The Chemistry of the C_{20}-Diterpene Alkaloids

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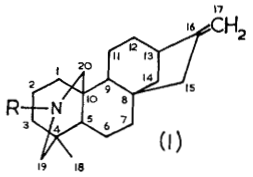
1 Introduction

Diterpene alkaloids[1] are widely distributed throughout the plant world and have long been of interest because of their pharmacological properties and complex structures. These alkaloids can be divided into two broad categories. The first group, which is the subject of this Review, includes a series of comparatively simple and relatively non-toxic amino-alcohols (alkamines) which are modelled on a C_{20}-skeleton. (This class is sometimes loosely referred to as the 'atisines'. In this Review a more restricted classification will be used. The term 'atisines' will refer only to those compounds modelled on an atisine skeleton.) These compounds are not extensively oxygenated and contain at most one methoxy group. One of the distinguishing chemical features of this group is the formation of phenanthrenes when subjected to selenium or palladium dehydrogenation. A few of these compounds occur in the plant as monoesters of acetic or benzoic acid. The second group comprises the highly toxic ester bases (aconitines) which are heavily substituted by methoxy and hydroxy groups. Hydrolysis of the aconitines furnishes the relatively non-toxic aconines which are modelled on a hexacyclic C_{19}-skeleton.

The C_{20}-diterpene alkaloids are derived from tetracyclic diterpenes in which carbon atoms 19 and 20 are linked with the nitrogen of a molecule of β-amino-ethanol, methylamine, or ethylamine to form a heterocyclic ring. Thus far two different types of skeleton have been encountered, the veatchine (1) and the atisine (3) types. The veatchine skeleton which occurs in the *Garrya* alkaloids, incorporates a phyllocladene skeleton (2) and obeys the isoprene rule. The atisine skeleton (3) differs from the veatchine type in that ring D is six- rather than five-membered; it does not obey the isoprene rule. All the C_{20}-diterpene alkaloids yet encountered in Nature are constructed on these two skeletal types. In certain alkaloids, such as songorine and kobusine, one or more additional ring fusions are present.

[1] Detailed reviews on various aspects of diterpene alkaloid chemistry have been published by (*a*) S. W. Pelletier, *Experientia*, 1964, **20**, 1; (*b*) S. W. Pelletier, *Tetrahedron*, 1961, **14**, 76; (*c*) H. G. Boit, 'Ergebnisse der Alkaloid-Chemie bis 1960', Academie-Verlag, Berlin, 1961, pp. 851–905, 1009–1001; (*d*) A. R. Pinder, in 'Chemistry of Carbon Compounds', vol. IVc, ed. E. R. Rodd, Elsevier, Amsterdam, 1960, pp. 2019–2033; (*e*) E. S. Stern, in 'The Alkaloids', vol. VII, ed. R. H. F. Manske, Academic Press, New York, 1960, pp. 473–503; (*f*) K. Wiesner and Z. Valenta, 'Progress in the Chemistry of Organic Natural Products', Springer-Verlag, Vienna, 1958, pp. 26–89.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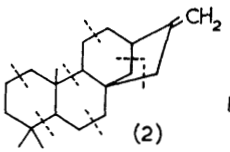
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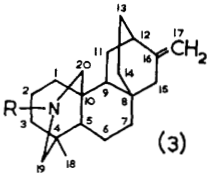
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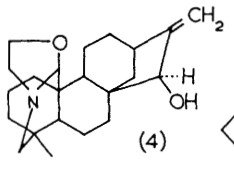
Careful chemical investigation of the alkloids of species of *Aconitum* and *Delphinium* was initiated by Walter A. Jacobs and his collaborators at the Rockefeller Institute in 1942. These workers carried out a number of meticulous degradations which laid the foundation for subsequent contributions in this field. In later work on the *Garrya* alkaloids, K. Wiesner paralleled Jacobs's early studies on atisine and pointed out the striking similarity in the chemistry of the two groups of alkaloids. Advances in one field then greatly assisted progress in the other. Since structures of the *Garrya* alkaloids were the first to be elucidated, these compounds will be considered first.

2 The *Garrya* Alkaloids

A. Vetachine and Garryine (*Garrya veatchii* Kellogg).[2]—Veatchine (4), $C_{22}H_{33}NO_2$, is a strong tertiary base (pK_a' 11·5) containing one acylatable hydroxyl, a C-CH_3 group, and an exocyclic methylene group. On treatment with base veatchine is converted into the isomeric garryine (5) (pK_a' 8·7). Reduction of either alkaloid with $LiAlH_4$ results in hydrogenolysis of the ether bridge to give the same dihydroveatchine (6) and catalytic hydrogenation of either alkaloid gives tetrahydroveatchine (7). Both dihydro- and terrahydro-veatchine show two active hydrogens and give O,O'-diacetate derivatives.[2]

Selenium dehydrogenation of veatchine or garryine yields 7-ethyl-1-methylphenanthrene and 7-ethyl-1-methyl-3-azaphenanthrene (8).[2] On the basis of these products and other degradations to be described structure (6) was suggested for dihydroveatchine. Veatchine and garryine were then formulated as the isomeric cyclic ethers (4) and (5) respectively. These structural assignments were confirmed by pK_a studies and by the results of degradations which will be briefly summarised.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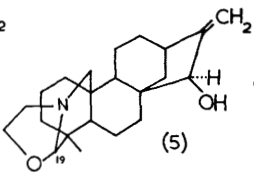
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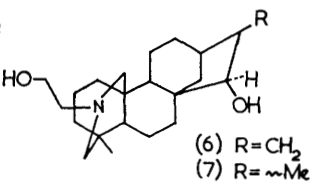
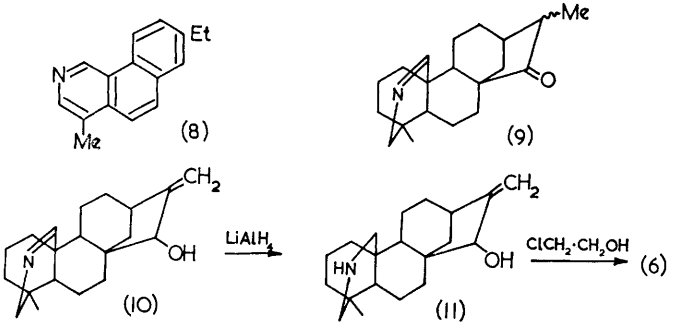

(6) R=CH_2
(7) R=~~Me

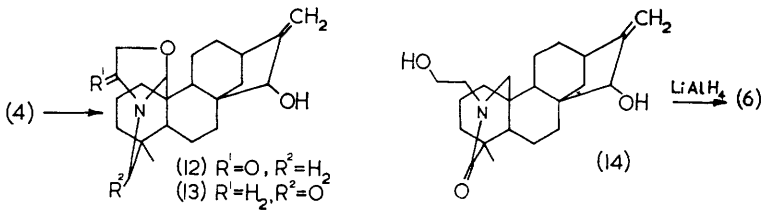
Pyrolysis of veatchine or garryine with selenium at 290° gave the isomeric pyrolysis bases (9) and (10). Reduction of (10) with $LiAlH_4$ gave the secondary base (11) which was alkylated with ethylene chlorohydrin to give dihydroveat-

[2] See ref. 1(*f*) for a series of papers on the *Garrya* alkaloids.

chine (6). Oxidation of the latter with one equivalent of osmium tetroxide in ether afforded garryine (5), cyclisation occurring at the less hindered 19-position. These reactions demonstrate the presence of an oxazolidine moiety in veatchine and garryine.[3,4]



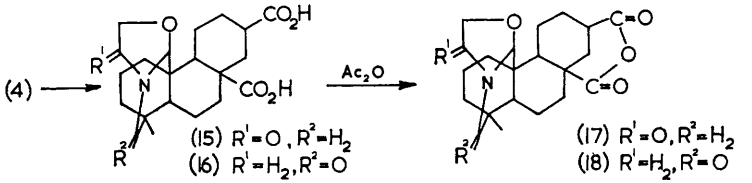
Oxidation of veatchine with potassium permanganate in acetone furnishes a γ-lactam, oxoveatchine-A (12), and an isomeric δ-lactam, oxoveatchine-B (13). Under the same conditions, garryine gives the δ-lactam, oxogarryine (14). Reduction of oxogarryine with $LiAlH_4$ furnishes dihydroveatchine (6).[3,5]



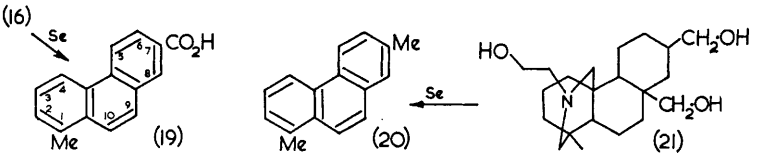
Under more vigorous conditions of permanganate oxidation, veatchine furnishes the lactam dicarboxylic acids (15) and (16), formed by cleavage of the five-membered ring bearing the -CHOH group. These acids are readily converted into the corresponding anhydrides (17) and (18), the infrared spectra of which are compatible with the presence of the γ-lactam (1700 cm.$^{-1}$) and δ-lactam (1640 cm.$^{-1}$), respectively, and of a glutaric anhydride grouping in each (1800, 1762 and 1800, 1775 cm.$^{-1}$, respectively). The dimethyl esters (no infrared hydroxyl absorption) of (15) and (16) on hydrolysis give monomethyl esters

[3] K. Wiesner, W. I. Taylor, S. F. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, *Chem. Ber.*, 1953, **86**, 800.
[4] K. Wiesner, R. Armstrong, M. F. Bartlett, and J. A. Edwards, *J. Amer. Chem. Soc.*, 1954, **76**, 6068.
[5] K. Wiesner, S. K. Figdor, M. F. Bartlett, and D. R. Henderson, *Canad. J. Chem.*, 1952, **30**, 608.

