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THE STEREOCHEMISTRY AND BIOSYNTHESIS OF CERTAIN COMPLEX DITERPENES

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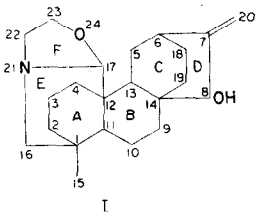
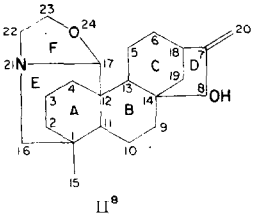
Abstract—From a consideration of the available data the absolute configurations of the atisine and garrya diterpenoid alkaloids have been derived.

The biosynthesis of these, and similar complex diterpenes, is discussed.[1]

THE relative stereochemistry at C(12) and C(13) in the atisine and garrya alkaloids, types I and II respectively, has not been unequivocally defined, but has been generally designated as *anti-* by analogy with other diterpenes.[2] The recent proof that at least five diterpenes, namely isodextropimaric acid,[3] rosenonolactone,[4] rosololactone,[5] 9-deoxyrosenonolactone[6] and cafestol[7] (XLI) have a *syn*-backbone shows that this assumption is not necessarily valid. *A priori*, the eight configurations III—X (and the corresponding enantiomers) are theoretically possible for atisine. The absolute stereochemistry may be deduced in the following manner.



I



II[8]

Atisine and ajaconine (XI) have the same skeletal configuration since both have been converted into the azomethine (XII).[10] It has also been established that atidine (XIII) has the same skeletal stereochemistry as atisine,[11] and that the allylic hydroxyl substituents in ajaconine, atisine and atidine occupy the same position and have the same stereochemistry.[11] The formation of the C(17)–C(9) ether bridge in ajaconine

[1] A preliminary draft of this communication was sent to Dr. O. E. Edwards in January (1960) and formed the basis of discussions in Bristol (November 1959) and other places.

[2] See e.g. K. Wiesner and Z. Valenta, *The Aconite-Garrya Alkaloid* , *Fortschritte der Chemie Organischer Naturstoffe* Vol. 16, p. 26. Springer-Verlag, Vienna (1958).

[3] B. Green, A. Harris, and W. B. Whalley, *J. Chem. Soc.* 4715 (1958); O. E. Edwards and R. Howe, *Canad. J. Chem.* **37**, 760 (1959); Le-Van-Thoi, *C.R. Acad. Sci., Paris* **247**, 1343 (1958).

[4] A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.* 1799 (1958).

[5] A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.* 1807 (1958)

[6] W. B. Whalley, B. Green, D. Arigoni, J. J. Britt and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5520 (1959).

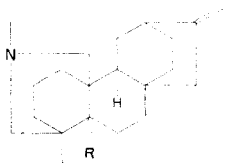
[7] R. A. Finnegan and C. Djerassi, *J. Amer. Chem. Soc.* **82**, 4342, (1960).

[8] The numbering system of Djerassi *et al.*,[9] for the garrya type alkaloids has been modified to make it analogous to that of the atisine alkaloids. The system used in I and II stems logically from the proposed mode of biosynthesis (p. 49). It would seem rational to number the phyllodadene system (XL) in the same manner.

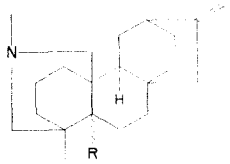
[9] C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, *J. Amer. Chem. Soc.* **77**, 4801 (1955).

[10] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 952 (1957).

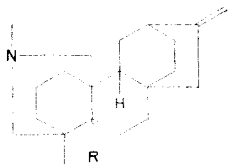
[11] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).



