General Methods of Alkaloid Synthesis. A New Approach to the Synthesis of the 5,10b-Ethanophenanthridine *Amaryllidaceae* Alkaloids. A Stereoselective Total Synthesis of *dl*-Elwesine (Dihydrocrinine)[1]

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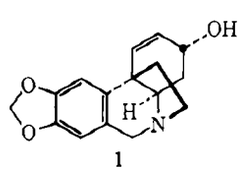
An efficient eight-stage stereoselective total synthesis of the *Amaryllidaceae* alkaloid elwesine (**2a**) and its C-3 epimer is portrayed. Key steps in this synthesis involved the methyl vinyl ketone annelation of a Δ^2-pyrroline to achieve the basic *cis*-octahydroindolone skeleton and the acid-catalyzed thermal rearrangement of cyclopropyl imines as a general device for the elaboration of the required Δ^2-pyrrolines.

The *Amaryllidaceae* family has been known for some time now to be a rich source of complex and intriguing alkaloids. The structural diversity which characterizes these interesting bases is quite remarkable and necessitates their classification into several skeletally homogeneous subgroups. One of these includes those alkaloids which incorporate the 5,10b-ethanophenanthridine nucleus and is usually referred to as the crinine group after the parent natural product **1**. A recent review[4] of these alkaloids lists 35 closely related members of this family, and from a careful inspection of their structures we conceived of a number of potentially general synthetic approaches which, perhaps with only minor modification, could be employed in the synthesis of selected members of this family.[5] We selected for our initial investigation elwesine (dihydrocrinine) **2a**, a minor alkaloid of *Galanthus elwesii* Hook. f.[6]



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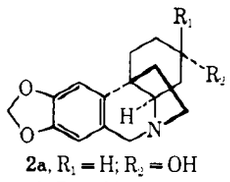
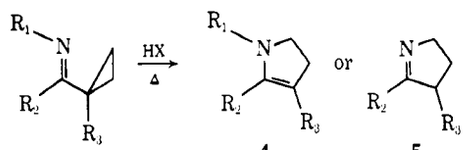


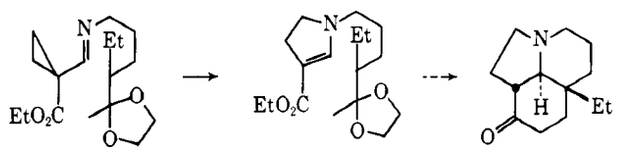
2a, $R_1 = H$; $R_2 = OH$
b, $R_1 = OH$; $R_2 = H$

The method of approach we decided to investigate first was a logical extension of two fundamental and increasingly important general principles of alkaloid synthesis which we, and others, have been developing. The first of these exploits, the acid-catalyzed, thermally induced rearrangement of cyclopropyl imines as a useful general approach to Δ^1- or Δ^2-pyrrolines (**3** → **4** or **5**), provided simple efficient syntheses of the pyridine alkaloids myosmine **6** and apoferrorosamine **7**[7] and constituted a key step in the synthesis of the hydrolulolidine *Aspidosperma* alkaloid intermediate **8**[8]



3 **4** **5**

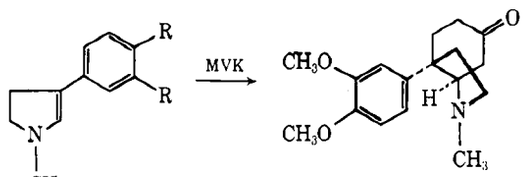
6 **7**



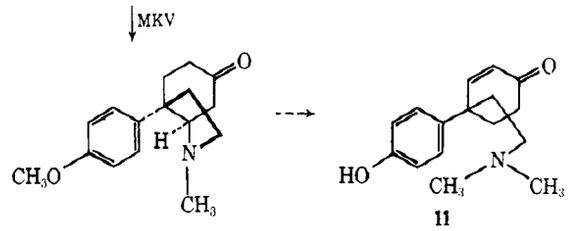
8

as well as the *Aizoaceae* alkaloid mesembrine **10**[9a,b] and the *Sceletium* base joubertiamine **11**.[10]

Also of importance in the synthesis of the latter two substances was the application of the methyl vinyl ketone (MVK) annelation to an endocyclic enamine (*e.g.*, **9** to **10**), a reaction which has also been employed



9 **10**



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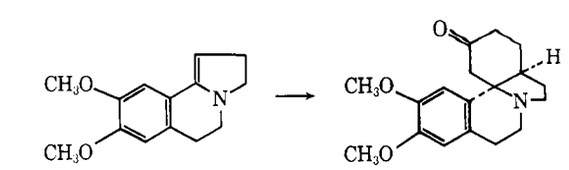

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(1) Preliminary communication: R. V. Stevens and L. E. DuPree, Jr., *Chem. Commun.*, 1585 (1970).

(2) A. P. Sloan Fellow, 1969–1971.

(3) National Science Foundation Predoctoral Fellow, 1968–present.

(4) W. C. Wildman in "The Alkaloids," Vol. II, R. H. F. Manske, Ed., Academic Press, London and New York, 1968, p 308.

(5) For previous synthetic work *cf.* (a) W. C. Wildman, *J. Amer. Chem. Soc.*, **80**, 2567 (1958); (b) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *ibid.*, **88**, 3670; (1966); (c) H. W. Whitlock, Jr., and G. L. Smith, *ibid.*, **89**, 3600 (1967); (d) B. Franck and H. J. Lubs, *Angew. Chem., Int. Ed. Engl.*, **7**, 223 (1968); (e) H. Irie, S. Uyeo, and A. Yoshitake, *J. Chem. Soc. C*, 1802 (1968); (f) M. Schwartz and R. Holton, *J. Amer. Chem. Soc.*, **92**, 1092 (1970); (g) J. B. Hendrickson, T. L. Bogard, and M. E. Fisch, *ibid.*, **92**, 5538 (1970); (h) I. Ninomiya, T. Naito, and T. Kiguchi, *Chem. Commun.*, 1669 (1970).