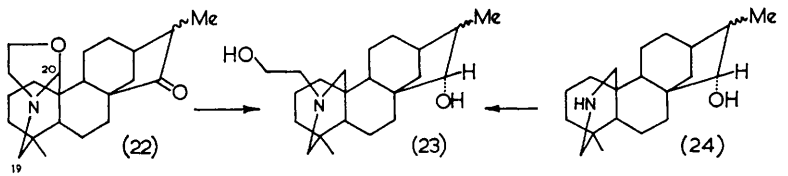
which are resistant to further hydrolysis, an indication of the hindered nature of one of the carboxyl groups in each compound.[4]



Dehydrogenation of acid (16) with selenium afforded 1-methylphenanthrene-7-carboxylic acid (19) and pimanthrene (20). Dehydrogenation of the triol (21), formed by lithium aluminium hydride reduction of the dimethyl ester of (16), also led to pimanthrene.[4]

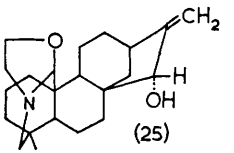


B. Cuauchichicine and Garryfoline.[6]—These alkaloids of *Garrya laurifolia* Hartiv. are isomeric with veatchine and garryine and can be separated from each other by countercurrent distribution. The infrared spectrum of cuauchichicine shows the absence of -OH or -NH absorption but a strong carbonyl band at 1730 cm.$^{-1}$ which can be attributed to a cyclopentanone ring. Kuhn–Roth determinations demonstrated the presence of two *C*-methyl groups and the lack of an exocyclic methylene group was confirmed by ozonisation. Selenium pyrolysis of cuauchichicine at 290° yielded a base (9), identical with that obtained earlier from veatchine by similar treatment. Moreover, reduction of the alkaloid with $LiAlH_4$ gives tetrahydroepiveatchine (23), a compound which has been synthesised from imine (9) by reduction to (24), followed by alkylation with ethylene chlorohydrin. Since the pK_a value of cuauchichicine (11·15) is comparable with that of veatchine (11·5) rather than that of garryine (8·7), in cuauchichicine the oxazolidine ring is fused at C(20) and the structure of the alkaloid may be formulated as (22).[6]



[6] C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor, and J. Herran, *J. Amer. Chem. Soc.*, 1955, 77, 4801.

Garryfoline is a tertiary base containing a *C*-methyl group, a secondary hydroxyl, and an exocyclic methylene group. The skeleton of garryfoline is the same as that of cuauchichicine (22) since it can easily be isomerised by acid to the latter compound. Garryfoline is reduced with $LiAlH_4$ to dihydrogarryfoline (26), a transformation analogous to the conversion of veatchine (4) into dihydroveatchine (6) and involving reductive cleavage of the oxazolidine ring. Like garryfoline, the dihydro-derivative (26) is isomerised with acid to a ketone, dihydrocuauchichicine (27), which is also obtained by catalytic reducion of cuauchichicine (22). On reduction with $LiAlH_4$, dihydrocuauchichicine yields tetrahydroepiveatchine (28), also obtainable by catalytic hydrogenation of garryfoline itself. These transformations indicate that garryfoline has the structure of 15-epiveatchine (25). The attachment of the oxazolidine ring at C(20) follows from a comparison of the pK_a' of garryfoline (11·8) with veatchine (11·5).[6] Base-catalysed isomerisation, comparable with the conversion of veatchine into garryine, also occurs with cuauchichicine and garryfoline.



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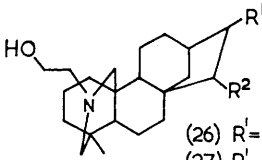
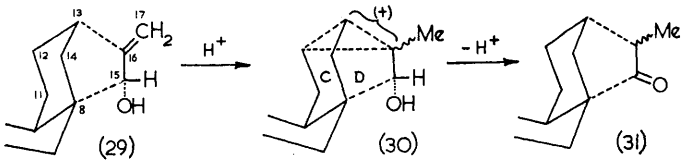


(26) $R^1 = CH_2$, $R^2 = \overset{H}{\underset{OH}{<}}$
(27) $R^1 = \sim Me$, $R^2 = O$
(28) $R^1 = \sim Me$, $R^2 = \overset{H}{\underset{OH}{<}}$

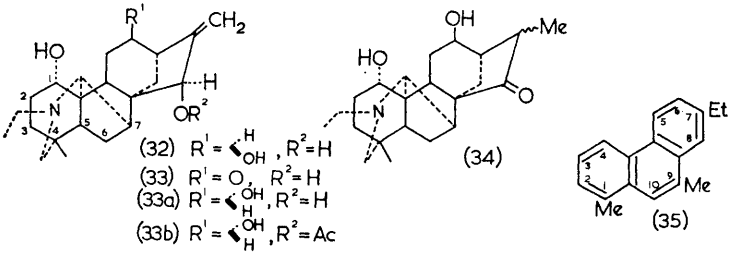
The acid-catalysed isomerisation of garryfoline (25) to cuauchichicine (22) and of dihydrogarryfoline (26) to dihydrocuauchichicine (27) requires comment in view of the stability of veatchine to acidic conditions. Reduction of dihydrocuauchichicine (27) with lithium and alcohol in liquid ammonia, conditions known to lead to the more stable epimeric alcohol, affords as the sole product tetrahydroepiveatchine (28); thus garryfoline is thermodynamically more stable than veatchine. Yet garryfoline is the epimer which undergoes rearrangement to cuauchichicine. The isomerisation can proceed only when the four centres involved are coplanar and the non-classical carbonium ion (30) from garryfoline (29) has been invoked as an intermediate in this isomerisation to the methyl ketone (31). In this cation the quasi-axial (with respect to the 5-membered D-ring) and C(15) hydrogen atom is coplanar with the bond joining C(12) and C(16).* This leads to the relative stereochemistry for garryfoline as (29); the hydroxyl groups at C(15) in garryfoline and veatchine are respectively quasi-equatorial and quasi-axial with reference to ring D.[6]

*The mechanism of this rearrangement has recently been investigated by M. F. Barnes and J. MacMillan [*J. Chem. Soc.* (*C*), 1967, 351] using the epimeric (−)-kaur-16-en-15-ols as models. The 15β-ol rearranges in mineral acid to 16*R*-(−)-kaur-15-one by a 15,16-hydride shift. The 16α-ol, like veatchine, is stable under these conditions.



(29) (30) (31)

C. Napelline, Songorine, and Luciculine.—Napelline, $C_{22}H_{33}NO_3$, and songorine, $C_{22}H_{31}NO_3$, occur in *Aconitum napellus* L. and *A. soongaricum*. Songorine is a ketonic base which on reduction with $LiAlH_4$ yields the corresponding secondary alcohol, napelline. Each base contains an *N*-ethyl, *C*-methyl, and exocyclic methylene group. The carbonyl group of songorine is part of a six-membered ring (1712 cm.$^{-1}$). Napelline is readily isomerised to isonapelline, which contains a cyclopentanone system (1740 cm.$^{-1}$) and two *C*-methyl groups, and in these respects resembles garryfoline in its tendency to undergo ketonisation in the presence of acid. The presence of a veatchine-type skeleton in these bases is indicated by formation of 7-ethyl-1-methyl-3-azaphenanthrene (8) on dehydrogenation of isonapelline. Selenium dehydrogenation of songorine gives 7-ethyl-1,9-dimethylphenanthrene (35). The chemistry of napelline (32), songorine (33), and isonapelline (34) will be discussed in terms of the structures ultimately derived.[1f,7]