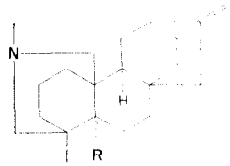
III (R = α–H)
VII (R = β–H)



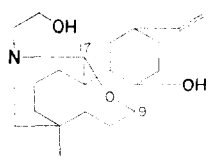
IV (R = α–H)
VIII (R = β–H)



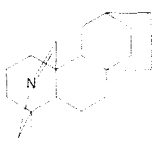
V (R = α–H)
IX (R = β–H)



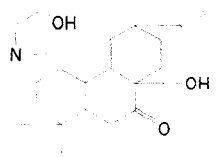
VI (R = α–H)
X (R = β–H)



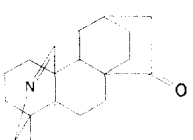
XI



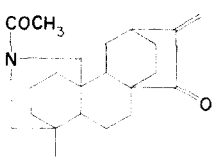
XII



XIII



XIV



XV

and its appropriate derivatives requires C(17) and the C(9) hydroxyl group to be *cis*- and *axial* with respect to ring B. Rings B/E constitute a perhydroisoquinoline system and the relationship between the A/B and the B/E ring systems is such that when the A/B junction is *cis*- the B/E junction has to be *trans*- and *vice versa*. In the *trans*- B/E ring system C(1) and C(17) are equatorial with respect to ring B: but, as indicated C(17) of ajaconine must be *axial* to ring B. To fulfil this requirement the B/E junction has to be *cis*- and thus the A/B junction must be *trans*- in ajaconine. From the correlation[11] between atisine and ajaconine it follows that the A/B ring junction in atisine must also be *trans*. This conclusion is implicit in Edward's earlier work on atisine.[12] Consideration is now restricted to the four A/B *trans*- configurations III–VI.

Sodium borohydride reduction of the ketones XIV and XV furnishes two epimeric alcohols in each case.[13,14] Both epimers are relatively unhindered and consequently the allylic hydroxyl group in atisine must be situated on the *trans*-bridge with respect

[12] D. Dvornik and O. E. Edwards, *Canad. J. Chem.* **35**, 860 (1957).
[13] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 623 (1958).
[14] S. W. Pelletier, *Chem. & Ind.* 1116 (1958).

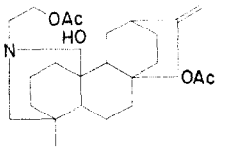
to C(17). This excludes configuration IV. The same evidence suffices to exclude configuration V, in which ring B must be a boat. In V, C(8) and the hydrogen at C(11) are at the stem and stern positions of the Boat B and hence the C(8) ketone (and the related epimeric alcohols) would be subjected to very considerably steric hindrance.

Of the remaining configurations, III and VI, only III is compatible *inter alia* with (a) the extreme ease of conversion of atisine diacetate (XVI) into the azomethine (XVII),[12] where the driving force for this remarkably facile elimination is undoubtedly provided by the tendency[12] of C(17) to assume the trigonal state, due to C(19)–C(17) and C(18)–C(17) hydrogen interaction, with (b) the ease of conversion of the azomethine (XVIII) into the isomer XVII[12] with (c), the co-occurrence in *Aconitum heterophyllum* of atisine and hetisine (probably XIX),[15] where the C(19), C(17) interaction has been eliminated by bond formation, the geometry of which requires an *anti*-backbone, as in III, and with (d), the large negative rotational shift ($[M.]_D$ — 439°) which accompanies the transformation of the methiodide derivative (XX) of ajaconine into the carbinolamine ether (XXI).[16] The initial product from opening of the ether bridge in ajaconine derivatives (e.g. XXI) will have ring B in the boat conformation XXII with the 9-hydroxyl group axially oriented. The unfavourable 1:4-stem-stern interactions between C(17) and the C(9) hydroxyl group will immediately "flip" the boat XXII into the chair conformation XX in which the 9-hydroxyl substituent is equatorial. Infra-red spectral evidence clearly shows that the hydroxyl group in XX is equatorial.[16] The conversion of XX into XXI must thus proceed by way of XXII with the transformation of ring B from a chair to a boat. The observed alteration in rotation[16] is completely compatible with this major conformational change. If ajaconine were to have configuration VI, with a *syn*-backbone, ring B would be forced to retain the boat conformation in the derivative XX, in which the 9-hydroxyl group would remain *axial*: this is contrary to the spectral evidence. Further, the conversion of XX into XXI could only distort, but not *invert*, ring B and thus the rotational changes involved would be relatively small. Thus atisine may be assigned the relative configuration III.[17]

