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# RECENT DEVELOPMENTS IN THE CHEMISTRY OF THE ATISINE-TYPE DITERPENE ALKALOIDS

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## I. INTRODUCTION

FROM ancient times man has been intrigued and fascinated by powerful plant poisons. Few there are who are not moved by reading Plato's account in the *Phaedo* of Socrates drinking the cup of poison hemlock or the accounts in medieval literature of the use of Monkshood, Ouabain, or Deadly Nightshade in the trials by ordeal. It is perhaps this same kind of fascination which accounts at least in part for the organic chemists' interest in the Aconite[3] alkaloids. These substances occur in the various species of *Aconitum* and *Delphinium*, which are widely distributed throughout the plant world, and have long been of great interest because of their intensely poisonous properties and their complex structures. Extracts of the roots and leaves of *Aconitum* species were employed in ancient times for such varied uses as animal poisons and the treatment of neuralgia, hypertension, gout and rheumatism.

The Aconite alkaloids may be divided into two broad categories. The first comprises the highly toxic ester bases called the Aconitines. These consist of relatively non-toxic, polyhydric C-19 bases (aconines) which are esterified with one or two simple organic acids such as acetic or benzoic acid. The second group which is designated as the "Atisine" class includes a series of relatively non-toxic alkamines containing few substituents and is modeled on a $C_{20}$-skeleton. It is this second class of "simpler" alkaloids that forms the subject for the present review. Since two recent reviews[4,5] have appeared which cover the literature to about the end of 1957, this survey will be concerned mainly with developments of the past three years, and in particular with only those alkaloids for which complete or at least plausible, if not rigorously demonstrated, structures have been advanced.

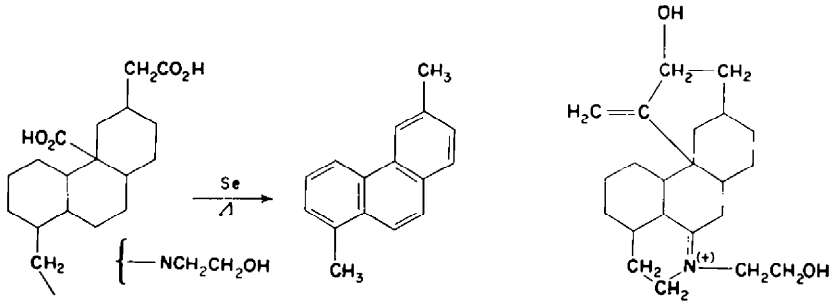
## II. THE CHEMISTRY OF ATISINE[6]

### A. *General remarks*

*Aconitum heterophyllum*, Wall (atis or atees), a plant native to the Himalayas, has long occupied an important place in Indian folk medicine. Thus, extracts of the plant have been used as a bitter tonic, expectorant, febrifuge and aphrodisiac, and in the

[1] Fellow of the American-Swiss Foundation for Scientific Exchange, 1960.
[2] The author's investigations of 1959–60, which are reported herein, were supported in part by Grants RG 5807, 5807 (C1) and 5807 (C2) from the National Institutes of Health, United States Public Health Service.
[3] The term "Aconite Alkaloids" was coined by W. A. Jacobs to designate bases of both the *Aconitum* and *Delphinium* species.
[4] K. Wiesner and Z. Valenta, *Progress in the Chemistry of Organic Natural Products* Vol. XVI, p. 26. Springer-Verlag, Vienna (1958).
[5] E. S. Stern in *The Alkaloids, Chemistry and Physiology* (Edited by R. H. F. Manske and H. L. Holmes) Vol. VII, p. 473. Academic Press, New York (1960).
[6] Atisine appears to be identical with anthorine, the alkaloid of *A. anthora* [A. Goris and M. Melin, *C. R. Acad. Sci., Paris* **180**, 968 (1925); A. Goris, *Ibid.* **205**, 1007 (1937)].

treatment of dyspepsia and dysentery. Whether the alkaloids of the plant are responsible for its reputed properties is unknown, but those which have been isolated in a pure state include atisine, atidine, hetisine, heteratisine and a benzoyl derivative of the latter. The predominant alkaloid, atisine, is a clear varnish-like base which was first described and named by Broughton in 1877.[7] Numerous crystalline derivatives were subsequently reported[8–10] but the correct molecular formula ($C_{22}H_{33}NO_2$) remained unknown until the work of Lawson and Topps[11]. The pioneering studies of the Aconite alkaloids by Walter A. Jacobs and his collaborators at the Rockefeller Institute were initiated in 1936 and provided an indispensible foundation for subsequent contributions in this field. Jacobs' work on atisine disclosed the relationship of functional groups and provided deep insight into the complex chemistry of this substance.[12] Unfortunately due to an incorrect assumption that a methyl group in 1,6-dimethylphenanthrene (2) could not have originated from a carboxyl group during dehydrogenation, Jacobs concluded that the dicarboxylic acid from isoatisine must bear an acetic acid residue as in structure (1). This situation, was largely responsible for the postulation of an incorrect skeleton (3) for atisine.[12]

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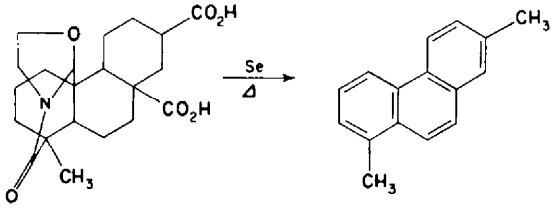
In subsequent work on the Garrya alkaloids,[13] Wiesner paralleled the early studies of Jacobs on atisine and was able to show convincingly that during dehydrogenation one of the carboxyls of oxoveatchine dicarboxylic acid-B (4) is in fact a precursor of a

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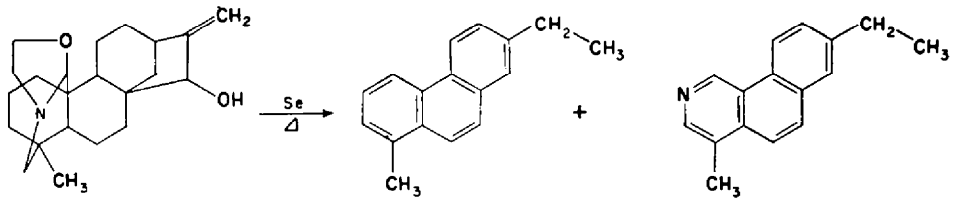
methyl group in pimanthrene (5).[14] Another key development leading to a clarification of veatchine chemistry was the elucidation, by X-ray crystallography and synthesis,

[7] J. Broughton, *Blue Book* 133 (1877).
[8] M. D. v. Wasowicz, *Arch. Pharm.* **214**, 193 (1879).
[9] A. Wright, *Yearbook Pharm.* 422 (1879).
[10] H. A. D. Jowett, *J. Chem. Soc.* **69**, 1518 (1896).
[11] A. Lawson and J. E. C. Topps, *J. Chem. Soc.* 1640 (1937).
[12] For leading references see W. A. Jacobs, *J. Org. Chem.* **16**, 1593 (1951).
[13] K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Canad. J. Chem.* **30**, 608 (1952); K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong and J. A. Edwards *Chem. Ber.* **86**, 800 (1953).
[14] K. Wiesner, J. R. Armstrong, M. F. Bartlett and J. A. Edwards, *J. Amer. Chem. Soc.* **76**, 6068 (1954).

of the structure of the $C_{16}H_{15}N$ azaphenanthrene (8) obtained by dehydrogenation of veatchine (6).[15a,16] With the veatchine structure clarified, the striking parallelism

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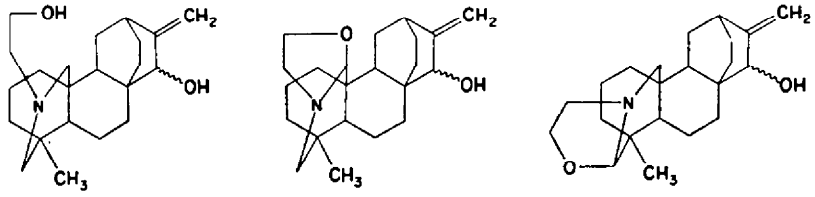
between the chemistry of atisine as uncovered by Jacobs[12], and that of veatchine led Wiesner to suggest a structure for dihydroatisine (9)[15a] and by implication for atisine (10) and isoatisine (11).[15b] Though the Wiesner postulate was based mainly on

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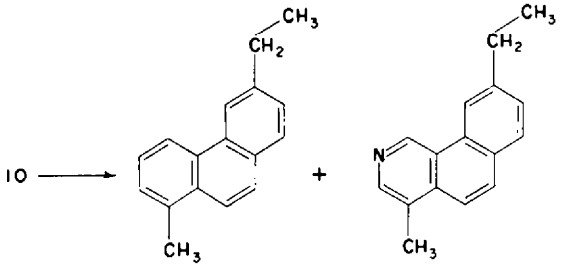
analogy, and direct evidence for many elements of this proposal was lacking, subsequent studies at the Rockefeller Institute and the National Research Council in Ottawa have provided the desired experimental proof for these structures. Thus rigorous proof for the existence of the oxazolidine moiety in atisine[17] and the $\beta$-hydroxyethyl group[18] in dihydroatisine, as well as valuable degradative data locating the site of functional groups and shedding general light on the structure,[19–23] was soon forthcoming. Recent advances include proof of the position of the nitrogen atom in atisine,[24] evidence for the presence of a 2,2,2-bicyclooctane system,[25] correlation of ajaconine,[26,27] atidine[27] and the Garrya alkaloids (veatchine and garryfoline) with atisine,[28] a method of removing the nitrogen atom from the diterpene alkaloids,[29] and elucidation of the stereochemistry of the atisine-type alkaloids.[30] These developments will now be surveyed.

[15a] K. Wiesner, J. R. Armstrong. M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954). [b] *cf. Experientia*, **11**, 255 (1955).
[16] M. F. Bartlett and K. Wiesner, *Chem & Ind.* 542 (1954).
[17] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **76**, 4496 (1954).
[18] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4144 (1956).
[19] O. E. Edwards and T. Singh, *Canad. J. Chem.* **32**, 465 (1954).
[20] S. W. Pelletier and W. A. Jacobs, *Chem. & Ind.* 1385 (1955).
[21] O. E. Edwards and T. Singh, *Canad. J. Chem.* **33**, 448 (1955).
[22] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4139 (1956).
[23] D. Dvornik and O. E. Edwards, *Canad. J. Chem.* **35**, 860 (1957).
[24] D. M. Locke and S. W. Pelletier, *J. Amer. Chem. Soc.* **80**, 2588 (1958); *Ibid.* **81**, 2246 (1959).
[25] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 623 (1958).
[26] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 952 (1957).
[27] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).
[28] S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).
[29] O. E. Edwards and R. Howe, *Proc. Chem. Soc.* 62 (1959).
[30] A. J. Solo and S. W. Pelletier, *Chem. & Ind.* 1108 (1960).

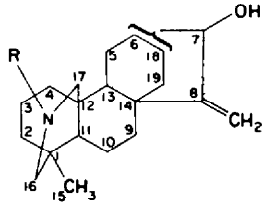
B. *Gross structural features*

An important piece of evidence bearing on the skeleton of atisine (10) is the structure of the $C_{16}H_{15}N$ base obtained initially by Lawson and Topps[11] and later by Jacobs[31] from the dehydrogenation of atisine. This base, together with the 1-methyl-6-ethylphenanthrene (12)[31,32] also obtained, accounts for all but three carbon atoms of atisine and relates the heterocyclic ring to the rest of the molecule. By analogy with veatchine chemistry,[33] it would be expected to have the structure of 1-methyl-6-ethyl-3-azaphenanthrene (13). This has been demonstrated by an unambiguous synthesis from 7-ethyltetralone-1.[24] This synthesis provides the first positive evidence fixing the position of the nitrogen atom with respect to the remainder of the atisine molecule.




12 13

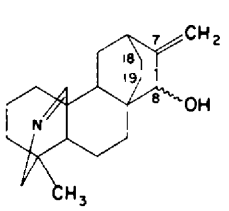
The relative positions of the secondary alcohol and exocyclic methylene groups in atisine were assigned on the basis of the selenium dehydrogenation products.[15a,17] Thus atisine, oxoisoatisine and tetrahydroatisine give 1-methyl-6-ethylphenanthrene (12) while the di- and tricarboxylic acids from isoatisine give 1,6-dimethylphenanthrene.[12,31,32] By analogy with veatchine (6) which gives 1, 7-disubstituted phenanthrenes,[13] the secondary hydroxyl and exocyclic methylene functions were located as in (10).[15a,17] Though cleavage between the carbons bearing the hydroxyl and methylene groups might be expected during dehydrogenation and would account for the formation of the 6-ethyl group, it is not inconceivable that the allylic alcohol and exocyclic methylene groups are reversed in position as in (14). Aside from the suggestive nature of the dehydrogenation data, all the above chemical evidence in both the atisine and veatchine series could have been accommodated as well by structures (14) and (15) respectively.




14 C(7)–C(6) bond
15 C(7)–C(18) bond

[31] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **143**, 589 (1942).
[32] C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.* **170**, 203 (1947).
[33] When dehydrogenated veatchine gave 1-methyl-7-ethylphenanthrene (7)[13] and 1-methyl-7-ethyl-3-azaphenanthrene (8)[16] while atisine gave 1-methyl-6-ethylphenanthrene (12)[31,32] and the unknown $C_{16}H_{15}N$ base.

Definitive evidence on this point is now available in the case of atisine. Dvornik and Edwards have shown that hydration of the $C_{20}$-azomethine alcohol (16)[34] gave the diol (17) which on reduction, acetylation, selective hydrolysis and oxidation gave a 7,8-*seco*-methylketo acid (18).[25] Treatment of the latter with trifluoroacetyl peroxide followed by hydrolysis and dichromate oxidation gave the bisnor-keto acid (19), 1712 $cm^{-1}$, 1602 $cm^{-1}$. Dibromination of (19) followed by dehydrohalogenation gave a crystalline phenol (20) [828, 1586, 1638 $cm^{-1}$, $\lambda_{max}$ 282 m$\mu$ shifting to 300 m$\mu$ in alkali], and a keto $\gamma$-lactone (1796, 1734, 1639 $cm^{-1}$). Formation of the latter,



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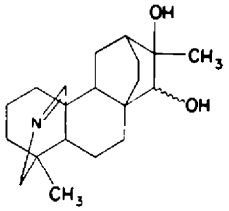

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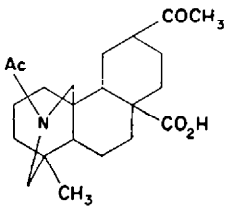

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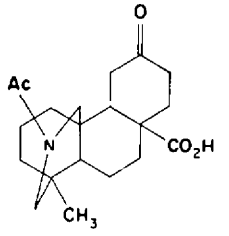

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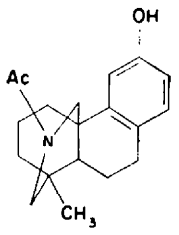

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involving displacement of bromine $\alpha$ to the keto group by carboxylate anion, demonstrates a 1,4 relationship of the ketone and carboxyl groups in (19). Thus these results, when taken with Jacobs dehydrogenation evidence for substitution at C-6,[12,32] show clearly that a 2,2,2-bicycloöctane system is present in atisine and that the terminal methylene group is located at C-7 (or C-18)[37] and the secondary hydroxyl at C-8 (or C-19)[37] respectively.[25] Further evidence on this point is provided by the following sequence of reactions.[38] Isomerization of isoatisine (11) with ethanolic hydrochloric acid gave a mixture of ketones (21) [1712 $cm^{-1}$] epimeric at the adjacent methyl group. That skeletal rearrangement had not occurred during the isomerization was shown by borohydride reduction of (21) to give a mixture from which the known $\alpha$-tetrahydroatisine (22)[39] was isolated. Removal of the keto group to give (23) could be effected only by Barton's procedure[40] for sterically hindered ketones. That the oxazolidine ring was opened is not surprising since it is well known that both atisine

[34] This unusual and valuable degradation product was first obtained as a by-product of the permanganate oxidation of atisine.[18,32,35] Subsequently a useful procedure of preparation involving a Hofmann degradation of atisine diacetate chloride was published.[25,36]

[35] S. W. Pelletier, Lecture, Gordon Research Conference on Steroids and Related Natural Products, New Hampton, N.H., August 24, 1955.