(6) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **48**, 406 (1961).

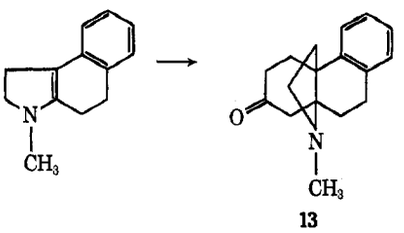
(7) R. V. Stevens, M. C. Ellis, and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5576 (1968).

(8) R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *Chem. Commun.*, 857 (1971).

(9) (a) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5580 (1968); (b) S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); (c) T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

(10) R. V. Stevens and J. Lai, *J. Org. Chem.*, in press.

to advantage in the synthesis of the *Erythrina*[11] and hasubanan[12] skeletons, **12** and **13**, respectively, as well as providing an alternative approach to the useful aspidospermine precursor **14**.[13] The rather similar



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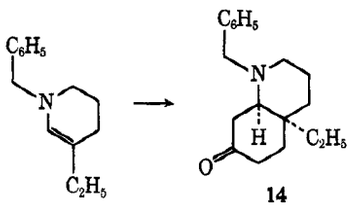
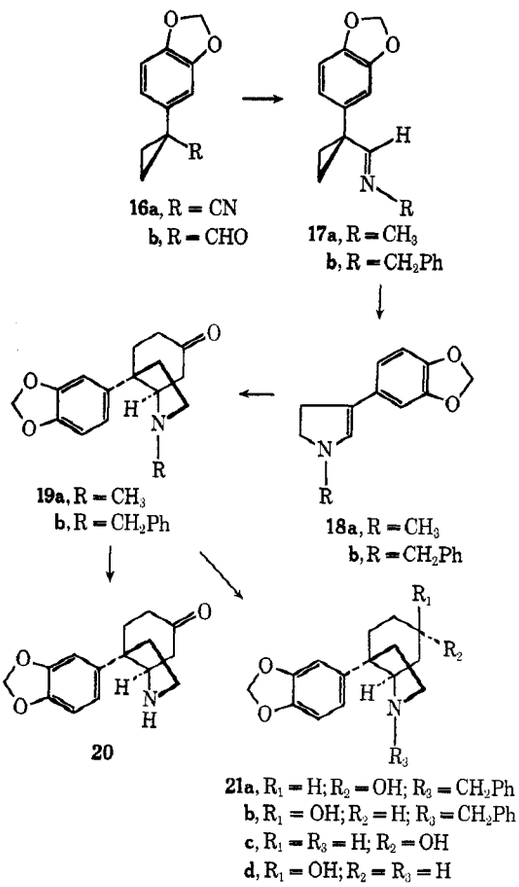


14

structural features of mesembrine (**10**) and various crinine-type alkaloids such as elwesine (**2a**) had, from the very beginning of our investigation,[14] captured our imagination and prompted additional study to more clearly define the utility of these two principles in the execution of alkaloid synthesis.

Thus, the now familiar approach to the synthesis of endocyclic enamines **18a** and **18b** was investigated and not found lacking. Lithium amide induced cyclopropanation of piperonyl cyanide with ethylene dibromide proceeded smoothly in glyme at room temperature in 65–75% yield. This result is in direct contrast to the employment of other strong bases such as sodium amide or sodium hydride, which gave at best very modest yields of **16a**, and is in agreement with our previous studies[9a] concerning the beneficial effect of generating the more covalent lithium salts in electronically destabilized carbanions of this type. Conversion of **16a** to the corresponding aldehyde **16b** was achieved in 75–85% yield by selective reduction with diisobutylaluminum hydride (DIBAL).[9b,13] Virtually complete conversion of **16b** to the *N*-methylimine **17a** was accomplished by exposure to a saturated benzene solution of methylamine in the presence of anhydrous magnesium sulfate. Rearrangement of this cyclopropyl imine **17a** to pyrroline **18a** was catalyzed by anhydrous HBr at 140–150°, providing another example of the utility of this process. By employing the same procedure developed previously in the synthesis of mesembrine[9a] (*cf.* **9** to **10**), a 42% yield of analytically pure *cis*-octahydroindole **19a** was obtained from the methyl vinyl ketone annelation of **18a**.[15] The identity of the highly diagnostic pmr spectrum of **19a** with that of mesembrine **10**[9a] in the significant aliphatic region confirmed the structural and stereochemical assignments. The cis stereochemistry observed in this annelation is in consonance with previously defined stereochemical arguments[9a] and is corroborated further by an increasing number of examples involving other structurally diverse endocyclic enamines (*cf.* **10–14**).[16] Attempts to demethylate **19a** to **20** by a variety of standard techniques were uniformally unsuccessful and in most instances were complicated by simple β elimination.[17] However, these results proved to be of value in the subsequent design and successful execution of the synthesis.



