloromethane–chloroform and chromatographed over 25 g of alumina. Elution gave 643 mg (57%) of nitrile as amorphous, pale yellow solid. Elution of the column with chloroform yielded more of the nitrile admixed with carbonyl-containing compounds.

Trituration of the nitrile with ethanol gave long needles, recrystallized from dichloromethane–methanol to give colorless needles: mp 240.5–243° (vacuum), $[\alpha]_D$ +6.7° (*c* 1.00, chloroform); $\lambda\lambda^{CHCl_3}$, 4.44 (–CN), 6.15 and 6.24 (C=C), 10.38 and 10.64 μm (*trans*-substituted enol thioether).[25]

Anal. Calcd for $C_{20}H_{23}N_3S$: C, 71.18; H, 6.87; N, 12.45; S, 9.50. Found: C, 70.99; H, 7.29; N, 12.31; S, 9.24.

Corynanthenitrile (2(*R*)-Cyanomethyl-3(*R*)-vinyl-1,2,3,4,6,7,12,-12b(*S*)-octahydroindolo[2,3-*a*]quinolizine) (11). Method A. To 6.5 ml of ethanolic slurry of Raney nickel (from W. R. Grace Co., deactivated as described below) was added a slurry of 603 mg of methioxycorynanthenitrile in 200 ml of absolute ethanol. The mixture was boiled under reflux and stirred vigorously for 3 hr, during which time the nitrile slowly dissolved. The mixture was then cooled to 40°, the nickel settled, and the solution was filtered through Supercel. The nickel was washed twice with 75 ml of hot absolute ethanol. The combined yellow ethanol solution was again filtered through Supercel, then distilled to dryness *in vacuo*. The green residue (560 mg) of crude corynanthenitrile was extracted with dichloromethane and the pale yellow extract filtered and dried over magnesium sulfate. Filtration and evaporation of the solvent left 454 mg (87%) of crystals. Recrystallization from chloroform–methanol gave 337-mg (65%) clusters of colorless needles, mp 280.2–283.1° (vacuum); $[\alpha]_D$ −7.4° (of the hydrochloride) (*c* 1.00, 1:1 chloroform–methanol).

For analysis, a sample of the nitrile in chloroform solution was filtered through alumina, then thrice recrystallized from chloroform–methanol.

Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 77.68; H, 7.34; N, 14.82.

The exact mass was 291.1738 (calcd 291.1735).

Method B. Methanolic Raney nickel (13 ml, W-2, deactivated as described below) and 1.30 g of methioxycorynanthenitrile in 600 ml of methanol were boiled under reflux and stirred vigorously for 2.5 hr, then further processed in methanol in a manner analogous to method A to yield 919 mg (82%) of crystalline corynanthenitrile.

1-Acetylcorynanthenitrile (12-Acetyl-2(*R*)-cyanomethyl-3(*R*)-vinyl-1,2,3,4,6,7,12,12b(*S*)-octahydroindolo[2,3-*a*]quinolizine). Acylation of the indole nitrogen of corynanthenitrile by the action of acetic anhydride and potassium acetate gave, after observation of the usual precautions and chromatography (elution from alumina by 1:1 dichloromethane–chloroform) an 87% yield of acetylcorynanthenitrile as an oil, characterized only by its infrared and nmr spectra: $\lambda\lambda^{CH_2Cl_2}$ (sharp NH at 2.88 is absent), 4.41 (–CN), 5.91 (C=O), 10.02 and 10.90 μm (–CH=CH_2); δ^{CDCl_3} 2.80 (sharp singlet, *Me*C=O), 5.03–6.42 ppm (complex absorption, –CH=CH_2).