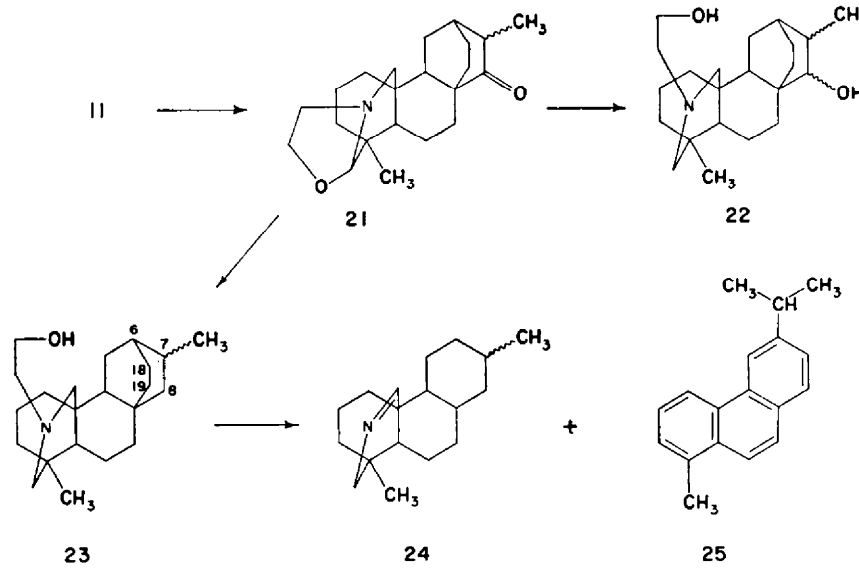
[36] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 248 (1956).

[37] Since the bicycloöctane system is symmetrical, the allylic alcohol system could be located on either the *cis*- or *trans*-branch. This point will be considered later under the section on the stereochemistry of atisine.

[38] S. W. Pelletier, *Chem & Ind.* 1116 (1958).

[39] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **143**, 589 (1942).

[40] D. H. R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.* 2056 (1955).




and isoatisine are reduced to dihydroatisine (9) when heated with ethanolic alkali at high temperatures.[41] Dehydrogenation of (23) with selenium gave the epimeric azomethines (24) and also 1-methyl-6-isopropyl phenanthrene (25).[38] Had the methylene group been located at C(8) or C(19)[37] one would expect to obtain either 1,6-dimethylphenanthrene or 1-methyl-6-n-propylphenanthrene. The formation of the isopropyl derivative is again clear evidence for assigning the methylene group to C(7) or C(18).[37,38] Aside from stereochemical features, which are discussed in another section, atisine is thus shown to have structure (10).

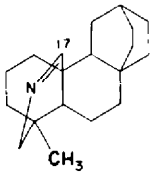
C. *Removal of the nitrogen from diterpene alkaloids*

Of significance relative to the problem of degrading the atisine alkaloids to diterpenes of established stereochemistry is the difficulty in removing the nitrogen atom. Since both positions $\beta$ to the nitrogen are quaternary, Hofmann type degradations are ineffective. What might appear to be a particularly susceptible group for an attack on the nitrogen is the azomethine linkage such as occurs in (26). This masked aldehyde manifests a remarkable stability to both acids and bases. Thus it survives boiling with 10 per cent hydrochloric acid[42] and also conditions of the Wolff-Kishner reaction.[23,43] The remarkable stability of this function is owing to the peculiar geometry of the system. Steric compression between the nitrogen and C(17) maintains the linkage in a closed position, thus effectively prohibiting reactions which would normally occur via the aldehyde.

Recently success in removing the nitrogen from (26) has been achieved through a mild reaction with aqueous nitrous acid.[29,44] Treatment with nitrous acid gave as the major product a hemiacetal (27) which was oxidized with bromine water to a $\delta$-lactone (1725 $cm^{-1}$). The hemiacetal was converted successively to a primary alcohol (28a),

[41] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **147**, 567 (1943).
[42] S. W. Pelletier, unpublished work.
[43] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 952 (1957).
[44] Reactions of a similar type have been studied in the case of amides and amines by R. Huisgen and his collaborators [*Leibigs Ann.* **599**, 161, 183 (1956); *Ibid.* **601**, 1 (1956)].

aldehyde (1696 $cm^{-1}$) (28b) and carboxylic acid (1675 $cm^{-1}$, $\lambda_{max}$ 225 m$\mu$, $\varepsilon$100) (28c). It is of interest to note that the sodium salt of (28c) is soluble in ether and that it has a



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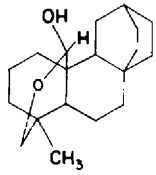

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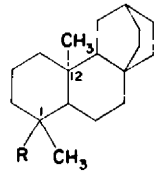


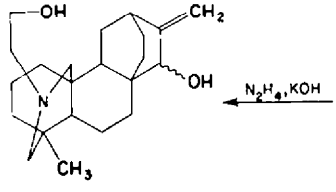
28a R = —$CH_2OH$
28b R = —CHO
28c R = —$CO_2H$

pKa of 9·6. The abnormal ultraviolet absorption of the acid and the displaced infrared maxima of the lactone, aldehyde and acid are attributed to the extreme steric hindrance of the carbonyl groups. That (28c) is an extremely weak acid is probably due to steric hindrance of solvation of the carboxylate ion.[29]

*Note added in proof:* Djerassi (private communication, Dec. 22, 1960) has shown in the case of the azomethine from garryfoline that the angular carboxyl is located at C(12) rather than at (C1). [Diterpene numbering, see formula 63a] Structure (27, 28a, b, c) should also be revised accordingly.

## III. THE STRUCTURE OF ATIDINE

Atidine, $C_{22}H_{33}NO_3$, has been isolated from the strongly basic fraction of extracts of *Aconitum heterophyllum*.[45] Chemical and infrared data indicate that two of the oxygen atoms exist as primary or secondary hydroxyls (diacetate) and the third as a ketone (oxime) in a six- or larger-membered ring (1695 $cm^{-1}$). Also present are an exocyclic methylene group (3086, 1658, 900 $cm^{-1}$; formaldehyde results from permanganate-periodate oxidation), a C-methyl group (1376 $cm^{-1}$) and a N—$CH_2CH_2OH$ group.[45] The conclusion that atidine is a keto dihydroatisine was shown to be correct by conversion of atidine (29) to dihydroatisine (30) by the Huang-Minlon procedure.[46] Possible sites for the keto group were indicated by observation that treatment of atidine with alkali under mild conditions led to extensive formation of polymeric material.[42] With a keto group at either position 9 or 19 one would expect the $\beta$-hydroxyketone to undergo facile cleavage of the retroaldol type to give the unstable acrolein derivative (31), thus accounting for the rapid destruction of atidine. Sub-



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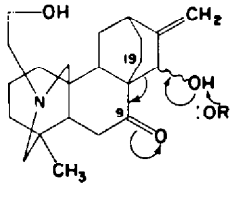

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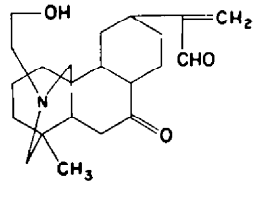

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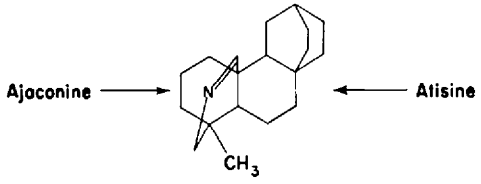
sequent correlation of atidine and ajaconine via the dihydro derivative (*vide infra*)[46]

[45] S. W. Pelletier, *Chem. & Ind.* 1016 (1956).
[46] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).

and the elucidation of the structure of ajaconine[47] allow the keto function to be assigned to position 9 in atidine (29).

## IV. THE CHEMISTRY OF AJACONINE

The delphinium alkaloid ajaconine[48] (*D. ajacas*), $C_{22}H_{33}NO_3$, is of especial interest since it is the first reported example of an atisine derivative occurring in a delphinium species.[43] Ajaconine was shown to have the same carbocyclic skeleton as atisine by conversion to the oxygen-free azomethine base (32), earlier obtained from atisine.[23,43]

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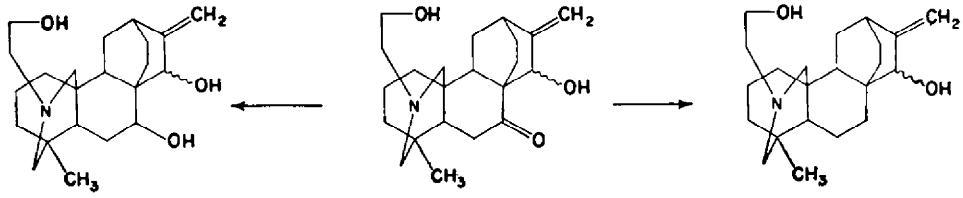
That the secondary allylic alcohol system also has the same position and stereochemistry in ajaconine as in atisine was shown by the reduction of atidine (29), a companion of atisine,[45] to a mixture of epimers, one of which is identical to dihydroajaconine

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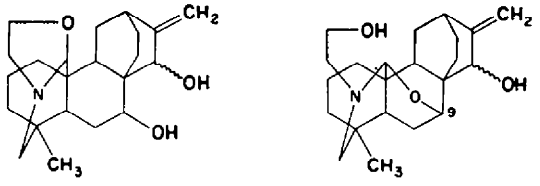
(33).[46] Since atidine had been previously converted to dihydroatisine (34), it is clear that ajaconine is a derivative of the latter.[46]

Initial observations on the behavior of ajaconine, including its high $pK_a'$ (11·3), formation of an anhydronium chloride (I.R., 1683 $cm^{-1}$, $\rangle C{=}\overset{+}{N}\langle$) and the smooth Hofmann-type elimination of the acetoxyethyl group of ajaconine triacetate to give an azomethine base, led Dvornik and Edwards to assume it contained an oxazolidine ring system (35) such as occurs in atisine.[43,49] Their later work, however, has shown

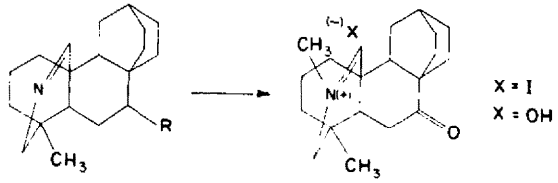



35 36

that the internal carbinolamine ether involves the 9-oxygen atom and is not derived from the N-2$\beta$-hydroxyethyl system as in atisine. The subsequent discussion of ajaconine chemistry will be based therefore on this revised structure (36).[47]

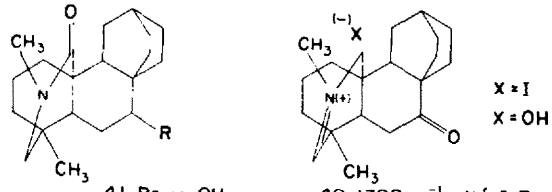
[47] D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.* 305 (1958).
[48] J. A. Goodson, *J. Chem. Soc.* 245 (1945).
[49] D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.* 280 (1958).

The position and character of the hydroxyl group resulting on opening of the ether ring was established as follows.[49] The $C_{19}$-alcohol (37) was oxidized to the corresponding ketone (38) and thence converted to the N-methyl carbinolamine (39). Hot methanolic alkali transformed (39) into a mixture of the corresponding iso compound (40) and a hydroxy lactam (41)3380, 1054, 1620 $cm^{-1}$. The latter was




37 -R=—OH
38 R==O

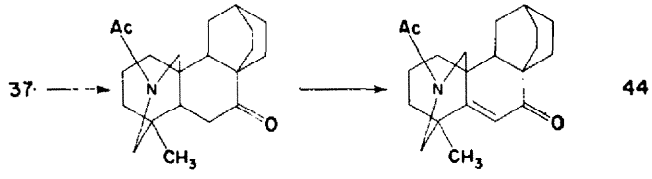
39 1705, 1688 $cm^{-1}$; pKa 11·7




41 R=····OH
42 R=—OH

40 1702 $cm^{-1}$; pKa 9·7

shown to result from an intramolecular Cannizzaro-type reaction. Oxidation of (41) followed by reduction gave the epimeric hydroxy lactam (42) with the hydroxyl in the original orientation of ajaconine. Spectroscopic data indicate that the hydroxyl in (41) is axial (1054 $cm^{-1}$) and in (42) is equatorial (1082 $cm^{-1}$). The above evidence demonstrates the hydroxyl in (41) is *trans* to the N-bridge and in (37) is *cis* thereto. The hydroxyl was shown to be at position 9 by the following sequence.[49] Azomethine (37)



43 1707, 1654 $cm^{-1}$

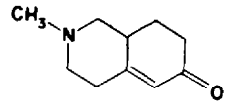
$\lambda_{max.}$ 290 m$\mu$ (e, 55)

44

was converted rationally to ketone (43). Bromination of the latter gave a monobromo ketone which on dehydrobromination gave the $\alpha,\beta$-unsaturated ketone (44), 1664 $cm^{-1}$, $\lambda_{max}$ 250 m$\mu$ ($\varepsilon$9300) and 328 m$\mu$ ($\varepsilon$96) in ethanol. The ultraviolet maximum at 250 m$\mu$ corresponds reasonably well with the calculated value of 244 m$\mu$[50,51] for a $\beta,\beta$-disubstituted exocyclic double bond, though certain basic $\alpha,\beta$-unsaturated ketones have been shown to absorb at abnormally short wave lengths, e.g. compound (45) is reported to absorb at 227·5 m$\mu$ in methanol,[52] and at 232 m$\mu$ in ethanol.[53]

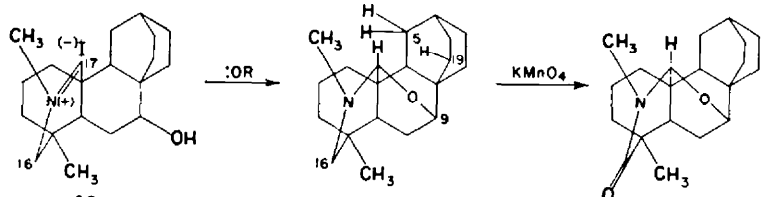
[50] R. B. Woodward, *J. Amer. Chem. Soc.* **63**, 1123 (1941); *Ibid.* **64**, 76 (1942).
[51] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene* p. 190. Reinhold, New York (1949).
[52] C. B. Clarke and A. R. Pinder, *J. Chem. Soc.* 1967 (1958).
[53] E. M. Kosower and D. C. Remy, *Tetrahedron* **5**, 281 (1959).

However, (45) may not be a good model since the geometry of the heterocyclic ring is different in (44).



