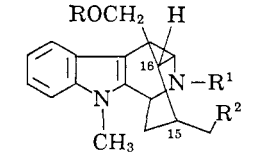
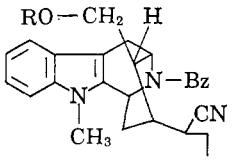
further characterized by converting them in more than 90% yield into the corresponding dihydroxy secondary amines **7′**, mp 208–209°, and **7a′**, mp 162–163°, with lithium aluminum hydride and then catalytic hydrogenation.

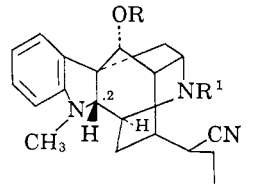
Conversion of **7** into the cyano compound **8** was readily achieved by treatment with hydroxylamine followed by benzoyl chloride in warm pyridine. The anion of **8** (triphenylmethylsodium–tetrahydrofuran) was treated with excess ethyl iodide to provide in 70% yield monoethyl compounds, from which a pure ethyl cyano compound **9**[8] was isolated in 60–70% yield. Brief treatment of **9** with sodium methoxide removed the benzoyl group from the ester to give a hydroxy compound (**10**), mp 202.5–204.5°. Similarly, **8a** was converted into **9a**[8] and **10a**.[8] Spectra[8] of **9**, **10**, **9a**, and **10a** were identical with those of the corresponding degradation products of ajmaline, as shown below.



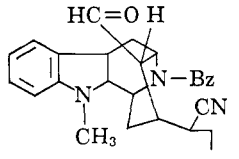
7, R = R¹ = Bz; R² = CHO
7′, R = R¹ = H; R² = CH_2OH
8, R = R′ = Bz; R² = CN



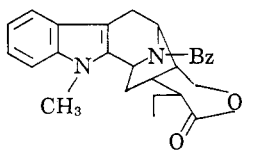
9, R = Bz
10, R = H
13, R = H
14, R = Bz



11, R = H; R¹ = Bz
17, R = Ac; R¹ = Bz
18, R = H; R¹ = $CH_2C_6H_5$
19, R = R¹ = H



12



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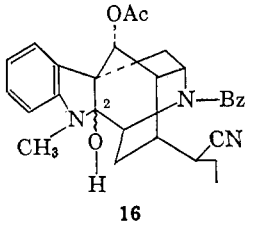

16

Compounds **7a**, **7a′**, **8a**, etc., are epimeric at C_{16} with **7**, **7′**, **8**, etc., respectively. Compounds **9** and **10** are racemates; **13** and **14** are the *d* (or *l*) isomers.

Treatment of ajmaline oxime[9] with benzoyl chloride in warm pyridine followed by sodium hydroxide provided a cyanobenzamide (**11**), mp 265–266°. Reaction of **11** with lead tetraacetate[3] followed by neutral work-up afforded an aldehyde (**12**), mp 219–220°, nmr ($CDCl_3$, 60°)[10] τ 0.45 (CHO) and 6.46 (N–CH_3), which was reduced with sodium borohydride to the corresponding hydroxy compound **13**, mp 228–230° and 261–262°, O-benzoate (**14**).[10] In the presence of alumina **12** was equilibrated with its epimer, **12a**; nmr ($CDCl_3$, 60°)[10] τ 0.32 (CHO) and 6.54 (N–CH_3), in a 3:7 ratio in favor of **12a**. Thus **12** and **12a** were interconvertible. The sodium borohydride reduction of **12a** provided a hydroxy compound (**13a**) which was converted with hydrochloric acid to a lactone (**15**), mp 312–313°. Compounds **13** and **13a** were oxidized with dimethyl sulfoxide and acetic anhydride (or carbodiimide)[11] to afford **12** and **12a**, respectively. Identity of spectral data[8] of **13**, **14**, **13a**, and **14a** with those of **10**, **9**, **10a**, and **9a**, respectively, established the structures and stereochemistry of synthetic intermediates.