Methyl Corynantheate (2(*R*)-Methoxycarbonylmethyl-3(*R*)-vinyl-1,2,3,4,6,7,12,12b(*S*)-octahydroindolo[2,3-*a*]quinolizine) (12). Method A. A slurry of 418 mg of corynanthenitrile in 30 ml of methanol was treated with 20 ml of concentrated hydrochloric acid, and the resulting solution was boiled under reflux for 5.5 hr, then cooled and distilled *in vacuo*. The oily residue was dissolved in methanol saturated with anhydrous hydrogen chloride, and the resulting solution was boiled under reflux for 12 hr, cooled in ice and neutralized with dilute ammonia. The mixture containing a white precipitate was diluted with ice water and extracted with dichloromethane. The organic extract was dried over magnesium sulfate, filtered, and evaporated to leave a yellow oil. A dichloromethane solution of the oil was chromatographed on 10 g of alumina. Elution with chloroform gave 352 mg (76%) of pale yellow solid. Filtration of an ether solution of the solid through a small column of alumina, then trituration with petroleum ether gave the ester as colorless needles, mp 118–121°. For analysis the ester was thrice recrystallized from ethyl acetate–petroleum ether to give colorless needles: mp 121.2–122.4° (vacuum); $[\alpha]_D$ −28.7° (*c* 1.00, ethyl acetate).

Anal. Calcd for $C_{20}H_{24}N_2O_2 \cdot C_4H_8O_2$: C, 69.88; H, 7.82; N, 6.79. Found: C, 70.40; H, 7.46; N, 7.85.

The exact mass was 324.1827 (calcd 324.1837).

Method B. A slurry of 391 mg of corynanthenitrile in 100 ml of methanol under nitrogen was treated with 5 g of potassium hydroxide in 25 ml of water. As the mixture was boiled under reflux the solid slowly dissolved to give a yellow solution. After 24 hr the solution was cooled in ice and neutralized with concentrated hydrochloric acid. The cold mixture was filtered and the filtrate was distilled *in vacuo*. Treatment of the residue with anhydrous methanolic hydrogen chloride under reflux for 22 hr, followed by concentration, ice cooling, potassium carbonate neutralization, and chloroform extraction, yielded 458 mg of yellow semisolid. Filtration of a chloroform solution through 10 g of activity I neutral Woelm alumina gave 400 mg (92%) of pale yellow, amorphous ester which could be crystallized on rechromatography in ether, then trituration with petroleum ether: $\lambda\lambda^{CH_2Cl_2}$ 5.77 (C=O), 6.09 (C=C), 10.00 and 10.83 μm (–CH=CH_2); δ^{CDCl_3} 3.70 (sharp singlet, *Me*OOC), 4.89–5.83 ppm (complex absorption, –C*H*=CH_2).

Desmethylcorynantheine (Methyl 16-Formylcorynantheate. 2(*S*)-(1′-Methoxycarbonyl-2′-oxoethyl)-3(*R*)-vinyl-1,2,3,4,6,7,12,12b(*S*)-

octahydroindolo[2,3-*a*]quinolizine) (13 and 14)). The use of serum caps, syringes, dry nitrogen, etc., to exclude oxygen and adventitious moisture was prerequisite to success. Dry methyl corynantheate (265 mg) in 20 ml of tetrahydrofuran was treated with 20.5 ml (2.46 mequiv, 150% of theory) of 0.12 *N* freshly prepared triphenylmethylsodium in ether. The first 8 ml of base was decolorized instantaneously as the indole anion formed; addition of the remainder caused the color of the trityl anion to persist. Methyl formate (4 ml) was then added to the solution; the red color was discharged instantaneously and there was moderate evolution of carbon monoxide. The resulting cloudy yellow solution was stirred at room temperature for 6 hr then concentrated *in vacuo* to remove remaining methyl formate, and diluted with 100 ml of ether followed by 100 ml of dilute potassium hydroxide. The aqueous extract was separated, exactly neutralized with dilute hydrochloric acid, and extracted twice with 125 ml of ether. The combined ether extract, dried over magnesium sulfate, yielded 129 mg (45%, not corrected for recovery of starting ester) of pale yellow amorphous solid.