16a, R = CN
b, R = CHO

17a, R = CH_3
b, R = CH_2Ph

19a, R = CH_3
b, R = CH_2Ph

18a, R = CH_3
b, R = CH_2Ph

20

21a, R_1 = H; R_2 = OH; R_3 = CH_2Ph
b, R_1 = OH; R_2 = H; R_3 = CH_2Ph
c, R_1 = R_3 = H; R_2 = OH
d, R_1 = OH; R_2 = R_3 = H

In view of the problems associated with attempts to demethylate **19a**, substitution of the adamant *N*-

(11) R. V. Stevens and M. P. Wentland, *Chem. Commun.*, 1104 (1968).

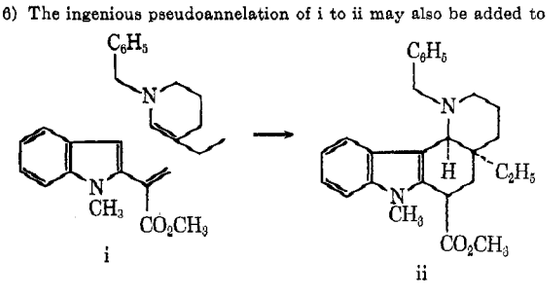
(12) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970); S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron*, **26**, 4729 (1970).

(13) R. V. Stevens, R. K. Mehra, and R. L. Zimmerman, *Chem. Commun.*, 1104 (1968).

(14) R. V. Stevens and M. C. Ellis, *Tetrahedron Lett.*, 5185 (1967).

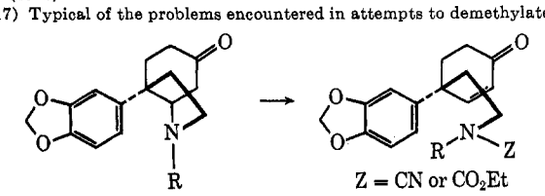
(15) In view of subsequent difficulties encountered in attempts to demethylate **19a**, no attempt was made to maximize its yield or that of its precursor, pyrroline **18a**.

(16) The ingenious pseudoannelation of i to ii may also be added to this ever-growing list: F. E. Ziegler and E. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3492 (1970).



i ii

(17) Typical of the problems encountered in attempts to demethylate **19a** or debenzylate **19b** by a variety of methods is their fate upon exposure to cyanogen bromide or ethyl chloroformate. In each case simple β elimination predominated.



19

Z = CN or CO_2Et

methyl function by the more labile benzyl group attracted our attention as a logical solution to this problem and required only a slight variation of the scheme and no compromise whatever in efficiency. Thus, aldehyde **16b** could be transformed to aldimine **17b** in 72–92% yield by simply stirring a benzene solution of the reactants (excess benzylamine) with anhydrous calcium chloride for 2–3 days. Considerable resinification accompanied the rearrangement of this aldimine when HBr was employed as the acidic catalyst. However, thermal rearrangement to pyrroline **18b** proceeded smoothly in 72–80% yield by employing ammonium chloride. We were rather surprised and annoyed to observe that the methyl vinyl ketone annelation of this intermediate produced only complex unstable mixtures containing little if any of the desired product, since the same procedure had been so successfully employed with other closely related substances. However, this frustration was only temporary when it was discovered that 56–67% yields of pure crystalline *cis*-octahydroindole **19b** could be secured by prior conversion of **18b** to its hydrochloride salt and admixture to a solution of methyl vinyl ketone in acetonitrile.[9c]

With the obtention of **19b** we were now in a position to affect its debenzylation. However, the facile β eliminations which plagued our efforts in the *N*-methyl series were no less conspicuous in the present case.[17] Presented with these difficulties, various alternatives were considered which involved modification of the menacing carbonyl function. Since this particular oxidation state is not that which is found in any of the naturally occurring crinine-type bases and elwesine (**2a**) in particular, the most obvious solution to this problem would be to reduce **19b** to the desired alcohol **21a**.[18]

Sodium borohydride reduction of **19b** yielded a 3:1 mixture of two epimeric alcohols which were readily separated by preparative layer chromatography. Catalytic debenzylation[19] of the major isomer (**21b**, *vide infra*, see discussion below) yielded **21d** (100%). Pictet–Spengler cyclization under carefully defined conditions[5c,21b] provided *dl*-3-*epi*-elwesine (**2b**)[20] in 65% yield.

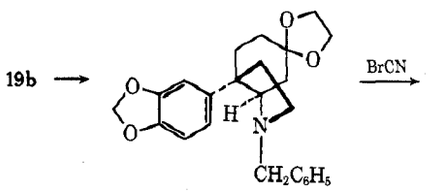
The unfavorable 3:1 product distribution of epimeric alcohols **21b** and **21a** obviously required adjustment if a truly effective synthesis of elwesine was to be achieved. This was accomplished by reducing ketone **19b** catalytically in isopropyl alcohol as solvent and 10% Pd/C catalyst. This provided a more than satisfactory ratio of 8:1 in favor of the desired alcohol **21a**. Subsequent debenzylation (100%) and Pictet–Spengler cyclization provided totally synthetic racemic elwesine **2a**[20] in 61% yield. Completion of this work establishes the validity and efficiency of the synthetic principles involved.

Spectral Data.—During the course of this investigation it became increasingly clear that we were dealing with a very subtle but important conformational equilibrium in our bicyclic intermediates **19** and **21**. The surprising revelation[21] that mesembrine (**10** = **22a**), both epimeric mesembranols (**21e** and **21f**), and their corresponding acetates prefer (in $CDCl_3$ or C_6H_6 solvent) a conformation in which the bulky aryl moiety occupies an axial configuration prompted a similar analysis in the present series. Our results are in consonance with these previous observations, and we present additional evidence which supports this striking conclusion.