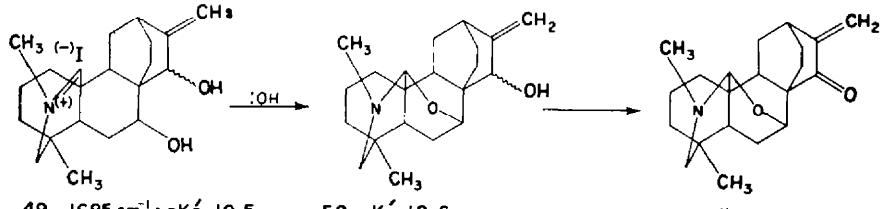
45

That the carbinolamine function in ajaconine is derived from the 9-oxygen is suggested by the behavior of the methiodide (46) with hot, methanolic alkali.[47] The product is a hydroxyl-free base (47) [p$K_a'$ 10] and hence must be an internal cyclization product derived from the 9-hydroxyl and carbon 17 or 16. Since oxidation of (47) with permanganate gives a carbinolamine ether lactam (48) [1655 cm$^{-1}$] with the amide



46 47 48

carbonyl at C(16),[54] it is clear that C(17) is involved in ether formation in (47). A second parallel series of transformations involving the methiodide (49) is more convincing since the products are more closely related to ajaconine.[47] Conversion of (49) to (50) with cold base and subsequent oxidation with manganese dioxide gave the



49. 1685 cm$^{-1}$; pKá 10·5 50 pKá 10·6 51

hydroxyl-free $\alpha,\beta$-unsaturated ketone (51), p$K_a'$ 9·0, 1706 cm$^{-1}$, $\lambda_{max}$ 222 m$\mu$ ($\varepsilon$6840). Since base 50 and ajaconine have identical p$K_a'$ values (10·6) and equal rotations, it is reasonable to believe they are analogous compounds.

The fact that the carbinol amine ethers (47) and (50) are not isomerized by alkali to C(16)—O—C(9) ethers led Edwards to postulate that the driving force for the atisine-isoatisine type isomerization is the relief of steric compression between the C(17) oxygen and the 5(H) atom.[47] While this explanation has some validity it will be shown later to be incapable, by itself, of accounting for the sizable free energy difference between atisine and isoatisine (see p. 91).

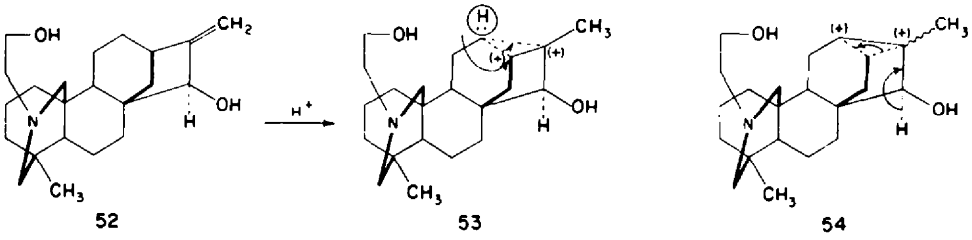
## V. THE CORRELATION OF THE ATISINE AND GARRYA ALKALOIDS

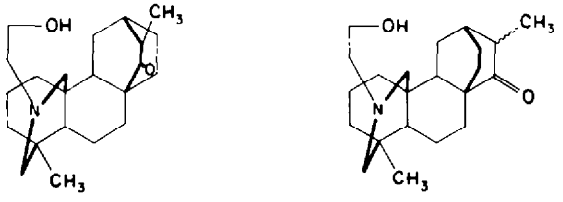
In a recent review Wiesner recounts an attempted correlation of the Garrya alkaloids and atisine by vigorous acid isomerization of dihydroveatchine.[55] It was

[54] Formation of a 17-carbonyl group by intermolecular oxidation is not possible because of the inaccessibility of the 17-hydrogen atom [facing C(19)].[47]

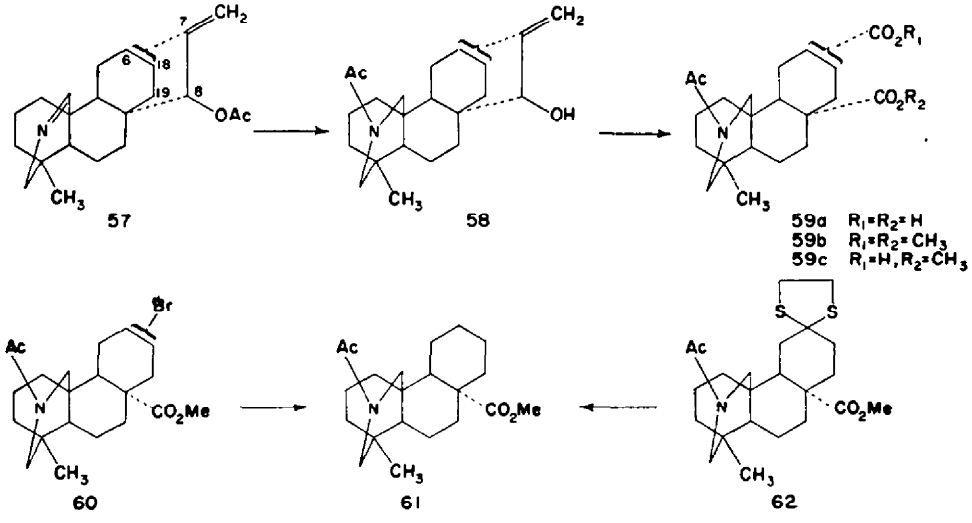
[55] Reference 4, page 52.

anticipated that the bridged cation (53) formed by protonization of dihydroveatchine (52) might be slowly transformed by a hydride shift to bridged cation (54) which could then ketonize as indicated to give "tetrahydro-ketoisoveatchine" (55). If atisine has the stereochemistry in the C/D rings predicted by Wenkert's biogenetic




scheme,[56] compound (55) should be identical with "tetrahydro-ketoatisine". Isomerization of dihydroveatchine under vigorous acidic conditions did indeed give a ketone (carbonyl frequency characteristic of a cyclohexanone) which was tentatively concluded to have structure (55). However, comparison with an authentic sample of "tetrahydro-ketoatisine", showed the compounds were *not* identical. Wiesner points out the uncertainty of the structure assigned to "tetrahydroketoisoveatchine", but suggests that the simplest interpretation of this work would be the assignment of structure (55) to "tetrahydro-ketoisoveatchine" and structure (56) to "tetrahydro-ketoatisine".[55] This would mean that if atisine has the usual *trans-anti* backbone




[56] E. Wenkert, *Chem & Ind.* 282 (1955).

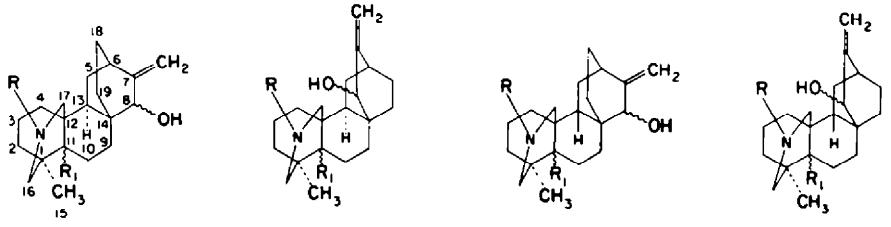
common to most diterpenes, the allylic alcohol would occupy the *cis* bridge (with respect to nitrogen) of the bicyclo-(2,2,2)-octane system. However, our own results[38] and those of Edwards[25] clearly indicated otherwise, so it was of interest to effect a correlation of atisine and the Garrya alkaloids by a less ambiguous procedure. This was accomplished by converting both atisine and veatchine, by a parallel sequence of degradations, to the same N-acetyl ester (61).[28] The respective azomethine acetates (57) derived from atisine [C(7)—C(6) bond] and veatchine [C(7)—C(18) bond] were converted to the N-acetyl derivatives (58) by reduction, acetylation and saponification. Oxidation of (58) with permanganate-periodate under carefully controlled conditions gave the respective dicarboxylic acids (59a). Saponification of the dimethyl esters (59b) gave (59c) which were transformed to the monobromides (60) utilizing the Hunsdiecker reaction. Reductive debromination of (60) with zinc in acetic acid gave (61). Compound (61) was also obtained from atisine by another route. Desulfurization of the thioketal (62) derived from (19)[25,58] gave a product identical with (61.)[57]

The formation of (61) from both atisine and veatchine demonstrates that these compounds as well as the related alkaloids, garryfoline,[59] atidine[46] and ajaconine,[47] all have the same stereochemistry.

## VI. STEREOCHEMISTRY OF THE ATISINE AND GARRYA ALKALOIDS

### A. *The carbon skeleton*

It has been common to assume that alkaloids of the atisine and veatchine types have the *trans-anti* skeleton which is common to most diterpenes, though until recently no evidence supporting this assumption was available.[23,25,38,59] *A priori*, eight *dl*-pairs, of which four are A/B-*trans*-isomers (63 a–d) and four are A/B-*cis*-



(63a) $R_1$ = α-H, (64a) $R_1$ = β-H (63b) $R_1$ = α-H, (64b) $R_1$ = β-H (63c) $R_1$ = α-H, (64c) $R_1$ = β-H (63d) $R_1$ = α-H, (64d) $R_1$ = β-H

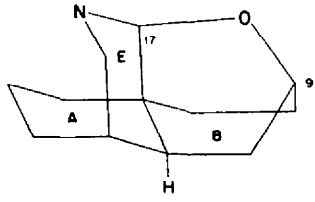
isomers (64 a–d), are possible on the basis of the chemistry discussed thus far for atisine. The work of Dvornik and Edwards[47] on ajaconine (see p. 83) is significant relative to the stereochemistry of atisine. Their results have been utilized recently by Solo and Pelletier to define certain aspects of the stereochemistry of atisine and the Garrya alkaloids.[30] Thus briefly, the existence of an ether bridge between C(9) and C(17) of ajaconine (36)[47] and its derivatives requires that the ether oxygen and C-17 be in a 1,4-*cis-diaxial* relationship to each other on ring B. Since it can be shown that only the *cis*-perhydroisoquinoline system with an A/B-*trans*-fusion (65) satisfies this

[57] S. W. Pelletier and D. M. Locke, unpublished work.

[58] We thank Dr. O. E. Edwards for placing at our disposal the experimental directions for the preparation of the intermediate diol (17).

[59] C. Djerassi, C. R. Smith, S. K. Figdor, J. Herran and J. Romo, *J. Amer. Chem. Soc.* **76**, 5889 (1954); *Ibid.* C. Djerassi, C. R. Smith, A. E. Lipmann, S. K. Fidgor and J. Herran, **77**, 4801, 6633 (1955).

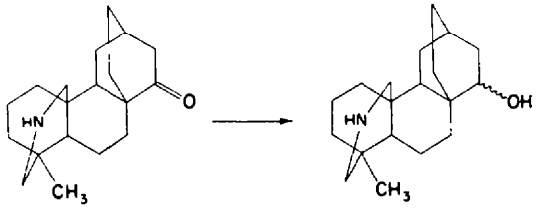
requirement, A/B-*trans*-isomers (63 a–d) remain for consideration.[30] Differentiation between isomers (63a and b), in which a *trans-anti* backbone is present, involves the choice of locating the allylic alcohol group on the *trans*-(isomer a) or *cis*-branch (isomer b) of the bicyclo [2,2,2] octane system. Reduction of ketones (66)[25] and (68)[38]



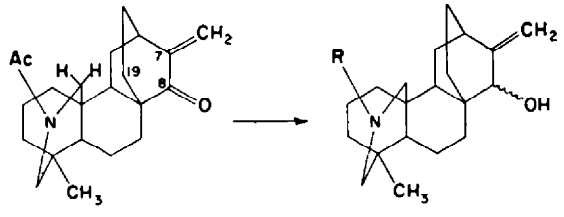

A/B-trans

65

with sodium borohydride gives in each case a pair of epimeric alcohols (67a, b and 69a, b), each of which readily forms an O-acetate. This relatively unhindered character of the hydroxyl groups supports location of the allylic alcohol group on the *trans*-bridge (isomer 63a) of the bicycloöctane system, for if the group were on the *cis*-branch (isomer 63b) only one epimer would be expected on reduction due to the severe crowding at C(19). Moreover, this view is confirmed by a study of the epimeric N-ethyl compounds (70a and b) and their $pK_a$'s.[38,42]

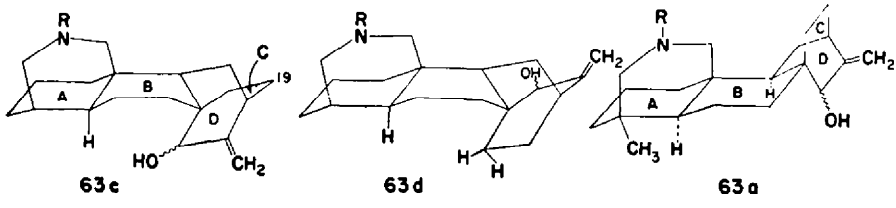



66 67 a,b



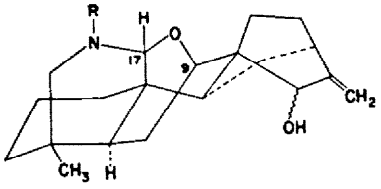

68 69 a,b, R = Ac
70 a,b, R = Et

The choice between isomer (63c) and (63d) of the *trans-syn*-perhydrophenanthrene system may be made by noting that the condition of relatively unhindered hydroxyls in (67), (69) and (70) is met only in (63d), but not in (63c). Thus the above arguments rigorously limit the stereochemistry of atisine to either (63a) or (63d).[30]




63c 63d 63a

Differentiation between 63a and 63d is possible on the basis of two observations from ajaconine chemistry:[30] i, a very large negative shift in rotation accompanies formation of the C(9)—C(17) oxide bridge and ii, spectral data show that the hydroxyl derived by opening the C(9) oxygen of ajaconine is *equatorial*.[47] If isomer (71) represents ajaconine, the open form (72) may be pictured as having ring B as a chair with an equatorial hydroxyl at C(9) which is transformed to a boat in the closed form. Since a major conformational change is involved in this transformation, one would expect a dramatic shift in rotation—which is in fact noted.

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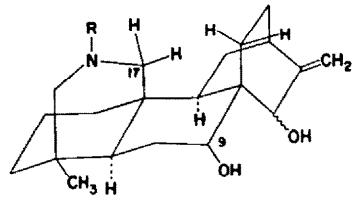
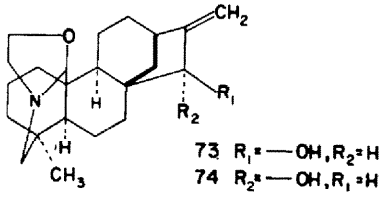



72

If, however, ajaconine has the stereochemistry of isomer (63d), the hydroxyl at C(9) must be pseudo-axial to be able to bridge to C(17). But the C(9) hydroxyl is known to be equatorial.[47,49] Furthermore, formation of an ether bridge between C(9) and C(17) would merely distort, but not invert ring B, thus not accounting for the observed rotation shift. Finally, the required bond distortion would create severe strain in the bicycloöctane system. For these reasons, it is clear that ajaconine and therefore atisine and atidine can have only the ABD *trans-anti-trans* skeleton of (63a).[30] Since veatchine and garryfoline have been correlated with atisine[28] they have the same stereochemistry and may be represented by structures (73) and (74) respectively.