The original ether layer, from which the product had been extracted by potassium hydroxide, was dried and treated with hydrogen chloride gas. The mixture was cooled and centrifuged and the hydrochloride was washed with fresh ether, then partitioned between ether and dilute ammonia. The dried ether extract yielded 182 mg of crystals, chromatographed in ether over 20 g of alumina. The first 25 ml of ether gave 26 mg of triphenylmethane; the next 75 ml of ether contained nothing. Elution with 225 ml of ether then gave 46 mg of methyl corynantheate; another 56 mg (total recovery of material suitable for reuse, 38%) was obtained by elution with 80 ml of chloroform.

The yield of desmethylcorynantheine, corrected for recovery of starting material, was thus 73%: exact mass of $C_{21}H_{24}N_2O_3$ 352.1769 (calcd 352.1787); $\lambda\lambda^{CHCl_3}$ 2.87 (sharp, NH), 3.00 (weak, intramolecular OH), 5.79 (ester and aldehyde unconjugated), 5.99 (conjugated, chelated ester), 6.14–6.21 (enol C=C), 10.01 and 10.86 μm (–CH=CH_2). The relative intensities of the three bands at 5.79, 5.99, and 6.21 were strikingly variable and depended in a nonreproducible way on the rate and direction of approach to neutrality in precipitating the formyl ester: δ^{CDCl_3} 3.63 and 3.83 (singlets of quite different intensity, MeOOC unconjugated and conjugated?), 4.82–5.97 (complex absorption, –CH=CH_2), 7.92 (broad singlet, NH), 9.90 ppm (weak, ill defined, –*CH*O).

The mass spectrum of this synthetic desmethylcorynantheine was, but for the shift of two mass units, indistinguishable in the high mass portion from that of desmethyldihydrocorynantheine obtained by degradation of natural material.

Corynantheine (Methyl 3-*trans*-Methoxy-2-(3(*R*)-vinyl-1,2,3,4,-6,7,12,12b(*S*)-octahydroindolo[2,3-*a*]quinolizin-2(*S*)-yl)acrylate (1)). A solution of 155 mg of desmethylcorynantheine in 100 ml of methanol was saturated with hydrogen chloride and boiled under reflux for 24 hr. It was then concentrated *in vacuo* to 20 ml, diluted with chloroform, and shaken with ice-cold dilute ammonia. The organic phase was dried over magnesium sulfate, filtered, and distilled *in vacuo* to leave 178 mg of yellow oil.

Examination of the oil by thin layer chromatography and infrared and mass spectroscopy showed it to contain about 40% corynantheine, 40% probably acetal **24**, and 20% other products. Filtration of a chloroform solution through alumina removed some dark material but returned 153 mg of oil. A dichloromethane solution was placed on 5 g of alumina; nothing was eluted by 30 ml of dichloromethane or by the first 75 ml of 9:1 dichloromethane–chloroform. Eight succeeding small fractions (10–20 ml) eluted a total of 102 mg. The first 22 mg showed a prominent carbonyl absorption at 5.80 μm (desmethylcorynantheine and/or its dimethyl acetal). The next five fractions (69 mg) were 85–90% pure (36% yield) corynantheine (absorption at 5.89 and 6.09 μm). Subsequent fractions, though still rich in corynantheine, were less pure.

The 69 mg rich in corynantheine was rechromatographed over alumina in 9:1 dichloromethane–chloroform and a center fraction (11 mg, 6.8% yield), the infrared spectrum of which was very similar to that of corynantheine, with only a small absorption at 5.80 μm, was taken for further purification. It was dissolved in acetonitrile and treated with ether saturated with hydrogen chloride. The precipitated hydrochloride was collected by centrifugation and the free base was regenerated by partitioning the hydrochloride between ether and dilute ammonia. The dried ether solution yielded 3.1 mg (1.9%) of corynantheine, identical with natural corynantheine[56] in respect of infrared spectrum in chloroform solution, mass spectrum, and behavior on tlc plates in two solvent systems. The exact mass of $C_{22}H_{26}N_2O_3$ was 366.1937 (calcd 366.1943).