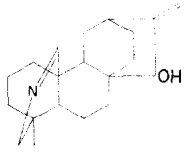
The phenol (XXIII)[13] derived from atisine has a negative rotation and thus most probably has the absolute configuration XXIII[13] with an antipodal *trans*- A/B ring junction. Hence atisine, ajaconine and atidine have the absolute configuration XXIV.[18a] The brilliant investigations of Przybylska and Marion have shown that lycoctonine (XXVI)[19] and aconitine[20] have the absolute configuration XXVI with the *trans-anti*-skeleton. These results together with the co-occurrence[10] of ajaconine, lycoctonine and its associate, delcosine, are compatible with the attractive suggestion,[21] that the atisines are the biogenetic precursors of the aconitine–lycoctonine alkaloids [cf. the sequence XXV → XXVI].

[15] A. J. Solo and S. W. Pelletier, *J. Amer. Chem. Soc.* **81**, 4438 (1959).
[16] D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.* 305 (1958).
[17] The same conclusion has been reached independently by Solo and Pelletier[18] whose work appeared in a preliminary communication during the preparation of this manuscript.
[18] A. J. Solo and S. W. Pelletier, *Chem. & Ind.* 1108 (1960).
[18a] For simplicity in representation and where the absolute configuration is not important the mirror image of XXIV is adopted for many formulae in this paper.
[19] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1843 (1959).
[20] M. Przybylska and L. Marion, *Canad. J. Chem.* **37**, 1116, (1959).
[21] K. Wiesner and Z. Valenta, *Chem. & Ind.* 354 (1956); R. C. Cookson and M. E. Trevett, *J. Chem. Soc.* 3121 (1956).

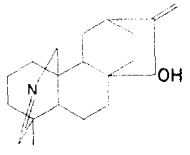
Atisine and veatchine (XXVII) have the same skeletal stereochemistry.[22] Hence veatchine (XXVII), garryine (XXVIII) and cuauchichicine (XXIX)[9] have the absolute configurations shown. Laurifoline[9] is 19-epi-veatchine. Since atisine, atidine and



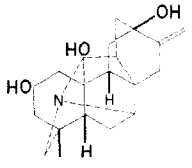
XVI



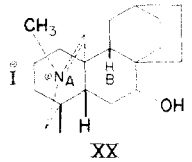
XVII



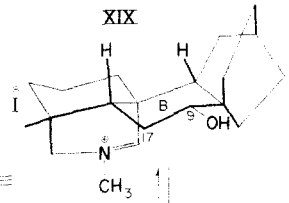
XVIII

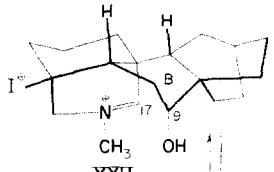


XIX

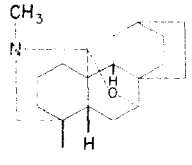


XX

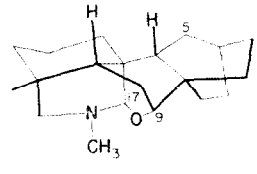




XXII



XXI



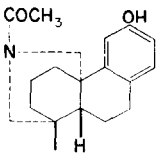
hetisine occur in *A. heterophyllum* it is most probable that hetisine has the absolute configuration XIX.

Although the diterpene alkaloids have an antipodal *trans*-A/B ring junction, the 2-hydroxyl group which has been regarded[23] as a characteristic concomitant of this configuration in sesqui- and di-terpenes, is absent. However, the existence of antipodal diterpenes, e.g. the garrya and atisine alkaloids and eperuic acid,[24] which are devoid of a 2-hydroxyl substituent, and of 'normal' diterpenes, e.g. cassaic acid,[25] which have this group indicate that the problem of the absolute configuration of polycyclic

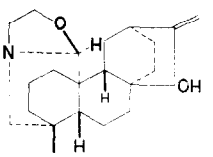
[22] S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).
[23] C. Djerassi, M. Cais and L. A. Mitscher, *J, Amer. Chem. Soc.* **81**, 2386 (1959).
[24] J. A. Barltrop and D. B. Bigley, *Chem. & Ind.* 1447 (1959); J. D. Crocker and T. G. Halsall, *J. Chem. Soc.* 4262 (1956); C. Djerassi and D. Marshall, *Tetrahedron* **1**, 238 (1957).
[25] W. J. Genser and G. M. Sherman, *Chem. & Ind.* 223 (1959); F. E. King, T. J. King and J. M. Uprichard, *J. Chem. Soc.* 3428 (1958).

