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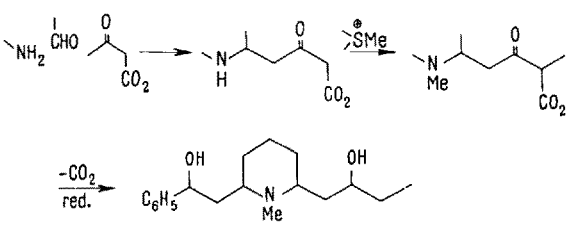
Alkaloid Biosynthesis*

By ERNEST WENKERT**

The last decade has witnessed rapid progress in the chemist's understanding of Nature's methods of synthesis of whole classes of naturally occurring substances. The acetate-polyacetate pathway, long accepted as the route to lipids[1], has been established as the basis of the biosynthesis of natural phenolic-enolic compounds[2] and has been suggested as that of macrolide antibiotics[2–4]. A slight variant, the acetate-mevalonate path, constitutes the acknowledged route to terpenes and steroids[5]. In contrast to these dramatic developments only little headway has been made in our knowledge of the biosynthesis of alkaloids[6].

The determination of the structures of alkaloids and their synthesis for the last forty years have led to the build-up of a vast body of biosynthetic theory whose main common thesis is the assumed intimate relationship between alkaloid biosynthesis and amino acid or protein metabolism[7]. This postulated consanguinity has yielded the impetus for experimentation on many *in vitro* syntheses of alkaloids from amino acids or their equivalents under 'physiological conditions'[7]. It has led to C^{14} tracer experiments being carried out almost exclusively with radioactive amino acids as starting substrates[6]. For a long time it even formed the basis for theories attempting to explain the reason for the existence of alkaloids in higher plants[8]. Despite this overwhelming unanimity of opinion it has been apparent for some time that parts or the whole of the skeleta of some alkaloids cannot be derived from a biosynthetic alkaloid-amino-acid affinity. The acetate unit appears to play an important role in the formation of alkaloids. Thus it appears as such or in a masked form[9] in many systems. As acetoacetate it is responsible for the 'acetone' moiety in the following types of bases: hygrine, cuscohygrine, cocaine, isopelletierine and pseudopelletierine[7,10], for the butyryl unit in pilocarpine[7] and for the hydroxybutyl sidechain in lelobanidine (I) and lobinine:



I

Three acetates appear responsible for the resorcinol unit in the acridone alkaloids[2,7] as well as C-2 and the *n*-amyl sidechain in the quinoline alkaloids of the Angostura bark[11]. Finally, the presence of isoprene units in many furoquinoline systems[7], in some tropane bases[12] and in a few isoquinoline alkaloids[13] as well as

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** Department of Chemistry, Iowa State College, Ames, Iowa, U.S.A.

[1] H. J. DEUEL, Jr., *The Lipids*, Vol. III: *Biochemistry* (Interscience Publishers, Inc., New York 1957).

[2] A. J. BIRCH, *Biosynthetic Relations of Some Natural Phenolic and Enolic Compounds*, in L. ZECHMEISTER, *Progress in the Chemistry of Organic Natural Products*, Vol. XIV (Springer Verlag, Vienna, Austria 1957); A. J. BIRCH, R. A. MASSY-WESTROPP, R. W. RICKARDS, and H. Smith, J. chem. Soc. (*1958*), 360.

[3] R. B. WOODWARD, *The Structure and Biogenesis of the Macrolides, A New Class of Natural Products*, in *Festschrift Arthur Stoll* (Birkhäuser, Basel 1957).

[4] V. MUSÍLEK and V. ŠEVČIK, Naturwiss. *45*, 86 (1958).

[5] H. RILLING, T. T. TCHEN, and K. BLOCK, Proc. Nat. Acad. Sci. *44*, 167 (1958).–J. W. CORNFORTH, R. H. CORNFORTH, G. POPJÁK, and I. Y. GORE, Biochem. J. *69*, 146 (1958).–D. ARIGONI, Exper. *14*, 153 (1958).–A. J. BIRCH, R. W. RICKARDS, and H. SMITH, Proc. chem. Soc. *1958*, 192.–A. J. BIRCH, R. W. RICKARDS, H. SMITH, A. HARRIS, and W. B. WHALLEY, Proc. chem. Soc. *1958*, 223.–J. J. BRITT and D. ARIGONI, Proc. chem. Soc. *1958*, 224.

[6] L. MARION, Bull. Soc. chim. France *1958*, 109.

[7] *Cf.* R. ROBINSON, *The Structural Relations of Natural Products* (Clarendon Press, Oxford, England 1955).

[8] *Cf.* K. MOTHES, *Über die Stellung der Alkaloide im Gesamtstoffwechsel*, in *Festschrift Arthur Stoll* (Birkhäuser, Basel 1957).

[9] *Cf.* R. B. WOODWARD, Nature *162*, 155 (1948).

[10] The derivation of the 'acetone' moiety from acetonedicarboxylic acid[7] is most unlikely because of the absence of dicarboxy alkaloid derivatives in nature and, more importantly, because of the unavailability of any realistic biochemical pathway leading to dicarboxyacetone (*cf.*: A. J. BIRCH, *Biosynthetic Theories*, in A. TODD, *Perspectives of Organic Chemistry* (Interscience Publishers, Inc., New York 1956)).

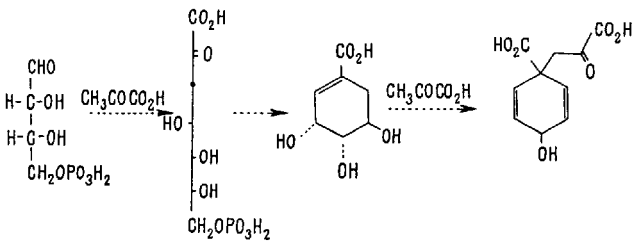
[11] C. SCHÖPF and G. LEHMANN, Ann. Chim. *497*, 7 (1932).–C. SCHÖPF and K. THIERFELDER, Ann. Chim. *518*, 127 (1935).

[12] W. DECKERS and J. MAIER, Chem. Ber. *86*, 1423 (1953).–J. B. JONES and A. R. PINDER, Chem. & Ind. *1958*, 1000.

[13] C. DJERASSI, S. K. FIGDOR, J. M. BOBBITT, and F. X. MARKLEY, J. Amer. chem. Soc. *79*, 2203 (1957).–C. DJERASSI, T. NAKANO, and J. M. BOBBITT, Tetrahedron *2*, 58 (1958).

the existence of monoterpene[14], diterpene and steroid alkaloids illustrate further utilization of the acetate building block.

