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STUDIORUM PROGRESSUS

The Role of Oxidation in the Biogenesis of Alkaloids

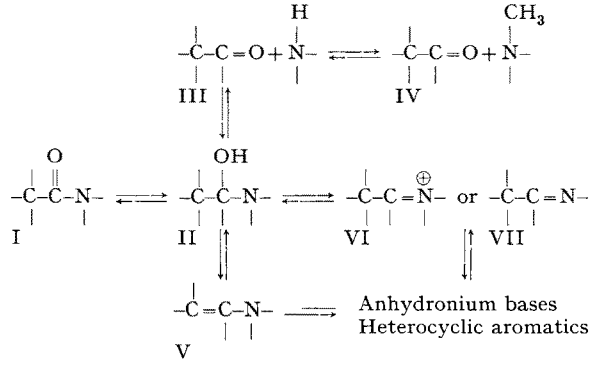
By E. WENKERT, Ames, Iowa[1].

The Mannich condensation involving the interaction between an amino group, a carbonyl function, and a carbanion center present in amines and aldehydes, derivable from amino acid precursors (except for acetonedicarboxylic acid, derivable from citric acid) has served as the basis for the successful correlation and even prediction of the chemical structure of alkaloids obtainable from various plants[2]. Whereas the overall carbon-nitrogen skeleton of most alkaloids can be formulated by this reaction, the latter sometimes being assumed to be the phytochemical process of alkaloid evolution in the plant[3], the finer points in the structure of alkaloids, i.e., the substituents, often remain unexplained.

The ever-recurring alicyclic N-methyl, aromatic O-methyl and methylene-dioxy groupings have been considered as arising from an interrupted basic biogenetic reaction, one wherein a reductive step follows the interaction of formaldehyde (derivable from glycine) and N–H or O–H (except for the methylene-dioxy group, which would be formed by the condensation of the second hydroxyl group with the OH-formaldehyde complex) and thus supercedes the normal carbanion attack on the amine-aldehyde complex[4]. This interpretation has been questioned and hypotheses involving transmethylation[4], or formylation followed by reduction[5] have been advanced.

The relatively high state of oxidation of the average alkaloid (at least as compared to its amino acid precursor) is another striking characteristic of the natural product. While the site of oxidation is located in both the aromatic and aliphatic or alicyclic parts of most alkaloids, only the former has aroused experimental and theoretical interest. Thus the biochemical introduction of oxygen atoms into the aromatic ring has been discussed and reviewed ably by WITKOP[6]. The oxidative phenyl-phenyl interaction has been a long-known phenomenon in the biogenesis of alkaloids[2]. The aporphine and morphine groups are examples of this oxidation, when it results in carbon-carbon bond formation (i.e., production of the diphenyl system), while the biscoclaurine group exemplifies the same reaction involving carbon-oxygen bond formation (i.e., diphenyl ether system). Oxidative nitrogen-phenyl interaction had been shown chemically possible in 1932[1], and is one of the steps in the formulated biogenesis of the alkaloids of the dehydrolaudanosoline[2] and other pyrrocoline types[3]. Finally, the oxidative cleavage of the aromatic nucleus was postulated elegantly by WOODWARD[4] as an important feature of the biogenesis of the strychnos alkaloids. This oxidation is incorporated now in the suggested biogenesis of alkaloids as varied as the cinchona, rauwolfia, alstonia species[5], emetine[5] and β-erythroidine[6].

Regarding the oxidation of the alicyclic portion of an alkaloidal ring skeleton, WITKOP recently suggested[7] that (at least in the case of the indole alkaloids) the likely sites of oxidation would be at positions adjacent to carbon-carbon and carbon-nitrogen double bonds. Since oxidized centers appear also at positions not activated by adjacent unsaturated bonds, the above mechanism is not unique. Curiously, however, the point of oxidation most repeated in a vast majority of alkaloids is the carbon atom bonded to a nitrogen atom. Thus amides (I), carbinolamines (II), amino ketones or aldehydes (III, IV), ene-amines (V), imines (VII), anhydronium salts (VI) and bases and heterocyclic-aromatic nuclei are continuously recurring functional groups in alkaloid chemistry. Since all these functions are related to carbinolamines, it becomes necessary to interpret the origin of this linkage.



On elementary inspection of the energetics of oxidation at centers of hydrogen, saturated carbon and nitrogen atoms, it is apparent that the last would be the most susceptible site to oxidation and that the primary product would be an amine oxide (or a hydroxylamine derivative)[8]. Furthermore, the latter would require simply a rearrangement to furnish a carbinolamine, the pre-

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[2] G. K. HUGHES and E. RITCHIE, Rev. pure App. Chem. *2*, 125 (1952).

[3] G. K. HUGHES and E. RITCHIE, Rev. pure App. Chem. *2*, 125 (1952). – R. F. DAWSON, Adv. Enzymology *8*, 203 (1948).

