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A POSSIBLE BIOSYNTHETIC RELATIONSHIP BETWEEN THE CYCLOPENTANOID MONOTERPENES AND THE INDOLE ALKALOIDS

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IN the well-known Barger-Hahn hypothesis[1,2] the carbon skeleton of yohimbine (I), is considered to be derived from tryptamine, phenylalanine and formaldehyde or its C_1 equivalent. This proposal later gained considerable support as a consequence of the attractive suggestion of Woodward,[3] that a related pathway involving the fission of a 3,4-dihydroxyphenylalanine-derived ring E with the incorporation of a single acetate unit, could simply explain the origin of strychnine. A most valuable consequence of this novel postulate has been the successful biosynthetic anticipation of the subsequently determined structures of a number of other indole alkaloids of varying degrees of complexity, e.g. corynantheine (II)[4] and echitamine (III),[5] and also the isoquinoline base, emetine (IV).[6]

Although in relation to the indole alkaloids the utilization of a tryptamine unit is almost self-evident and has indeed recently been demonstrated

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[1] G. Barger and C. Scholz, Helv.Chim.Acta 16, 1343 (1933).

[2] G. Hahn and H. Werner, Liebigs Ann. 520, 123 (1935).

[3] R.B. Woodward, Nature, Lond. 162, 155 (1948).

[4] M.M. Janot, R. Goutarel and V. Prelog, Helv.Chim.Acta 34, 1207 (1951).

[5] Miss J.A. Hamilton, T.A. Hamor, J. Monteath Robertson and G.A. Sim, Proc.Chem.Soc. 63 (1961).

[6] Sir Robert Robinson, Nature, Lond. 162, 524 (1948).

by the incorporation of tryptophan-2-^{14}C into ajmaline (V),[7] even in the relatively straightforward application of the Barger-Hahn scheme to yohimbine, the details of the required modifications of the phenylalanine precursor are less clear. The ability of C_1 units to substitute into the tyrosine nucleus has been established in the Streptomyces antibiotic novobiocin,[8] however, in this instance substitution occurs at the position meta to the original carbon side chain. The difficulty in adequately explaining the position of the yohimbine carbomethoxy group has been stressed by Robinson[9], who proposed a mechanism involving the expansion of ring E to a tropolone intermediate, with subsequent extrusion of the carboxyl group at carbon-16 (cf. I).

More recently Wenkert and Bringi[10] have drawn attention to the following limitations of the Barger-Hahn scheme: (a) it does not readily account for the predominantly aliphatic character of those indole alkaloids containing a carbocyclic ring E; (b) it is inconsistent with the observation that carbon-15 appears to possess a unique absolute configuration[10] (the single known exception being ψ-akuammicine[11]); (c) the postulated origin of the carbomethoxy group involving a tropolone intermediate is considered to be inadequate.

An ingenious alternative scheme was proposed by these authors in which the alicyclic precursors of phenylalanine, namely shikimic acid and prephenic acid were utilized directly. A key step in this subsequent hypothesis is a 1,2 migration of the pyruvyl side chain of a hydrated

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[7] E. Leete, Chem. & Ind. 692 (1960).

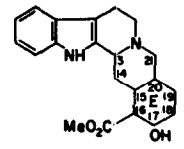
[8] A.J. Birch, D.W. Cameron, P.W. Holloway, R.W. Rickards, Tetrahedron Letters No.25, 26 (1960); K. Chambers, G.W. Kenner, M.J. Temple Robinson and B.R. Webster, Proc.Chem.Soc. 291 (1960).

[9] Sir Robert Robinson, Structural Relations of Natural Products p.110. Clarendon Press, Oxford (1955).

[10] E. Wenkert and N.V. Bringi, J.Amer.Chem.Soc. 81, 1474 (1959).