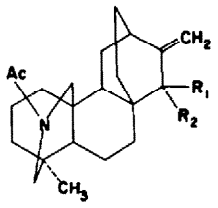

73 $R_1$ = —OH, $R_2$ = H
74 $R_2$ = —OH, $R_1$ = H

B. *The configuration of the allylic hydroxyl in atisine*

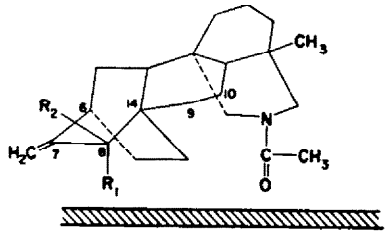
The tentative assignment of the allylic hydroxyl in atisine was originally made on the basis of the marked difference in absorption behavior toward alumina of the epimeric alcohols (75a) and (75b). Since models suggest that a hydroxyl with the configuration as in (75a) (OH *cis*- to nitrogen) is slightly more shielded than (75b), the less firmly bound epimer (with the natural configuration) was assumed to be (75a).[39] However, the difference in steric environment seems too small to account for the great difference in absorption behavior of these compounds. Further consideration[60] reveals that in isomer (75a), the hydroxyl and N-acetyl group are so oriented that they may be absorbed simultaneously on the alumina surface. This may most clearly be seen by viewing the molecule along the plane described by atoms C(6), C(7), C(8), C(14), C(9) and C(10) as shown below. In isomer (75b) the hydroxy land N-acetyl

[60] S. W. Pelletier and D. M. Locke, unpublished observation.

group are on opposite sides of the molecule and therefore cannot be absorbed by the alumina at any given time. The more strongly absorbed isomer must be (75a) in which hydroxyl and N-acetyl absorption reinforce each other. Atisine, which has the



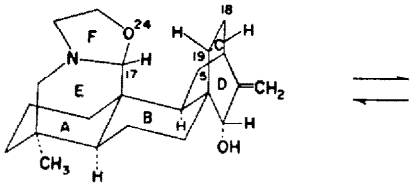
75a $R_1$ = OH, $R_2$ = H
75b $R_1$ = H, $R_2$ = OH



configuration of the less strongly absorbed of the two isomers, must be represented by the configuration of (75b). Since atidine and ajaconine have been correlated with dihydroatisine,[27] the allylic alcohol group in these compounds would also have the α-configuration as in (75b). It is interesting to note that the allylic hydroxyl in garryfoline also has the α-configuration.[59]

C. *The conformation of the E/F rings in atisine*

There remains the question of the steric arrangement of the E and F rings of atisine (76) and its bearing on the atisine-isoatisine type of isomerization.[61] The



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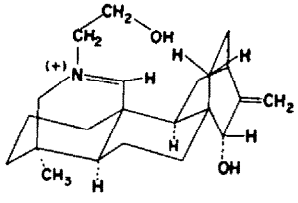
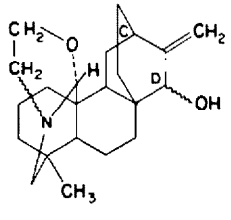


77

piperidine ring E of atisine could in principle exist in either a boat or chair conformation and, to each of these, ring F could be fused so as to give two *cis*-forms and one *trans*-form, giving a total of six conformers. Three of these may be eliminated by the following argument. Very great hindrance is known to exist between the 17-methylene group and the C(18)—C(19) bridge of atisine (76).[15b,20] Since the oxazolidine ring may be reformed easily from derivatives in which C(17) is trigonal (77),[20] the 24



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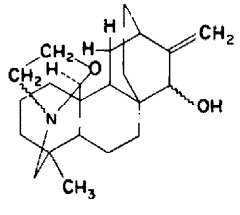
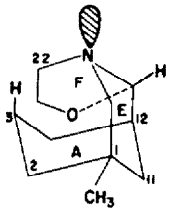


79

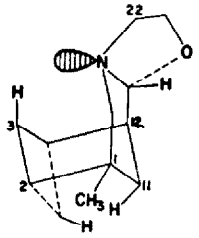
oxygen atom in atisine must be substituted on the less hindered side of C-17—i.e. the side away from ring C (formula 78). The three conformers corresponding to 79 are thereby eliminated.[61]

[61] A. J. Solo and S. W. Pelletier, *Proc. Chem. Soc.* 14 (1961).

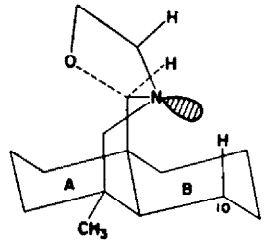
The conformers, (X,Y,Z), corresponding to (78) may now be considered. Conformer (X) in which ring-A is a chair with C(22) axial is unlikely since the A and F rings are strongly opposed. The free electron pair on nitrogen is hindered by a hydrogen on C(3) in conformer (Y) and by a hydrogen on C(10) in conformer (Z). The interaction at C(3) in (Y) is relieved with ring A as a boat but such a change introduces new interactions. It should be noted that with either form the ring system of atisine must be distorted so as to accommodate the very serious interactions between rings C and E. This distortion has the effect of relieving the N—$H_{C(10)}$ interaction in (Z) but of increasing the interaction of the hydrogen atoms in the flagpole positions of boat A in (Y). Moreover, the the five-membered F-ring is *trans*-fused to E in (Y) and this tends to distort E in such a way as to increase the hindrance encountered by the nitrogen. In rotamer (Z), however, the *cis*-fused E/F junction tends to relieve the interaction suffered by nitrogen with the hydrogen on C(10). Finally, as will be shown below, the oxygen of oxazolidine ring-F is seriously hindered in (Y) but is not in (Z). Therefore, these factors indicate that conformation (Z) should be at least as stable as (Y).[61]




78x




78y




78z

It has been noted that conversion of C(17) in atisine derivatives from a quaternary to a trigonal form results in a considerable decrease in strain.[4] This reduction in steric hindrance provides the accepted explanation for the high $pK_a$ of atisine (12·8)[20] and also provides a reasonable explanation for the fact that the diacetate of isoatisinium chloride is readily isomerized to the corresponding atisine derivative.[21] Since both atisine and isoatisine have quaternary C(17) groups, it is necessary to look further for the reason for the facile isomerization of atisine to isoatisine, or in other words for the greater stability of isoatisine over atisine (a free energy difference of at least 3 kilocalories is required).[62,63] Dvornik and Edwards have explained the stability difference on the basis of an interaction between the C(24) oxygen of ring-F and the C(5)-hydrogen which occurs in atisine, but not in isoatisine.[47] This interaction may be observed in models of rotamer (Y), but not in (Z). To the extent that steric strain results from this interaction, rotamer (Z) should be favored over (Y). Therefore

[62] A. J. Solo and S. W. Pelletier, unpublished work.

[63] The statement that $\Delta F$ for the atisine-isoatisine conversion equals 3 kcal minimum assumes that at 25°C the equilibrium atisine ⇌ open form lies at least 93 per cent toward the open form and that in refluxing ethanol the open form is converted at least to the extent of 91 per cent to isoatisine.

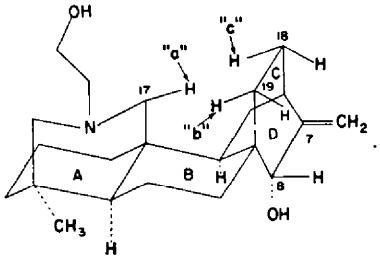
Thus $\Delta F = RT \ln K = 4{\cdot}58 \times 298 \log 93/7 = 1{\cdot}52$ kcal.

and $\Delta F = RT \ln K = 4{\cdot}58 \times 338 \log 91/9 = \dfrac{1{\cdot}56 \text{ kcal.}}{3{\cdot}08 \text{ kcal.}}$

If the equilibria lie less far to the right than assumed, $\Delta F_{min}$ must be reduced, but it will certainly be far more than the 0·4 kcal which Edwards' O(24)—C(5)H interaction makes available through entropy factors, (see footnote 64).

unless (Z) can be shown to be less stable than (Y), this interaction by itself cannot explain the free energy difference between atisine and isoatisine.[64]

If dihydroatisine (80) is constructed using Dreiding[65] or other models in which atoms have no bulk, but in which the bonds are rigid, tetrahedral angles are preserved, free rotation about single bonds is possible and covalent bond distances are correct; then, hydrogen "a" on C(17) may be seen to be strongly hindered by hydrogens on the C(18)—C(19) bridge. Depending on the staggering of the bicycloöctane system, the distance between hydrogen "a" and hydrogen "b" on C(19) varies from 1·26 to 1·38 Å, while the distance between "a" and "c" varies from 1·27 to 1·66 Å—all without introducing angular strain.[62] These distances are all well under the required internuclear separation of approximately 2·4 Å (2 × the van der Waals radius of hydrogen = 2 × 1·2 Å). Since the energy required to deform bond angles of a molecule is always less than the energy gained by moving interfering groups apart,[66] the steric compression of hydrogen "a" will be accommodated by distortion of the dihydroatisine ring system. To relieve the steric hindrance, it is necessary that the bonds from the perhydrophenanthrene system ABD to C(18) and C(19) should bend away from the bond to C(17) and vice-versa. (Formula 80). While the greater part of the indicated accommodation undoubtedly affects mainly the B—C—D system, movement




80

of C-17 is also important. The motion which C-17 may undergo involves bending away from ring C and rotating in such a way as to make the axial bond on C-17 even more axial and the equatorial bond—more equatorial.

This rotation of the C-17 group is in the direction opposite to that which would be required to form the (angular strain-free) conformer (78Z) of atisine. In isoatisine C-17, not being part of the oxazolidine system, is free to undergo essentially the same rotation as it undergoes in dihydroatisine. The greater free energy of atisine as compared to isoatisine may therefore be attributed to the increased steric hindrance in atisine caused by the restriction which ring F imposes on the rotation of C-17. The steric compression is of course still accommodated by the distortion of the molecule as a whole, but the net effect is an increase in bond distortion with a concomitant increase in energy.[61]

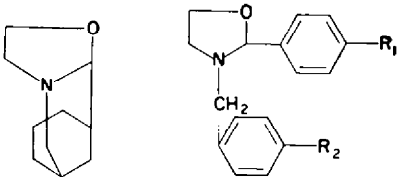
Leonard has recently studied the isomerization of a tricyclic oxazolidine model of

[64] Position C(16) is relatively unhindered, therefore in isoatisine the oxygen of ring F may be attached to either side of ring E. This extra degree of freedom should permit an extra conformer (ring-E as a chair with C(22) equatorial but with *cis*-E/F-fusion) to exist in isoatisine. The resulting increase in entropy for isoatisine could contribute a maximum of approximately 0·4 kcal. (RT ln 2) toward increasing the stability of isoatisine over atisine.

[65] A. S. Dreiding, *Helv. Chim. Acta* **42**, 1339 (1959).

[66] F. H. Westheimer, *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) Chap. 12. John Wiley, New York (1956).

the AEF-ring system of the diterpene alkaloids, viz. 6-aza-3-oxatricyclo [6.3.1.$0^{2,6}$] dodecane (81).[67] Isomerization of this model, in which there is no steric driving



81



82a $R_1 = H, R_2 = OCH_3$

82b $R_1 = OCH_3, R_2 = H$

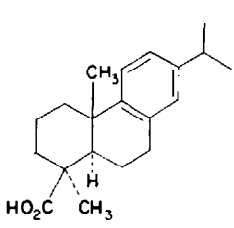
force to rearrangement of the oxazolidine ring, required more strenuous conditions than atisine, veatchine or garryfoline. In another model system of the arylaralkyl-oxazolidine type (82a,b) in which there was no steric differentiation between the two $\alpha$ N-carbons but in which the protons on these carbons were more acidic than in the diterpene alkaloids, isomerization did not occur under conditions which lead to formation of the "iso" alkaloids. These findings indicate that isomerization of ternary iminium compounds is not a general phenomenon but is very dependent upon steric factors and reaction conditions. Incidental to this study a new method of oxidative cyclization for the synthesis of oxazolidines from $\beta$-3° aminoalcohols was developed using mercuric acetate. A detailed subsequent study showed that mercuric acetate oxidation of several piperidino- and pyrrolidino-alcohols gave good yields of bicyclic oxazolidines and tetrahydro-1,3-oxazines.[68]

D. *Absolute configuration*

The absolute configuration of the atisine alkaloids has not yet been settled but the scanty evidence available suggests that atisine bears a mirror image relationship to that of the common diterpenes and hence to the above formulas.[25] Thus the phenol (20) derived from atisine shows a strong negative rotation ($M_D$-314°) whereas the molecular rotations of dehydroabietic acid (83), ferruginol acetate (84) and podocarpic acid (85) are strongly positive. For this reason the atisine phenol has been assigned the configuration shown in formula (86).[25] The fact that lycoctonine and aconitine have been shown to have a configuration antipodal to the common diterpenes[69] is in agreement with this assignment.

*Note added in proof:* Djerassi and Vorbrüggen (private communication) have recently converted the azomethine from garryfoline to a hydrocarbon via the aldehyde analogous to (28b). This hydrocarbon is not identical with either $\alpha$- or $\beta$-dihydrophyllocladene. Since the rotatory dispersion curves of ring-D ketones of garryine are substantially identical with those of the corresponding ketones of the phyllocladene series, these workers conclude that the absolute configuration of the A/B ring juncture in the alkaloids is antipodal to that of the steroids and common diterpenes.

[67] N. J. Leonard, K. Conrow and R. R. Sauers, *J. Amer. Chem. Soc.* **80**, 5185 (1958).
[68] N. J. Leonard, and W. K. Musker, *J. Amer. Chem. Soc.* **82**, 5148 (1960).
[69] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1843 (1959).

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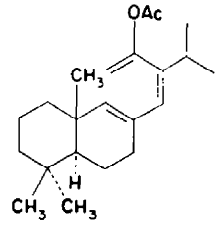


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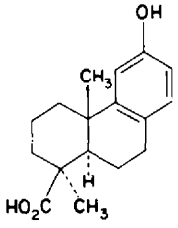


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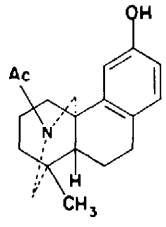


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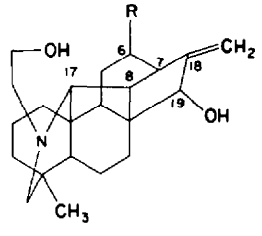
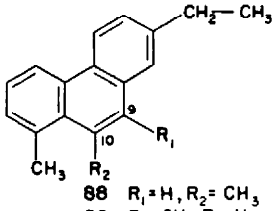
## VII. NAPELLINE AND SONGORINE (NAPELLONINE)

As a result of a careful series of investigations, Wiesner was led to assign structure

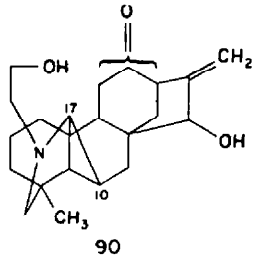



87

(87) to napelline (R = – – –OH) and napellonine (R = O).[70] Subsequently, Kuzovkov showed the identity of napellonine and songorine and that selenium dehydrogenation of the latter gave a trisubstituted phenanthrene which was identified by synthesis as 1,10-dimethyl-7-ethylphenanthrene (88).[71] He pointed out that this result confirmed the presence of a substituent at the C(1) position and the joining of the five-membered ring at C(7), but made improbable a bond between C(17) and C(8). Instead, bonding from C(17) to C(10) was suggested and structure (90) proposed for songorine[71,72].



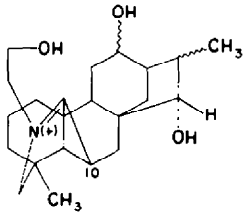

88 $R_1$ = H, $R_2$ = $CH_3$
89 $R_1$ = $CH_3$, $R_2$ = H




90

[70] K. Wiesner, Z. Valenta, J. F. King, R. K. Maudgal, L. G. Humber and S. Itô, *Chem. & Ind.* 173 (1957).
[71] A. D. Kuzovkov, *J. Gen. Chem.* **28**, 2320 (1958). English translation.
[72] A. D. Kuzovkov, *J. Gen. Chem.* **29**, 1706 (1959). English translation.