Two recent discoveries have yielded clues regarding the biosynthetic origin of the majority of alkaloids, those not derivable from acetate units. Firstly, the biosyntheses of the non-resorcinol-phloroglucinol aromatic nucleus[15] and the indole ring[16] have been clarified and, secondly, this disclosure has been utilized successfully in the interpretation of the absolute configuration of the yohimbé, strychnos and cinchona alkaloids[17]. The brilliant work by DAVIS[15] and by SPRINSON[15] has shown that such aromatic systems as anthranillic and oxygenated benzoic acids, phenylalanine and tyrosine are synthesized in bacterial cells from carbohydrates via D-erythrose-4-phosphate (II), 2-keto-3-desoxy-7-phospho-D-glucoheptonic acid (III), shikimic acid (IV) and prephenic acid (V):



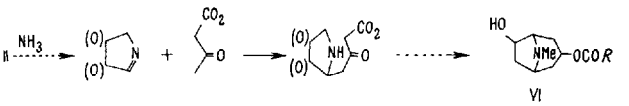
II III IV V

The revelation of this biosynthetic route was followed rapidly by suggestions of its possible universality. Thus the shikimate-prephenate pathway could account for the origin of major structural features of depsides and the tannins[18], flavonoid plant constituents[18,19] and was proved experimentally to be responsible for the C_6-C_3 units of lignin[20].

The surprisingly wide distribution of C_6–C_1, C_6-C_2 and C_6–C_3 units among alkaloid structures, if not as part of the alkamine moieties then as the prosthetic groups, suggests strongly that even in this vast realm of naturally occuring substances the predominant route of biosynthesis is the shikimate-prephenate pathway. It is the purpose of the ensuing discussion to illustrate this relationship between alkaloid biosynthesis and carbohydrate metabolism in light of present-day knowledge in biochemistry. As will become apparent, all alkaloids are derivable, at least formally, from formaldehyde, acetate, pyruvate, erythrose, shikimate and prephenate units by routes which are analoguous in every detail to well-known enzymic reactions.

The C_4 Unit

The origin of the pyrrolidine moiety, appearing in both masked and unmasked fashion as part of the structures of many alkaloids, has been associated for a long time with the metabolism of ornithine or its equivalents[6,7]. While the biosynthetic importance of the amino acid cannot be ignored, its equivalence at this time with erythrose, an early intermediate in the shikimate-prephenate scheme, as a pyrrolidine precursor may be more than coincidence. Thus the tropane alkaloids, whose alkamines occur naturally as esters of, among others, benzoic acid, a dehydration product of shikimic acid, and tropic acid, an aldol product of formaldehyde and prephenate units, may well have their C_4-N ring originate from variously oxygenated succindialdehyde equivalents, themselves derivable from erythrose. The highly oxidized bases, e.g. teloidine (VI), are most likely to find their genesis in this pathway[21]:



VI

Similarly, in the absence of any knowledge regarding the origin of the alkaloidal nitrogen atom the carbohydrate route of biosynthesis cannot be ignored even for the hygrine, nicotine and senecio bases.

The C_4 unit appears to be an important structural moiety in alkaloids derivable from anthranillic acid (VII), itself probably produced from shikimate[15]. A combination of an aminated C_4 unit and reduced anthranillate leads to vasicine (VIII)[7,22], while a slightly varied anthranillate-erythrose complex may be

[14] K. WIESNER, Z. VALENTA, B. S. HULBERT, F. BICKELHAUPT, and L. R. FOWLER, J. Amer. chem. Soc. *80*, 1521 (1958).

[15] B. D. DAVIS, *Biosynthesis of the Aromatic Amino Acids*, and D. B. SPRINSON, *The Biosynthesis of Shikimic Acid from Labeled Carbohydrates*, in W. D. MCELROY and H. B. GLASS, *A Symposium on Amino Acid Metabolism* (The Johns Hopkins Press, Baltimore, Maryland 1955).–P. R. SRINIVASAN, M. KATAGIRI, and D. B. SPRINSON, J. Amer. chem. Soc. *77*, 4943 (1955).–E. B. KALAN, B. D. DAVIS, P. R. SRINIVASAN, and D. B. SPRINSON, J. biol. Chem. *223*, 907, 913 (1956).

[16] C. YANOFSKY, J. biol. Chem. *223*, 171 (1956), *224*, 783 (1957).–L. W. PARKS and H. C. DOUGLAS, Biochim. Biophys. Acta *23*, 207 (1957).

[17] E. WENKERT and N. V. BRINGI, J. Amer. chem. Soc. *81*, 1474 (1959).

[18] *The Chemistry of Vegetable Tannins, A Symposium*, Croydon, Society of Leather Trades' Chemists (G. Marshall and Co., Ltd. London 1956).

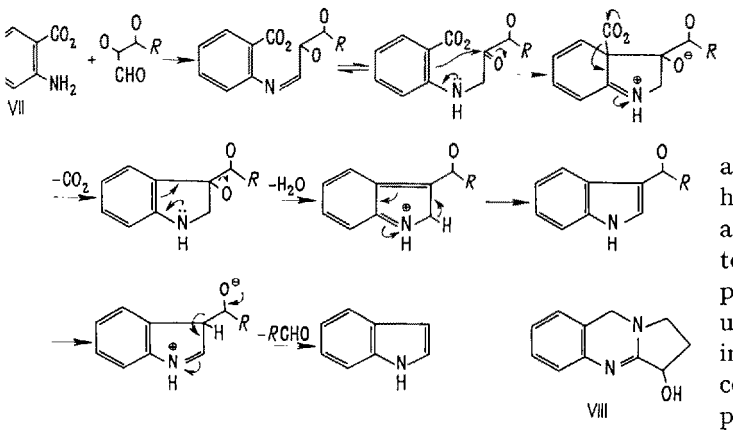
[19] E. W. UNDERHILL, J. E. WATKIN, and A. C. NEISH, Can. J. Biochem. Biophys. *35*, 219, 229 (1957).–T. A. GEISSMAN and T. SWAIN, Chem. & Ind. 984 (1957).–S. SHIBATA and M. YAMAZAKI, Chem. Pharm. Bull. *6*, 42 (1958).

[20] S. N. AZERBO, W. J. SCHUBERT, and F. F. NORD, J. Amer. chem. Soc. *80*, 1990 (1958) and preceding papers.

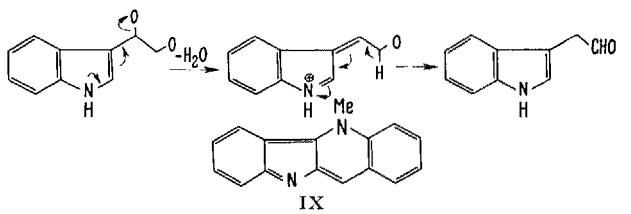
[21] Unfortunately former labelling experiments[6] in this field are inadequate to differentiate between the amino acid and carbohydrate routes. Contrary to claim, the *in vivo* C^{14} incorporation of atropine from labelled ornithine does not prove the latter to be a progenitor of the tropane base. It merely illustrates that the amino acid is an efficient producer of a succindialdehyde equivalent, ROBINSON's brilliantly conceived hypothetical precursor of the tropane alkaloids (R. ROBINSON, J. chem. Soc. *111*, 762 (1917)), but leaves the actual origin of the C_4 unit open to question.