Compound **12** upon treatment with hydrochloric acid in acetic acid and acetic anhydride underwent cyclization to afford in 65% yield compound **16**, which was hydrogenated with platinum catalyst in 6 *N* hydrochloric acid to yield in 60% yield compound **17**, mp 202–204°, and the corresponding 2 epimer in 30% yield.[12,13] Reduction of **17** with lithium triethoxyaluminum hydride provided the corresponding benzyl derivative **18**, mp 170.5–171.5°, which was in turn hydrogenolyzed to a secondary amine (**19**), mp 260–262°.[9] Since **19** has already been converted into **1** with lithium aluminum hydride,[9] we have completed the first synthesis of ajmaline.[14]

Acknowledgment. The authors are grateful to the National Research Council of Canada for financial support.

(9) F. A. L. Anet, D. Chakravarti, R. Robinson, and E. Schlittler, *J. Chem. Soc.*, 1242 (1954).

(10) All compounds containing the benzamide group showed temperature-dependent nmr spectra.

(11) A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 1762 (1966), and references cited therein.

(12) Compound **16** existed exclusively in the indoleninium form under these conditions: λ_{max}^{6NHCl} 294 mμ (ε 7200), 244 (11,700), and 236 (13,200).

(13) Catalytic hydrogenation of 21-deoxyajmalal-A[3] and 2-hydroxyvincamedine under acidic conditions proceeded from the α side of the compounds to yield 2-*epi* series of ajmaline type compounds [J. Gosset-Garnier, J. Le Men, and M.-M. Janot, *Bull. Soc. Chim. France*, 676 (1965)]. Dreiding models of these compounds reveal that the α and β sides present only a slight difference in steric hindrance toward hydrogenation. The exclusive α attack reported above was presumably due to the presence of the protonated nitrogen atom in the α side. In accord with this view, **16**, in which the amine was benzoylated, provided predominantly a compound of the normal series.

(14) Compound **15** was readily converted into N-methyl-10-desoxydihydrosarpagine[3] through a sequence of four steps in 35% over-all yield.

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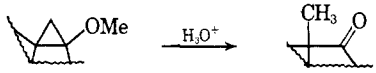
The Stereospecific Introduction of a Vicinally Functionalized Angular Methyl Group. A Synthesis of *l*-Valeranone

Sir:

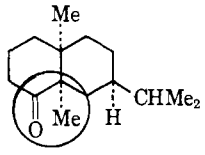
The molecular rearrangement accompanying the transformation of β-diketones and related substances into monoketones by the action of zinc and acid has been interpreted in terms of reductive formation of cyclopropanols followed by acid-induced ring cleavage.[1]

(1) (a) E. Wenkert and E. Kariv, *Chem. Commun.*, 570 (1965); (b) B. R. Davis and P. D. Woodgate, *J. Chem. Soc.*, 2006 (1966), and references therein.

The high specificity of protolysis of a fused, polycyclic methoxycyclopropane recently isolated from a Clemmensen reduction (in methanol solution) which had been quenched at an early stage (a → b)[2] strongly recommended the use of cyclopropyl ethers in organochemical synthesis in general and for the construction of quaternary carbon sites next to oxygenated carbon centers in particular. We now wish to report a seven-step synthesis of *l*-valeranone (I)[3] whose biosynthetically anomalous α-methylketo moiety (encircled structural unit in I) made this sesquiterpenic ketone an ideal object for exploitation of the new synthetic procedure.[4]