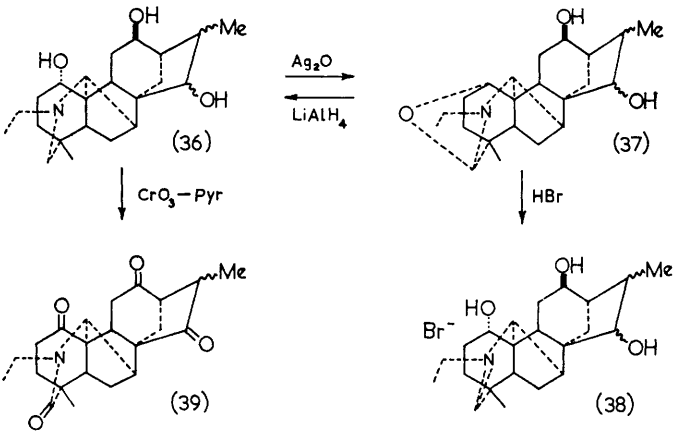
(32) R^1 = , R^2 = H
(33) R^1 = O, R^2 = H
(33a) R^1 = , R^2 = H
(33b) R^1 = , R^2 = Ac

(34) (35)

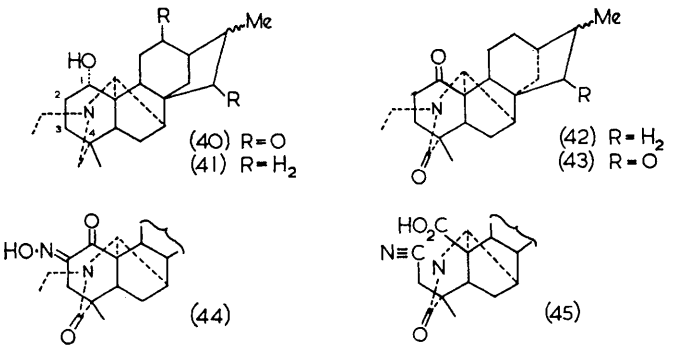
Silver oxide converts dihydronapelline (36) into a weakly basic carbinolamine ether (37), pK_a' 6·77, which forms a ternary iminium salt (38). Reduction of (37) with $LiAlH_4$ regenerates dihydronapelline. Oxidation of (36) with CrO_3–pyridine gives a triketolactam (39).[1f]

Isosongorine (40) available from the allylic rearrangement of songorine (33), gave on Huang–Minlon reduction the deoxy-derivative (41). Oxidation of the latter with CrO_3–pyridine gave a keto-δ-lactam (42) [1707, 1635 cm.$^{-1}$]. The latter gave an amorphous monobenzylidine derivative and exchanged 1·82 atoms of deuterium when equilibrated in the presence of NaOD in MeOD and D_2O. These results indicate the presence of one methylene group adjacent to the keto-function and therefore limit the site of the ring-A hydroxyl in napelline to either

[7] T. Sugasawa, *Chem. and Pharm. Bull. (Japan)*, 1961, **9**, 889, 897.



C(1) or C(3). To distinguish between these possibilities the dioxolactam (43) was treated with isopentyl nitrite to give the isonitroso-derivative (44). Cleavage of the latter with benzenesulphonyl chloride and alkali gave a nitrile (45) which was stable at its melting point and did not decarboxylate in boiling ethanolic hydrogen chloride. These results permit assignment of the hydroxyl in ring A to C(1); napelline and songorine are therefore represented by structures (32) and (33), respectively.[7] Reduction of songorine with $LiAlH_4$ gives luciculine (33a), the alkamine of lucidusculine (33b). The structure and absolute configuration of the latter has been determined by an *X*-ray analysis.[8]

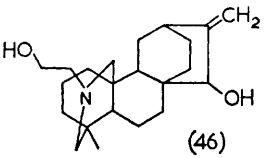


D. The Structure of Atisine.—(i) *General structural considerations.* Atisine, $C_{22}H_{33}NO_2$, the predominate alkaloid of *Aconitum heterophyllum*, is a tertiary base which contains an exocyclic methylene, a secondary hydroxyl, and a *C*-methyl group. *N*-Alkyl determinations indicate the presence of an *N*-ethyl

[8] T. Okamoto, M. Natsume, Y. Iitaka, A. Yoshino, and T. Amija, *Chem. and Pharm. Bull. (Japan)*, 1965, **13**, 1270.

group or suitable precursor in the molecule.[9] Atisine is a very strong base (pK_a' 12·8) which can easily be isomerised to isoatisine (pK_a' 10·3). Reduction with hydride gives a dihydro-derivative analogous to dihydroveatchine. Oxidation of isoatisine with potassium permanganate gives a lactam, oxoisoatisine, $C_{22}H_{33}NO_3$, analogous to oxogarryine (14). Atisine contains one active hydrogen and on hydrogenation gives a mixture of tetrahydro-derivatives.

(ii) *Skeleton of atisine.* One important difference noted between atisine and the *Garrya* alkaloids is their behaviour on selenium dehydrogenation. While veatchine gives 7-ethyl-1-methylphenanthrene and 7-ethyl-1-methyl-3-azaphenanthrene, atisine gives 1-methylphenanthrene, 6-ethyl-1-methylphenanthrene, and 6-ethyl-1-methyl-3-azaphenanthrene (49).[10,11] This behaviour prompted the suggestion that the difference between atisine and the *Garrya* alkaloids lies in the position of attachment of ring D. In particular structure (46) was suggested for dihydroatisine and structures (47) and (48) for atisine and isoatisine, respectively.[12,13]



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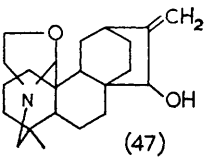

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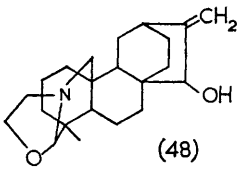

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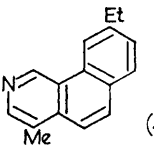
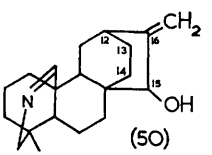


(49)

The relative positions of the secondary alcohol and exocyclic methylene group are determined by two independent studies. Dvornik and Edwards[14] converted the azomethine alcohol (50) into the bisnor-keto-acid (51). Dibromination of the latter followed by dehydrohalogenation gave a crystalline phenol (52) and a keto-γ-lactone (53) [bridging of ether oxygen either at C(11) or C(13)]. Formation of the latter, involving displacement of bromine α to the ketone by carboxylate anion, demonstrates a 1,4-relationship of the ketone and carboxyl groups in (51). These results, taken with dehydrogenation evidence for substitution at

[9] C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, 1948, **174**, 1001.
[10] C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.*, 1947, **170**, 203.
[11] D. M. Locke and S. W. Pelletier, *J. Amer. Chem. Soc.*, 1959, **81**, 2246.
[12] K. Wiesner, R. Armstrong, M. F. Bartlett, and J. A. Edwards, *Chem. and Ind.*, 1954, 132.
[13] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1954, **76**, 4496.
[14] D. Dvornik and O. E. Edwards, *Canad. J. Chem.*, 1964, **42**, 137.

C(12) [C(6) on phenanthrene nucleus], show clearly that a bicyclo[2,2,2]octane system is present and that the exocyclic methylene is located at C(16) [or C(13)] and the secondary hydroxyl at C(15) [or C(14)], respectively. (Since the bicyclo-octane system is symmetrical, the allylic alcohol system could be located on either the *cis*- or *trans*-branch. This point is considered later.) Additional



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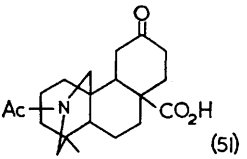

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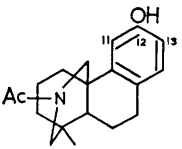

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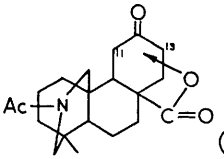
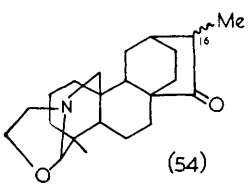
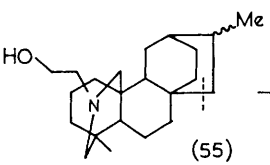


(53)

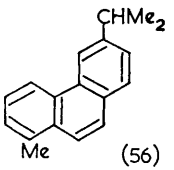
evidence on this point is available from the following sequence of reactions. Isomerisation of isoatisine (48) with ethanolic hydrochloric acid gave a mixture of epimeric 16-methyl ketones (54). Wolff–Kishner reduction of (54) gave the deoxy-derivative (55) and dehydrogenation of the latter with selenium afforded 6-isopropyl-1-methylphenanthrene (56). The formation of the isopropyl derivative constitutes additional evidence for assigning the methylene to C(16) [or C(13)].