[22] C. SCHÖPF and F. OECHLER, Ann. Chim. *523*, 1 1936).

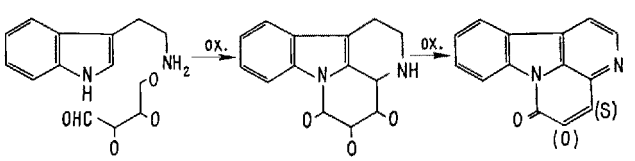
the phytochemical precursor of the indole bases coexisting with vasicine in *Peganum Harmala*. The reaction sequence responsible for the formation of the indole ring has ample analogy in the indole biosynthesis in bacteria, which recently has been shown to emanate from anthranillate and simple monosaccharides[16], and whose pathway can be portrayed mechanistically in the following manner:



While a combination of thus-derived indole and an anthranillate unit can account for the structure of cryptolepine (IX)[7], most indole bases are substituted tryptamines or tryptophols whose origin has been considered to be tryptophan[7], itself arising from anthranillate, via indole, as above[16]. But again, the amino acid pathway is indistinguishable from its carbohydrate counterpart at this time. Thus the following dehydrative break-up of an anthranillate-erythrose complex presents a simpler, alternate route to indole alkaloids:

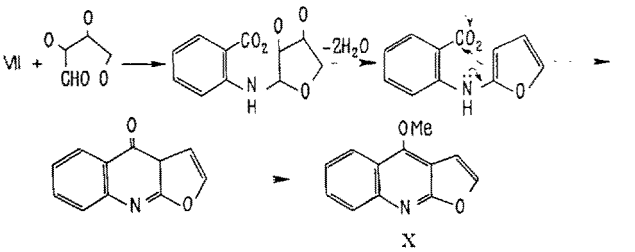


The Piptadenia[23], Physostigma[7] and Calycanthus[7] bases evolve readily from the resulting aldehyde. Plants producing the Harmala and Evodia bases appear to utilize only the shikimate-prephenate scheme—the biosynthetic components being tryptamine, pyruvate, formaldehyde, and anthranillate[7]. Even the structurally unusual 'canthine' bases[7] are derivable from similar precursors, tryptamine and erythrose:

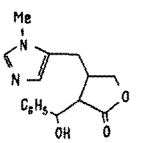


[23] M. S. FISH, N. M. JOHNSON, and E. C. HORNING, J. Amer. chem. Soc. *77*, 5892 (1955).

A slight variant of the above interactions of anthranillate and erythrose lead to the furoquinoline alkaloids, e.g. dictamnine (X):



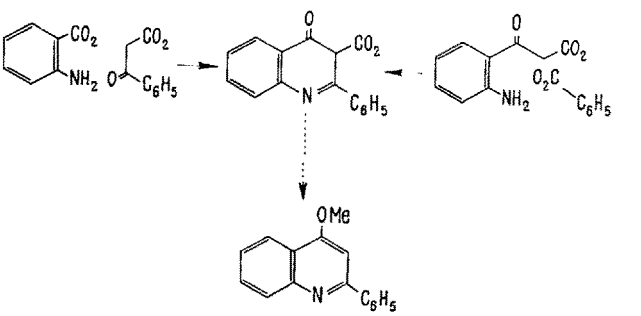
The demonstration of the derivation of the sidechain and two nuclear carbon atoms of histidine from carbohydrate sources[24] strongly suggests that imidazole alkaloids also are derived from sugars in paths parallel to the biosynthesis of histidine[7]. It is of interest that a prephenate unit, histamine and hexose moieties make up the structure of casimiroedine, a recently described imidazole alkaloid[25], while a prephenate is part of the condensed carbon skeleton in the Jaborandi alkaloid pilosine (XI).



XI

The C_6–C_1 Unit

The variously substituted benzoate group, derivable from shikimate (C_6–C_1), has been shown already to be a conspicuous part of many alkaloid structures. In most previous cases it has appeared along side C_4 or acetate units, but in many alkaloids it is revealed in conjunction with a prephenate moiety, e.g. the alkaloids of the Angostura bark and the Lunasia base, 4-methoxy-2-phenylquinoline (XII)[26]:



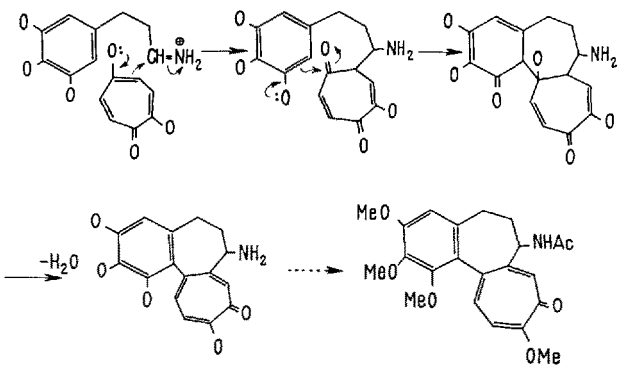
XII

[24] H. S. MOYED and B. MAGASANIK, J. Amer. chem. Soc. *79*, 4812 (1957).– B. N. AMES, J. biol. Chem. *226*, 583 (1957), and preceding papers.

[25] C. DJERASSI, C. BANKIEWICZ, A. L. KAPOOR, and B. RINIKER, Tetrahedron *2*, 168a (1958).

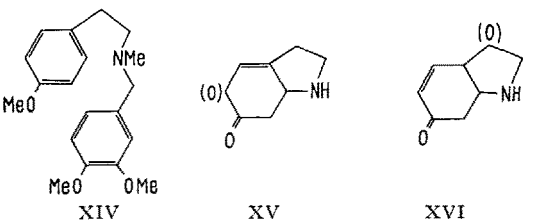
[26] S. GOODWIN, A. F. SMITH, and E. C. HORNING, J. Amer. chem. Soc. *79*, 2239 (1957).