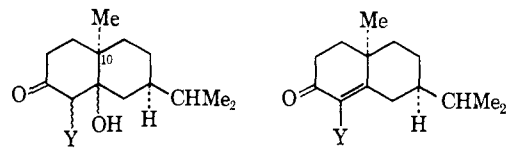


a b



I

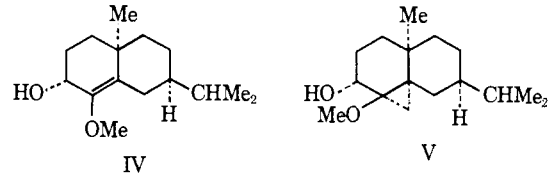
Condensation of *d*-carvomenthone with 1,4-dimethoxy-2-butanone,[5] the *in situ* precursor of methoxymethyl vinyl ketone,[6,7] under the influence of ethanolic potassium hydroxide in ether solution[8] produced a mixture of ketol and isomeric enones, predominating (4.5:1) in the 10α-methyl configuration, from which the liquid ketol IIa [36%; infrared (neat): 2.90 (OH, m), 5.81 μ (C=O, s); pmr ($CDCl_3$): one-proton singlet at δ 3.99 (methoxymethine), three-proton singlet at 3.50 (methoxyl), 1.25 (angular Me), six-proton broad doublet at 0.83 (J = 6.0 cps, isopropyl methyls). *Anal.* Found: C, 70.94; H, 10.40] could be isolated. The structure of this ketol was determined by its conversion into the demethoxy derivative IIb [79%; infrared (neat): 2.84 (OH, m), 5.85 μ (C=O, s). *Anal.* Found: C, 74.37; H, 10.70] on lithium–ammonia reduction, followed by transformation of the latter on acid-induced dehydration[9] into the unsaturated ketone IIIb (91%, mp 28–28.5°) whose optical rotatory dispersion curve was the mirror image of the known enantiometer.[10] The ketones IIb and IIIb also were the products of a base-catalyzed condensation[8] of *d*-carvomenthone and methyl vinyl ketone.



II III

a, Y = OMe; b, Y = H

Treatment of the ketol IIa with ethanolic potassium hydroxide yielded the enone IIIa [78%; $[\alpha]^{21}D$ −163° (c 1.0, $CHCl_3$); infrared (neat): 5.96 (C=O, s), 6.21 μ (C=C, m); λ_{max} (EtOH) 257 mμ (ε 8500); pmr ($CDCl_3$): three-proton singlet at δ 3.61 (methoxyl), 1.27 (angular Me), six-proton pair of doublets at 0.97, 0.87 (J = 5.5 cps, isopropyl methyls). *Anal.* Found: C, 76,21; H, 10.15] whose lithium aluminum hydride reduction produced the alcohol IV [94%; $[\alpha]^{24}D$ +25.7° (c 1.2, $CHCl_3$); infrared (neat): 2.99 (OH, m), 6.01 μ (C=C, m); pmr ($CDCl_3$): one-proton multiplet at δ 4.44 (hydroxymethine), three-proton singlet at 3.58 (methoxyl), 1.14 (angular Me), six-proton pair of doublets at 0.94, 0.85 (J = 6.0 cps, isopropyl methyls). *Anal.* Found: C, 75.95; H, 10.71]. Simmons–Smith reaction[11] of this allyl alcohol[12] led to the cyclopropane derivative V [91%; $[\alpha]^{21}D$ −38.9° (c 0.8, $CHCl_3$); infrared (neat): 2.90 (OH, m), 3.25 μ (probably cyclopropyl H, w); pmr ($CDCl_3$): one-proton multiplet at δ 4.34 (hydroxymethine), three-proton singlet at 3.36 (methoxyl), 0.92 (angular Me), six-proton broad doublet at 0.83 (J = 5.5 cps, isopropyl methyls), one-proton doublets at 0.66, 0.21 (J = 6.0 cps, cyclopropyl methylene). *Anal.* Found: C, 76.33; H, 11.12].