The infrared (ir) spectrum of **21a** in tetrachloroethylene exhibits a free hydroxyl stretching absorption at 3620 cm^{-1} (sharp) and a broad hydrogen-bonded band at approximately 3500 cm^{-1} which disappears in solutions ≤ 0.025 *M*, thus demonstrating the intermolecular nature of this hydrogen bond. By contrast, **21b** has but one hydroxyl stretching band at 3325 cm^{-1} typical of a strongly hydrogen-bonded hydroxyl. Furthermore, this absorption persists and no free hydroxyl band appears at concentrations as low as 0.0083 *M*, a fact which strongly suggests intramolecular hydrogen bonding. Conclusive evidence to support this conclusion was obtained by the method of successive dilution.[22]

The ir spectra of **21c** and **21d** are very similar to those of their precursors **21a** and **21b**, respectively. Compound **21c** exhibits a sharp free OH stretching band at 3620 cm^{-1} and a broad absorption at 3360 cm^{-1}. This broad absorption can be attributed to a hydrogen-bonded hydroxyl and/or the NH stretching band of the secondary amine. Epimeric alcohol **21d**, however, shows only a broad band centered at 3340 cm^{-1}. No free OH band appears at concentrations as low as 0.0125 *M*. The successive dilution technique was not applied in this case, as the contribution of the NH band could not be determined. However, the data are consistent with intramolecular hydrogen bonding in compound **21d**. When coupled with the

(18) Alternatively, the marked tendency for these compounds to β eliminate could be suppressed by conversion of **19b** to the corresponding ketal iii.



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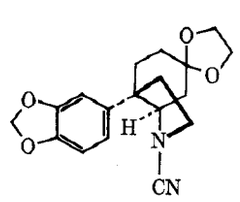


iv

This was achieved with partially gratifying consequences, since exposure of this substance to cyanogen bromide finally resulted in removal of the benzyl function. However, subsequent transformation of iv into useful synthetic intermediates proved to be a rather more arduous task than we had envisaged.

(19) According to the procedure of G. Büchi, D. Coffen, K. Korsis, P. Sonnet, and F. Ziegler, *J. Amer. Chem. Soc.*, **88**, 3099 (1966).

(20) The structural and stereochemical assignments were confirmed by comparison of solution infrared spectra and tlc behavior with those of an authentic optically active specimen and by oxidation to the known racemic ketone, mp 171.5–174.5° (lit.[5c] mp 171–173°). We are most grateful to Professor W. C. Wildman for providing us with these authentic samples.

(21) (a) P. W. Jeffs, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, **91**, 3831 (1969); *cf.* P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970). We are grateful to Professor Jeffs for communicating these results to us prior to their publication. (b) H. Taguchi, T. Oh-ishi, and H. Kugita, *Chem. Pharm. Bull.*, **18**, 299, 1008 (1970), and references cited therein.

(22) M. Tichy in "Organic Chemistry: Methods and Results," Vol. 5, 1965, p 115.

following pmr data this information provides conclusive evidence concerning the preferred conformations of each of these intermediates.

The assignment of specific resonances in the pmr spectra of these compounds to the conformationally diagnostic protons on C_6 and C_{7a} were made as follows. A one-proton triplet at δ 3.22 in the spectrum of ketone **22b** was readily assigned to the C_{7a} proton, since this is the only proton in the molecule capable of providing such a signal and is consistent with average chemical shift data for a methine located adjacent to an amine function.[23]

On reduction of ketone **22b** to the two epimeric alcohols **21a** and **21b**, a triplet attributable to the C_{7a} proton is no longer clearly visible, having become obscured by the methylene signals. However, new multiplets appear at δ 4.02 and 4.11 in the spectra of **21b** and **21a**, respectively, which integrate for one proton. Based on the fact that these signals appear on reduction of the ketone they were tentatively assigned to the C_6 protons. Unambiguous confirmation of these assignments was obtained by reduction of the ketone with $NaBD_4$, which provided the two epimeric alcohols **21h** and **21g** (*vide infra*, *cf.* also discussion above) in a 2:1 ratio. The pmr spectra of these compounds lacked the absorptions at δ 4.02 and 4.11, respectively, thus confirming the original assignment. After debenzylation the epimeric monodeuterated alcohols **21i** and **21j** also lacked absorptions at δ 4.00 and 3.97 found in the spectra of their nondeuterated partners **21c** and **21d** and made it possible to assign these peaks to the C_6 protons and additionally those at δ 3.67 and 3.71 to the C_{7a} protons (Table I).

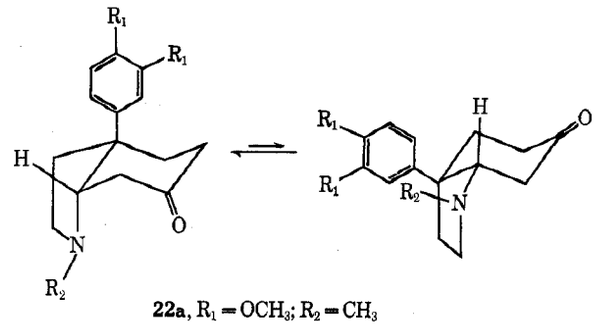
TABLE I
PERTINENT PMR DATA ($CDCl_3$)

	C-6 hydrogen		C-7a hydrogen	
Compd	δ	$W_{1/2}$, Hz	δ	J_{app} or $W_{1/2}$, Hz
19b			3.22	J_{app} = 3.5
21a	4.11	18	Obscured	
21b	4.02	8	Obscured	
21c	4.00	21	3.67	$W_{1/2}$ = 10
21d	3.97	8	3.71	$W_{1/2}$ = 7.8