Another shikimate-prephenate interaction is apparent from the structure of colchicine (XIII). The tropolone ring may arise either from a C_6–C_1→C_7 change or, in analogy with mold metabolites[27], directly from acyclic carbohydrate precursors[28]. The following portrays a possible biosynthetic route:



XIII

The Amaryllidaceae represent a class of alkaloids whose biosynthesis also involves the union of a C_6–C_1 entity and prephenate. In an early hypothesis the structure of lycorine (XVII), one of the most abundant bases of this class, was envisaged to be derived from the interaction of two dioxyphenylalanine equivalents and a formaldehyde unit by way of an oxidative phenyl-phenyl coupling and a retro-Michael extrusion of a twocarbon residue[29]. While this accounted for the presence of the C_6–C_1 fraction, it did not support readily the hydroaromatic state of oxidation of ring C[7]. Unfortunately this drawback also plagues a more recent scheme[30], wherein oxidative phenyl-phenyl couplings led to ketonic intermediates, which would be expected to enolize (and thus aromatize ring C) in a cellular environment. However, all difficulties are overcome, if it be assumed that hydroaromatic precursors are involved in the formation of the hydrodiphenyl system. Hence the C_6–C_1 residue corresponds to a shikimate (or IV + formaldehyde–CO_2), while the remaining C_6–C_2N moiety must emanate from prephenate. With the exception of belladine (XIV)[31], whose genesis lies in the oxidation of shikimyl 'prephenyl' amine, all Ammaryllidaceae bases most probably originate from XV and XVI, whose own biosynthesis will be discussed in the Prephenate Section.



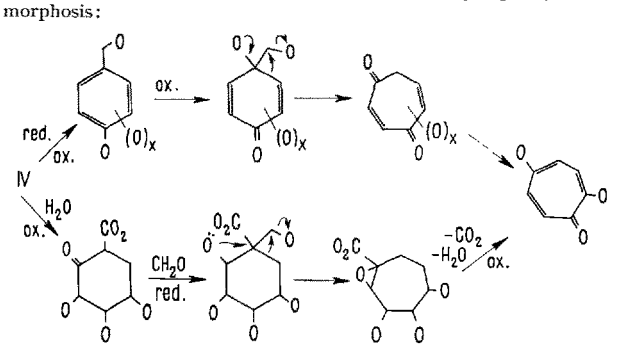
XIV XV XVI

As illustrated in Chart I, internal Michael condensation of a shikimyl derivative of XV, followed by hydration-dehydration, oxidation-reduction changes, leads to alkaloid skeleta characteristic of the lycorine group of substances, e.g. lycorine (XVII), lycorenine (XVIII)[32]. Similarly, the shikimyl derivative of XVI acts as the progenitor of the crinine group (XIX), e.g.: crinine (XXII)[33], the galanthamine variety (XX), e.g.: narwedine (XXIII)[34], and the tazettine type of alkaloids (XXI), e.g.: tazettine (XXIV)[35]. It is noteworthy that the present scheme accounts accurately for the location of oxygen atoms in the Amaryllidaceae alkaloids[36].

The tannins are a group of non-alkaloidal plant products whose structures reveal their carbohydrate-shikimate origin[18]. To account for the presence of the often recurring gallate unit, usually in oxydiphenyl or diphenyl ether form, it has been tempting to suggest

[27] R. BENTLEY, Biochim. biophys. Acta *29*,666 (1958).

[28] The route involving a transformation of shikimate to tropolone (or carboxytropolone) would require the intermediacy of shikimyl alcohol, or its equivalent, which could arise by direct phytochemical reduction of the carboxy group or by the introduction of a formaldehyde unit and the extrusion of CO_2. Furthermore, the state of oxidation of the substrate undergoing ring expansion cannot be described with certainty at this time. The following schemes illustrate two possible extreme representations of the C_6—C_1→C_7 metamorphosis:



Finally, the interaction of the C_7 unit with prephenate might occur at the tropolone or any of the pre-tropolone stages.

[29] E. WENKERT, Chem. & Ind. *1953*, 1088.

[30] D. H. R. BARTON and T. COHEN, in *Festschrift Arthur Stoll* (Birkhäuser, Basel 1957), p. 117.

[31] E. W. WARNHOFF, Chem. & Ind. *1957*, 1385.

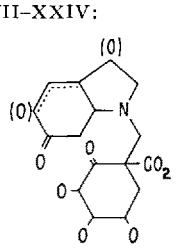
[32] T. KITAGAWA, W. I. TAYLOR, S. UYEO, and H. YAJIMA, J. chem. Soc. *1955*, 1066.–S. TAKAGI, W. I. TAYLOR, S. UYEO, and H. YAJIMA, J. chem. Soc. *1955*, 4003.

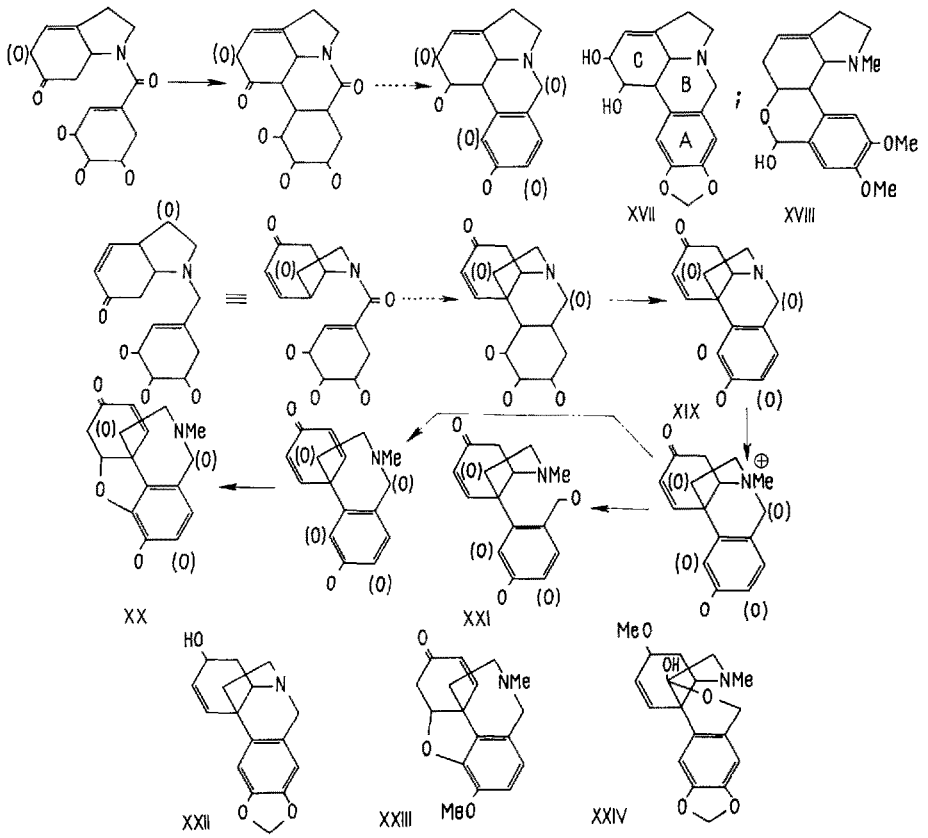
[33] W. C. WILDMAN, J. Amer. chem. Soc. *80*, 2567 (1958).