IV V

Jones oxidation of V produced the ketone VIa [54%; mp 40.5–42.0°; $[\alpha]^{20}D$ −39.8° (c 0.8, $CHCl_3$); infrared (neat): 3.30 (probably cyclopropyl H, w), 5.92 μ (C=O, s); pmr ($CDCl_3$): three-proton singlet at δ 3.47 (methoxyl), 1.12 (angular Me), six-proton pair of doublets at 0.83, 0.81 (J = 5.5 cps, isopropyl methyls). *Anal.* Found: C, 76.96; H, 10.21] whose

(2) E. Wenkert and J. Zylber, unpublished observations.

(3) H. Hikino, Y. Hikino, Y. Takeshita, K. Meguro, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 1408 (1965), and references therein.

(4) J. A. Marshall, W. I. Fanta, and G. L. Bundy, *Tetrahedron Letters*, 4807 (1965), have executed a synthesis of *d*-valeranone along traditional lines.

(5) G. F. Hennion and F. P. Kupiecki, *J. Org. Chem.*, **18**, 1601 (1953).

(6) While neither this vinyl ketone nor the keto diether appears to have found use in Robinson annelation reactions heretofore, the condensation of 2-methyl-3-hydroxy-2-cyclohexenone with a mixture of 3-methoxy-4-diethylamino-2-butanone and 1-methoxy-4-diethylamino-2-butanone (also an *in situ* precursor of methoxymethyl vinyl ketone), derived from a Mannich condensation of methoxyacetone, formaldehyde, and diethylamine, is on record [J. Szmuszkovicz, *ibid.*, **19**, 1424 (1954)].

(7) Even though the Robinson ring annelation reaction is nowadays part of the standard repertoire of organochemical synthesis, the choice of the all-important vinyl ketone component in the Michael condensation is limited usually to compounds with no more daring structural variation than different alkyl substituents. The recent utilization of carbomethoxymethyl vinyl ketone in an annelation process was of immense value in diterpene synthesis [E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964)]. Methoxymethyl vinyl ketone or its equivalents can be expected to assume similar importance in the future.

(8) *Cf.* N. C. Ross and R. Levine, *J. Org. Chem.*, **29**, 2341 (1964).

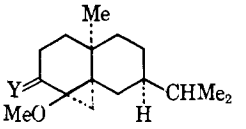
(9) *Cf.* E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 2318 (1956).

(10) C. Djerassi, J. Burakevich, J. W. Chamberlin, D. Elad, T. Toda, and G. Stork, *ibid.*, **86**, 465 (1964).

(11) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

(12) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963); W. G. Dauben and A. C. Ashcraft, *ibid.*, **85**, 3673 (1963).

Wolff–Kishner reduction yielded the tricyclic ether VIb [80%; $[\alpha]^{21}D$ −55.6° (*c* 0.8, $CHCl_3$); infrared (neat): 3.30 μ (probably cyclopropyl H, w); pmr ($CDCl_3$): three-proton singlet at δ 3.25 (methoxyl), 0.91 (angular Me), six-proton doublet at 0.86 (J = 6.0 cps, isopropyl methyls), one-proton doublets at 0.30 and 0.16 (J = 5.0 cps, cyclopropyl methylene). *Anal.* Found: C, 81.49; H, 11.94]. Exposure of the latter to aqueous, methanolic hydrochloric acid afforded a quantitative yield of *l*-valeranone (I), identical in all respects with the natural plant product.[13]



VIa, Y=O
b, Y=H_2

(13) The authors are indebted to Dr. T. Takemoto (Tohoku University) for a gift of natural *l*-valeranone and to the National Science Foundation for partial support of this work.

(14) Public Health Service predoctoral fellow, 1965–.