[11] P.N. Edwards and G.F. Smith, Proc.Chem.Soc. 215 (1960).

prephenic acid with the retention of configuration; in this respect the mode of formation of the substituted ring E carbon skeleton is less direct than that of the Barger-Hahn scheme, although a reasonable analogy was cited in the known pathway leading to homogentisic acid. The opening of ring E corresponding to the Woodward fission, is suggested by Wenkert and Bringi to involve the retro-aldol cleavage of a β-oxycyclohexanone ring.



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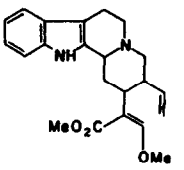

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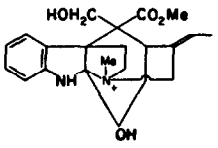

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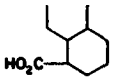

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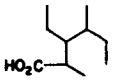

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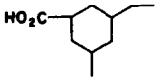
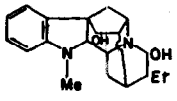


X

XI



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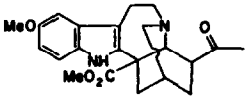

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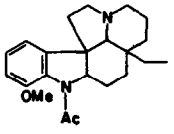

IX

The primary value of such speculations to date, has been the biosynthetic correlation of two major types of C_{10} unit (VI and VII) among the indole alkaloids (existing also as C_9 units where the carbomethoxy group is absent). Two other variants of these C_{10} and C_9 units can be recognized in the indole alkaloids related to voacryptin (VIII)[12] and aspidospermine (IX),[13] the corresponding non-tryptamine moieties being derivatives of X and XI respectively.

[12] V. Renner and D.A. Prins, Experientia 17, 106 (1961).

[13] J.F.D. Mills and S.C. Nyburg, Tetrahedron Letters No.11, 1 (1959). H. Conroy, P.R. Brook and Y. Amiel, Ibid. No.11, 4 (1959).

The purpose of the present paper is to propose a relatively simple scheme for the biosynthesis of the indole alkaloids which appears to satisfy the above criteria. This can be best illustrated in terms of the C_{10}-pyridine alkaloid gentianine (XII), which also has the carbon skeleton VII and whose biosynthesis has been previously interpreted on the basis of both the Barger-Hahn-Woodward[14] and the Wenkert-Bringi[10] hypotheses. It is now suggested that a more direct route is one which would involve the ring fission of a cyclopentanoid monoterpene related to the alkaloids actinidine (XIII) and skytanthine (XIV).[15]

This alternative pathway could equally account for the origin of the glucosides oleuropein (possible structure XV,[16] which in some respects resembles emetine IV), swertiamarine (XVI),[17] and its related lactam bakankosin (XVII),[12] which all contain the C_{10} skeleton VII. Thus on structural grounds, their derivation from non-nitrogenous cyclopentanoid monoterpenes related to verbenalin (XX),[18] genepin (XVIII),[19] and asperuloside (XIX)[20] would be readily explicable.

It would appear to be particularly significant that the esterified carboxyl in most of these compounds is substituted at the carbon atom which would correspond to carbon-16 in yohimbine and the related 17,18-seco series. The absence of this carbomethoxy group in certain indole alkaloids

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[14] T.R. Govindachari, K. Nagarajan and S. Rajappa, Experientia 14, 5 (1958).

[15] C. Djerassi, J.P. Kutney, M. Shamma, J.N. Schoolery and L.F. Johnson, Chem. & Ind. 210 (1961); G.C. Casinovi, J.A. Garbarino and G.B. Marini-Bettolo, Ibid. 253 (1961).

[16] L. Panizzi, M.L. Scarpati and G. Oriente, Gazz.Chim.Ital. 90, 1449 (1960). For alternative structure, cf. B. Shasha and J. Leibowitz, J.Org.Chem. 26, 1948 (1961).