[34] H. G. BOIT, W. DÖPKE, and A. BEITNER, Chem. Ber. *90*, 2197 (1957).

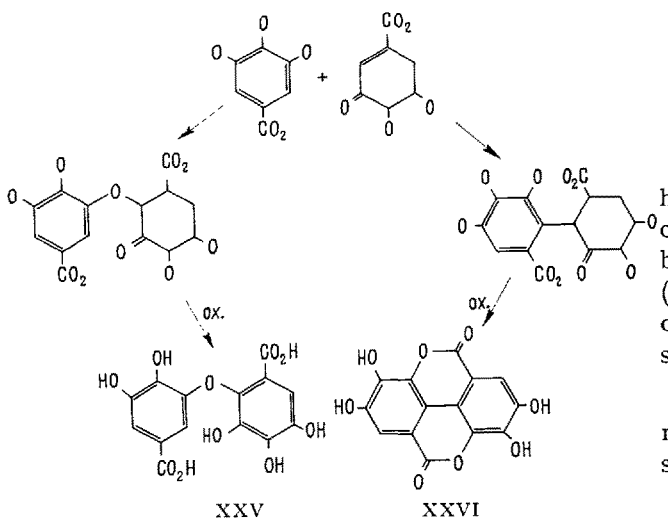
[35] T. IKEDA, W. I. TAYLOR, Y. TSUDA, S. UYEO, and H. YAJIMA, J. chem. Soc. *1956*, 4749.

[36] Since it is not clear whether the benzyl carbon atom on the shikimate unit is the penultimately reduced carboxyl carbon of shikimic acid itself or a formaldehyde unit introduced at an early stage, the following system is an alternative derivative of XV or XVI which requires an internal aldol condensation (rather than a Michael reaction), followed by decarboxylative dehydrations and oxidations, to lead to structures XVII–XXIV:

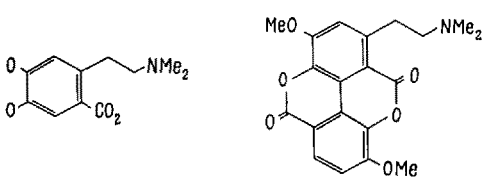




that oxidative phenol coupling of gallate is responsible for the common structure patterns among the tannins[30,37]. As in the case of the Amaryllidaceae alkaloids above, this need not be the sole biosynthetic pathway. Since undoubtedly gallate is derived from dehydro shikimate by oxidation, the latter also may be involved in the dimerization. In this event the coupling process, a Michael condensation, in the genesis of such compounds as dehydrodigallic acid (XXV) or ellaigic acid (XXVI) would take on a similar appearance to that of the Amaryllidaceae alkaloids:



A like interaction of shikimate and the intermediate XXVII, itself obtainable from prephenate (*vide infra*), rather than the previously proposed oxidative degradation of aporphine[38], may represent one of the last stages in the biosynthesis of the alkaloid taspine (XXVIII).



XXVII XXVIII

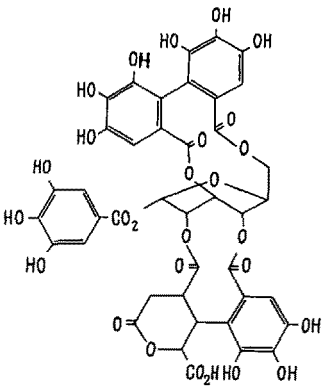
The hypothesis regarding the Michael addition of hydroaromatic intermediates being preferred in some cases to the oxidative coupling of aromatic systems is best supported by the structure of chebullagic acid (XXIX)[39], wherein the lactone ring appears in a state of oxidation which makes its derivation from dehydro shikimate more likely than from gallate.

Structure XXIX also reveals that a shikimate unit may exist naturally as an acyclic or heterocyclic system. Thus the lactonic acid moiety in XXIX may

[37] H. ERDTMAN and C. A. WACHTMEISTER, in *Festschrift Arthur Stoll* (Birkhäuser, Basel 1957), p. 144.

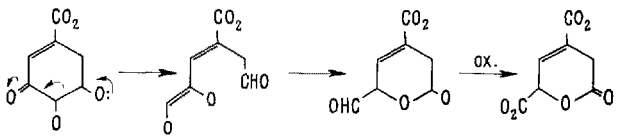
[33] G. F. SMITH, Chem. Soc. Ann. Rep. *53*, 242 (1956).

[34] O. T. SCHMIDT, R. H. HEUSLER, and P. STEPHAN, Ann. Chim. *609*, 186 (1957).

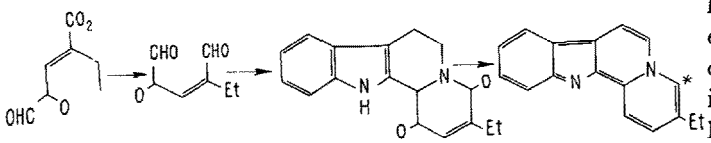


XXIX

arise from a retro-aldol process on dehydroshikimate, followed by oxidation:



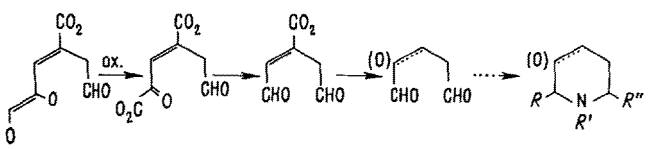
Interaction of a slightly more reduced **intermediate** with a tryptamine unit leads to the skeleton of flavopereirine (XXX):



XXX

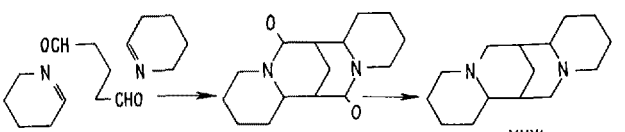
This scheme suggests that a shikimate or shikimate-formaldehyde complex[40] accounts for ring D of the unusual indole alkaloid. A formerly suggested route involving the loss of an acetaldehyde component from a corynantheine derivative[41], presents similar disadvantages to those inherent in an early portrayal of the biosynthesis of the Amaryllidaceae bases[29].

A further consequence of the shikimate cleavage is the possibility of the C_6–C_1 system serving as progenitor of the piperidine unit:

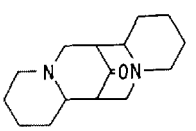


Whereas the construction of the piperidine bases has been associated usually with the metabolism of lysine or close relatives of this amino acid[7,42], nothing unfortunately is known about the origin of the all-important nitrogen atom. In the absence of these data no differentiation can be made between the amino acid and carbohydrate backgrounds of the biointermediates leading to the piperidine nucleus, δ-aminovaleraldehyde, glutaraldehyde, α-oxyglutaraldehyde, glutaconaldehyde and their equivalents. The presence of prephenate units in the alkaloids of black pepper and the Lobelia species suggests that at least in some piperidine bases the carbohydrate scheme may prevail.