[4] F. CHALLENGER, Chem. Rev. *36*, 315 (1945).

[5] F. CHALLENGER, Chem. Rev. *36*, 315 (1945). – Cf.: S. KIRKWOOD and L. MARION, Can. J. Chem. *29*, 30 (1951).

[6] B. WITKOP and S. GOODWIN, Exper. *8*, 377 (1952).

[1] R. ROBINSON and S. SUGASAWA, J. Chem. Soc. *1932*, 789. – C. SCHOEPF and K. THIERFELDER, Ann. Chem. *497*, 22 (1932).

[2] J. EWING, G. K. HUGHES, E. RITCHIE, and W. C. TAYLOR, Nature *169*, 618 (1952).

[3] E. WENKERT, Chem. Ind., *1953*, 1088.

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

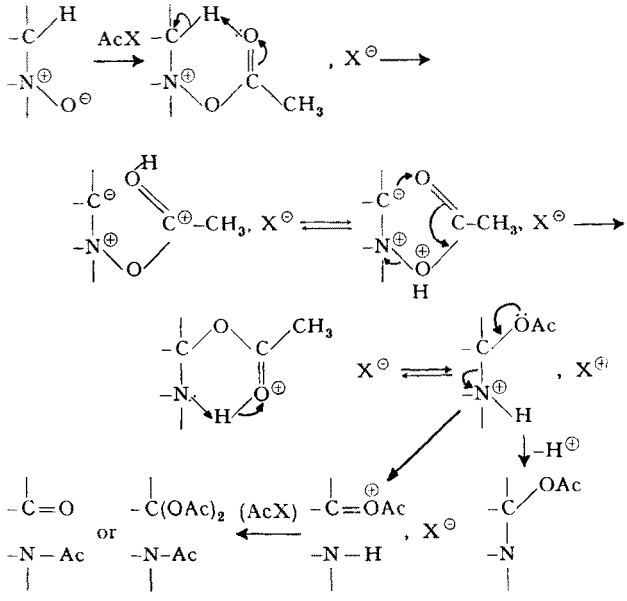
[5] G. K. HUGHES and E. RITCHIE, Rev. pure App. Chem. *2*, 125 1952).

[6] V. BOEKELHEIDE, J. WEINSTOCK, M. F. GRUNDON, G. L. SAUVAGE, and E. J. AGNELLO, J. Amer. Chem. Soc. *75*, 2550 (1952).

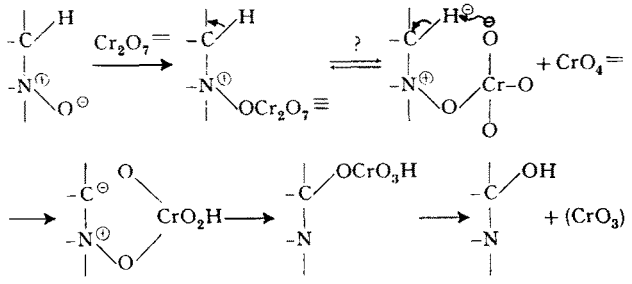
[7] B. WITKOP, J. Amer. Chem. Soc. *75*, 3361 (1953). – B. WITKOP and S. GOODWIN, J. Amer. Chem. Soc. *75*, 3371 (1953).

[8] One previous suggestion regarding the use of a N-oxide as a biogenetic intermediate was made by ROBINSON [Chem. Ind. *1952*, 358] in his interpretation of the origin of the 7-hydroxy group in natural hydroxyindole derivatives. The mechanism of this oxidation, however, was not explained.

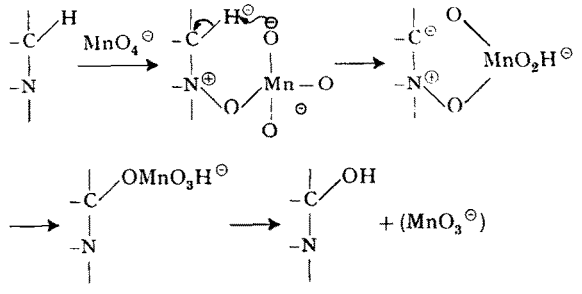
cursor to the various functional groups discussed above. Such rearrangements are common in the chemical literature and probably the most representative among them is the Polonovski reaction[1]. While this reaction,—the spontaneous decomposition of a quaternary acyloxy-



ammonium salt into a carbinolamine acylate or its equivalent[2],—has been used mainly with acetic anhydride on N-methyl containing alkaloids (almost always yielding the N-acetyl-nor compounds), other conditions are also possible[1]. In fact, the dichromate (or chromate)-induced N-oxide-to-carbinolamine conversion may proceed by a similar route:



Generally the reaction proceeds past the carbinol amine stage and produces amides (or N-dealkylated amides)[2], but primary oxidation products,—e.g.: norcodeine and pseudostrychnine (along with 18-oxostrychnine) from the N-oxides of codeine and strychnine respectively[3],—also have been obtained. The oxidation of amines by permanganate probably takes an identical course:

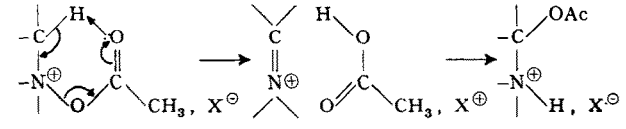


Carbinolamines, amides or further reaction products thereof are the consequence (e.g., nornicotine, nortropine, oxylupanine from nicotine[4], tropine[5] and lupanine[6] respectively[7]). Various other inorganic reagents foster the N-oxide rearrangement especially in heterocyclic aromatic systems[8], although some of them may be applicable in alicyclic nitrogen compounds.

It would appear that in principle any active biologically available ions or enzyme surfaces would be capable of the simple electron transfer inherent in the N-oxide-to-carbinolamine transformation. Furthermore, the alkaloid skeleton, oxidized to the amine oxide by a plant oxidase, would not survive generally as such but be metabolized to the carbinolamine or its equivalents. It is thus not surprizing that only few amine-oxide-

[1] M. Polonovski and M. Polonovski, Bull. Soc. chim. *39*, 1147 (1926), and succeeding papers. – This is a much-neglected reaction even though it seems to be as good as, if not superior to, the von Braun cyanogen bromide degradation of tertiary amines.

[2] The mechanism of the Polonovski reaction (vide supra), never seriously suggested before, most likely involves the internal abstraction of a proton from the carbon adjacent to the positive nitrogen atom thus forming an ylid which cyclically breaks up yielding the carbinol amine acylate or its conjugate acid. The original removal of a proton is reminiscent of the strychnine-to-neostrychnine conversion [R. B. Woodward and W. J. Brehm, J. Amer. Chem. Soc. *70*, 2107 (1948)] and the general formation of ylides [G. Wittig, Angew. Chem. *63*, 15 (1951)]. Whereas these examples are higher energy reactions involving external bases and the production of mesomeric benzyl or allyl carbanions, the case of the Polonovski reaction must be due to the availability of the internal base, the neighboring acetoxyl group. The carbanion, once formed, then could displace acetic acid from nitrogen, possibly even in a concerted reaction, e.g.:



But this mechanism at least cannot be general since the reaction also proceeds on compounds containing nitrogen at a bridgehead thus precluding the formation of a $-C=\overset{\oplus}{N}-$ intermediate [M. Polonovski, M. Darmon, and P. Rajzman, C. r. Acad. Sci., Paris *234*, 108 (1952)]. Consequently, the carbanion must attack the carbonyl group with a concommitant cleavage of the N–O bond. This phase of the reaction is the five-membered cyclic analogue to the three-membered cyclic mechanism of the Stevens rearrangement [G. Wittig, vide supra], while the unorthodox attack on the carbonyl group is the same as the one proposed for the zinc reduction of α-halo-, α-oxy- [R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, J. Amer. Chem. Soc. *74*, 4223 (1952)], α-amino-, and α-thioketones [N. J. Leonard and J. Figueros, Jr., J. Amer. Chem. Soc. *74*, 917 (1952), and preceding papers].

[1] M. Polonovski and M. Polonovski, Bull. Soc. chim. *39*, 1147 (1926), and succeeding papers.

[2] P. J. Scheuer, W. I. Kimoto, and K. Ohinata, J. Amer. Chem. Soc. *75*, 3029 (1953).

[3] P. J. Scheuer, W. I. Kimoto, and K. Ohinata, J. Amer. Chem. Soc. *75*, 3029 (1953). – O. Diels and E. Fischer, Ber. dtsch. chem. Ges. *49*, 1721 (1916).

[4] E. Spaeth, L. Marion, and E. Zajic, Ber. dtsch. chem. Ges. *69*, 251 (1936).

[5] G. Merling, Amer. Chem. J. *216*, 343 (1883). – R. Willstätter, Ber. dtsch. chem. Ges. *29*, 1579, 1637 (1896).