terpenoids is not associated with the 2-hydroxyl group and is of a more fundamental nature.[26]

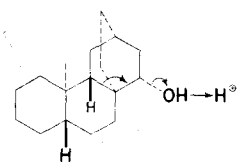
In atisine, the piperidine ring E may have the boat or chair conformation. To



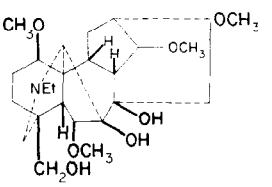
XXIII



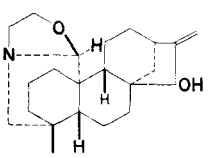
XXIV



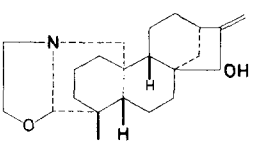
XXV



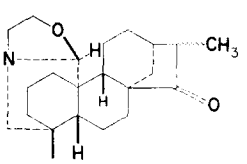
XXVI



XXVII



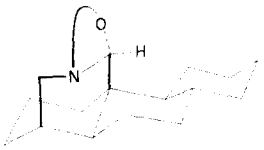
XXVIII



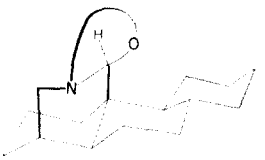
XXIX

each of these the oxazolidine ring may be fused to furnish two *cis*-isomers and one *trans*-isomer XXX–XXXV. The strong steric hindrance between C(17) and the C(18)–C(19) bridge is well established,[2] yet the original oxazolidine ring is readily reformed from a trigonal C(17) derivative of type XXXVI.[12] It thus follows that the oxazolidine ring is attached to the lesser hindered side of C(17) and *not* as in XXXI, XXXII or XXXIII. The strong steric interaction between rings A and F in XXXV seems to exclude this isomer. An unequivocal decision between the remaining alternatives, XXXIV and XXX, does not appear feasible at present, but since the difference between XXXIV and XXX is conformational and not configurational it follows that the absolute configuration of the E/F ring junction is defined as in XXIV. Similar considerations indicate that the E/F ring junction in the garrya alkaloids is also of the XXX or XXXIV type. Geometrical considerations require ring E in the

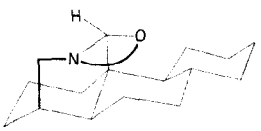
[26] cf. W. B. Whalley in *Recent Development in the Chemistry of Natural Phenolic Compounds.* Pergamon Press (in press).



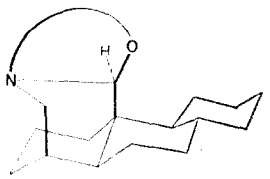
XXX cis



XXXI trans



XXXII cis



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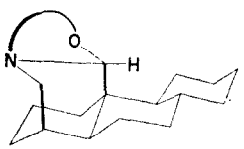
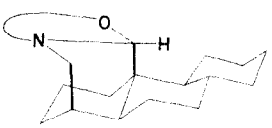
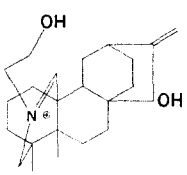


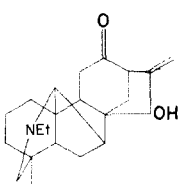
XXXIV cis



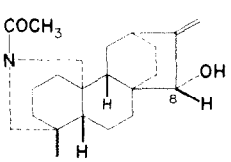
XXXV cis



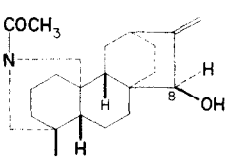
XXXVI



XXXVI a



XXXVII



XXXVIII

aconitine–lycoctonine alkaloids type XXVI, in songorine[27] (XXXVIa) (and its congeners) and in those derivatives of ajaconine with the C(9)–C(17) ether bridge to have the chair conformation XXXV. Similarly, hetisine (XIX) and its associates must have ring E in the boat conformation XXX.