In connection with biosynthetic proposals for the various pelletierines and lupanines the interaction of lysine units with formaldehyde and acetone-dicarboxylic acid fragments, or with γ-keto-α,α'-diaminopimelic acid, has been invoked[7,43]. While the unrealistic aspects of the utilization of dicarboxyacetone as a biosynthetic intermediate have been discussed already above, it is noteworthy that its incorporation in the build-up of the lupanines is in violation of known biochemical processes. Irrespective of the exact mode of interaction, the ketonic precursor was considered to be responsible for the formation of the central carbon atoms in the tetracyclic system XXXII. As no lupin alkaloids are oxygenated on the one-carbon bridge, as in XXXII, the latter required reduction to a methylene group. However, such reductions in physiological environment proceed via alcohol and olefin stages, an unallowed route in the present system because of the impossibility of locating a double bond toward the bridgehead of a [3,1,3]-bridge. Instead, the central two rings of an alkaloid such as sparteine (XXXI) must arise from the participation of a third glutaraldehyde unit:



XXXI



XXXII

The C_6–C_2 and C_6–C_3 Units

With the exception of the naturally occurring phenylethylamines, the ephedra bases, a few β-carbolines and substances already discussed above, most alkaloids, whose structures are hypothetically divisible into C_6–C_2 or C_6–C_3 units, are composed of two or more of these fragments. As has been demon-

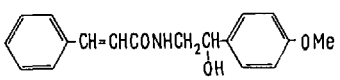
[40] Just as it is impossible to assign rigorously at this time the location of the shikimate ring rupture or the exact state of oxidation of the biointermediates, it is not certain that the carboxyl group in shikimate becomes the starred atom in flavopereirine. The latter might originate from a formaldehyde unit in analogy with the alternate biosyntheses of colchicine and the Amaryllidaceae alkaloids.

[41] Footnote 14 in E. BÄCHLI, C. VAMVACAS, H. SCHMID, and P. KARRER, Helv. chim. Acta *40*, 1167 (1957).

[42] *Cf.* E. LEETE, J. Amer. chem. Soc. *80*, 4393 (1958).

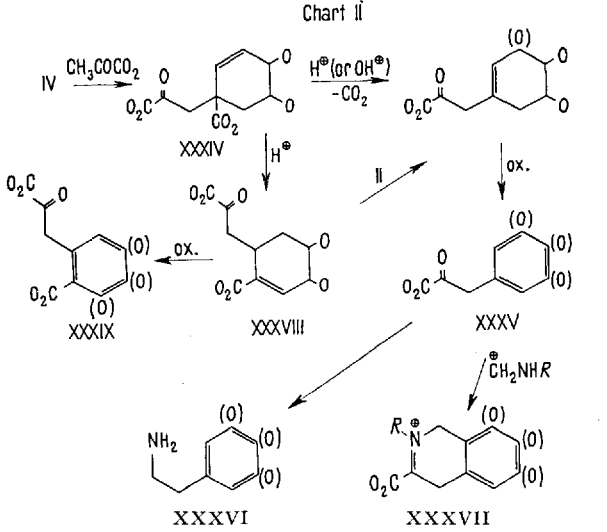
[43] E. ANET, G. K. HUGHES, and E. RITCHIE, Austr. J. Sci. Res. *3A*, 635 (1950).–C. SCHÖPF, G. BENZ, F. BRAUN, H. HINKEL, and R. ROKOL, Angew. Chem. *65*, 161 (1953).–E. E. VAN TAMELEN and J. E. BARAN, J. Amer. chem. Soc. *80*, 4659 (1958).

strated in connection with the biosynthesis of indole alkaloids[17], these structural units can originate from hydrated prephenate (XXXIV) through almost every modification of hydration-dehydration, oxidation-reduction, decarboxylation, aldol-retroaldol and Mannich condensations. Chart II portrays the formation of phenylpyruvate (XXXV) and phenylethylamine (XXXVI). A combination of these two substances may lead to products such as aegelin (XXXIII)[44], or alkaloids of the benzylisoquinoline, aporphine, morphine, cularine and bisbenzylisoquinoline types[7]. The creation of the diphenyl and diphenyl ether linkages in the last four classes can occur, as in afore-mentioned cases, at either the aromatic or the hydroaromatic stages, although recent elegant tracer studies have revealed that in the morphine group, at least, the prephenate units are aromatized prior to the coupling process[45]. Formalation of phenylpyruvate (XXXV) yields XXXVII, the precursor of the protoberberine and protopine alkaloids[7]. Since the conversion of XXXIV into a phenylpyruvate (XXXV) system can proceed by direct decarboxylation and aromatization or by prior 1,2-migration of the pyruvate sidechain, the intermediate (XXXVIII) resulting from such rearrangement might be expected to be trapped as an o-carboxyphenylpyruvate (XXXIX). Indeed, the latter serves as the basis for the structures of taspine (XXVII→XXVIII) and the phthalide-isoquinoline alkaloids[46].

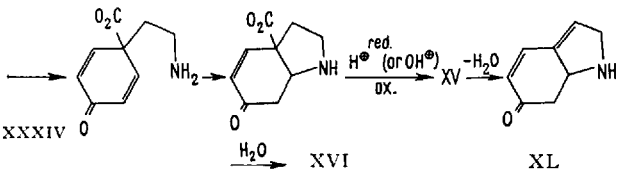


XXXIII

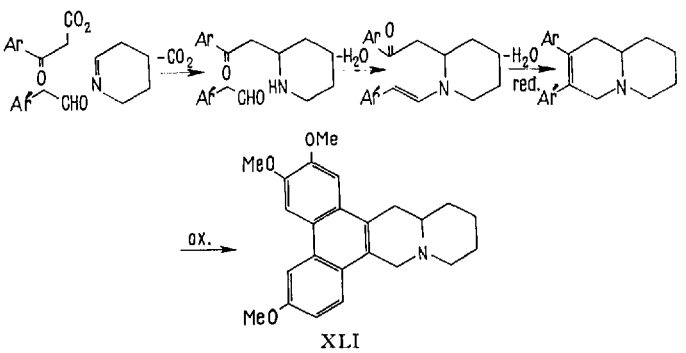
Chart II



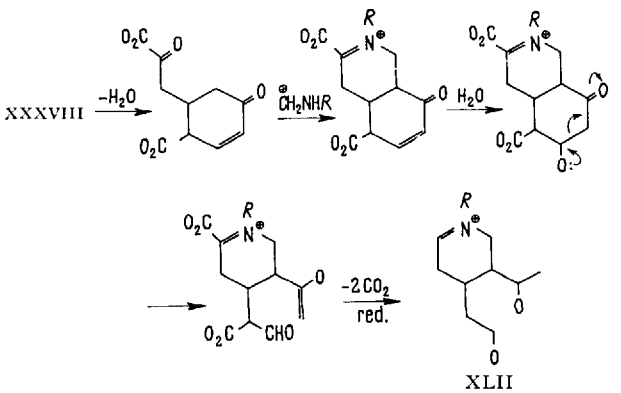
Amination of the prephenate unit (XXXV) at an early stage can lead to a ketamine which may act as the progenitor of the hydroindole portion of the erythrina (XL) and Amaryllidaceae alkaloids (XV and XVI)[47]:



In view of the presence of the active methylene group on the sidechain of the phenylpyruvate unit or its precursors (XXXIV–XXXV) it is not surprising that this position would be the site of further formation of carbon-carbon bonds. Thus direct C-methylation on the sidechain[7] leads to such bases as corydaline, in the protoberberine family, and corycavine, in the protopine class, while aldol condensation at the same site between two prephenate moieties results in the production of alkaloids of the α-naphthaphenanthridine group[48] as well as tylophorine[49] and crytopleurine (XLI)[49]:



Many of the bases in the vast realm of indole and biosynthetically related alkaloids have been shown to revolve around the all-important intermediate XLII, readily derived from XXXVIII[17]:



XLII

[44] R. N. CHAKRAVARTI and B. DASGUPTA, J. chem. Soc. *1958*, 1580.

[45] A. R. BATTERSBY and B. J. T. HARPER, Chem. & Ind. *1958*, 363.–E. LEETE, Chem. & Ind. *1958*, 977.

[46] This scheme now supersedes the previous suggestion regarding the biosynthesis of this group of alkaloids, i.e. their derivation from the protoberberine bases by oxidation[7]. Sir ROBERT ROBINSON has kindly informed the author of his similar views on this subject.

[47] *Cf.* H. PLIENINGER, Exper. *14*, 57 (1958).

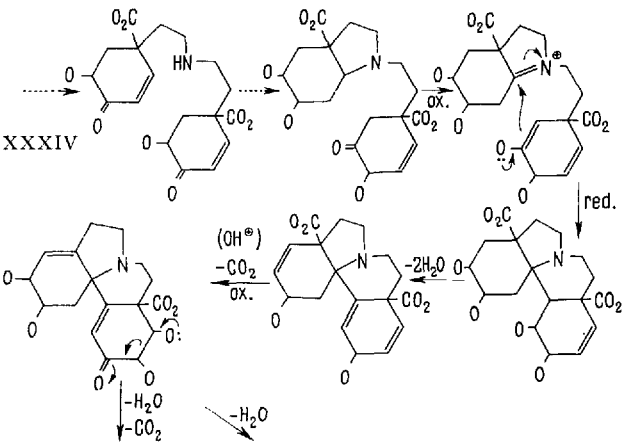
[48] R. H. F. MANSKE in R. H. F. MANSKE and H. L. HOLMES, *The Alkaloids* (Academic Press, Inc., New York 1954), p. 1.

[49] T. R. GOVINDACHARI, M. W. LAKSHMIKANTHAM, K. NAGARAJAN, and B. R. PAI, Chem. & Ind. *1957*, 1484.–P. MARCHINI and B. BELLEAU, Can. J. Chem. *36*, 581 (1958).

Not only are the above intermediates responsible for the genesis of the Yohimbé, Strychnos, Cinchona and Ipecac bases, but they also lay the foundation for the creation of the oxindole[50] and the calebash curare bases[51].

The monotonous consistency with which many alkaloids reveal a twocarbon sidechain in their skeleta strongly hints at the wide distribution of one all-important enzyme, a retroaldolase on the basis of the present theory, which is responsible for the scission of the prephenate unit at a specific site. On this assumption even those alkaloids not based on XLII might be expected to have their prephenate moiety cleaved at the same position. Two such classes appear to exist, the erythrina alkaloids and the indole bases whose dehydrogenation leads to 3,5-dialkylpyridines.

The erythrina bases are made up of two prephenate units, the evolution of one of which has already been illustrated (*cf.* XL). The other structural half is transformed into a phenylethyl group as in the aromatic bases (XLIII) or into a C_5–C_2 lactone as in α-erythroidine (XLIV)[52] and its β isomer. The following indicates their possible biosynthesis:



[50] J. C. SEATON and L. MARION, Can. J. Chem. *35*, 1102 (1957).–J. C. SEATON, R. TONDEUR, and L. MARION, Can J. Chem. *36*, 1301 (1958).

[51] K. BERNAUER, H. SCHMID, and P. KARRER, Helv. chim. Acta *41*, 1408 (1958), and preceding papers.–A. R. BATTERSBY and H. F. HODSON, Proc. chem. Soc. *1958*, 287.

[52] V. BOEKELHEIDE and G. C. MORRISON, J. Amer. chem. Soc. *80*, 3905 (1958).