(54)



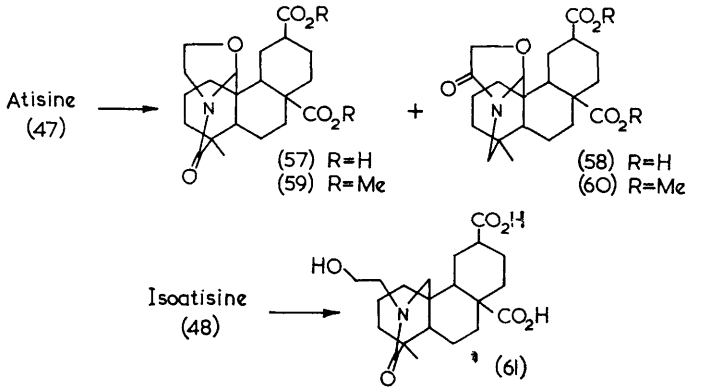
(55)



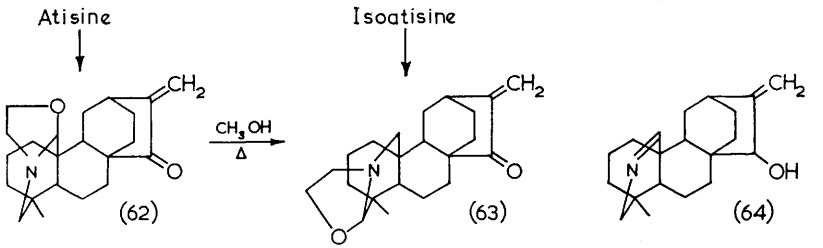
(56)

(iii) *Oxazolidine ring system.* Evidence for the existence of an oxazolidine ring in atisine and isoatisine is derived from two experiments.[13,15] Oxidation of atisine (47) with permanganate in acetone gives lactam dicarboxylic acids (57) and (58) whose methyl esters (59 and 60) show no infrared absorption for a hydroxyl group and give negative tests for active hydrogen. A similar oxidation of isoatisine furnishes oxoisoatisinedicarboxylic acid (61) [compare oxidation of garryine (5) to oxogarrine (14)] which has been related to (57) by catalytic reduction of the latter. The second piece of evidence is the oxidation of both atisine

[15] S. W. Pelletier and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, 1965, **87**, 777.



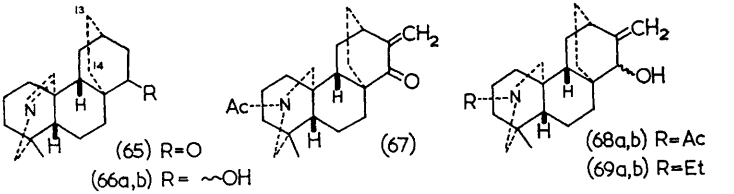
and isoatisine to conjugated enones [(62) (λ_{max} 229 mμ, 9500) and (63) (λ_{max} 227 mμ, 8070), respectively] which show no infrared hydroxy absorption and give negative tests for active hydrogen. Refluxing (62) in methanol gives a good yield of the iso-enone (63), a reaction which parallels the easy veatchine → garryine and atisine → isoatisine isomerisations. Final confirmation of the presence of an



oxazolidine moiety has been provided by reconstitution of atisine from the imino-alcohol (64).[16]

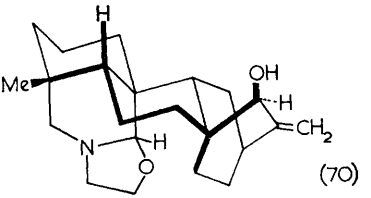
(iv) *Stereochemistry of atisine.* At the time when the selenium dehydrogenation results mentioned above were available it was assumed that atisine possessed the *trans-anti* skeleton which is common to most diterpenes. Conformational arguments[17] relative to the structure of the related alkaloid ajaconine have shown that A/B-*trans* stereochemistry is present in atisine. Further, reduction of ketones (65) and (67) with sodium borohydride gives in each case a pair of epimeric alchols (66a,b and 68a,b) each of which readily forms an *O*-acetate. This relatively unhindered character of the hydroxyl groups supports location of the allylic alchol group on the *trans* bridge of the bicyclo-octane system, for if the group were on the *cis* bridge only one epimer would be expected on reduction owing to the severe crowding at C(14).[15,18] Moreover this view is confirmed by a study of the pK_a's of the epimeric *N*-ethyl compounds (69a,b) and their

[16] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1956, **78**, 4144.
[17] A. J. Solo and S. W. Pelletier, *Chem. and Ind.*, 1960, 1108.
[18] D. Dvornik and O. E. Edwards, *Chem. and Ind.*, 1958, 623.



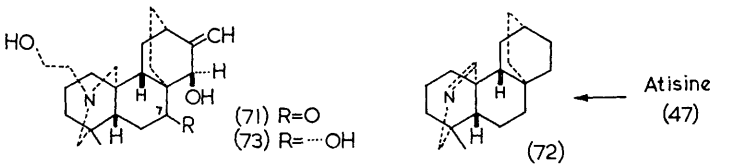
acetates. Detailed studies indicate that the complete relative stereochemistry of atisine is expressed by structure 70.[1b,19]

The assignment of configuration of the secondary hydroxyl in atisine is made difficult by the high degree of symmetry of the bicyclo[2,2,2]octane system. A tentative assignment of the β-configuration as in (70) has been made on the basis of the difference in the absorption of the epimeric alcohols (68a,b) on alumina.[1b,15] The absolute configuration of atisine is considered under Section 4C.



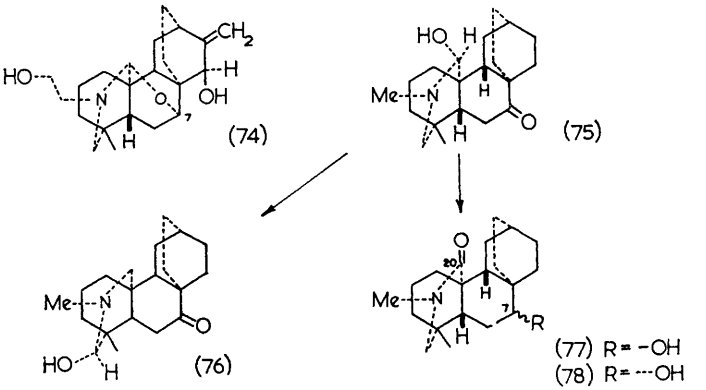
E. The Structure of Atidine.—Atidine, $C_{22}H_{33}NO_3$, another constituent of *Aconitum heterophyllum*, is a tertiary base possessing two hydroxy groups (diacetate), a ketone function (oxime) in a six-membered ring, an exocyclic methylene, a *C*-methyl, and an N-CH_2·CH_2OH group. Atidine is shown to be an oxodihydroatisine (71) by Huang-Minlon reduction to dihydroatisine (46). A correlation of atidine and ajaconine *via* the dihydro-derivative (see below) allows the keto-function to be assigned to C(7) in atidine.[20]

F. The Chemistry of Ajaconine.[19–21]—Ajaconine, $C_{22}H_{33}NO_3$, an alkaloid of *Delphinium ajacas* L., has been shown to have the same carbocyclic skeleton as atisine by conversion into the oxygen-free azomethine base (72), obtained earlier from atisine.[21] That the allylic alcohol system of ajaconine has the same position and stereochemistry as in atisine was shown by reduction of atidine (71) (previously correlated with dihydroatisine) to a mixture of epimers, one of which is dihydroajaconine (73).[20]



[19] D. Dvornik and O. E. Edwards, *Tetrahedron*, 1961, **14**, 54.
[20] S. W. Pelletier, *J. Amer. Chem. Soc.*, 1965, **87**, 799.
[21] D. Dvornik and O. E. Edwards, *Chem. and Ind.*, 1957, 952.

The work of Dvornik and Edwards has shown that ajaconine (74) contains a carbinolamine ether involving an oxygen atom at C(7).[19] The *N*-methylcarbinolamine (75) derived from ajaconine was transformed by methanolic alkali into a mixture of the iso-compound (76) and a hydroxy-lactam (77). This unusual product results from an intramolecular Cannizzaro-type reaction involving a transannular hydride transfer from C(20) to C(7).