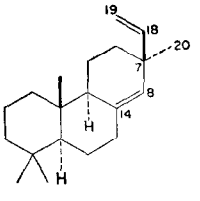
A comparison of the difference in adsorption upon alumina of the epimeric alcohols XXXVII and XXXVIII showed the natural epimer to be the less firmly bound and it was suggested[14] that this would be the epimer XXXVII in which the allylic hydroxyl group and the nitrogen bridge are in a *cis*-relationship. However,

[27] E. Ochiai, T. Okamoto, S. Sakai, T. Sugasawa and T. Onouchi, *Chem. & Pharm. Bull.* **7**, 542 (1959).

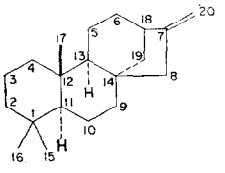
this interpretation appears to be incorrect. In the *cis*-isomer XXXVII the nitrogen and hydroxyl groups are almost co-planar and since no other portion of the atisine molecule projects through this plane they may be adsorbed simultaneously onto a surface.[28] Consequently the less firmly held epimer should be XXXVIII in which the nitrogen bridge and the C(8) hydroxyl substituent are *trans*. Thus atisine, ajaconine and atidine have an 8β-hydroxyl group as in XXXVIII. This also applies to laurifoline:[9] veatchine and garryine have 8α-hydroxyl substituents.[9]

Biosynthesis

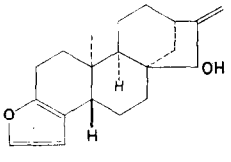
Wenkert has postulated[29] that pimaradienes of type XXXIX are the biogenetic precursors of the tetracyclic diterpenes, e.g. phyllocladene (XL), and of the diterpenoid alkaloids types I and II. The suggestion that only those pimaradienes with quasi-axial C(7) vinyl residues would occur naturally has been invalidated by the proof[3] that dextro- and isodextropimaric acid are epimeric at C(7). Further, the facile transformation of ring C from a half-chair to a half-boat (and *vice versa*) would change the conformation of a quasi-equatorial C(7) vinyl group to quasi-axial. Consequently the biosynthesis of tetracyclic diterpenes from pimaradienes in which the C(7) vinyl substituent is initially either quasi-axial or quasi-equatorial might be expected: in more general terms the C(7) vinyl substituent may be α- or β-oriented. This view is substantiated by the fact that the garrya II and atisine (I) alkaloids and mirene[30] (XLVII) are derived from precursors with a C(7) quasi-axial vinyl substituent, but the pimaradienes which yield cafestol (XLI), phyllocladene (XL), (−)kaurene[30] and gibberellic acid (XLII)[31] must have C(7) quasi-equatorial vinyl groups. Hence it follows that the Wenkert hypothesis *does not* uniquely define the stereochemistry of rings C and D in these tetracyclic diterpenes, despite implications to the contrary.[29]



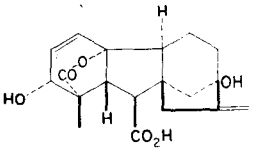
XXXIX



XL



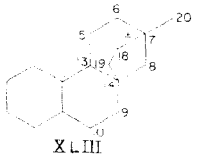
XLI



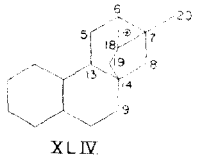
XLII

[28] We are informed by Professor Pelletier that he has reached the same conclusion.
[29] E. Wenkert, *Chem. & Ind.* 282 (1955).
[30] L. H. Briggs, B. F. Cain, R. C. Cambie and B. R. Davis, *Tetrahedron Letters* No. 24, 18 (1960).
[31] O. E. Edwards, A. Nicolson, J. W. Apsimon and W. B. Whalley, *Chem. & Ind.* 624 (1960) and references cited therein.