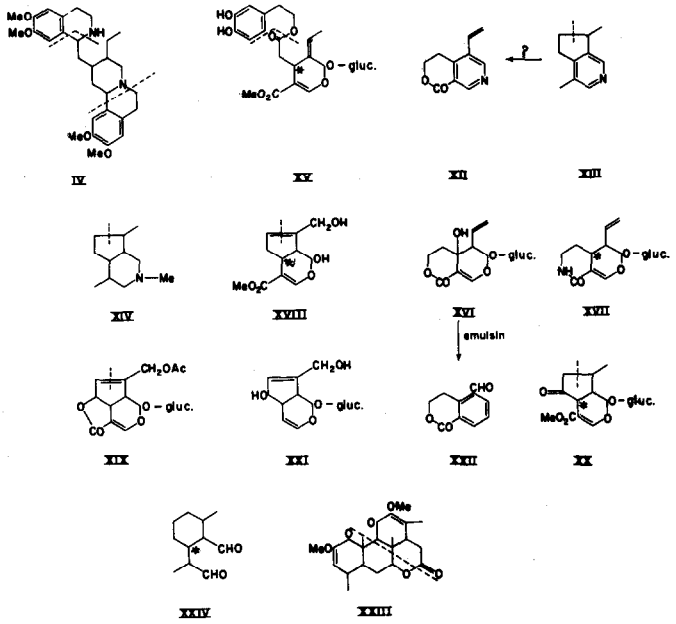
[17] T. Kubota and Y. Tomita, Tetrahedron Letters No.5, 176 (1961).

[18] G. Buchi and R.E. Manning, Tetrahedron Letters No.26, 5 (1960).

[19] C. Djerassi, T. Nakano, A.N. James, L.H. Zalkow, E.J. Eisenbraun and J.N. Schoolery, J.Org.Chem. 26, 1192 (1961).

[20] J. Grimshaw, Chem. & Ind. 403 (1961).

such as ajmaline and also in emetine, finds a parallel in the monoterpenoid series in the bitter substance aucubin (XXI).[21]



On the basis of these structural comparisons, e.g. between swertiamarin (XVI) and asperuloside (XIX), it would seem that unless a biosynthetic interrelationship is involved, the degree of coincidence would be remarkable. The above scheme could be reasonably extended to include the relevant indole alkaloids, with the proviso that the yohimbine alkaloids containing a homocyclic ring E (corresponding to VI) would result from the cyclization of a derivative of the acyclic C_{10} unit VII. This sequence is in direct contrast to that proposed in the previously mentioned hypotheses, however, an analogous ring closure is apparent in the enzymatic degradation of swertiamarin (XVI). Thus, following hydrolysis of the β-glucoside with emulsin, the aglucone

[21] S. Fujise, H. Obara and H. Uda, Chem. & Ind. 289 (1960); J. Grimshaw and H.R. Juneja, Ibid. 657 (1960).

undergoes cyclization to the benzenoid product erythrocentaurin (XXII)[17] (cf. the indole alkaloid alstoniline in which ring E is benzenoid).

A related homocyclic (non-aromatic) structure is contained in the bitter principle quassin whose probable structure (XXIII),[22] would on this basis require the oxidative coupling of two identical monoterpenoid units (containing the same carbon skeleton as VI), in a manner similar to the suggested mode of formation of gossypol.[23]

By analogy with swertiamarin, a parallel cyclization of oleuropein (XV) and also bakankosin (XVII) would yield a hydroaromatic ring in which the stereo-chemical integrity of the carbon asterisked in XV and XVII, would probably be maintained. This asymmetric centre would correspond to the hypothetical precursor of carbon-15 of ring E of the indole alkaloids. While the absolute configurations at this position in oleuropein and bakankosin have not yet been described, the equivalent carbon in genepin (XVIII) is known to be substituted by an α-hydrogen,[19] which is consequently in accordance with Wenkert and Bringi's criterion.[10] The same α-configuration has also been established for all the other members of this group of monoterpenoid compounds studied thus far, including verbenalin (XX), nepetalactone, the ant lactones iridomyrmecin and iridodial (XXIV) and the related product plumieride.[18,19,24]

A biosynthesis of iridodial has been proposed which involves the cyclization of citronellal and this mechanism was simulated in a laboratory synthesis.[25] The subsequently required cleavage of the cyclopentane ring

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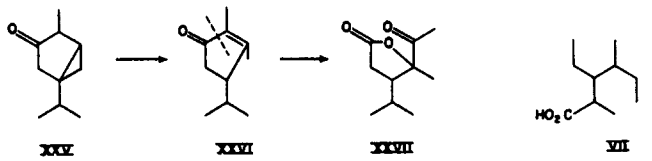
[22] Z. Valenta, S. Papadopoulos and C. Podesva, Tetrahedron In press (1961); R.M. Catman and A.D. Ward, Tetrahedron Letters, No. 10, 317 (1961).