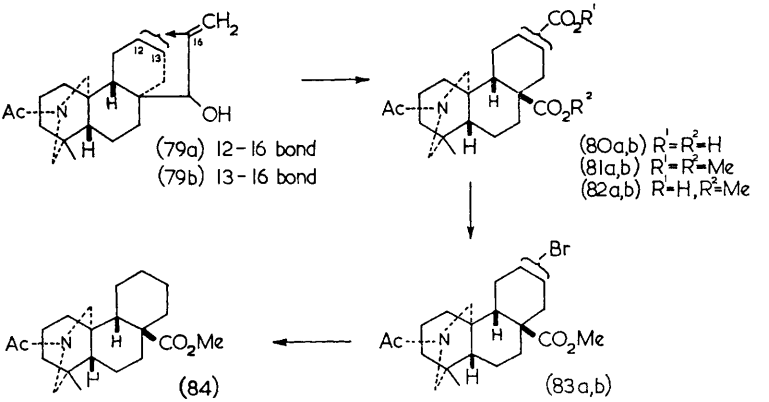
The absolute configuration indicated for ajaconine (74) and its derivatives follows from its correlation with atisine and atidine.[19,20]

4 Correlations and Absolute Stereochemistry of *Atisine* and *Garrya* Alkaloids

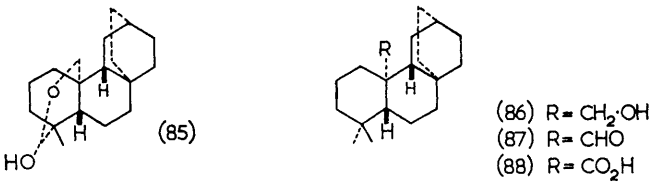
A. Correlation of *Atisine* and *Garrya* Alkaloids.—The *Atisine* and *Garrya* alkaloids have been interrelated by converting both atisine and veatchine, by a parallel sequence of degradations, into the same *N*-acetyl ester (84).[22] The respective *N*-acetyl derivatives (79a) and (79b) derived from atisine [12–16 bond] and veatchine [13–16 bond] were converted by oxidation with permanganate–periodate to the respective carboxylic acids (80a,b). Hydrolysis of the dimethyl esters (81a,b) gave (82a,b) which were transformed into the corresponding monobromides (83a,b) by the Hunsdiecker method. Reductive debromination of (83a) and (83b) with zinc dust in acetic acid gave the same acetyl ester (84). This correlation demonstrates that the *Garrya* alkaloids have the same stereochemistry of ring fusions as atisine.

B. Correlation of the *Atisines* with Diterpenes.—(i) *Removal of the nitrogen from diterpene alkaloids.* Degradation of diterpene alkaloids to diterpenes of established configuration was delayed by the lack of a suitable method of removing the nitrogen atom. Since both positions β to the nitrogen are quaternary, Hofmann-type degradations are ineffective. Success in removing the nitrogen from (72) has been achieved through a mild reaction with aqueous nitrous acid.[23]

[22] S. W. Pelletier and D. M. Locke, *J. Amer. Chem. Soc.*, 1965, **87**, 761.
[23] J. W. Ap Simon and O. E. Edwards, *Canad. J. Chem.*, 1962, **40**, 896.



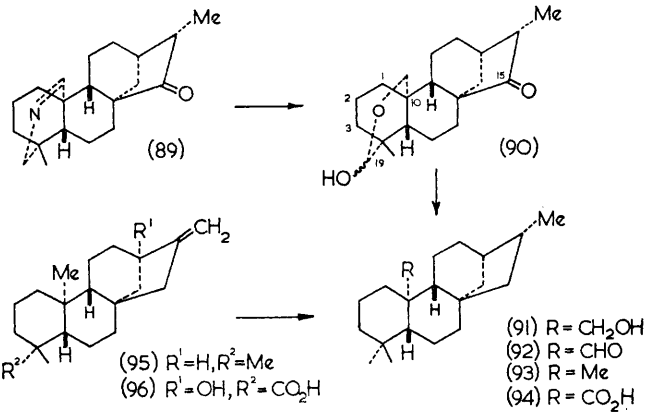
The major product is the hemiacetal (85). This hemiacetal has been converted successively into a primary alcohol (86), aldehyde (87), and carboxylic acid (88). The same procedure has been applied with success to the azomethines derived from the *Garrya* alkaloids (see below).



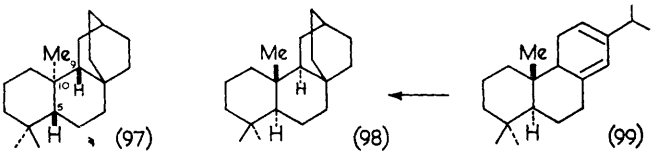
(ii) *Correlation of garryfoline with kaurene and stevane-B.*[24] The azomethine (89) derived from garryfoline was converted into the hemiacetal (90) by treatment with nitrous acid. Wolff–Kisner reduction of (90) effected simultaneous reduction of the 15-oxo- and masked 19-aldehydo-functions. Oxidation of the resulting primary alcohol (91) with CrO_3–pyridine gave aldehyde (92) which was transformed by vigorous Wolff–Kishner conditions into the hydrocarbon (93). This hydrocarbon was identical with (—)-'β'-dihydrokaurene, the minor hydrogenation product of (—)-kaurene (95), and with 'stevane-B', a degradation product of steviol (96). The evidence for structure (90) for the hemiacetal is based on the extremely hindered nature of the derived aldehyde (92) and acid (94) [pK^*_{MCS} 9·49].

(iii) *Correlation of atisine and the resin acids.* The aldehyde (87) derived from atisine has been converted by Wolff–Kishner reduction into the hydrocarbon (97) which is enantiomorphic with a hydrocarbon (98) prepared by a long degradative sequence from abieta-6,8-diene (99).[25] This work represents the first correlation of the tetracarbocyclic ring system of atisine with the resin

[24] H. Vorbrueggen and C. Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 2990.
[25] W. A. Ayer, C. E. McDonald, and G. G. Iverach, *Tetrahedron Letters*, 1963, No. 17,1095.



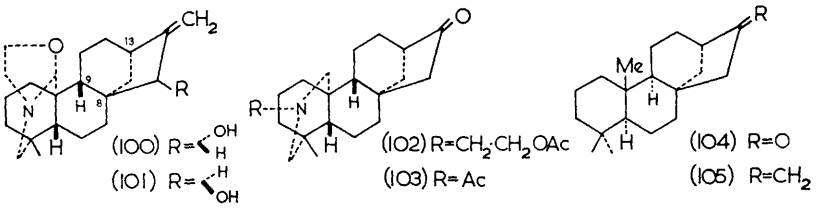
acids and confirms the mirror-image relationship at C(5), C(9), and C(10). Hydrocarbon (99) has also been synthesised from abietic acid *via* maleopimaric acid.[26]



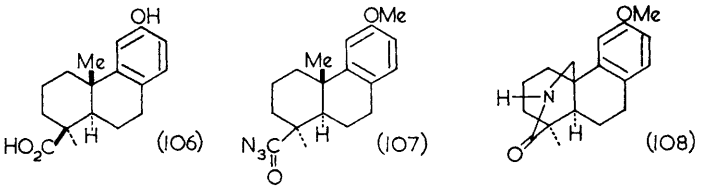
C. Absolute Configuration of *Atisine* and *Garrya* Alkaloids.[24]—Vorbrueggen and Djerassi[24] have converted veatchine (100) and garryfoline (101) into the 17-nor-16-ketones (102) and (103). These compounds exhibit a positive Cotton effect of amplitude similar to that observed for the 17-nor-16-ketone (104) from phyllocladene (105). Since the absolute configuration of phyllocladene has been established and since the configuration at C(9) should not effect the sign of the Cotton effect, the absolute configuration at C(8) and C(13) of the *Garrya* alkaloids [and hence of C(8) and C(12) of atisine] is established. The correlation of garryfoline with (—)-'β' dihydrokaurene (93) has been discussed previously. These results lead to the complete absolute configurational representations (100) and (101) for veatchine and garryfoline. In view of the correlation[22] of atisine and veatchine, this absolute configurational assignment also applies to atisine (70) and its relatives such as ajaconine (74) and atidine (71).

Independent evidence for the absolute configuration of atisine is provided by a synthesis from podocarpic acid (106) of the antipode of the phenol (52) originally obtained by degradation of atisine. The synthesis involved photolysis of the azide (107) derived from the methyl ether of podocarpic acid. One of the products

[26] L. H. Zalkow and N. N. Girotra, *J. Org. Chem.*, 1964, **29**, 1299.

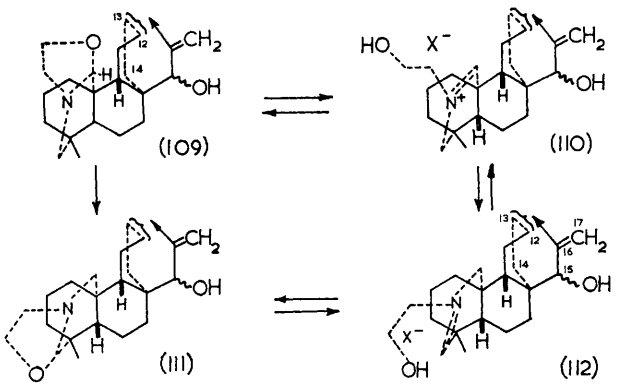


of the photolysis reaction was the δ-lactam (108) which was converted by conventional procedures into the enantiomer of (52).



5 The Ternary Iminium Salts of the *Atisine* and *Garrya* Alkaloids

Atisine, veatchine, garryfoline, and cuauchichicine are isomerised by dilute base to the iso-type bases, isoatisine, garryine, isogarryfoline, and isocuauchichicine, respectively,[1a,3,6] The isomerisation (109) → (111) proceeds even at room temperature in alcohol without external base. Members of these pairs of isomers manifest a remarkable difference in basic strengths. In 50% methanol, atisine has a pK_a' of 12·8 while isoatisine has a value of 10·35. Similar differences exist for the *Garrya* alkaloid pairs.