Wiesner pointed out the incompatibility of this structure with formation of a carbinolamine ether from dihydronapelline by oxidation with silver oxide.[4,73] Thus it is clear that a C(17)—C(10) bond in the salt form of the carbinolamine ether (91) is impossible. Subsequently, Wiesner *et al.* showed that formation of glyoxal by oxidation with lead tetraacetate is not a specific reaction for the N—$CH_2CH_2OH$ group and that napelline contains an N-ethyl group.[4,73] The carbinolamine ether was then formulated by Wiesner as (92) and its salt as (93),with a C(17)—C(10) bond. Other



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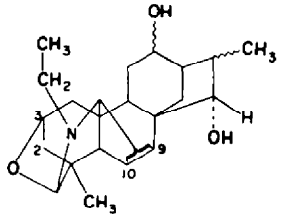

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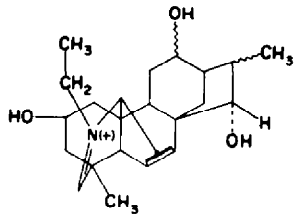


93

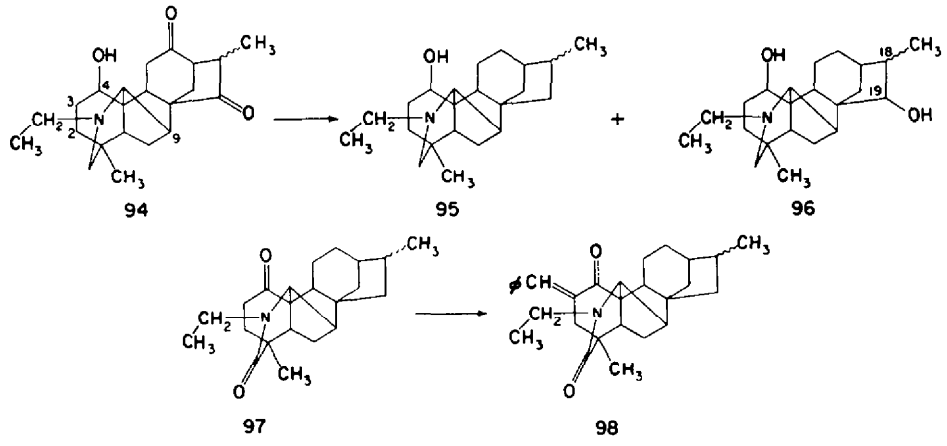
sites for the location of the ether oxygen are of course possible at C(2) or C(4). In considering an alternative and biogenetically more plausible structure for songorine, Wiesner made the attractive hypothesis that rearrangement of the 10-methyl group into the less hindered 9-position had occurred in the last step of Kuzovkov's synthesis of 1,10-dimethyl-7-ethylphenanthrene. The "natural" phenanthrene should then be 1,9-dimethyl-7-ethylphenanthrene (89) and songorine would possess a C(17)—C(9) bond.[4,73] This perceptive suggestion has been shown to be correct by Ochiai *et al.* who have demonstrated that the songorine hydrocarbon is in fact (89) by unambiguous syntheses.[74] It is interesting to note that (89), as well as a small amount of 1,3,9-trimethyl-7-isopropylphenanthrene, is also obtained by the dehydrogenation of isodesoxysongorine (100) hydrochloride.[75,76]

Recently Sugasawa has questioned the assignment of a hydroxyl at C(3) in songorine and in fact has accumulated rather compelling evidence for location of a hydroxyl at C(4).[76,77] This evidence will now be outlined.

Isosongorine (94), [1736, 1695 $cm^{-1}$], available from the allylic rearrangement of songorine with palladium charcoal, gave on Huang-Minlon reduction dideoxyisosongorine (95) and a small yield of the glycol (96) [3310–3500 $cm^{-1}$]. Oxidation of (95) with an excess of chromium trioxide-pyridine gave a neutral product which was formulated as a keto $\delta$-lactam (97) [1707, 1635 $cm^{-1}$]. The latter gave a compound containing 1·82 atoms of deuterium when equilibrated in the presence of NaOD, MeOD and $D_2O$ and an amorphous monobenzylidine derivative (98) as judged by ultraviolet absorption (300 m$\mu$, log $\varepsilon$, 4·73),[77,78] (98 in contrast to 97 gave a negative Zimmerman reaction). These results indicate the presence of one methylene group adjacent to the keto function and consequently limit the site of the hydroxyl in songorine to either C(2) or C(4).

Isodeoxysongorine (100), prepared by isomerization of deoxysongorine (99), on

[73] K. Wiesner, S. Itô and Z. Valenta, *Experientia* **14**, 167 (1958).
[74] E. Ochiai, T. Okamoto, S. Sakai, T. Sugasawa and T. Onouchi, *Chem. & Pharm. Bull.* **7**, 542 (1959).
[75] T. Sugasawa, *Chem. & Pharm. Bull.* In press.
[76] We thank Dr. Sugasawa for giving us manuscripts prior to publication in which these results are presented.
[77] T. Sugasawa, *Chem. & Pharm. Bull.* In press.
[78] The monobenzylidine derivative of cyclohexanone shows absorption at 290 m$\mu$ (4·05) while the dibenzylidine derivative shows absorption at 330 m$\mu$ (4·40).

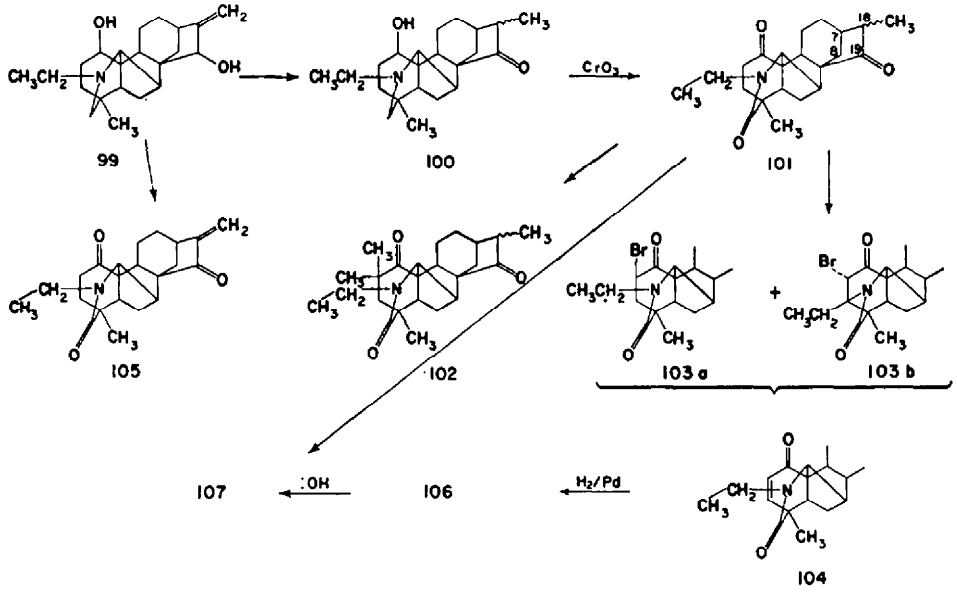


94 95 96

97 98

oxidation with chromium trioxide–pyridine gave the diketo lactam, (101), [1733, 1713, 1633 $cm^{-1}$]. Treatment of the latter with methyl iodide and potassium t-butoxide in t-butanol afforded a gem-dimethyl derivative (102) [1733, 1698, 1638 $cm^{-1}$] which unlike (101) did not form a benzylidine derivative. Bromination of (101) in glacial acetic acid gave a pair of epimeric ketones [(103a), 317 m$\mu$ (2·81); (103b), 299 m$\mu$ (2·11)]. Both bromides showed absorption at 1720 $cm^{-1}$. Dehydrohalogenation of the mixed bromides with lithium chloride in boiling dimethylformamide gave a product (104) with spectral properties characteristic of an $\alpha,\beta$-unsaturated ketone in a six-membered or larger ring (1738, 1668, 1638 $cm^{-1}$). Evidence that bromination had occurred in ring A and not ring D was provided by oxidation of (99) to a neutral product (105) containing the conjugated enone in the five-membered D-ring. [1710, 1725, 1640 $cm^{-1}$; 233 m$\mu$ (4·17); 295 m$\mu$ (2·06)].

It appears that dehydrohalogenation of (103) in the presence of lithium chloride is accompanied by partial epimerization of the methyl group at C(18), for reduction of



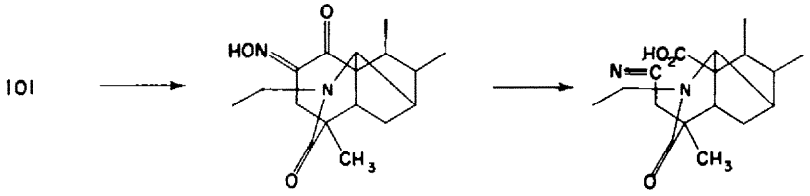
99 100 101

105 102 103a 103b

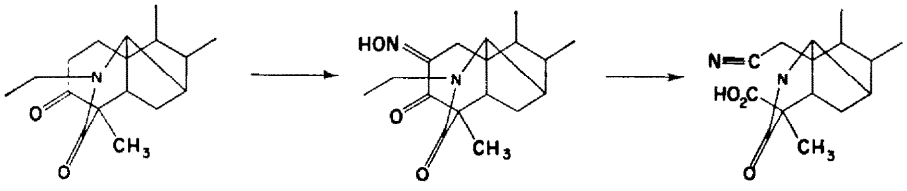
107 106 104

the product (104) over palladium gave a mixture of products [(106), 1733, 1635, 1713 $cm^{-1}$], which was not identical with (101). However, treatment of both (101) and (106) in methanolic sodium hydroxide gave the same equilibrium mixture of epimers, (107), as judged by the usual criteria.

To ascertain whether the hydroxyl in ring A is situated at C(2) or C(4), the diketo-lactam (101) was reacted with isoamylnitrite to give the isonitroso derivative (108) and the latter was cleaved with benzenesulfonyl chloride and alkali to the nitrile [(109), 2260 (—C≡N), 2500–2700 ($CO_2H$), 1730 (CO in 5-ring and $CO_2H$), 1612, 1630, $\rangle N-C=O---HO-\underset{|}{C}=O$ and $\rangle N-\underset{|}{C}=O$]. Since the latter was stable up to its melting point (185°) and did not decarboxylate when boiled in ethanolic hydrogen chloride, it is probable that the keto function in (108) is at C(4). Had it been at C(2), as represented in (110) and (111), the product of the reactions would be the malonamide (112), a type of compound which is known in the ignavine series to decarboxylate easily either when heated to 140–170° or when boiled in the presence of acid.

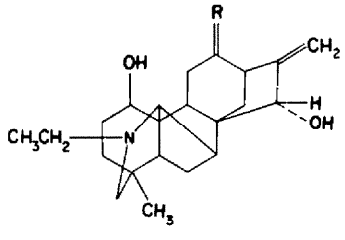



108 109




110 111 112

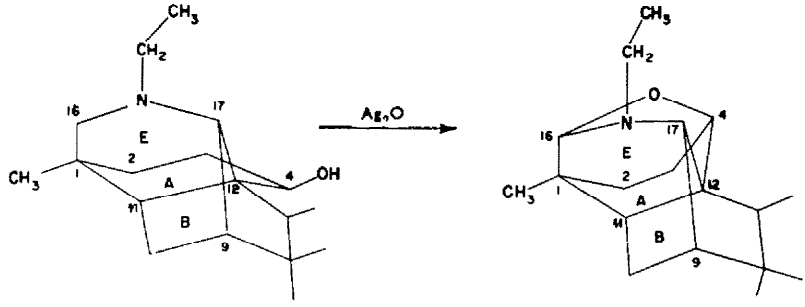
The above transformations led Sugasawa to assign the hydroxyl in ring A to C(4) and therefore songorine may be represented by (113, R = O), while napelline is the




113

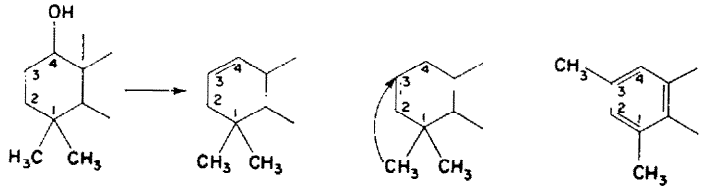
ring C equatorial alcohol (R = ---OH). In order to be able to form a carbinolamine ether by oxidation of the C(4) hydroxyl, models show that this hydroxyl must be equatorial and that ether formation is accompanied by an inversion of ring A from the chair to boat form as shown in formulas (114–115).

It must be admitted that formation of 1,3,9-trimethyl-7-isopropylphenanthrene by dehydrogenation of isodeoxysongorine (100) hydrochloride is difficult to explain on the basis of structure (113) for songorine. Sugasawa's attempted rationalization




114 115

for the formation of this hydrocarbon assumes that initial cleavage of the C(16)—N bond gives a 1-gem-dimethyl compound. Elimination of the C(4) hydroxyl as water would create unsaturation at C(3)—C(4). Under the drastic conditions of the dehydrogenation, this double bond might migrate to C(2)—C(3). One of the gem-dimethyls might then undergo a rearrangement to the allylic position at C(3). Until further evidence is forthcoming, this scheme must be regarded as purely speculative.




## VIII. THE CHEMISTRY OF HETISINE

Hetisine, $C_{20}H_{27}NO_3$, which occurs as a companion of atisine in *Aconitum heterophyllum*, was first isolated by Jacobs and Craig in 1942.[79] The alkaloid represents an unusual structural type and presents a very difficult structural problem both because of its complicated molecular architecture and because of the unusual rearrangements certain of its derivatives undergo.

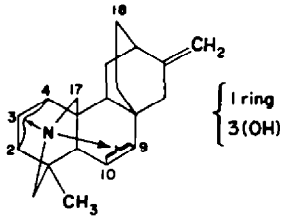
The alkaloid has one double bond which can be hydrogenated,[79] three active hydrogens,[79] a tertiary nitrogen atom and no vicinal hydroxyl groups.[80] N-alkyl and methoxyl determinations are negative.[79] The presence of an exocyclic methylene group is shown by the infrared (3003, 1659, 899 $cm^{-1}$)[81] and NMR spectra ($\tau$ = 5·28, 5·46),[62] and confirmed by the isolation of formaldehyde upon ozonolysis.[81] C-methyl determinations and infrared absorption (1379 $cm^{-1}$) indicate the existence of one C-methyl group in hetisine and two in dihydrohetisine.[42] This is confirmed by the appropriate NMR spectra ($\tau$ for C-methyl in hetisine = 9·02).[62] Since the near ultraviolet spectrum of dihydrohetisine is normal,[4] it is clear that hetisine must have a heptacyclic skeleton.

The nature of the oxygen functions is indicated by formation of a crystalline

[79] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **143**, 605 (1942).
[80] W. A. Jacobs and C. F. Huebner, *J. Biol. Chem.* **170**, 189 (1947).
[81] A. J. Solo and S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).

diacetate (3247, 1742, 1252, 1225 $cm^{-1}$) and an amorphous triacetate, both of which regenerate hetisine on saponification.[42] Furthermore, the alkaloid is inert to both periodate and lead tetraacetate[80] and does not form an acetonide.[42] Thus hetisine possesses three acetylable hydroxyls which are non-vicinal and not in a 1,3-*cis*-diaxial relationship.