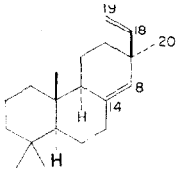
According to the Wenkert hypothesis[29] the biosynthesis of the atisine and garrya alkaloids from a pimaradiene type XXXIX is initiated by protonation of the 8:14 double bond. A garrya alkaloid may then result by way of the bridged cation XLIII. Alternatively transformation of XLIII into the bridged cation XLIV by a hydride shift (or its equivalent) will yield an atisine alkaloid.



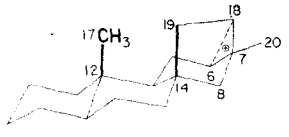
XLIII



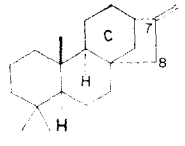
XLIV



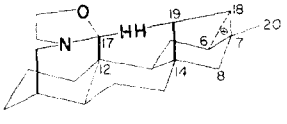
XLV



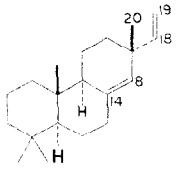
XLVI



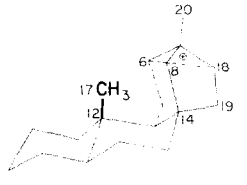
XLVII



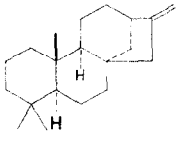
XLVIII



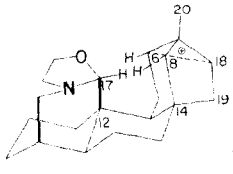
XLIX



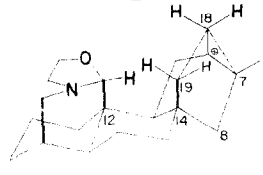
L



LI



LII

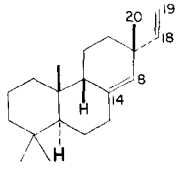


LIII

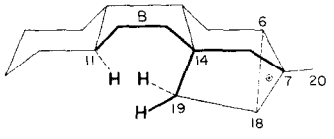
We now suggest that the configurations of the atisines, the garrya alkaloids and the known tetracyclic diterpenes, e.g. phyllocladene, are compatible with the hypothesis that the configuration of the intermediate cations, XLIII and XLIV, is subject to *steric* control.

The formation of the cation LV from the pimaradiene LIV is energetically very unfavourable due to severe steric interactions between the C(11) hydrogen and C(19) which occupy flagpole positions in boat B. On the other hand this steric effect is absent from the ion LVIII derived from the diene LVII. Here ring B has a skew boat conformation and in addition the five-membered ring D distorts ring B so that the

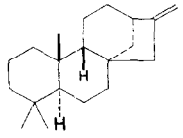
C(8)–C(14) bond is bent *away* from the C(11) hydrogen. Consequently the biosynthesis of the atisine system (VI) and of the garrya and phyllocladene systems of configuration LVI may be considered improbable, but tetracyclic diterpenes of type