The salts of these alkaloids exist in the ternary iminium form. In hydroxylic solvents the 'normal' bases (109) exist almost completely as the ternary iminium hydroxides (110; X = OH), whereas the 'iso'-bases exist mainly in the oxazolidine form (111). The reasons for the preponderance of the ternary iminium

hydroxide in the 'normal' base equilibria have been reviewed.[1a,1f,27] In solution, isomerisation of the 'normal' bases proceeds through the ternary iminium forms (110) and (112) by prototropy. Since steric factors are responsible for the 'iso'-bases having a lower free energy than the 'normal' bases, the equilibrium is shifted toward the sterically more favoured 'iso-' forms.[1a,1f,27,28]

In the case of the salts of the 'normal' and 'iso'-bases, the reverse of the situation described for the bases prevails. The 'normal' salts are more stable than the iso-salts.[29] Thus isoatisinium chloride (112; X = Cl, 12–16 bond) can be converted into atisinium chloride (110; X = Cl, 12–16 bond) by refluxing in such solvents as dimethyl sulphoxide, dimethylformamide, diethylformamide, or high-boiling alcohols. Garryinium chloride (112; X = Cl, 13–16 bond) in similar conditions is isomerised to veatchinium chloride (110; X = Cl, 13–16 bond). Since the normal salts can be readily converted, without isomerisation, into the corresponding bases by treatment with cold, aqueous alkali, this thermal isomerisation of the salts provides a convenient practical method of reversing the easy 'normal' base (109) → 'iso'-base (111) isomerisation. Detailed rate studies on this reaction in several organic solvents have been carried out.[29]

6 The Chemistry of Alkaloids with a Modified Alkaline Skeleton

In recent years a wide range of *Aconitum* species native to Japan and India have been examined for alkaloids. Among those encountered are several which are modelled on an atisine skeleton but possess additional ring fusions. This section will survey the chemistry of these compounds.

A. The Chemistry of Hetisine.—Hetisine, $C_{20}H_{27}NO_3$, a minor constituent of *Aconitum heterophyllum*,[30] represents an interesting variant of the atisine skeleton. The alkaloid has one hydrogenatable double bond, three active hydrogen atoms, an exocyclic methylene group, one *C*-methyl group, and a tertiary nitrogen atom. *N*-Alkyl and methoxyl determinations are negative. Since dihydrohetisine shows no adsorption in the near-ultraviolet region, it is clear that hetisine must have a heptacyclic skeleton.[31]

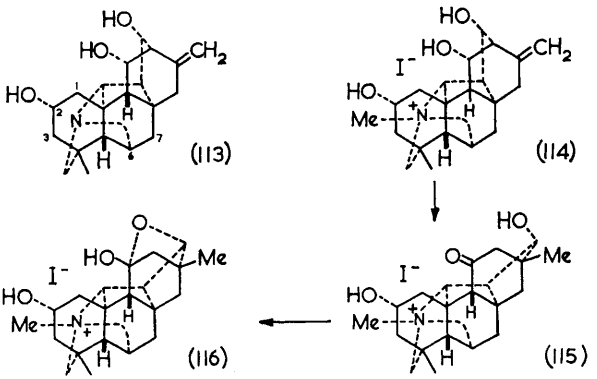
The nature of the oxygen functions is indicated by formation of a crystalline diacetate and an amorphous triacetate, both of which regenerate hetisine on hydrolysis. Further, the alkaloid is inert to both periodate and lead tetra-acetate and does not form an acetonide. It therefore possesses three acylatable hydroxyls which are non-vicinal and are not in a 1,3-*cis*-diaxial relationship.

Dehydrogenation of hetisine yields a complex mixture of hydrocarbons from which pimanthrene (20) has been isolated. The fact that hetisine lacks a free *N*-alkyl group and compares in basicity (pK_a' 9·85) with quinuclidine (10·3),

[27] K. Wiesner and J. A. Edwards, *Experientia*, 1955, **11**, 255.
[28] S. W. Pelletier, K. W. Gopinath, and K. Kawazu, *Chem. and Ind.*, 1966, 28.
[29] S. W. Pelletier, K. Kawazu, and K. W. Gopinath, *J. Amer. Chem. Soc.*, 1965, **87**, 5229.
[30] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, 1942, **143**, 605.
[31] A. J. Solo and S. W. Pelletier, *J. Amer. Chem. Soc.*, 1959, **81**, 4439; *J. Org. Chem.*, 1962, **27**, 2702.

suggests a quinuclidine-type structure with bonding from the nitrogen to either C(1), C(2), C(3), C(6), or C(7). One additional ring and three hydroxyl groups are necessary to complete the structure. An *X*-ray diffraction study[32] has established the correct structure of hetisine as (113).

Under mild conditions of quaternisation hetisine forms a methiodide (114) which undergoes Hofmann degradation to give demethylhetisine. The latter possesses an exocyclic methylene group and a new double bond, both of which can be hydrogenated. Under more vigorous conditions the methiodide rearranges with participation of the original exocyclic methylene group. This rearrangement has been interpreted as proceeding *via* the ketone (115) to the hemiketal structure (116).[33]



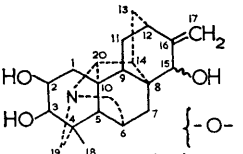
B. Ignavine and Anhydroignavinol.[34]—This alkaloid occurs in the roots of *Aconitum sanyoense* Nakai, *A. tasiromontanum* Nakai, and *A. japonicum*. Ignavine, $C_{27}H_{31}NO_6$, lacks methoxy, methylenedioxy-, or *N*-methyl groups and is unreactive toward the usual carbonyl reagents. Hydrolysis of ignavine gives one mol. of benzoic acid and anhydroignavinol, $C_{20}H_{25}NO_4$.

Of the six oxygens in ignavine, two occur in the benzoyloxy-group and four in hydroxyls. One of these hydroxy groups is adjacent to the benzoyloxy-group since the hydrolysis product is susceptible to periodate cleavage while ignavine is not. Diacyl derivatives are formed which contain a mol. of water less than calculated and are therefore anhydroignavinol derivatives. Hydrolysis of these derivatives does indeed afford anhydroignavinol.

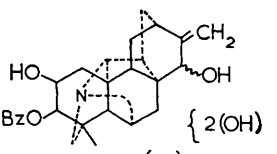
That the exocyclic methylene group in ignavine is involved in a secondary allylic alcohol system as in atisine was demonstrated by catalytic isomerisation to a methyl ketone (1692 cm.$^{-1}$) and by oxidation to a conjugated enone (1615, 1687 cm.$^{-1}$).[34]

[32] M. Przybylska, *Canad. J. Chem.*, 1962, **40**, 566; *Acta Cryst.*, 1962, **16**, 871.
[33] K. Wiesner, Z. Valenta, and L. G. Humber, *Tetrahedron Letters*, 1962, No. 14, 621.
[34] E. Ochiai and T. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 550; *ibid.*, p. 556.

Dehydrogenation of anhydroignavinol yields a complex mixture of hydrocarbons from which 1,7-dimethyl-6-n-propylphenanthrene, 3-ethyl-1,8-dimethylphenanthrene, and 3-isopropyl-1,8-dimethylphenanthrene have been isolated. These products account for 19 of the 20 carbon atoms of anhydroignavinol. The assumption of a bicyclo[2,2,2]octane–allyl alcohol system in ignavine is given credence by oxidation of de-*N*-methyloxoanhydroignavinol to a related dicarboxylic acid in which one of the carboxyl groups is tertiary. Further, the three phenanthrene dehydrogenation products suggest a bond between C(14) and C(20) and a methyl group at C(1). Numerous degradations have established the position of the nitrogen and shown the presence of hydroxyls at C(2) and C(3) in anhydroignavinol. Since ignavine has no *N*-alkyl group, a third bond must extend from nitrogen to one of the rings. The data suggest C(6) as the most likely site.



(117)



(118)

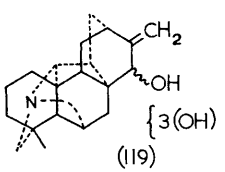
The published data clarify the nature of four of the six oxygens of ignavine and three of the four of anhydroignavinol. The fourth oxygen in anhydroignavinol is probably an ether since no hydroxyl band is observable in the infrared spectra of tribenzoylanhydroignavinol and certain other anhydro-derivatives. It is therefore likely that loss of water accompanying many of the reactions of ignavine involves *ether* rather than double-bond formation. Possible positions for the hydroxyls involved in the elimination assuming a β-glycol moiety are C(11–13), C(7–14), C(7–9), and C(5–9). Since ignavine has a normal pK_a' value (7·7) for a tertiary amine, it is unlikely that a hydroxyl is at C(19) or C(20). In view of the above, anhydroignavinol and ignavine have been provisionally represented by partial structures (117) and (118), respectively. (The absolute configuration shown is based on analogy to that of the other diterpene alkaloids.)