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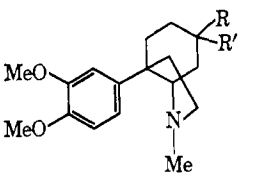
Biosynthesis of Mesembrine. The Incorporation of One-Carbon Units and the Origin of the C_6 Unit[1]

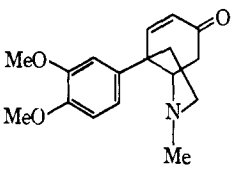
Sir:

The alkaloid mesembrine (**1**, R = R′ = O) along with several cogeners, mesembrinol (**1**, R = OH; R′ = H) and mesembrinine (**2**), occur in several plants of the *Aizoacea* family.[2] The biosynthesis of these alkaloids is of interest since the skeletal framework would appear to contain a C_6–C_2–N unit, which in the case of mesembrine is comprised of the cyclohexanone ring and the attached C_2–N bridge, and a C_6 unit represented by the aromatic ring. The presence of an isolated C_6 unit is an unusual structural feature, and its biosynthetic origin is therefore of interest. We report the results obtained which provide information on a precursor to this unit and also the results obtained from the incorporation of the label from methionine-S-methyl-C^{14} into mesembrine.

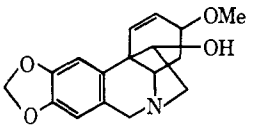
The labeled compounds were fed to *Sceletium strictum* L. Bol.,[3] and after periods ranging from 3 to 22 days the plants were harvested and the mesembrine isolated by using inactive mesembrine as a carrier. The results are summarized in Table I and are for mesembrine of constant activity. When the mesembrine derived



1



2



3

from the methionine feeding experiment was demethylated to give the activities for the O-methyl and N-methyl groups separately, the total activity was, within the limits of experimental error, the same as in the alkaloid. Furthermore, the ratio of the activities for the two methoxyls and the N-methyl group was 2:1. This suggests that each of these one-carbon sites makes an equal contribution to the total activity, in accordance with expectation for the result of a transmethylation process involving the S-methyl group of methionine.[4]

Table I. Incorporation of Radioactive Compounds into Mesembrine[a]

Precursor	Injected, μcuries	Isolation, days	Incorporation, %[b]
Methionine S-methyl-C^{14}	50	3	0.75
Tyrosine-3-C^{14}	50	10	0.051
Phenylalanine-2-C^{14}	50	10	<0.001
Phenylalanine [uniformly labeled in the ring with C^{14}]	50	22	0.059
	50	10	0.053

[a] Samples were counted on a Nuclear Chicago Unilux scintillation counter in toluene or dioxane–methanol–water scintillator solutions. [b] This figure may be regarded as a minimum since it was calculated on the basis of the weight of inactive mesembrine added to the plant extract.

These results were independently confirmed by the degradation of radioactive mesembrine to veratric acid and demethylation of the latter to protocatechuic acid. The relative activities of the products of the degradation sequence are shown in Table II.

Radioactive mesembrine derived from phenylalanine [C^{14}-ring labeled] was converted to veratric acid which was degraded further to protocatechuic acid. The relative activities of the degradation products indicate that the aromatic ring of phenylalanine is incorporated intact into the aromatic ring of mesembrine and that the label is restricted to this portion of the molecule. These results, when considered in conjunction with the results of the incorporation of radioactivity from tyrosine-3-C^{14} and the lack of activity in the mesem-

(1) Supported by National Science Foundation Grant GB-4361 and a grant-in-aid from Eli Lilly Co.

(2) A. Popelak, E. Haak, G. Lettenbauer, and H. Spengler, *Naturwissenschaften*, **47**, 150, 231 (1960); E. Smith, N. Hosansky, M. Shamma, and J. B. Moss, *Chem. Ind.* (London), 402 (1961); M. Shamma and H. Rodriguez, *Tetrahedron Letters*, 4847 (1965).

(3) We are indebted to Mr. H. Herre, Stellenbosch, South Africa, for supplying these rare botanicals, and to Mr. J. N. McQuay, Botany Department, Duke University, for invaluable help with their cultivation.

(4) See R. N. Gupta and I. D. Spenser, *Can. J. Chem.*, **43**, 133 (1965).