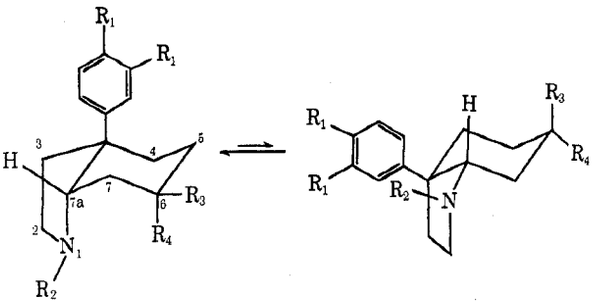
The employment of pmr spectroscopy to establish preferred ground state conformations is rather well established. Thus, the distinction between an axial and an equatorial alcohol in an epimeric pair can usually be made on the basis of relative chemical shift data and/or the half band width ($W_{1/2}$) properties of the methine hydrogen signal, especially when this signal is poorly resolved. Typically, an equatorial proton of this type exhibits a $W_{1/2} \cong$ 5–10 Hz, and an axial one a value of about 15–30 Hz.[21,24] The widths at half-height for the diagnostic hydrogens at C_6 and C_{7a} listed in Table I lead to only one possible conclusion: all of these substances, regardless of the nature of the substituent on nitrogen (*i.e.*, H, CH_3, $PhCH_2$), prefer the conformation in which the C_{7a} proton is equatorial and the adjacent aryl group is axial. The infrared data cited above are fully in accord with this conclusion.

(23) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," Wiley, New York, N. Y., 1967.

(24) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).



22a, $R_1 = OCH_3$; $R_2 = CH_3$
b, $R_1 = -OCH_2CH_2O-$; $R_2 = CH_2Ph$
c, $R_1 = -OCH_2CH_2O-$; $R_2 = CH_3$



21a, $R_1 = -OCH_2O-$; $R_2 = CH_2Ph$; $R_3 = OH$; $R_4 = H$
b, $R_1 = -OCH_2O-$; $R_2 = CH_2Ph$; $R_3 = H$; $R_4 = OH$
c, $R_1 = -OCH_2O-$; $R_2 = H$; $R_3 = OH$; $R_4 = H$
d, $R_1 = -OCH_2O-$; $R_2 = H$; $R_3 = H$; $R_4 = OH$
e, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = H$
f, $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = OH$
g, $R_1 = -OCH_2O-$; $R_2 = CH_2Ph$; $R_3 = OH$; $R_4 = D$
h, $R_1 = -OCH_2O-$; $R_2 = CH_2Ph$; $R_3 = D$; $R_4 = OH$
i, $R_1 = -OCH_2O-$; $R_2 = H$; $R_3 = OH$; $R_4 = D$
j, $R_1 = -OCH_2O-$; $R_2 = H$; $R_3 = D$; $R_4 = OH$

Experimental Section[25]

1-(3,4-Methylenedioxyphenyl)cyclopropane Carbonitrile (16a).—The general method was as follows: x g of piperonyl cyanide, x g of $LiNH_2$, $2x$ ml of ethylene dibromide, and $10x$ ml of dry glyme were combined in a dry flask equipped with N_2 blanket and mechanical stirrer. The reaction may be followed by tlc or by a color change from an initial light tan to a chocolate brown upon completion. The glyme was evaporated *in vacuo*, H_2O was added cautiously to the residue, and the mixture was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. Removal of the solvent left a dark oil which upon distillation provided reasonably pure product in 65–75% yield, bp 120° (0.2 mm). The distillate solidified upon standing. Two recrystallizations from petroleum ether (bp 30–60°) gave needles: mp 74.8–75.5° (sublimation at 80° (0.2 mm) is also a suitable method of purification); ir ($CHCl_3$) 2200 and 1040 cm^{-1}; pmr δ 1.44 (sym m, 4 H), 5.9 (s, 2 H), 6.7 (s, 3 H).

Anal. Calcd for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.66; H, 5.02; N, 7.33.

1-(3,4-Methylenedioxyphenyl)cyclopropane Carboxaldehyde (16b).—Nitrile **16a** (10 g, 0.054 mol) was dissolved in 100 ml of dry benzene in a flask equipped with a N_2 atmosphere, dropping funnel, and magnetic stirrer. A solution of 1.25 equiv of diisobutylaluminum hydride in toluene was added dropwise to the stirred solution and stirring was continued for an additional hour after addition was complete. The mixture was then cautiously poured into 5% aqueous H_2SO_4 (foaming!), the layers were separated, and the aqueous phase was extracted with ether. The organic phases were combined, dried ($MgSO_4$), and freed of solvent. The residual oil was dissolved in a minimum amount

(25) Infrared spectra were obtained on a Beckman IR-8 spectrometer. Pmr spectra were secured from a Varian A-56/60a spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-110 high resolution spectrometer. Melting points and boiling points are uncorrected. Microanalyses were performed by the Elek Microanalytical Laboratory, Torrance, Calif. Preparative layer chromatography operations employed Brinkmann precoated 20 × 20 cm plates of silica gel F-254, 2 mm thick.

of hot cyclohexane from which the pure aldehyde crystallized upon cooling (75–85%): mp 62.5–63.5°; mp (2,4-DNP) 232–232.5°; ir (CCl_4) 1715 cm^{-1}; pmr (CCl_4) δ 1.24 (t, 2 H), 1.41 (t, 2 H), 5.88 (s, 2 H), 6.66 (s, 3 H), 9.3 (s, 1 H).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.30. Found: C, 69.67; H, 5.46.