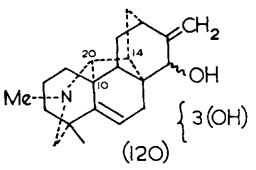
C. Hypognavine and Hypognavinol.[35–38]—Certain varieties of *A. sanyoense* contain an ester alkaloid which has one less oxygen atom than ignavine and is in many respects similar to it. This alkaloid hypognavine, $C_{27}H_{31}NO_5$, is a benzoyl ester, has no methoxly or *N*-methyl group, fails to react with the usual carbonyl-test reagents, and contains one hydrogenatable double bond. Like ignavine, it has two acylatable hydroxy groups and an exocyclic methylene group. In con-

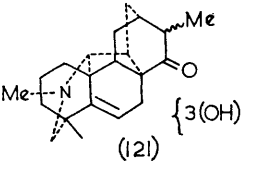
[35] E. Ochiai, T. Okamoto, S. Hara, S. Sakai, and M. Natsume, *Pharm. Bull. Japan*, 1958, **6**, 327.
[36] S. Sakai, *J. Pharm. Soc. Japan*, 1956, **76**, 1054.
[37] S. Sakai, *Chem. and Pharm. Bull. (Japan)*, 1958, **6**, 448.
[38] S. Sakai, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 50, 55.

trast to ignavine, hypognavine can be hydrolysed to an alkamine (hypognavinol, $C_{20}H_{27}NO_4$) without loss of a mol. of water. Acylation reactions and methiodide formation are also straightforward in the case of hypognavinol. Reactions analogous to those previously described afford clear evidence for the existence of a secondary allyl alcohol system such as occurs in atisine, ignavine, and songorine.

Selenium dehydrogenation of hypognavinol furnishes 1,8-dimethyl-phenanthrene, 1,7-dimethyl-6-n-propylphenanthrene, and 3-ethyl-1,8-dimethylphenanthrene, the latter two being characteristic products of anhydroignavinol. This suggests that hypognavine has the same skeleton as derived for ignavine. Formula (119) will be used as a basis for interpreting the chemistry of hypognavinol.

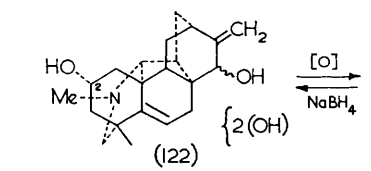

(119)

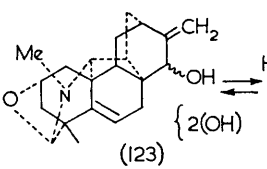

(120)

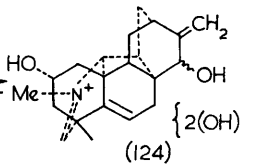

(121)

Hofmann degradation of hypognavinol methiodide gave the de-*N*-base (120) and the isomerisation product (121). The resistance of de-*N*-methylhypognavinol toward a second Hofmann degradation is well accommodated by (120), for the β positions to the nitrogen at C(4) and C(10) bear no hydrogen and formation of a double bond between C(14) and C(20) would violate Bredt's rule. The size of the heterocyclic ring is indicated by oxidation of hypognavinol derivatives to δ-lactams.

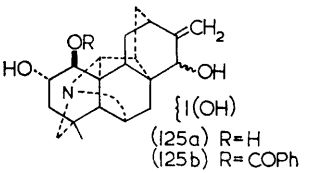
The three remaining oxygen atoms of hypognavinol exist as hydroxyls of which two are acylatable. The non-acylatable hydroxyl is shown to be tertiary by oxidation experiments. Detailed transformations have shown that the α-glycol system in hypognavinol is masked by a benzoyloxy-group in hypognavine. The location of the α-glycol system in ring-A of hypognavinol is fixed by oxidation of de-*N*-methylhypognavinol (122) with silver oxide or alkaline ferrocyanide to a carbinolamine ether (123) from which (122) can be regenerated by reduction with $NaBH_4$. Salts (124) of the carbinol-amine ether show infrared absorption typical of the $>C = N^+<$ group (1686–1679 cm.$^{-1}$) and regenerate the parent base on treatment with alkali. Models show that an axial hydroxyl at C(2) is most favourable for ether formation.


(122)

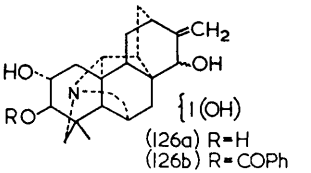

(123)


(124)

The assignment of the second hydroxyl of the glycol system at C(1) or C(3) is not yet settled. Periodate cleavage experiments indicate that a *trans*-glycol system is present. The benzoyloxy-group in hypognavine is accordingly assigned a 1β- or 3β-configuration. The site of the tertiary hydroxyl is unknown. Hypognavinol is thus represented by structure (125a) or (126a) and hypognavine by (125b) or (126b).



(125a) R=H
(125b) R=COPh



(126a) R=H
(126b) R=COPh

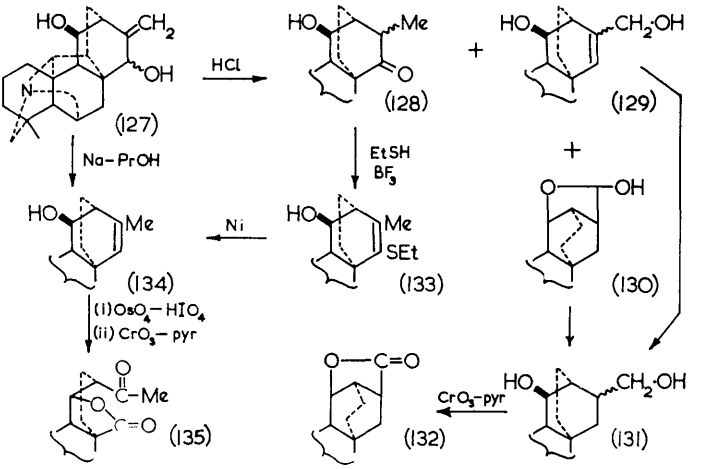
D. Kobusine.[39–41]—This alkaloid, $C_{20}H_{27}NO_2$, has been isolated from *A. Kamtschaticum* (*fischeri*), *A. sachalinense* Fr. Schmidt, *A. luciduseulum* Nakai, and *A. yesoensis* Nakai. It possesses two secondary hydroxy groups in six-membered rings, one of which is involved in an allyl alcohol grouping. Selenium dehydrogenation furnished 1,7-dimethyl-6-n-propylphenanthrene, a characteristic product obtained also from ignavine and hypognavine. These results suggest that kobusine has the same skeleton as ignavine and hypognavine. The chemistry of kobusine will be discussed in terms of the ultimately derived structure (127).

When kobusine (127) is warmed with dilute HCl, compounds (128)–(130) are formed. Compounds (129) and (130) are reducible to the same glycol (131). Oxidation of (131) with CrO_3–pyridine gave a γ-lactone (132) showing the proximity of the two hydroxyls. Treatment of kobusine with sodium in propanol gave the dehydroxyl derivative (134) which was related to the methyl ketone (128) *via* (133). Oxidation of (134) with OsO_4–HIO_4 followed by CrO_3–pyridine gave a γ-lactone (135), thus establishing the relationship between the two hydroxyl groups.

E. Pseudokobusine.[41,42]—Isolated from *A. yesoensis* Nakai and *A. luciduseulum* Nakai, this alkaloid, $C_{20}H_{27}NO_3$, is closely related to kobusine. It is a tertiary base containing three acylable hydroxyls (tribenzoate), an exocyclic methylene involved in an allyl alcohol group, a *C*-methyl group, and no methoxy. Oxidation experiments show that the allylic hydroxyl and one other are on six-membered rings and the third hydroxyl is tertiary since it is inert to Kiliani's reagent.

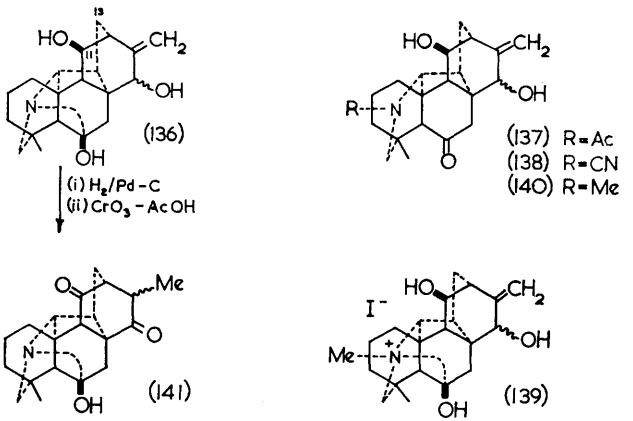
Selenium dehydrogenation of pseudokobusine gave 1,7-dimethyl-6-n-propylphenanthrene, a result which suggests that pseudokobusine has the same

[39] M. Natsume, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 539.
[40] T. Okamoto, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 44.
[41] T. Okamoto, M. Natsume, H. Zenda, S. Kamata, and A. Yoshino, Abstr. I.U.P.A.C. Symposium, Kyoto, 1964, 115.
[42] M. Natsume, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 879.