Early dehydrogenation studies by Jacobs showed that hetisine gave a complex mixture of hydrocarbons and bases.[80] From the mixture a small amount of the compound identified as pimanthrene was isolated. Recent work utilizing gas phase chromatography to separate the complex dehydrogenation mixture confirms this identification.[62] Since hetisine and atisine are companion alkaloids, one would expect them to be biogenetically and structurally related. While hetisine affords pimanthrene,[62,80] atisine furnishes 1-methyl-6-ethylphenanthrene.[31,32] Dehydrogenation of an isoatisine derivative lacking the secondary allylic hydroxyl, however, gives 1-methyl-6-isopropylphenanthrene,[38] indicating that the presence of the hydroxyl alters the course of the dehydrogenation. Since hetisine gives pimanthrene, it was suspected that the substitution adjacent to the exocyclic methylene group is different than in atisine. The fact that hetisine lacks a free N-alkyl group on the nitrogen[82] and compares in basicity ($pK_a'$ 9·85) with quinuclidine (10·3) suggests a quinuclidine type structure.[62] Models show that only positions 2, 3, 4, 9 and 10 are available for bonding to the nitrogen. The data considered thus far allow one to tentatively deduce skeleton (116) containing one additional ring and three hydroxyl groups. The interest-



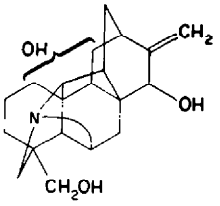

116

ing work on hypognavinol[83] provides an analogy for this kind of skeleton and also suggests bonding for the remaining ring, (see p. 107). The provisional skeleton advanced for hypognavinol on the basis of dehydrogenation data features a nor-quinuclidine type nitrogen with an extra bridge between C(17) and C(19).

At this point it will be advantageous to consider some of the older Hofmann data of Jacobs[80] since it has an important bearing on certain structural features of hetisine. Hetisine methiodide undergoes a one-stage Hofmann degradation to yield desmethylhetisine. This compound yields starting material when subjected to a second stage Hofmann degradation. Since hetisine has one double bond which can be hydrogenated, one would expect that desmethylhetisine would absorb two moles of hydrogen. However, only a dihydroderivative could be prepared. Dihydrohetisine was also found to undergo a single stage of the Hofmann degradation. The product, desmethyldihydrohetisine, unlike the isomeric dihydrodesmethylhetisine, absorbed one mole of hydrogen. It is evident that the hydrogenable double bond is the newly created one and not the exocyclic methylene. The latter has apparently suffered some kind of change.

[82] This is indicated by the Herzig–Meyer determination and N.M.R. spectrum of hetisine.
[83] S. Sakai, *Chem. & Pharm. Bull.* **6**, 448 (1958).

In an effort to explain these puzzling data, Wiesner proposed structure (117) for hetisine and (118) for desmethylhetisine.[84] To account for disappearance of the double



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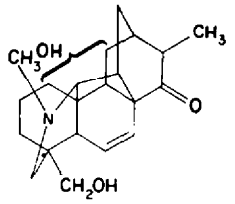
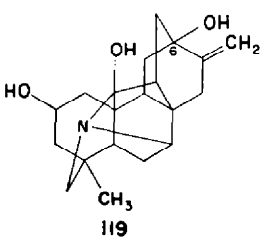


118

bond during the Hofmann degradation, an allylic rearrangement such as is known to occur readily in isoatisine[38] and garryfoline[59] was invoked. However, hetisine is known to have one C-methyl group (I.R., Kuhn–Roth, NMR) and desmethylhetisine shows no carbonyl absorption in the infrared.[42,62] Furthermore, hetisine gives mono- and dicarbonyl derivatives which are not conjugated enones.[42,81] Therefore, it cannot contain the hydroxy methylene and the secondary allylic alcohol shown in (117).

It is clear that the Hofmann data require an allylic rearrangement and therefore one of the hydroxyls must be α- to the $>C{=}CH_2$ group. Since a secondary allylic system is ruled out, the only other site for this hydroxyl is at C(6), i.e. a tertiary allylic alcohol. The remainder of the discussion of hetisine chemistry will be based on formula (119) which has been proposed recently.[81]

The degradations described above may be represented as shown in formulas (120) to (122). Hofmann degradation of hetisine methiodide (120) gives an incipient ketone



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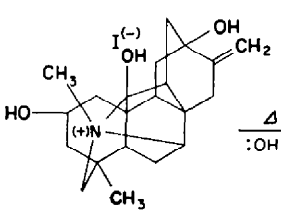

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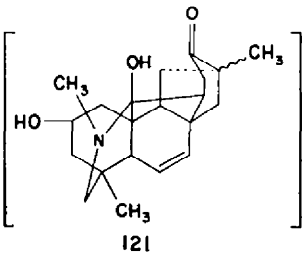

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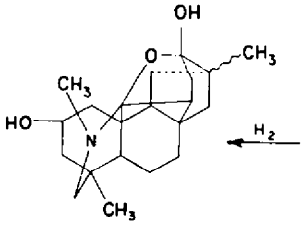

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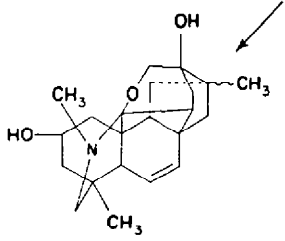
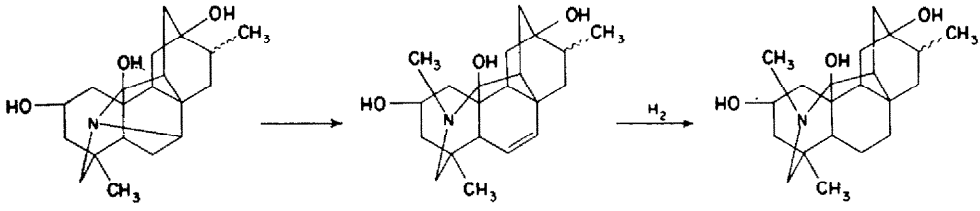


122

(121) which can participate in hemiketal formation with a suitably located hydroxyl on C(17) to give desmethylhetisine (122). The infrared spectrum of the latter shows new bands at 1143 and 1112 $cm^{-1}$ which may be ascribed to the hemiketal. The absorption of one mole of hydrogen by desmethylhetisine is also compatible with

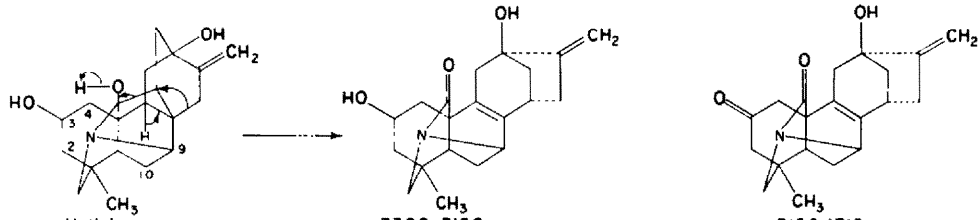
[84] Reference 4, page 62.

structure (122). Dihydrohetisine (124) on the other hand, undergoes a normal Hofmann degradation to give a product (125) absorbing one mole of hydrogen to give (126).



124 125 126

Evidence for the location of an oxygen atom at C(17) in hetisine follows from oxidation experiments with chromium trioxide in pyridine.[42] The products formulated in (127) and (128) are bicyclic lactams possessing a bridgehead nitrogen and arise from a skeletal rearrangement. Hydrolysis of (127) and (128) in base gave the respective amino carboxylates (1575 $cm^{-1}$).[81] Since this kind of system is incapable of resonance on

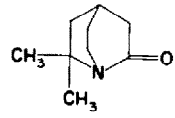


Hetisine

127: 3300, 3106, 1718, 1652 (w), 883 $cm^{-1}$

128: 3106, 1718, 1653 (w), 892 $cm^{-1}$

theoretical grounds, it would be expected to have properties of an aminoketone rather than of a lactam. In agreement with this, these compounds are basic ($pK_a'$ 8·1, 6·7 respectively), form stable hydrochlorides and methiodides, and show ketonic rather than lactam absorption in the infrared (1718 $cm^{-1}$). The first simple example of such a system is 2,2-dimethyl quinuclidone-6 (129) which is basic ($pK_a'$ 5·33), forms a hydrochloride and shows carbonyl absorption characteristic of a ketone (1733) rather than a lactam.[85,86] A comparison of the carbonyl absorption of (127) and (128) with that of 2,2-dimethyl quinuclidone-6 (1733 $cm^{-1}$) is the basis of the assignment of



129

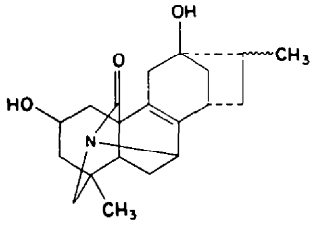
an N—C(9) bond (bicyclo-2,2,2 system) rather than a N—C(10), N—C(2) or N—C(3) bond (bicyclo-2,2,1 system) in hetisine. The latter system would be expected to show absorption in the region of a cyclopentanone.

Some evidence for the course of this unusual oxidation is available from a study

[85] H. Pracejus, *Chem. Ber.* 988 (1959).

[86] Wildman *et al.* [*J. Amer. Chem. Soc.* **80**, 2590 (1958); *Ibid.* **81**, 197 (1960)] have described a series of alkaloid oxidation products containing a quinuclidone-2 conjugated with an aromatic ring. Here too, the infrared absorption is characteristic of a cyclohexanone (conjugated with the phenyl ring).

of (128). It absorbs two moles of hydrogen to give a tetrahydro derivative (130) which shows the presence of two active hydrogens, a diminished carbonyl peak at 1704 $cm^{-1}$ and no exocyclic methylene absorption. Furthermore, NMR data indicate the absence



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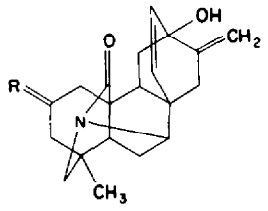
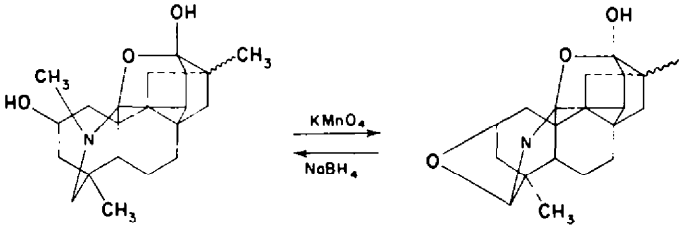


131 R = OH
R = O

of a hydrogen atom on the double bond.[62] These data rule out structure (131) which was originally suggested for these bicyclic lactams.[81,86a] It must be emphasized that though the structures proposed for these bicyclic lactams are in accord with the properties observed thus far, they are to be regarded as tentative.

Oxidation of dihydro-desmethylhetisine (123) with permanganate gave a crystalline product, $C_{21}H_{29}NO_3$, which shows weak hydroxyl absorption, but no carbonyl absorption in the infrared. Reduction with sodium borohydride regenerates starting material. The oxidation product is represented as a carbinolamine ether (132). The spectrum of the latter shows absorption at 1153, 1143, 1124 and 1103 $cm^{-1}$ which is attributed to O—C—O and O—C—N linkages. Analogy for this type of reaction is seen in the oxidation of desmethylhypognavinol with alkaline ferricyanide and dihydronapelline with silver acetate to carbinolamine ethers.[73,83,102] The third hydroxyl group is located tentatively at C(3) rather than C(4) because of the stability of the

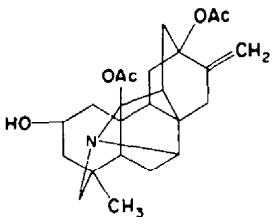



123 132

hydrolysis product from the keto-bridgehead lactam (128) [amino keto carboxylate]. If at C(4), the hydrolysis product would be a $\beta$-keto carboxylate and hence thermally unstable.

The acetylation products of hetisine require comment. The diacetate is represented as a ditertiary acetate (133) since on oxidation it furnishes a ketodiacetate (134) which may be saponified to give the parent dihydroxy ketone (1716 $cm^{-1}$; oxime). It may appear strange that two tertiary hydroxyls are acetylated in preference to a secondary hydroxyl. However, because of the bridgehead positions, the tertiary hydroxyls are relatively accessible, whereas the secondary hydroxyl is $\beta$-axial and can hydrogen bond to the nitrogen in such a way as to make acetylation difficult.

[86a] Structures 127 and 128 were first suggested on mechanistic grounds by Prof. Gilbert Stork. (Private communication).

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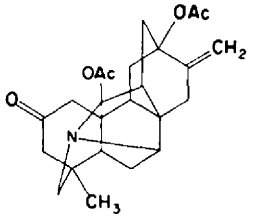



134

## IX. THE CHEMISTRY OF IGNAVINE, HYPOGNAVINE AND KOBUSINE

In recent years a wide range of *Aconitum* species native to Japan have been examined for alkaloids. Among those encountered are three, ignavine, hypognavine and kobusine which have been the subject of considerable investigation and now appear to have the same skeleton. Since most of the chemistry of these compounds has been published within the past three years, they will be covered in some detail.

### A. *Ignavine*

From the root nodules of *Aconitum sanyoense* Nakai[87], *A. tasiromontanum* Nakai[87,88] and *A. japonicum*,[89] the Ochiai school has isolated several toxic ester alkaloids and a simple-type alkaloid named ignavine. Early studies showed that ignavine, $C_{27}H_{31}NO_6$, does not contain a methoxyl, methylenedioxy, or an N-methyl group and is unreactive toward the usual carbonyl reagents. Hydrogenation with a palladium–charcoal catalyst gave a dihydroderivative. Saponification of ignavine with methanolic potassium hydroxide gives one mole of benzoic acid and an alkamine, designated as anhydroignavinol, $C_{20}H_{25}NO_4$, m.p. 302°. Methiodide formation is also accompanied by the loss of a mole of water from ignavine.[87]

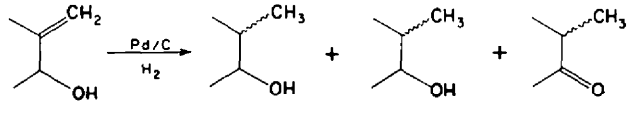
Of the six oxygens in ignavine, two occur in the benzoyloxy group and four in hydroxyls. One of these hydroxyls is on a carbon α- to that bearing the benzoyloxy group as shown by the fact that the hydrolysis product is susceptible to periodate cleavage while ignavine is not.[87] Two of the hydroxyls are acylable as is shown by the preparation of mon- and di-benzoates, di-*p*-bromobenzoates and di-*p*-nitrobenzoates.[90] These acyl derivatives are all characterized by the fact that they contain a mole of water less than would be calculated on the basis of ignavine and thus are anhydroignavinol derivatives. Saponification of these derivatives affords anhydroignavinol. It is thus evident that ignavine contains an unusual hydroxyl which on methiodide formation or acylation is eliminated as water. Early evidence was interpreted in favor of double bond formation, but recent studies favor ether formation accompanying dehydration.

Hofmann degradation of the methiodide of anhydroignavinol gives a des-N-methyl derivative, $C_{21}H_{27}NO_4$, m.p. 265–267°, which is reported to absorb one mole of hydrogen when reduced in methanol over Pd, Pt/C[90] and two moles over platinum in acetic acid.[91] Application of the Hofmann degradation to the methiodide of the

[87] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani and H. S. Hai, *J. Pharm. Soc. Japan* **27**, 816 (1952).
[88] E. Ochiai, T. Okamoto, T. Sugasawa and H. Tani, *J. Pharm. Soc. Japan* **27**, 1605 (1952).
[89] E. Ochiai, T. Okamoto, S. Sakai, M. Kaneko, K. Fujisawa, U. Nagai and H. Tani, *J. Pharm. Soc. Japan* **76**, 550 (1956).
[90] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani, S. Sakai, H. S. Hai and H. Endo, *Pharm. Bull.* **1**, 60 (1953).
[91] E. Ochiai and T. Okamoto, *Chem. & Pharm. Bull.* **7**, 556 (1959).