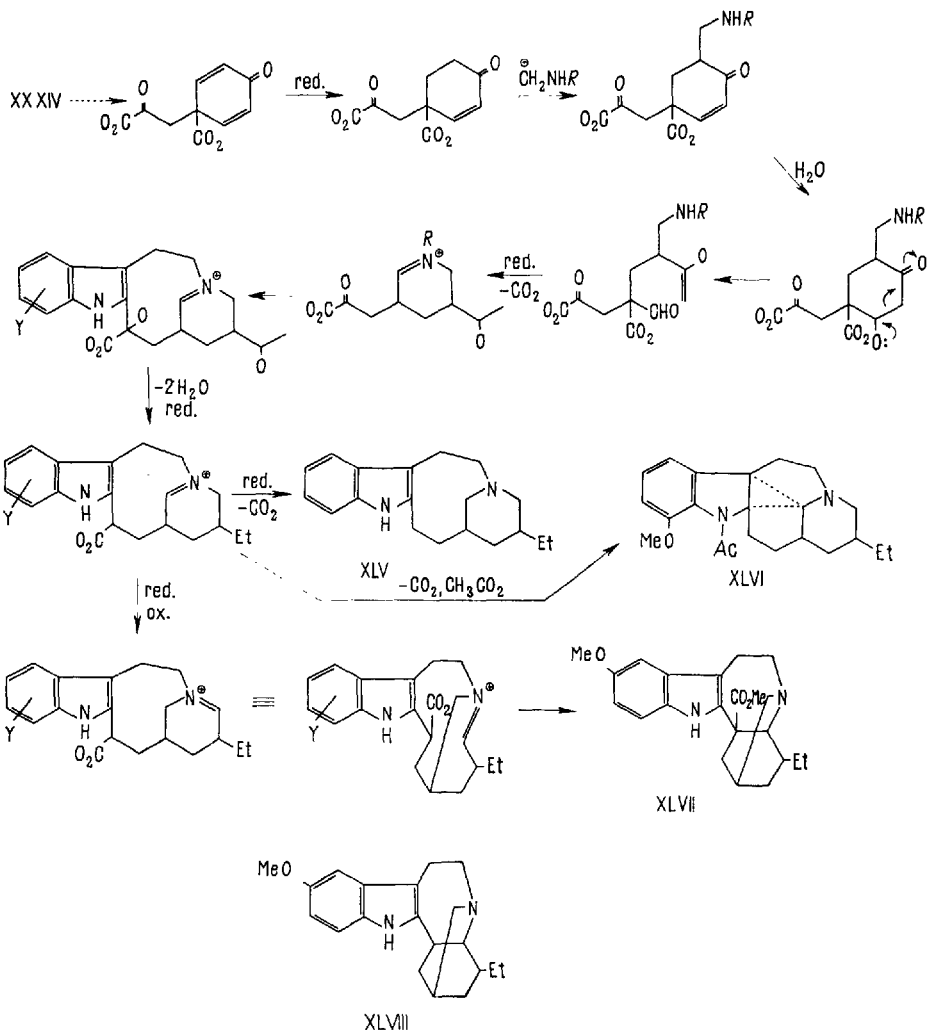
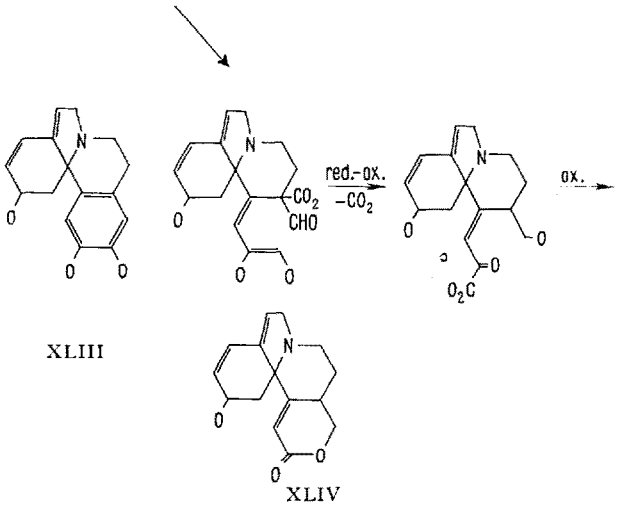


Chart III



XLIII XLIV

The structural features of several of the indole bases isolable from the aspidosperma, iboga and voacanga species reveal their derivation from prephenate, however, not by way of route XXXVIII→XLII. It would seem that in these cases, as in the case of the erythrina bases, the unrearranged skeleton XXXIV itself is the progenitor of the alkaloids under consideration. Formalation and ring opening at now well-determined positions are the initial steps in the pathway to natural products of such structures as quebrachamine (XLV)[53] aspidospermine (XLVI)[53] voacangine (XLVII)[54] and ibogaine (XLVIII)[54]. Their biosynthesis is illustrated in Chart III, pag. 172.

General Observations

The afore-going discussion has attempted to portray the strong likelihood of the biosynthetic derivation of plant alkaloids from carbohydrates, with the exception of the minor intervention of acetate and the possible interposition of ornithine, lysine. This novel unifying theory of alkaloid biosynthesis will now have to be put to a rigorous experimental test, the results of which will be of major interest.

The present theory requires a drastic change in view in connection with at least some hypotheses regarding the reason for the very existence of alkaloids in plants. While it sheds no direct light on this question, it suggests that the answer may be found in the field of the metabolism of plant carbohydrates, rather than amino acids. Thus, for example, should alkaloid production be associated with the plant's mechanism of tangential removal of excess biointermediates from its main metabolic pathways, it would imply that the plant's sugar supply may be excessive. In fact, perhaps this would suggest that alkaloid formation is related to the overabundance of pyruvate, the major intermediate in the shikimate-prephenate scheme.

On the basis of the rapidly emerging patterns of the biosynthesis of plant products, both theoretical and experimental, it is possible to categorize, albeit yet crudely, natural substances into two classes, one based to a large extent on acetate and, hence, on genetically and enzymatically easy routes, and the other founded to a major degree on non-acetate material, i.e. substances farther along in the tricarboxylic acid cycles, and hence, enzymatically difficult, circuitous routes. If it be assumed that the evolution of life processes, i.e. the structure and mechanism of enzymes, through geologic time proceeded from simple to more complex patterns, a correlation of paleobotany with the chemistry of natural products would be on hand. Substances originating from acetate would be expected present in the oldest plants. On this basis the structure of the Lycopodium alkaloid annotinine[55] is no surprise, nor is the discovery of triterpenes from petroleum[56] and coal[57] deposits.

Zusammenfassung

Es wird eine neue Theorie der Alkaloidbiosynthese vorgeschlagen, die alle Alkaloidtypen vereinigt. Die Grundidee dieser Theorie beruht auf der Überlegung, dass die Alkaloide eher mit Kohlehydraten als mit Aminosäuren genetisch verwandt sind. Alle Strukturtypen der Alkaloide sind hypothetisch teilbar in C_4, C_6–C_1, C_6–C_2 und C_6–C_3-Fragmente, und können daher in Beziehung zum Davis-Sprinson-Schema, welches die Biosynthese aromatischer Naturstoffe behandelt, gebracht werden.

[53] Whereas the structures of quebrachamine and aspidospermine have not been fully established, formulas XLV and XLVI are in agreement with available experimental data. These structures were first presented as working models by Professor H. CONROY at the 9th Annual Seminar in the Chemistry of Natural Products, University of New Brunswick, Fredericton, New Brunswick, Canada, October 23–25, 1957 (*cf.* H. CONROY, P. R. BROOK, M. K. ROUT, and N. SILVERMAN, J. Amer. chem. Soc. *80*, 5178 (1958)). Professor SANDOVAL has kindly informed the author of his present use of XLV as a working hypothesis for the structure of quebrachamine (*cf.* B. WITKOP, J. Amer. chem. Soc. *79*, 3193 (1957).–F. WALLS, O. COLLERA, and A. SANDOVAL, Tetrahedron *2*, 173 (1958)).

[54] M. F. BARTLETT, D. F. DICKEL, and W. I. TAYLOR, J. Amer. chem. Soc. *80*, 126 (1958).–W. I. TAYLOR, Exper. *13*, 454 (1957).

[55] K. WIESNER, W. A. AYER, L. R. FOWLER, and Z. VALENTA, Chem. & Ind. 564 (1957).–E. LEETE, Tetrahedron *3*, 313 (1958).

[56] D. H. R. BARTON, W. CARRUTHERS, and K. H. OVERTON, J. chem. Soc. *1956*, 788.

[57] V. JAROLÍN, M. STREIBL, M. HORÁK, and F. ŠORM, Chem. & Ind. *1958*, 1142.