***N*-Methylaldimine (17a).**—The procedure was essentially that described previously in the mesembrine synthesis:[9a] bp 105.5–106.5° (0.45 mm); ir (film) 1663 cm^{-1}; pmr ($CDCl_3$) δ 1.16 (sym m, 4 H), 3.2 (d, 3 H), 5.84 (s, 2 H), 6.68–6.8 (m, 3 H), 7.47 (q, 1 H).

Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; mol wt, 203.23. Found: C, 70.89; H, 6.46; mol wt, 203.

1-Methyl-3-(3,4-methylenedioxyphenyl)-2-pyrroline (18a).—Aldimine **17a** (490 mg) and 25 mg of NH_4Cl were introduced into a small flask equipped with N_2 blanket and magnetic stirrer and heated to 140–150°. After 1 hr the imine band at 1663 cm^{-1} had completely disappeared and the orange oil was allowed to cool, whereupon the mass solidified. Extraction with several portions of hot hexane, filtration to remove residual NH_4Cl, and removal of the solvent provided a yellow solid which was conveniently purified by sublimation at 80° (0.4 mm), providing 293 mg (60%) of pure pyrroline. An analytical sample was recrystallized from hexane: mp 109–110°; ir ($CHCl_3$) 1612 and 1040 cm^{-1}; pmr ($CDCl_3$) δ 2.5–3.3 (m, 4 H), 2.63 (s, 3 H), 5.88 (s, 2 H), 6.26 (t, 1 H), 6.57–6.8 (m, 3 H).

Anal. Calcd for $C_{12}H_{13}O_2N$: C, 70.92; H, 6.45; mol wt, 203.23. Found: C, 70.98; H, 6.69; mol wt, 203.

Amino Ketone 19a.—The procedure was essentially that described in the mesembrine synthesis.[9a] Except for methylenedioxy rather than the dimethoxy absorption, the pmr spectra of this material and those of *dl*-mesembrine (**10**) were virtually identical in the diagnostic aliphatic region.

***N*-Benzylaldimine (17b).**—Aldehyde **16b** (7.75 g, 0.048 mol) and 10 ml of benzylamine were dissolved in 50 ml of benzene, and 5 g of $CaCl_2$ was added to the stirred solution. After 12 hr no carbonyl absorption could be detected in the ir. The solution was filtered and freed of solvent, and the excess benzylamine was removed *in vacuo* at room temperature. Distillation provided a clear oil which solidified upon standing, bp 168–170° (0.1 mm) (72–92%). An analytical sample was obtained by sublimation at 110° (0.4 mm) providing needles: mp 67–67.5°; ir (film) 1655 cm^{-1}; pmr (CCl_4) δ 1.22 (m, 4 H), 4.5 (d, 2 H), 5.89 (s, 2 H), 6.7–6.85 (m, 3 H), 7.25 (s, 5 H), 7.9 (t, 1 H).

Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.40; H, 6.13; mol wt, 279.32. Found: C, 77.60; H, 6.11; mol wt, 279.

1-Benzyl-3-(3,4-methylenedioxyphenyl)-2-pyrroline (18b).—Aldimine **17b** was heated with a catalytic amount of NH_4Cl at 135° under a N_2 atmosphere. The reaction was followed by observing the disappearance of C=N absorption. The resultant dark orange oil was extracted with boiling hexane which upon cooling precipitated the product (72–80°). Sublimation at 100° (0.3 mm) provided an analytical sample: mp 62.5–63°; ir [tetrachloroethylene (TCE)] 1618 and 1045 cm^{-1}; pmr (TCE) δ 2.5–3.4 (m, 4 H), 3.99 (s, 2 H), 5.51 (t, 1 H), 5.86 (s, 2 H), 6.56–6.76 (m, 3 H), 7.33 (s, 5 H).

Anal. Calcd for $C_{18}H_{17}O_2N$: C, 77.40; H, 6.13; mol wt, 279.32. Found: C, 77.52; H, 6.31; mol wt, 279.

Amino Ketone 19b.—The procedure was essentially that of Curphey.[9c] Pyrroline **18b** was dissolved in dry ether and treated with anhydrous HCl gas, thus precipitating the salt. The ether was then removed *in vacuo*, the residue was dissolved in dry CH_3CN, and a slight excess of freshly distilled methyl vinyl ketone was added. The solution was then brought to reflux for 9 hr in a N_2 atmosphere. Upon cooling the reaction mixture was poured into dilute HCl, washed with ether to remove neutral materials, basified with KOH, and extracted three times with ether. The ether extracts were combined, washed with brine, dried over $MgSO_4$, and finally freed of solvent, leaving a white solid, mp 98–99.5° with softening at 94°. Recrystallization from cyclohexane–benzene provided reasonably pure product (56–67%). An analytical sample was secured by sublimation at 120° (0.2 mm) and melted at 98.5–101°: ir (TCE) 1725 cm^{-1}; pmr (TCE) δ 1.8–3.2 (m, 11 H), 2.98 (d, 1 H, J = 12 cps), 4.06 (d, 1 H, J = 12 cps), 5.85 (s, 2 H), 6.65–6.85 (m, 3 H), 7.12 (s, 5 H).

Anal. Calcd for $C_{22}H_{23}O_3N$: C, 75.62; H, 6.63; mol wt, 349.41. Found: C, 75.62; H, 6.85; mol wt, 349.

Sodium Borohydride Reduction of 19b. Synthesis of Amino Alcohols 21a and 21b.—Amino ketone **19b** was reduced with excess sodium borohydride in EtOH solution. The epimeric alcohols were readily separated by preparative layer chromatography (1:1 $CHCl_3$–Et_2O).