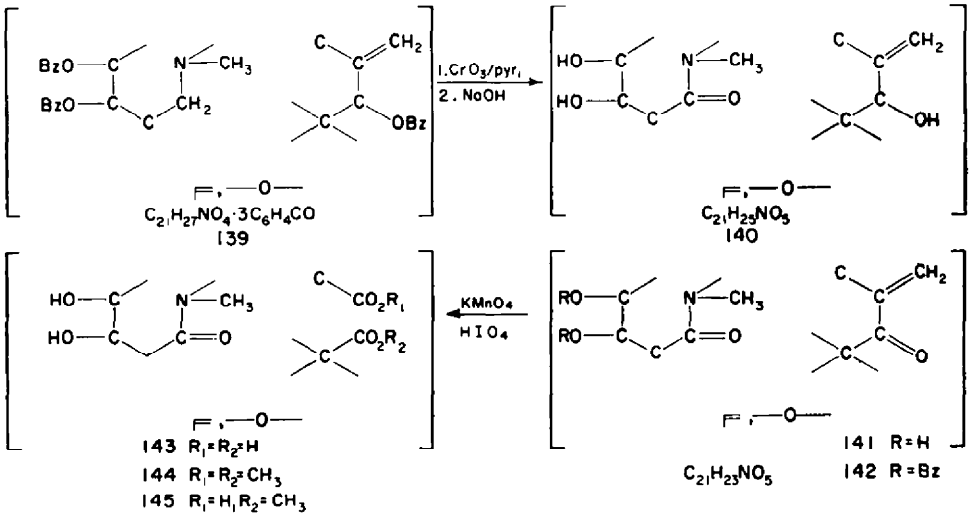
des-N-base regenerated des-N-methylanhydroignavinol. Failure to carry the Hofmann reaction through a second stage is reminiscent of the behavior encountered with des-N-methylhetisine.[80]

The presence of an exocyclic methyl group in anhydroignavine was indicated by the infrared spectrum (1645 and 892 $cm^{-1}$) and by the formation of formaldehyde on ozonization.[90] Careful study of the hydrogenation of ignavine (135) over palladized charcoal has resulted in the isolation of three different products, dihydroignavine (136), $C_{27}H_{33}NO_6$, m.p. 173°, anhydrodihydroignavine (137), $C_{27}H_{31}NO_5$, m.p. 236° and a compound assumed to be a cyclohexanone (1692 $cm^{-1}$), anhydrodihydroignavinone (138), $C_{27}H_{29}NO_5$, m.p. 260°. Formation of the latter two compounds involved the loss of a mole of water during hydrogenation. The appearance of a ketone (1692 $cm^{-1}$) among the hydrogenation products of a terminal methylene group is typical of the behavior of hypognavine[97] and kobusine[109] and involves rearrangement of an allyl alcohol system to a methyl ketone. These reactions confirm the presence of a secondary allyl alcohol system in ignavine.[92]




$C_{27}H_{31}NO_6$ 135 | $C_{27}H_{33}NO_6$ 136 | $C_{27}H_{31}NO_5$ 137 | $C_{27}H_{29}NO_5$ 138

Further operations on the secondary allylic system were carried out utilizing des-N-methylanhydroignavinol tribenzoate (139) as a substrate.[92] Oxidation of (139) with chromium trioxide–pyridine gave a lactam tribenzoate (1645 $cm^{-1}$; $\delta$-lactam) which on saponification afforded the parent $\delta$-lactam (140) [1615 $cm^{-1}$]. Further oxidation of the latter with chromium trioxide–pyridine furnished an $\alpha,\beta$-unsaturated ketone (141) with absorption bands characteristic of the conjugated enone (1615, 1687 $cm^{-1}$) and $\delta$-lactam (1590 $cm^{-1}$). Oxidation of the dibenzoate (142) with permanganate–periodate followed by hydrolysis furnished a dicarboxylic acid (143),



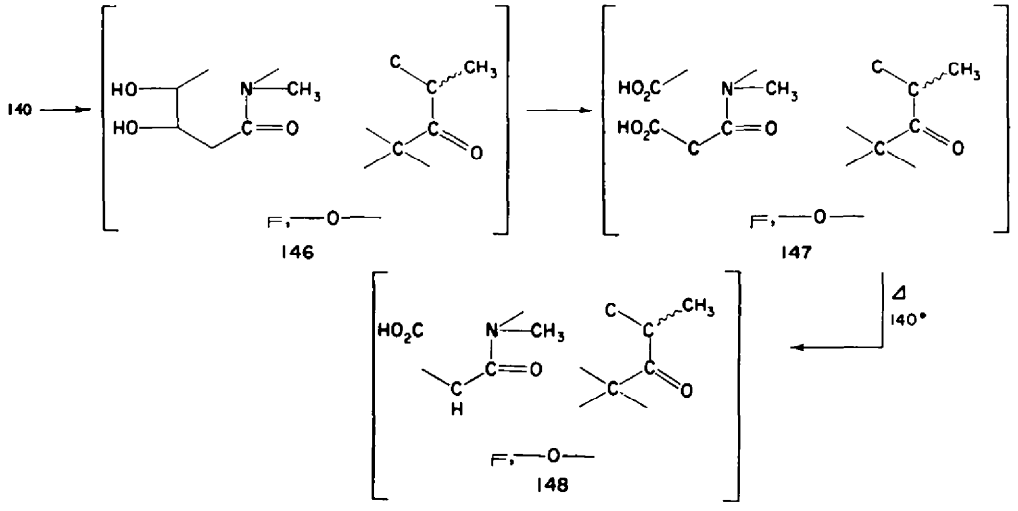

$C_{21}H_{27}NO_4 \cdot 3C_6H_4CO$ 139 | $C_{21}H_{25}NO_5$ 140 | $C_{21}H_{23}NO_5$ 141 R=H 142 R=Bz

143 $R_1=R_2=H$
144 $R_1=R_2=CH_3$
145 $R_1=H, R_2=CH_3$

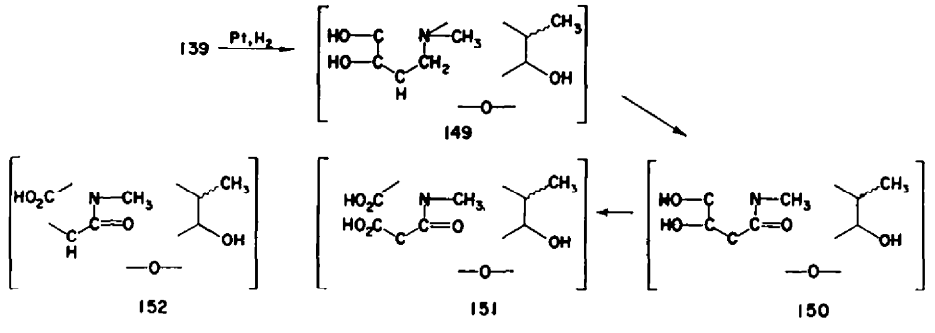
[92] E. Ochiai, and T. Okamoto, *Chem. & Pharm. Bull.* 7, 550 (1959).

(1690, 1708, 1585 $cm^{-1}$). Saponification of dimethylester (144) gave a mono-methyl ester (145) indicating one of the carboxyls in (143) is tertiary.[92]

The presence of a glycol system in (140) was demonstrated by cleavage to dicarboxylic acid (147). The exocyclic methylene group of (140) was rendered immune to oxidation by acid catalyzed rearrangement to the methyl ketone (146) (1700 $cm^{-1}$). Treatment with permanganate gave an amorphous dicarboxylic acid (147) which eliminated $CO_2$ at 140°. A parallel series of reactions was also carried out on one of




the isomeric tetrahydroderivatives (149) obtained when des-N-methylanhydrohypognavinol (139) was hydrogenated over platinum. Oxidation of (149) as the tribenzoate followed by saponification gave the $\delta$-lactam (150). Further oxidation with perman-

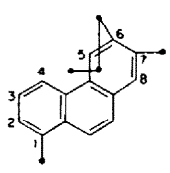



ganate gave an amorphous dicarboxylic acid (151) [1708 $cm^{-1}$, 1637 $cm^{-1}$], which again lost carbon dioxide at low temperature (140–170°) to give a monocarboxylic acid 152, (1712, 1620 $cm^{-1}$). The facile elimination of carbon dioxide suggests the presence of a malonamide moiety in acids (148) and (151) and supports the partial structure about the nitrogen atom as represented in the above formulas.[92]

Careful selenium dehydrogenation experiments on anhydroignavinol have yielded four alkyl phenanthrenes as well as alkyl benzenes and naphthalenes.[93] Two of the alkylphenanthrenes are crystalline: a $C_{19}H_{20}$ hydrocarbon, m.p. 82–84°, picrate,

[93] E. Ochiai, T. Okamoto, T. Sugasawa and S. Sakai, *Pharm. Bull. Japan* **2**, 388 (1954).

142°, TNB, 156° and a $C_{19}H_{20}$ or $C_{19}H_{18}$ hydrocarbon, m.p. 145–147°, picrate 135°, TNB, 160°. The two liquid phenanthrenes have picrates of m.p. 173–175° and 175–177°. It is a tribute to the patient and meticulous work of the Japanese workers that three of the four hydrocarbons have been recently identified by synthesis. The 82–84° hydrocarbon is 1,7-dimethyl-6-n-propylphenanthrene (153),[94] the liquid with the picrate melting at 173–175° is a 1,8-dimethyl-3-ethylphenanthrene (154)[95] and the one with the picrate melting at 175–177° is 1,8-dimethyl-3-isopropylphenanthrene (155).[95] These products account for nineteen of the twenty carbon atoms of anhydroignavinol.



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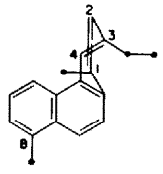

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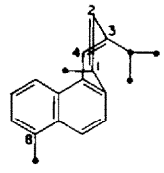

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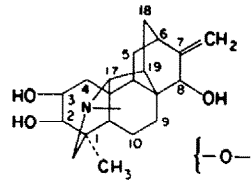


156

In view of the diterpenoid nature of the aconitum alkaloids and the demonstrated presence of an allylic alcohol system in ignavine, it is reasonable to assume the alkaloid contains a bicyclo-2,2,2-octane-allyl alcohol system such as occurs in atisine and which is shown in (156). This is given further credence by the oxidation of des-N-methyl-oxo-anhydroignavinol (140) to a dicarboxylic acid (143) in which one of the carboxyls is tertiary.[92] The dehydrogenation products (153, 154, 155) suggest a bond between C(19) and C(17) and a methyl group at C(1). Considering the partial structure involving the nitrogen which was deduced above, and the analogy to other diterpene alkaloids, one may place the nitrogen between C(16) and C(17) and hydroxyls at C(2) and C(3). Since ignavine shows no N-alkyl group, it is evident that a third bond must extend from nitrogen to one of the rings. The Japanese authors select C(10) as the most likely site. The remainder of anhydroignavine chemistry will be discussed on the basis of formula (157).

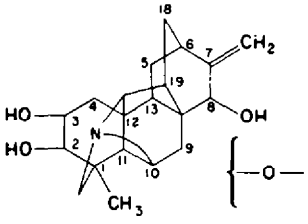
The fact that anhydroignavinol consumes one mole of periodic acid in two hours whereas ignavine is resistant to the reagent suggests that the α-glycol system which is present in anhydroignavinol is masked by the benzoyloxy group in ignavine. Oxidation of ignavine with chromium trioxide–pyridine gives a mixture of mono- and diketones. The diketone showed bands at 1708 and 1630 for the conjugated enone system and also bands assignable to a ketol benzoate at 1740 and 1722 $cm^{-1}$. Saponification gave a ketol as indicated by its behavior toward Tollins reagent and triphenyltetrazolium chloride. Location of the benzoyloxy group at C(2) rather than C(3) is suggested by the positive Zimmerman reaction given by the ketobenzoate.[91]

The published data clarify the nature of four of the six oxygens of ignavine and three of the four of anhydroignavinol. The fourth oxygen in anhydroignavinol is thought to exist as an ether since no hydroxyl band is observable in the infrared spectra of tribenzoyl anhydroignavinol, tribenzoyl-des-N-methylanhydroignavinol

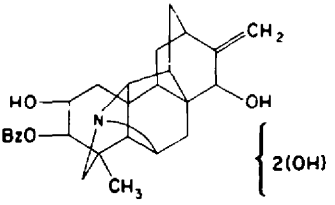
[94] E. Ochiai, T. Okamoto, S. Hara, S. Sakai and M. Natsume, *Chem. & Pharm. Bull.* **6**, 327 (1958).

[95] Personal communication from Prof. T. Okamoto. The author cordially thanks Prof. Okamoto for placing a manuscript by S. Hara and Y. Tokushige at his disposal which describes the synthesis of the two oily hydrocarbons. The pure synthetic hydrocarbons show the following constants: (154), m.p. 52–53°, TNB, m.p. 176–177·5°, picrate, 161–162°; (155), m.p. 74–76°, TNB, m.p. 182–183°, picrate, m.p. 162–163°. *Note added in proof:* The work cited has since been published in *Chem. & Pharm. Bull.* **8**, 976 (1960).

and tribenzoyl-des-N-methyl-oxo-anhydroignavinol. It is therefore probable that the loss of water accompanying many of the reactions of ignavine, e.g. saponification, reduction, acylation, involves *ether* rather than double bond formation. Possible positions for the hydroxyls involved in the elimination assuming a $\beta$-glycol moiety are, C(5–18), C(9–19), C(9–13) and C(11–13). Since ignavine has a normal $pK_a'$ value (7·7) for a tertiary amine, it seems unlikely hydroxyls could be at C(17) or C(16). In view of the above, anhydroignavinol and ignavine have been represented by partial structures (157) and (158) respectively.[91]




157




158

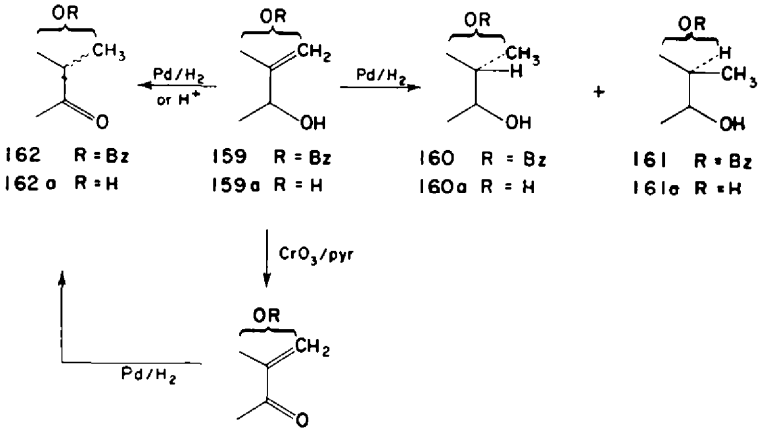
B. *Hypognavine*

Certain varieties of *Aconitum sanyoense* have been shown to contain an ester alkaloid called hypognavine which contains one less oxygen atom than ignavine and is in many respects similar to it.[96] Thus hypognavine, $C_{27}H_{31}NO_5$, is a benzoyl ester, has no methoxyl or N-methyl group, fails to react with the usual carbonyl-test reagents and contains one hydrogenable double bond. Like ignavine, it has two acylable hydroxyls and an exocyclic methylene group (1666, 895 $cm^{-1}$, ozonization gives formaldehyde).[96,97] However, in contrast to ignavine, hypognavine may be saponified to give an alkamine (hypognavinol, $C_{20}H_{27}NO_4$) without loss of a mole of water. Acylation reactions and methiodide formation are also straightforward in the case of hypognavine.[96]

The exocyclic methylene group in hypognavinol manifests the same characteristics as that in songorine and ignavine, namely partial rearrangement to a methyl ketone on catalytic hydrogenation with palladium charcoal or treatment with acids.[97] Thus hydrogenation of hypognavine (159) gave a mixture from which three products were isolated: dihydrohypognavine (160), m.p. 235°, allodihydrohypognavine (161), m.p. 252° and dihydrohypognavinone (162), m.p. 296° (1704, 1689 $cm^{-1}$). The latter was also obtained from hypognavine in small yield by heating with aqueous 10 per cent sulfuric acid. The alkamines corresponding to these hydrogenation products were obtained by alkaline saponification and can be designated as dihydrohypognavinol (160a), m.p. 302°, allodihydrohypognavinol (161a), m.p. 270°, and dihydrohypognavinolone (162a), m.p. (·HBr) 348° (1712 sh, 1701 $cm^{-1}$). The vinyl band at 895 $cm^{-1}$ was absent in all the above products. Hypognavine was oxidized to an $\alpha,\beta$-unsaturated ketone (163) in 30 per cent yield with manganese dioxide and 70 per cent yield with chromium trioxide–pyridine. The product, hypognavinone, showed absorption typical of the benzoyl group (1709, 1600, 1580 $cm^{-1}$) and conjugated enone [1705, 1630 $cm^{-1}$; $\lambda_{max}$ 231 (4·35)] and when reduced with palladium charcoal

[96] E. Ochiai, T. Okamoto, T. Sugasawa, H. Tani and S. Sakai, *Pharm. Bull. Japan* **1**, 152 (1953).
[97] S. Sakai, *J. Pharm. Soc. Japan* **76**, 1436 (1956).