[23] D.H.R. Barton and T. Cohen, Festschrift Arthur Stoll (Edited by A. Stoll) p.117. Birkhauser, Basle (1957).

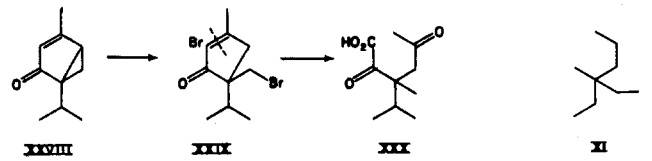
[24] G.W.K. Cavill, Rev.Pure Appl.Chem. 10, 69 (1960).

[25] K.J. Clark, G.I. Fray, R.H. Jaeger and Sir Robert Robinson, Tetrahedron 6, 217 (1959).

(leading to VII) finds an analogy in an established sequence of degradations of thujone (XXV).[26] Thus, under the influence of cold concentrated sulphuric acid, the cyclopropane ring of thujone is opened, yielding isothujone (XXVI) which possesses the same carbon skeleton as iridodial, genepin, etc. (this reaction is consequently compatible with an alternative biosynthetic derivation of the cyclopentanoid monoterpenes via the more commonly occurring cyclohexanoid series such as limonene). Isothujone can then undergo oxidative fission of the cyclopentane ring to give the keto lactone (XXVII), which contains the same carbon skeleton VII present in gentianine, oleuropein, swertiamarin and bakankosin, thus simulating the key step of the presently proposed biosynthetic scheme.



XXV XXVI XXVII VII



XXVIII XXIX XXX XI

The thujone analogue umbellulone (XXVIII) is known to undergo an alternative cleavage of the cyclopropane ring which may be significant in relation to the aspidospermine (IX) alkaloids. Thus, the bromination product dibromoumbellulone (XXIX) is a substituted cyclopentenone containing a quaternary carbon, which can be reduced with zinc and acetic acid to bromodihydroumbellulone and subsequently oxidized with permanganate to yield the diketo acid XXX.[26] An analogous biosynthetic sequence involving the loss of one

[26] P. de Mayo, Chemistry of Natural Products (Edited by K.W. Bentley) Vol. II, Chap. 3. Interscience, New York (1959).

of the gem-dimethyl groups through oxidation and decarboxylation (as is apparent in aucubin formation) would yield the carbon skeleton of the non-tryptamine moiety (XI) of aspidospermine and related alkaloids. These bases could therefore in theory be related to the yohimbine group through a common bicyclic monoterpene precursor of the thujone type. However, in view of the recognized facility with which the terpenes undergo rearrangement, this latter pathway represents only one of a number of possibilities.

It is similarly possible to arrive at various hypothetical schemes for the formation of the cyclohexanoid moiety of indole alkaloids related to voacryptin (VIII). However, it would be of primary importance to test the scheme in relation to the origin of the more common yohimbine group using labelled acetate and mevalonate (XXXI). If its validity could be verified in this way, then subsequent studies, as employed in the investigation of the biosynthesis of gibberellic acid[27] and trichothecin,[28] would provide information on the nature of the rearrangements involved in the construction of the units X and XI, present in voacryptin and aspidospermine respectively. The poor incorporation of acetate into trichothecin indicates the limited value of this precursor, relative to mevalonate, for the detection of terpenes.