Alcohol **21b** was removed from the plate and triturated with Et_2O, which induced crystallization. Recrystallization from Et_2O gave transparent cubes: mp 105–106°; pmr ($CDCl_3$) δ 1.0–2.6 (m, 10 H), 2.8–3.3 (m, 2 H), 3.12 (d, 1 H, J = 12.5 cps), 3.96 (poorly resolved quintet, 1 H, J = 2 cps), 4.39 (d, 1 H, J = 12.5 cps), 5.86 (s, 2 H), 6.7–6.85 (m, 3 H), 7.25 (s, 5 H); mol wt, 351. A picrate, mp 229–231°, was analyzed.

Anal. Calcd for $C_{28}H_{28}O_{10}N_4$: C, 57.93; H, 4.86. Found: C, 58.28; H, 4.94.

Alcohol **21a** was removed from the plate and it crystallized upon removal of the solvent. One recrystallization from ether provided an analytical sample: mp 135.5–136°; pmr ($CDCl_3$) δ 1.0–2.5 (m, 10 H), 2.7–3.2 (m, 2 H), 3.13 (d, 1 H, J = 13 cps), 3.8–4.35 (m, 1 H), 4.17 (d, 1 H, J = 13 cps), 5.87 (s, 2 H), 6.7–6.85 (m, 3 H), 7.25 (s, 5 H).

Anal. Calcd for $C_{22}H_{23}O_3N$: C, 75.19; H, 7.17; mol wt, 351.43. Found: C, 74.83; H, 7.21; mol wt, 351.

Catalytic Reduction of 19b. Stereoselective Synthesis of Amino Alcohol 21a.—The reduction of 2.38 g of the ketone was carried out in 200 ml of *i*-PrOH solution employing PtO_2 catalyst and an initial pressure of 42 psi in a Paar hydrogenator. After 48 hr the catalyst was removed and the filtrate was freed of solvent, leaving 2.3 g of a white residue (96%) whose tlc revealed that it was cleanly a mixture of the two epimeric alcohols **21a** and **21b**. These isomers were separated on a silica gel column eluting with 1:39 Et_2O–benzene mixture. The ratio of **21a** to **21b** was 8:1.

Debenzylation of 21b.—The method was essentially that of Büchi, *et al.*[19] The alcohol was dissolved in dry ether and the hydrochloride salt was precipitated with HCl gas. Excess HCl and solvent were then removed *in vacuo* and the dry salt was dissolved in MeOH. Hydrogenation at room temperature and 1 atm over 10% Pd/C catalyst was continued until hydrogen uptake ceased. Filtration and removal of the solvent gave essentially pure amine hydrochloride **21d** (100%). One recrystallization from MeOH–THF gave a white powder, mp 246–251.5°, in a vacuum-sealed capillary. The free amine was recrystallized from benzene–Et_2O and sublimed at 110° (0.45 mm) to give an analytical sample, mp 179–180°, in a vacuum-sealed capillary: pmr of HCl salt (D_2O) δ 1.5–2.5 (m, 8 H), 3.2–3.8 (m, 2 H), 3.9–4.35 (m, 2 H), 4.61 (s, HDO), 5.94 (s, 2 H), 6.85–7.05 (m, 3 H).

Anal. Calcd for $C_{15}H_{15}O_3N$: C, 68.94; H, 7.33; mol wt, 261.30. Found: C, 68.59; H, 7.62; mol wt, 261.

Debenzylation of 21a.—The same procedure as above provided a quantitative yield of amine hydrochloride **21c** which was recrystallized from MeOH–ether and dried *in vacuo* at 60°. The resultant white powder melted at 241.5–242° dec in a vacuum-sealed capillary, but the pmr spectrum revealed the presence of 0.25 mol of methanol of crystallization. The free amine could be recrystallized from benzene–Et_2O and sublimed at 90° (0.3 mm) to provide an amorphous powder: mp 154–156.5; pmr of HCl salt (D_2O) δ 1.4–2.6 (m, 8 H), 3.41 (s, 7 H, CH_3OH), 3.52 (broad t, 2 H), 4.05–4.45 (m, 2 H), 4.61 (HDO, s), 5.96 (s, 2 H), 6.9–7.1 (m, 3 H).

Anal. Calcd for $C_{15}H_{18}O_3N \cdot {}^1/_4CH_3OH$: C, 59.89; H, 6.92; mol wt, 261.30. Found: C, 59.78; H, 7.02; mol wt, 261.

***dl-epi*-Elwesine (2b).**—The procedure was essentially that of Whitlock and Smith.[5c] The hydrochloride salt of **21d** (234 mg) obtained in the debenzylation step was converted to the free amine and dissolved in 10 ml of 36% formalin and 10 ml of methanol. After 5 min 20 ml of 8 *N* HCl was added and the reaction was allowed to stand for 2 hr at room temperature. The mixture was then diluted with 25 ml of H_2O, extracted twice with 20-ml portions of ether to remove neutral materials, and basified with solid KOH. The resultant cloudy solution was then extracted with three 50-ml portions of $CHCl_3$, and the extracts were dried over K_2CO_3 and freed of solvent to give 275 mg of a white solid. Recrystallization from benzene–cyclohexane gave 139 mg (65%) of a white powder, which had mp 184–188°. Prolonged drying *in vacuo* at 60° (required to remove traces of benzene) raised the mp to 187–188.5° with softening at 185°. The solution ($CHCl_3$) ir spectrum of this substance was identical with that of an authentic sample[20] as was its behavior on tlc using a variety of solvents and solvent systems.