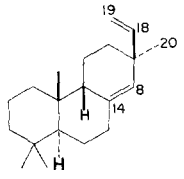
LIV



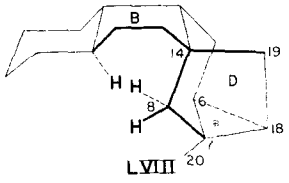
LV



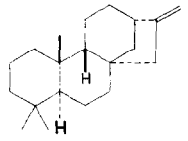
LVI



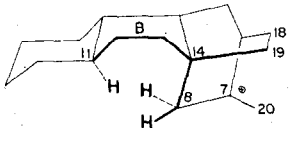
LVII



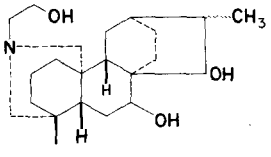
LVIII



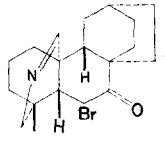
LIX



LX



LXI



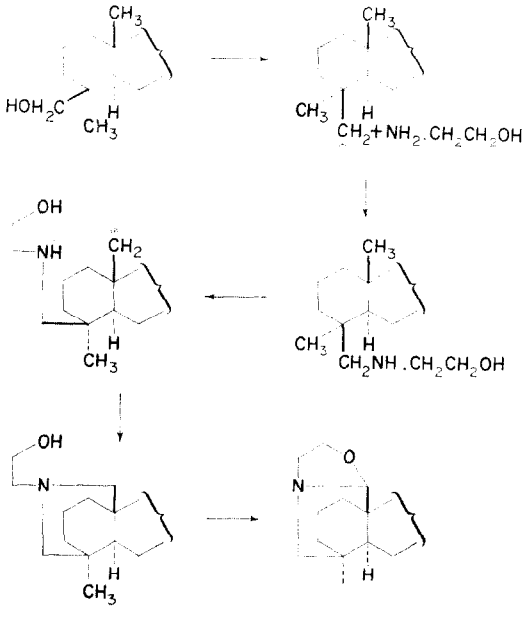
LXII

LIX could be produced. Although no garrya alkaloids of configuration LIX are known the tetracyclic diterpenes, (—)-kaurene[30] and cafestol (XLI)[9] belong to this series. The strong C(11) hydrogen, C(8) flagpole interaction across the boat ring B in the cation LX makes it formation from LVIII, and hence the biosynthesis of an atisine of configuration V, most unlikely.

The 1:3-diaxial interaction between the C(12) methyl substituent and the C(14)–C(19) bond in the cation XLVI derived from the pimaradienes (XLV) may be accommodated by lateral displacement of these substituents, particularly C(17), in the C(12), C(17), C(14), C(19) plane.[32] The corresponding C(12) methyl, C(8)–C(14) bond interaction in the cation L, derived from XLIX, may be similarly accommodated in the C(12), C(17), C(8), C(14) plane. Thus the formation of tetracyclic diterpenes of configurations XLVII and LI appears possible and indeed phyllocladene[33] (XL) has the conformation LI whilst mirene[30] has the configuration XLVII. Therefore, *a priori* the biosynthesis of garrya alkaloids of configurations XLVII and LI and hence of atisines of types III and IV seems feasible. However, there is an even chance that

[32] J. S. E. Holker and W. B. Whalley (in preparation).
[33] P. K. Grant and R. Hodges, *Tetrahedron Letters* No. 10, 21 (1959); P. K. Grant and R. Hodges, *Tetrahedron* **8**, 261 (1960).

the biosynthesis[34] of rings E and F, which may readily be envisaged as proceeding by a sequence such as:-



precedes the formation of ring D. Then the biosynthesis of the cation LII would be energetically most unfavourable because of the C(8)–C(17), C(6)–C(17) hydrogen: hydrogen and the C(6) hydrogen-24 oxygen interactions. Further in the ion LII, the E/F/A ring fusion makes the lateral displacement of C(17) in the C(12), C(17), C(8), C(14) plane very difficult. The steric interactions would thus have to be diminished by a partial flattening and distortion of ring B. Consequently the biosynthesis of garrya alkaloids of configuration LI and of atisines type IV, is improbable. The formation of the cation XLVIII is energetically much more favourable: the C(19)–C(14) bond is not truly axial with respect to ring B and hence the C(19), C(17) interaction is much less than the C(8)–C(17) interaction in the ion LII. In addition the C(6)–C(17) hydrogen:hydrogen and the C(6) hydrogen:24 oxygen interactions are absent. Since the steric interactions in the cations XLVIII and LIII are very similar XLVIII could furnish a garrya alkaloid XLVII directly or an atisine III indirectly, in which the steric interactions are similar to those of the parent cations. The trigonal C(7) in XLVII substantially distorts ring C from a perfect chair and consequently the C(6)–C(17) and C(6):24 oxygen interactions are less than in the structurally associated cation LII. It may be noted that the interactions in the atisine configurations III and IV are virtually identical but steric control of the cyclization (electronic effects are the same) excludes configuration IV.

Consequently of the four *trans*-A/B atisines, only configuration IV is predicted from these considerations, in agreement with deductions from chemical evidence.

[34] The di-N-alkylated ethanolamine bridge in these alkaloids, the N:N-dimethyl ethanolamine ester residue of the Erythrophleum alkaloids[35] and the N-ethyl group of the delpheline-lycoctonine alkaloids have obvious affinities with a common phytochemical progenitor.