Although the present concept, requiring the combination of tryptamine with a monoterpene is far removed from the Barger-Hahn and Wenkert-Bringi hypotheses, it would be entirely consistent with the recently elucidated mode of biosynthesis of another class of indole alkaloids, namely, the ergot group,[29] where the precursors were, in fact, shown to be tryptophan

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[27] A.J. Birch, R.W. Rickards, H. Smith, J. Winter and W.B. Turner, Chem. & Ind. 401 (1960).

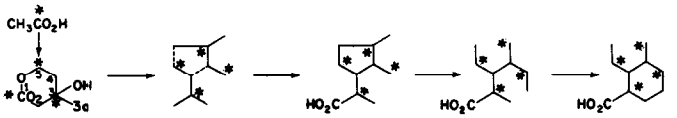
[28] J. Fishman, E.R.H. Jones, G. Lowe, and M.C. Whiting, Proc.Chem.Soc. 127 (1959).

[29] A.J. Birch, B.J. McLouglin and H. Smith, Tetrahedron Letters No.7, 1 (1960).

and mevalonic acid. Echinulin[30] is an isoprenoid fungal indole which is also probably derived from these precursors.

In summary, it is suggested on the basis of the structural relationships noted above, that the biosynthesis of gentianine, oleuropein, swertiamarin and bakankosin is related to that of the non-tryptamine moiety of the indole alkaloids and that the hypothetical pathway possesses the following features: (a) the C_{10} unit VII may be derived from two units of mevalonate via a cyclopentanoid monoterpene in such a way that the berberine bridge of yohimbine (carbon-21) would correspond to carbon-5 of this precursor (also equivalent to the carboxyl-carbon of acetate). The carbomethoxy group would be derived from either carbon 2 or 3a of mevalonate (equivalent to the methyl carbon of acetate). Neither ring E substituent would be specifically derived from C_1 units, as required by the earlier hypotheses; (b) the alkaloids containing the acyclic C_{10} unit VII would represent the skeletal precursors of the homocyclic ring E group (corresponding unit VI), which would be formed in an analogous manner to that involved in the cyclization of swertiamarin (XVI) to erythrocentaurin (XXII); (c) the C_{10} series (containing the units VI and VII) would be expected to represent the parent structures, giving rise to the C_9 series by decarboxylation.

The overall biosynthetic sequence may be outlined thus:



XXXI VII VI

In the specific instance of strychnine, in which the decarboxylated skeleton VII carries an additional C_2 unit, as pointed out by Woodward[3], this is probably derived from another acetate unit. The present scheme

30 C. Cardini, G. Casnati, F. Piozzi and A. Quilico, Tetrahedron Letters No.16, 1 (1959).

would consequently require this part of the strychnine molecule to have a mixed acetate and mevalonate origin. This combination of precursors has been demonstrated by tracer studies to lead to mould products of widely differing structure, e.g. mycophenolic acid,[31] trichothecin[28] and herqueinone.[32] It is worth noting, however, that the carboxymethyl group on the side chain of mycophenolic acid, arises by the oxidative removal of the isopropyl component of an isoprenoid unit, thus providing a possible alternative to the direct incorporation of acetate into the lactam ring of strychnine, *via* the degradation of a cyclopentanoid sesquiterpene.

The present scheme is consistent with taxonomic considerations; thus, aucubin (XXI) from *Buddlea* spp. and bakankosin (XVII), which with a number of indole alkaloids occurs in the genus *Strychnos*, are examples of hypothetically related products from genera classified in the same family (*Loganaceae*). However, in view of the isolation of cyclopentanoid monoterpenes from ants, the significance of this association may be gratuitous. The principal advantage, relative to the two previously suggested hypotheses, is the considerable simplification of the steps required to arrive at the indole alkaloid non-tryptamine skeleton, *via* the rearrangement of a cyclic monoterpenoid precursor.

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[31] A.J. Birch, R.J. English, R.A. Massy-Westropp and H. Smith, *J.Chem.Soc.* 369 (1958).

[32] R. Thomas, *Biochem. J.* *78*, 807 (1961).