The hydrochloride showed the following properties: 167–188° (micro hot stage); $[\alpha]^{25}D$ 37 ± 3° (*c* 0.14, methanol), lit.[10] (values for the natural mixture) $[\alpha]D$ 43° (*c* 1.00, methanol), mp 170–192°.

Desmethyldihydrocorynantheine (Methyl 16-Formyl-18,19-dihydrocorynantheate, 2(*S*)-(1′-Methoxycarbonyl-2′-oxoethyl)-3(*R*)-ethyl-1,2,3,4,6,7,12,12b(*S*)-octahydroindolo[2,3-*a*]quinolizine). Pure dihydrocorynantheine[56] (1.009 g) was cleaved by the action of hydrogen chloride in anhydrous acetone (dried over molecular sieves) essentially as described,[47] for the mixture of corynantheine and dihydrocorynantheine. For success it was necessary that the hydrogen chloride be passed into an acetone solution (originally ice cold) of the alkaloid at such a rate that the solution became quite hot, then was cooled back to 0°. If care were taken that the temperature did not rise, then the ether was not cleaved and all the alkaloid was recovered. There was obtained 411 mg (42%) of desmethyldihydrocorynantheine after purification.

The spectra showed the material to be present in both tautomeric forms; thus the infrared spectrum showed bands at 5.78, 5.81, 6.02, and 6.23 μm, these being attributed, respectively, to ester, aldehyde, chelated α,β-unsaturated ester, and enol double bond. The nmr spectrum showed methoxyl singlets at 3.58 (nonconjugated) and 3.70 ppm (conjugated ester). The parent ion peak at 354 was clearly visible in the mass spectrum; it was 62% of the intensity of the base peak at *m/e* 171.

Raney Nickel for Desulfurization.[41] Deactivation of Active Catalyst (supplied by W. R. Grace and Co.). The active catalyst (no. 28, in water) was boiled under reflux and vigorous stirring in acetone for 2.5 hr, cooled, and left for 15 hr. The acetone was decanted and the nickel was washed thrice with ethyl acetate, covered with fresh ethyl acetate, and again boiled under reflux with vigorous stirring for 3 hr. Ethyl acetate was decanted from the cooled mixture. The nickel was washed thrice with 95% ethanol, then thrice with absolute ethanol, then stored under absolute ethanol in a sealed bottle. Owing to the extreme variability of the activity of the catalyst as originally supplied, the deactivated nickel gave a good yield of desulfurization without reduction of the vinyl group, or gave no reaction at all, or gave only fully reduced product heavily contaminated with carbonyl-containing compounds.

Deactivation of W-2 Raney Nickel. W-2 Raney nickel, prepared and stored as described by Mozingo,[57] was deactivated as follows. The ethanolic slurry of nickel (45 ml) was transferred with acetone, washed four times by decantation with acetone, then heated under reflux with 200 ml of acetone for 3 hr. The cooled solvent was decanted and the nickel was washed several times with water, thrice with 95% ethanol, and thrice with methanol. The deactivated catalyst was stored in a bottle completely filled with methanol and sealed. The nickel so prepared was relatively reproducible from batch to batch in its ability to desulfurize the enol thioether without saturating the resulting vinyl group.

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(56) Corynantheine and dihydrocorynantheine were obtained by countercurrent distribution as described.[13] The natural mixture (7.0 g, *ca.* 30% corynantheine by nmr spectroscopy, from S. B. Penick & Co.) yielded 2.42 g of a corynantheine fraction about 80% pure, and 3.30 g of pure dihydrocorynantheine. The corynantheine fraction, on chromatography over alumina in ether, gave 933 mg of corynantheine at least 95% pure.

(57) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.