dl-**Elwesine (Dihydrocrinine) 2a.**—Amine **21c** (234 mg) was freed from its hydrochloride salt by dissolution in water, addition of 3 *M* NaOH, and extraction of the precipitated free base with ether. The ether was removed and the free base was dissolved in 5 ml of MeOH to which 2.4 ml of 37% formalin was added. After 10 min of stirring at room temperature the mixture was poured into 80 ml of 6 *N* HCl and stirred overnight. The slightly yellow solution was treated with charcoal, neutralized with concentrated NH_4OH, and extracted three times with $CHCl_3$. The organic extracts were combined, washed with H_2O, and dried over Na_2SO_4. Removal of the solvent provided 130 mg (61%) of a white crystalline solid which was essentially pure elwesine. Recrystallization from MeOH and drying *in vacuo* provided crystals, mp 216–220°. The solution ir spectra ($CHCl_3$) of this substance and that of an authentic sample[20] of elwesine were identical, as was their behavior on tlc.

Registry No.—*dl*-**2a**, 33531-72-5; *dl*-**2b**, 32209-87-3; **16a**, 33522-14-4; **16b**, 33522-15-5; **16b** (2,4-D), 33522-16-6; **17a**, 33522-17-7; **17b**, 32042-34-5; **18a**, 33608-35-4; **18b**, 33522-19-9; **19b**, 32209-88-4; **21a**, 33531-75-8; **21b**, 33531-76-9; **21b** (picrate), 33531-77-0; **21c**, 33531-78-1; **21c** (HCl), 33531-79-2; **21d**, 32209-89-5; **21d** (HCl), 33531-81-6.

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The Synthesis of (±)-Guaiol and (±)-7-Epiguaiol

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The synthesis of guaiol was carried out in two stages. In the first stage methyl *cis*-4-methyl-1(9)-octalin-2-one 10-carboxylate (**1**) was converted *via* enol acetylation and reduction ($NaBH_4$ followed by mesylate formation and Li–NH_3 reduction) to *cis*-5-methyl-10-hydroxymethyl-1(9)-octalin (**5**). Ring contraction *via* ozonolysis of the corresponding benzyl ether and aldol cyclization of the resulting ketoaldehyde afforded *cis*-7-methyl-7a-benzyloxymethyl-2,4,5,6,7,7a-hexahydroindene 3-carboxaldehyde (**8**). This intermediate was subjected to deconjugation–reduction through treatment of the enolate with ethanolic sodium borohydride followed by hydrogenolysis of the derived mesylate with Li–NH_3–*tert*-BuOH to give *cis*-3,7-dimethyl-7a-hydroxymethyl-5,6,7,7a-tetrahydroindan (**11**). The corresponding mesylate derivative upon acetolysis afforded *cis*-6,10-dimethylbicyclo[5.3.0]dec-1(7)-en-3-yl acetate (**13**) stereoselectively. The second stage of the synthesis was concerned with the introduction of a 1-methyl-1-hydroxyethyl grouping at the 3 position of this acetate. This transformation was finally achieved through carbonation of the Grignard reagent derived from the corresponding bromide. The sequence afforded a 2:1 mixture of acids in which the 7-epi isomer **16b** predominated. Equilibration of the derived methyl esters gave a 1:1 mixture of cis and trans esters **17a** and **17b** which yielded (±)-guaiol (**18**) and (±)-7-epiguaiol in the same ratio upon treatment with methyllithium. These epimeric alcohols were separated by preparative gas chromatography and identified through comparison with authentic material.

A major problem of synthesis relating to hydroazulene natural products[2] is the rational control of stereochemistry. An examination of molecular models clearly indicates the inherent stereochemical ambiguities of synthetic approaches which allow equilibration of chiral centers on the hydroazulene ring system. Thus particular effort must be made to avoid reactions and intermediates where such equilibration might occur. An especially fruitful approach to substituted hydroazulenes utilizes as a key step the skeletal rearrangement of relatively rigid bicyclic systems under conditions such that epimerization does not take place.[3] Such schemes have employed cyclohexane rings to good advantage for the control of stereochemistry in the various bicyclic precursors. This report describes a partially successful approach of this type to the total synthesis of guaiol, the structural prototype and first recognized member of the guaiane family of sesquiterpenes.[4–6]

Our synthetic plan was based on the expected rearrangement of a bicyclo[4.3.0]nonyl derivative through a formal ring expansion of the six-membered ring facilitated by homoallylic participation. This type of reaction has been examined in some detail by Tadanier using C-19 functionalized Δ^5 steroids as substrates.[7] Applications to bicyclo[4.3.0]nonyl systems have recently been reported by us[8] and by Scanio.[9] Our previous studies indicated that the methanesulfonate **12** (Chart I) would be the intermediate of choice for a projected synthesis of guaiol along these lines.[8] Accordingly, the known *cis*-methyloctalonecarboxylic ester **1**[10] was subjected to deconjugation–reduction *via* treatment of the enol acetate **2**[11] with ethanolic sodium borohydride.[12] The resulting hydroxy ester **3** readily lactonized upon work-up unless care was taken to avoid heating. Further reduction was effected through treatment of the methanesulfonate derivative **4** with lithium–ammonia–*tert*-butyl alcohol to give the unsaturated alcohol **5**, which was protected as the benzyl ether **6**.

The requisite ring contraction of octalin **6** was achieved through ozonolysis and subsequent aldol cyclization of the intermediate ketoaldehyde **7**. Double-

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