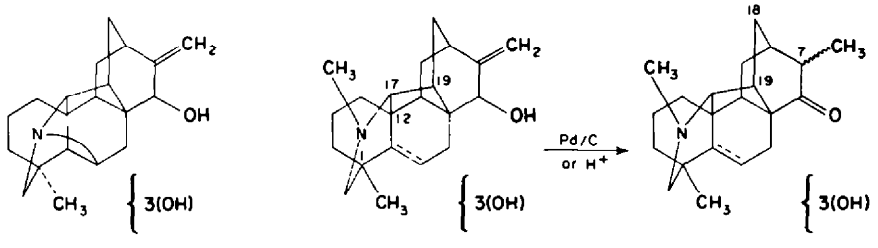
gave the known dihydrohypognavinone (162). These reactions[98] afford clear evidence for the existence of a secondary allyl alcohol system such as occurs in atisine,[25,38] ignavine,[92] and songorine.[70]




162 R = Bz; 162a R = H; 159 R = Bz; 159a R = H; 160 R = Bz; 160a R = H; 161 R = Bz; 161a R = H

163

Selenium dehydrogenation of the alkamine hypognavinol gives a small amount of 1,8-dimethyl phenanthrene,[97] 1,7-dimethyl-6-n-propyl phenanthrene[94] and 1,8-dimethyl-3-ethyl phenanthrene,[99] the latter two being characteristic products also obtained from anhydroignavinol.[95] In addition a weakly basic fraction was obtained in small yield with a ultraviolet spectrum in some respects similar to that of 3-azaphenanthrene.[100] It is therefore likely that hypognavine has the same general type of diterpene alkaloid skeleton as that derived for ignavine. The formula (164) will be used as a basis for interpreting other reactions of hypognavinol. The alternate structure with a N—C(3) bond is less probable because it does not easily explain oxidation data obtained with dihydrohypognavinone and des-N-methylhypognavinol (*vide infra*).




164 165 166

Hofmann degradation of the methiodide of hypognavinol gave a des base (165),

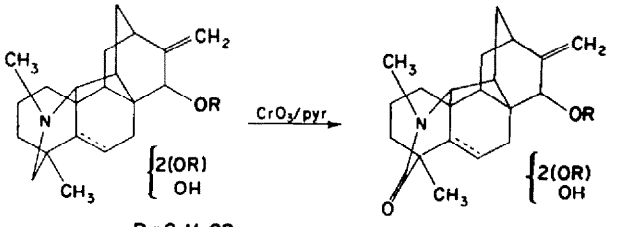
[98] The indicated configuration of the methyl groups is purely arbitrary. It is interesting to note that the ketobase hydrobromide, m.p. 346°, obtained by catalytic reduction of hypognavinol (159a) is not identical with the dihydrohypognavinolone hydrobromide (162a) obtained by catalytic reduction of hypognavine and subsequent saponification. The nonidentity is probably due to the difference in configuration of the newly formed methyl group.

[99] The author gratefully acknowledges receipt of this unpublished information from Professor Okamoto. See footnote 95.

[100] S. Sakai, *Chem. & Pharm. Bull.* 6, 448 (1958).

in 70% yield and a by-product, m.p. 225°, which has been identified as a des-N-methyldihydrohypognavinolone (166).[100,101] Des-N-methylhypognavinol on treatment with palladium–charcoal or acid undergoes an allylic rearrangement to give two isomeric methyl ketones, one of which is identical with the Hofmann by-product (166). The resistance of des-N-methylhypognavinol toward a second Hofmann degradation is well accommodated by structure (165), for the β-positions to nitrogen at C(1) and C(12) carry no hydrogen and formation of a C(17)—C(19) double bond would violate Bredt's Rule.

The size of the heterocyclic ring in (164) is indicated by oxidation of triacyl des-N-methylhypognavinol derivatives (167) to δ-lactams.[102] Thus oxidation of tribenzoyl and tri-*p*-nitrobenzoyl hypognavinol gave lactams (168) with amide absorption at 1656 and 1630 $cm^{-1}$ respectively. A similar oxidation of the triacetyl-des-N-ethyl-hypognavinol gave a lactam showing absorption at 1635 $cm^{-1}$. Saponification of the latter gave a product with amide absorption at 1614 $cm^{-1}$. All these values are within the range characteristic of δ-lactams.[103]

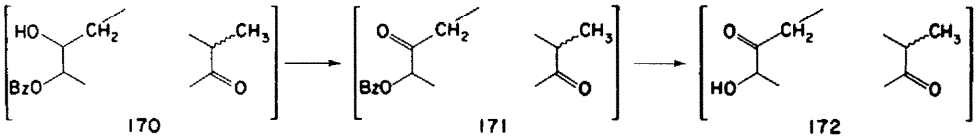



R = $C_6H_5CO$

167 R = p—$NO_2$—$C_6H_5CO$ 168

The three remaining oxygen atoms of hypognavinol exist as hydroxyl groups of which two are acylable. The nonacylable hydroxyl is tertiary since tribenzoyl hypognavinol (dibenzoylhypognavine) can be recovered unchanged from oxidation with chromium trioxide–pyridine. Oxidation of dihydrohypognavinone (170) under the same conditions gives a diketoester (171) which has a methylene group adjacent to the newly created carbonyl. (Zimmerman color reaction.) Saponification of the diketoester gave a pair of epimeric diketoalkamines (172) which undergo the usual reducing reactions for α-ketols and in contrast to the diketoester (171) consume one mole of periodic acid. It is thus clear that the new carbonyl group together with the benzoyloxy group comprises an α-ketol ester.[101]

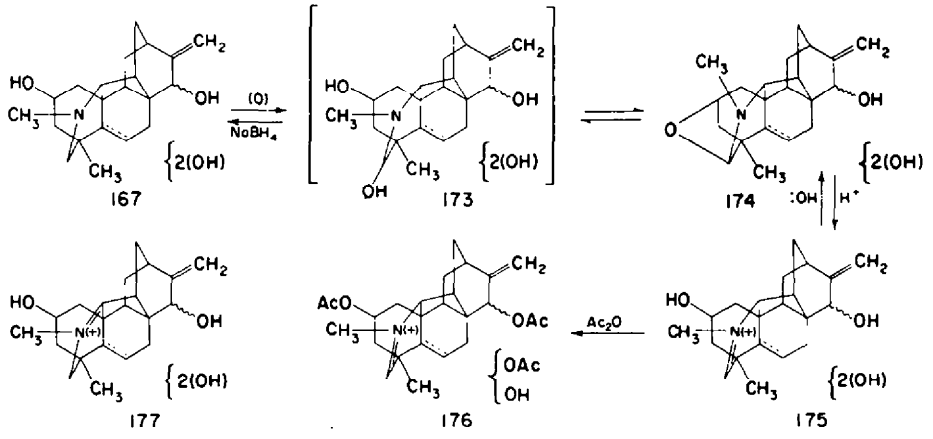
The location of this α-glycol system in ring A of the hypognavinol skeleton is provided by the following data. Oxidation of des-N-methylhypognavinol (167) with silver oxide in ether or alkaline ferricyanide affords a crystalline carbinolamine ether




170 171 172

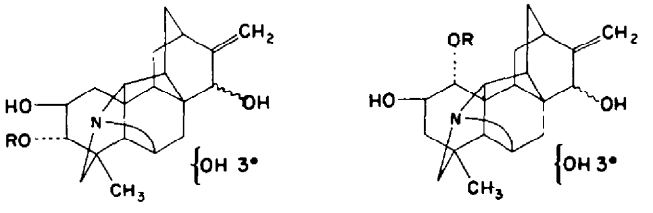
[101] S. Sakai, *Chem. & Pharm. Bull.* 7, 50 (1959).
[102] S. Sakai, *Chem. & Pharm. Bull.* 7, 55 (1959).
[103] Treatment of 169 for two hours with 50 per cent sulfuric acid at 135° gave no detectable acetic acid. Hence, the band at 1614 $cm^{-1}$ is due to lactam absorption and not an N-acetyl group.

(174), $C_{21}H_{27}NO_4$, $pK_a'$ 5·33, from which the starting material may be regenerated by reduction with sodium borohydride. Salts (175) of the carbinolamine ether show infrared absorption typical of the $>C=\overset{+}{N}<$ group (1686–1679 $cm^{-1}$) and regenerate the parent base on treatment with alkali. Acetylation of the perchlorate of (175) gives a triacetate (176) with a $pK_a'$ of 10·5 (50 per cent cellosolve). The Japanese workers explain the formation of a carbinolamine ether by assuming that oxidation proceeds initially at C(16) [or C(17)] to give 173. Subsequent elimination of water between the hydroxyl and a properly disposed neighboring hydroxyl would give the required ether. Models show that an axial hydroxyl at C(3) is most favorable for this closure. Moreover, it is to be noted that oxidation at C(17) is unlikely since the open form (salt) of




this carbinolamine ether (177) would violate Bredt's Rule. These transformations parallel the formation of the carbinolamine ether from des-N-methylhetisine and songorine and have been represented as involving an axial 3-hydroxyl group and the C(16) methylene group as illustrated.[100,102]

The question of whether the second hydroxyl of the glycol system is at C(2) or C(4) has not been settled. Since the diketoalkamines (172) consume one mole of periodate in twenty hours whereas hypognavinol and des-N-methylhypognavinol (167) require several hundred hours for the consumption of a mole of periodate or tetraacetate, it was inferred that a *trans*-glycol system is present. The benzoyloxy group in hypognavine was accordingly assigned a 2-α or 4-α configuration. The site of the tertiary hydroxyl is unknown. Hypognavine is thus represented by structure (179a) or (179b) and hypognavinol by (178a) or (178b).[102]



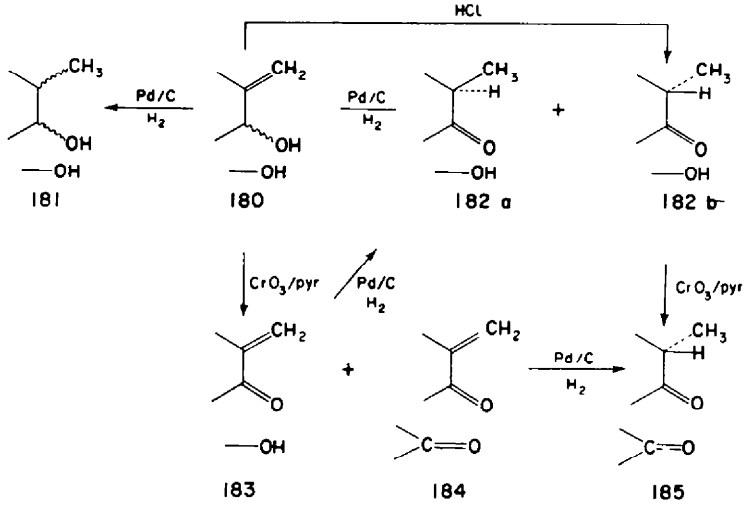

178 a, R = H
179 a, R = $COC_6H_5$

178 b, R = H
179 b, R = $COC_6H_5$

C. *Kobusine*

Though twenty years have elapsed since kobusine, $C_{20}H_{27}NO_2$, was first isolated from *Aconitum sachalinense* Fr. Schmidt by Singinome,[104,105] its structure has only recently begun to be clarified. In the early work one oxygen was shown to exist as a hydroxyl and the other thought to be in an ether linkage. The presence of one double bond was shown by hydrogenation.[108] Subsequent work by the Okamoto school has revealed many similarities between the chemistry of kobusine and ignavine and hypognavine and allowed the skeleton to be derived with reasonable certainty.[109,110]

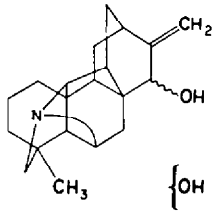
The later work has demonstrated the presence in kobusine of a secondary allyl alcohol moiety (180) (1648, 888 $cm^{-1}$) such as is common to atisine, ignavine and hypognavine. Thus reduction over palladium–charcoal gave dihydrokobusine (181) and two isomeric ketones, α-dihydrokobusinone (182a) and β-dihydrokobusinone (182b) which result from rearrangement of the allyl alcohol system. Spectral properties were in accord with a ketone in a six-membered ring (1705 $cm^{-1}$). The β-dihydrokobusinone could be obtained from the α-isomer or from kobusine itself by treatment with 5 per cent hydrochloric acid. Oxidation of kobusine with chromium trioxide–pyridine gave a monoketoalcohol, kobusinone (183) (3100, 1692, 1632 $cm^{-1}$) and a diketone, ketokobusinone (184) (1721, 1708, 1628 $cm^{-1}$) both of which compounds are α,β-unsaturated ketones. Catalytic hydrogenation of ketokobusinone gave a saturated diketone (185) (1707 $cm^{-1}$) which was identified with the product obtained by oxidation of β-dihydrokobusinone. A similar hydrogenation of kobusinone (183) gave α-dihydrokobusinone (182a). It is rather interesting that ketokobusinone (184) gave a compound with the configuration of the methyl group epimeric




[104] H. Suginome and F. Shimanouchi, *Liebigs Ann.* **545**, 220 (1940).
[105] Kobusine has also been isolated from *A. luciduscul*um[106,107] and *A. sachalinense*.[107]
[106] H. Suginome, S. Kakumoto and J. Sonoda, *J. Fac. Sci., Hokkaido Univ.* (*Ser. III, Chem.*) **4**, 25 (1950); *Chem. Abstr.* **46**, 1007 (1952).
[107] H. Suginome and S. Imato, *J. Fac. Sci., Hokkaido Univ.* (*Ser. III, Chem.*) **4**, 33 (1950); *Chem. Abstr.* **46**, 1008 (1952).
[108] H. Suginome and S. Umezawa, *J. Fac. Sci., Hokkaido Univ.* (*Ser. III, Chem.*) **4**, 15 (1950); *Chem. Abstr.* **46**, 1007 (1952).
[109] T. Okamoto, *Chem. & Pharm. Bull.* **7**, 44 (1959).
[110] M. Natsume, *Chem. & Pharm. Bull.* **7**, 539 (1959).

to that obtained from kobusinone. The above reactions demonstrate that kobusine contains a $CH_2$=C—C—OH group and another secondary hydroxyl in a six- or larger-membered ring.[109]

Selenium dehydrogenation of kobusine gives 1,7-dimethyl-6-n-propylphenanthrene, the characteristic product of anhydroignavinol[94] and hypognavinol[94] and two aromatic bases which have not yet been identified. On the basis of the isolation of 1,7-dimethyl-6-n-propylphenanthrene and by analogy with ignavine and hypognavine, it is reasonable to suppose that kobusine is modeled on the same skeleton. Only one hydroxyl remains to be located and the partial structure of kobusine may be represented by (186).[110]

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