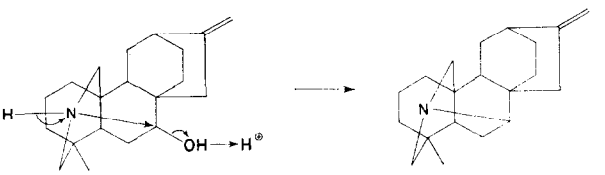
[35] G. Dalma in *The Alkaloid* (Edited by R. H. F. Manske and H. L. Holmes) Vol. IV, p. 265. Academic Press, New York (1954).

As previously indicated (p. 45) the aconitine–lycoctonine alkaloids belong to the atisine stereochemical series. Our concept of the steric control of biogenesis combined with the suggestion[21] that the atisines are the precursors of the lycoctonine group make it tempting to suggest that all aconitine–lycoctonine alkaloids have the unique atisine-type configuration III.

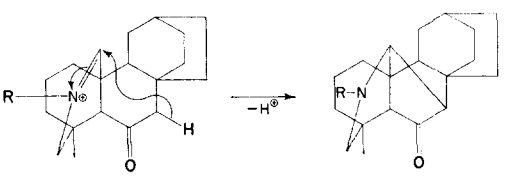
The resistance of C(19) and C(17) in the atisine and garrya alkaloids to lateral displacement in the C(12), C(17), C(19), C(14) plane has been emphasised (p. 52). However, lateral displacement of C(19) (and of the C18–C19 bridge system) in the C(8), C(19), C(9), C(6) plane, i.e. at right angles to the C(12), C(17), C(14), C(19) plane is readily effected by the conversion of ring B into a boat as in XXII, with C(9) and C(17) at the stem and stern positions. This displacement is energetically feasible only when the C(9), C(17) interactions are diminished. The frequent conversion, in the atisine series, of ring B into a boat in which the stem-stern interaction is decreased by various processes may thus be interpreted as a direct consequence of the C(17)–C(19) interaction. The principal reactions of this type are:

(a) The formation of the C(9)–C(17) ether bridge in the ajaconine series.

(b) The production of the nitrogen–C(9) bridge in hetisine (XIX) and its congeners. This reaction probably occurs as follows:



(c) The formation of the C(9)–C(17) link in the aconitine–lycoctonine series. This reaction most probable occurs at the atisine precursor stage by way of a Mannich type reaction:



The presence of an oxygen function at C(10) in the majority of the aconitine–lycoctonine alkaloids is biogenetically significant. The C(9)–C(17) bridge in songorine (XXXVIa) and its associates which will be similarly produced, provides an interesting example of the conversion of ring B, in a garrya type alkaloid, into a boat consequent upon the C(17)–C(19) interaction.

(d) The occurrence of ring B in the boat conformation in the bromoketone (LXII) derived from ajaconine.[36]

Ring B in atidine (XIII) probably has a boat conformation. This view is substantiated by a comparison of the p*Ka* value of 7·5 for atidine, with that of 8·47 for tetrahydroatidine (LXI) where ring B must have the chair conformation. It does not

[36] D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.* 280 (1958).

seem possible to define the conformation of the piperidine ring E in the atidine series or in the F-dihydro-atisine or garrya alkaloids.

It is significant that atisine, ajaconine and atidine have an 8β-oriented hydroxyl group (cf. XXXVIII). Since the α-configuration is required for the lycoctonine type shift XXV $\rightarrow$ XXVI it is tempting to suggest that these atisine structures survive because they have the *wrong* configuration at C(8). No naturally occurring C(8) epimeric atisines are known, but both 8α- and 8β-hydroxyls occur in the garrya series. However, in neither orientation are the C(13)–C(14) bond and the hydroxyl bond co-planar and thus a lycoctonine shift of type XXV $\rightarrow$ XXVI cannot occur. The general reactions[9] of the garrya alkaloids are in agreement with this view. It may thus be predicted that lycoctonine alkaloids of the garrya series do not occur naturally.

Acknowledgement—The author thanks Dr. O. E. Edwards, Ottawa, for helpful correspondence.