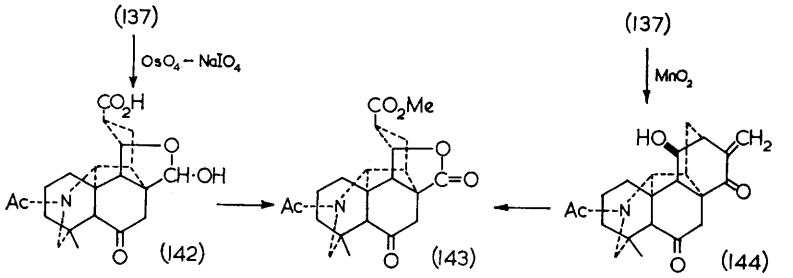
structure as kobusine, with the addition of one tertiary hydroxy group. The chemistry of pseudokobusine will be discussed in terms of structure (136).

Acetylation of pseudokobusine gave besides the normal *O*-acetate, an *N*-acetyl-seco-derivative (137). An analogous *N*-cyano-seco-derivative (138) was prepared with cyanogen bromide. Both seco-compounds regenerated kobusine when hydrolysed with 20% potassium hydroxide. Pseudokobusine methiodide (139) gave with ammonium hydroxide the *N*-methylketone (140) (1675 cm.$^{-1}$), which regenerated (139) when treated with hydriodic acid.

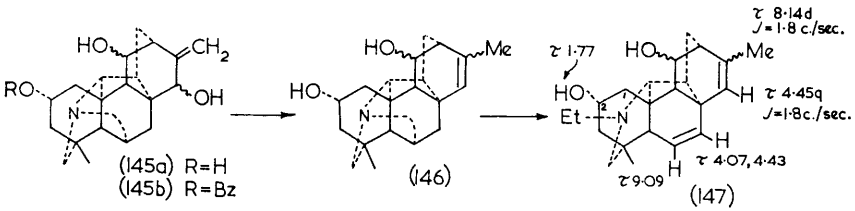


The location of the third hydroxyl group was determined by the following sequence. Oxidation of *N*-acetyl-seco-pseudokobusine (137) with OsO_4–$NaIO_4$ gave a hemiacetal monocarboxylic acid (142), (1720, 1650 cm.$^{-1}$), the methyl ester of which was oxidised with CrO_3–pyridine to the γ-lactone (143) (1778,

1728, 1699, 1630 cm.$^{-1}$). The same γ-lactone was obtained by oxidation of (144) with OsO_4–$NaIO_4$, followed by esterification. These transformations limit the position of the third hydroxyl group to position C(11) or C(13). That C(11) is the correct locus for the hydroxyl was shown by correlation of pseudokobusine with kobusine.



F. Isohypognavine.[43,44]—This alkaloid $C_{27}H_{31}NO_4$ (145b) occurs in the roots of *A. majimai* Nakai and *A. japonicum* Thumb and is a benzoate of the alkamine, isohypognavinol (145a). The latter has three acylatable hydroxyls, one of which is involved in the typical allyl alcohol system. Isohypognavine (145b) has been correlated with kobusine (127). Reduction of isohypognavinol (145a) with sodium in propanol gave a deoxy-derivative (146), the ethiodide of which afforded on Hofmann degradation a tertiary base (147). Nuclear magnetic resonance studies on (147) support the assignment of an α-hydroxyl group at C(2).



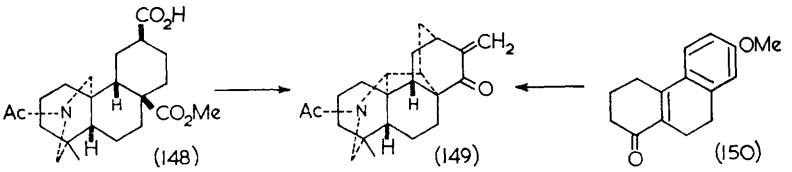
7 Synthesis of Diterpene Alkaloids

There has been such a flurry of activity in this area in the past few years that only a few significant developments will be cited.

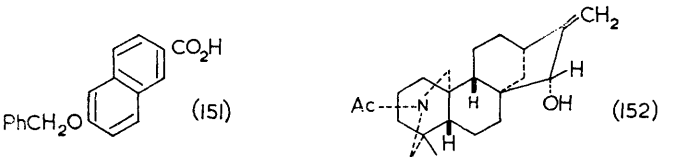
The *N*-acetyl ester (148), a key intermediate in the correlation of the *Atisine* and *Garrya* alkaloids, has been converted *via* (149) into atisine (70) by a twelve-step sequence.[45] The first complete stereospecific synthesis of (±)-atisine was reported by Nagata *et al.*[46] starting from ketone (150), which by a 23-step process

[43] E. Ochiai, T. Okamoto, S. Sakai, and S. Inoue, *J. Pharm. Soc. Japan*, 1955, **75**, 638.
[44] E. Ochiai, T. Okamoto, S. Sakai, M. Kaneko, K. Fujisawa, U. Nagai, and H. Tani, *J. Pharm. Soc. Japan*, 1956, **76**, 550.
[45] S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, 1963, No. 4, 205.
[46] W. Nagata, T. Sugasawa, M. Narisuda, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, 1963, **85**, 2342.

was also converted into ketone (149). A synthesis of (±)-garryine and (±)-veatchine involving intermediates from the atisine synthesis has also been reported by Nagata *et al.*[47]



A totally different synthesis of the diterpene alkaloids has been reported by Masamune starting from (151).[48] He has also converted compound (152), obtained from veatchine azomethine acetate, by a multistep procedure into the monoester carboxylic acid (148). Since (148) has already been converted into atisine,[45] this work completes in a formal sense the synthesis of atisine also.



Still a third synthesis of the *Garrya* alkaloids has been reported by Valenta, Wiesner, and Wong starting with 5-methoxy-2-tetralone.[49] In recent papers the New Brunswick group[50] has described two new synthetic sequences which can be used to elaborate both atisine- and *Garrya*-type structures.

Several other interesting approaches to the synthesis of the diterpene alkaloids have been reported.[51–71]

The Reviewer's work was supported by grants from the National Institutes of Health, U.S. Public Health Service.

[47] W. Nagata, M. Narisuda, T. Wakabayashi, and T. Sugasawa, *J. Amer. Chem. Soc.*, 1964, **86**, 929.
[48] S. Masamune, *J. Amer. Chem. Soc.*, 1964, **86**, 288, 290, 291.
[49] Z. Valenta, K. Wiesner, and C. M. Wong, *Tetrahedron Letters*, 1964, No. 36, 2437.
[50] R. W. Guthrie, A. Philipp, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1965, No. 34, 2945.
[51] I. Iwai, A. Ogiso, and B. Shimizu, *Chem. and Ind.*, 1962, 1288.
[52] I. Iwai and A. Ogiso, *Chem. and Ind.*, 1963, 1084.
[53] B. Shimizu, A. Ogiso, and I. Iwai, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 333, 766.
[54] A. Ogiso, B. Shimizu, and I. Iwai, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 770, 774.
[55] A. Ogiso and I. Iwai, *Chem. and Pharm. Bull. (Japan)*, 1964, **12**, 820.
[56] A. A. Othmann and N. A. J. Rogers, *Tetrahedron Letters*, 1963, No. 20, 1339.
[57] W. L. Meyer and A. S. Levinson, *Proc. Chem. Soc.*, 1963, 15; *J. Org. Chem.*, 1963, **28**, 2859.
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[59] N. N. Girotra and L. H. Zalkow, *Tetrahedron*, 1965, **21**, 101.
[60] T. Matsumoto and A. Suzuki, *Bull. Chem. Soc. Japan*, 1961, **34**, 274.
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[62] R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, 1965, **30**, 4145.
[63] D. H. R. Barton and J. R. Hanson, *Chem. Comm.*, 1965, No. 7, 117.
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[65] A. Tahara, K. Hirao, and Y. Hamazaki, *Tetrahedron*, 1965, **21**, 2133; *Chem. and Ind.*, 1965, 850.
[66] K. Wiesner and A. Philipp, *Tetrahedron Letters*, 1966, No. 14, 1467.
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[68] R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1966, No. 38, 4645.
[69] K. Wiesner and J. Santroch, *Tetrahedron Letters*, 1966, No. 47, 5939.
[70] A. A. Othmann, M. A. Qasseem, and N. A. J. Rogers, *Tetrahedron*, 1967, **23**, 87.
[71] R. W. Guthrie, W. A. Henry, H. Immer, C. M. Wong, Z. Valenta, and K. W. Wiesner, *Coll. Czeck. Chem. Comm.*, 1966, **31**, 602.