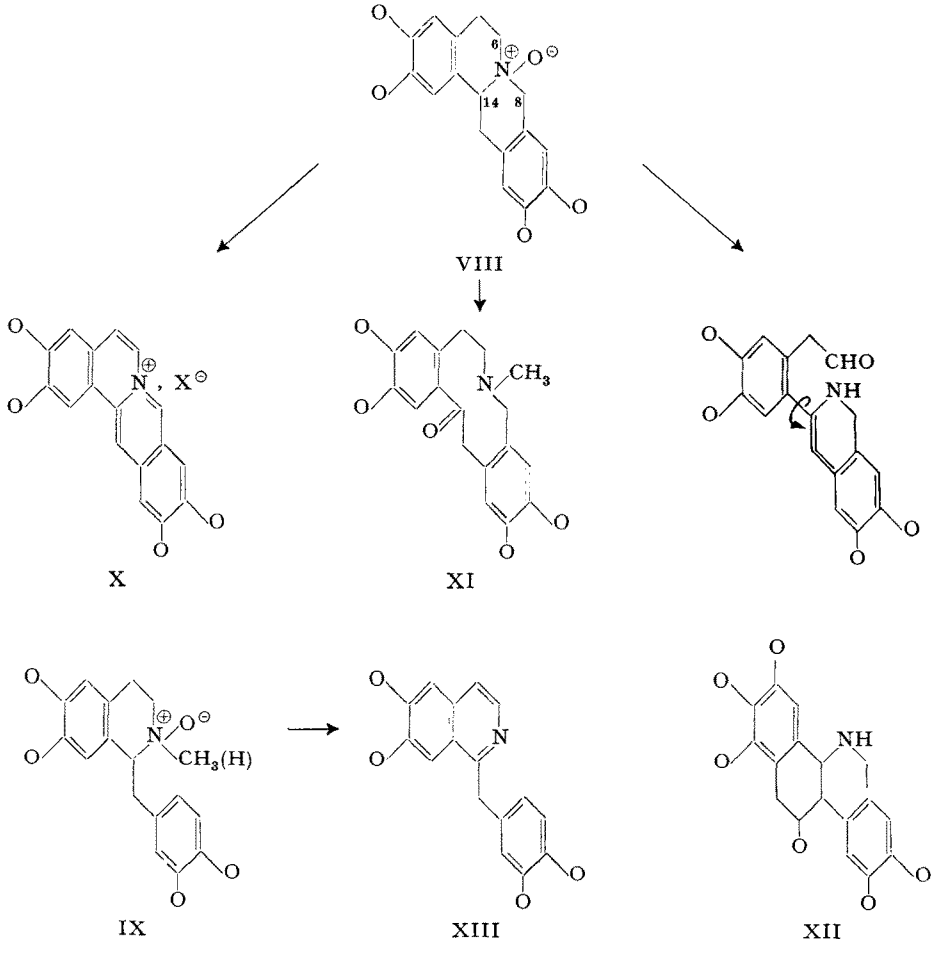
[6] G. R. Clemo and R. Raper, J. Chem. Soc. *1933*, 644, and preceding papers.

[7] It is noteworthy that in the case of the permanganate oxidation of benzyldialkylamines, benzyloxy compounds are the main products. This would be expected on the basis of a lower-energy transition state involving a benzyl carbanion.

[8] E. Ochiai, J. Org. Chem. *18*, 534 (1953).

containing alkaloids have been discovered (e.g.: geneserine, trachelanthine, trilupine, oxymatrine, dilupine, oxychelidonine). They all, however, are in close biological and chemical association with alkaloids of one higher or lower oxidation state.

Amine oxides seem to be the missing link in the often-discussed biogenetic interrelationship of alkaloids[1]. Thus the N-oxides (VIII) and (IX) of compounds derivable from two molecules of dioxyphenylalanine and one of glycine are the likely intermediates in the formation of the berberine (X), cryptopine (XI), benzophenanthridine (XII) and benzylisoquinoline (XIII) alkaloids. Participation of carbons 6-8-14, 14, 6-14, and 6-(8)-14 respectively in N-oxide rearrangements would be required.

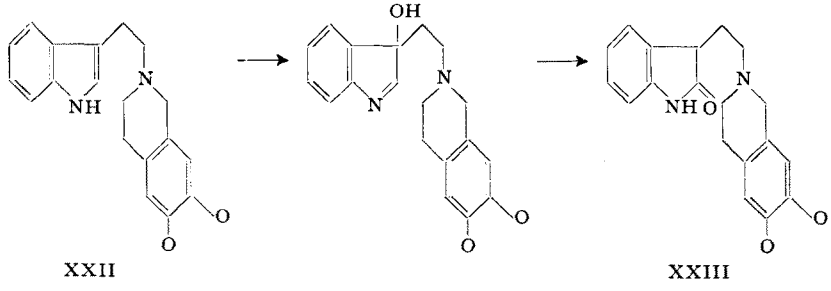


In like fashion the N-oxides XIV, XV and XVI of compounds derivable from tryptophan, dioxyphenylalanine and glycine are the logical precursors of sempervirine (XVII) (and some alkaloids of the alstonia and rauwolfia species), cinchonamine (XVIII) (quinamine and the quinoline-type cinchona alkaloids), vomicine (XIX) (via first the normal biogenetic pathway of the strychnos alkaloids[2]), some mitragyna species (XX)[3]

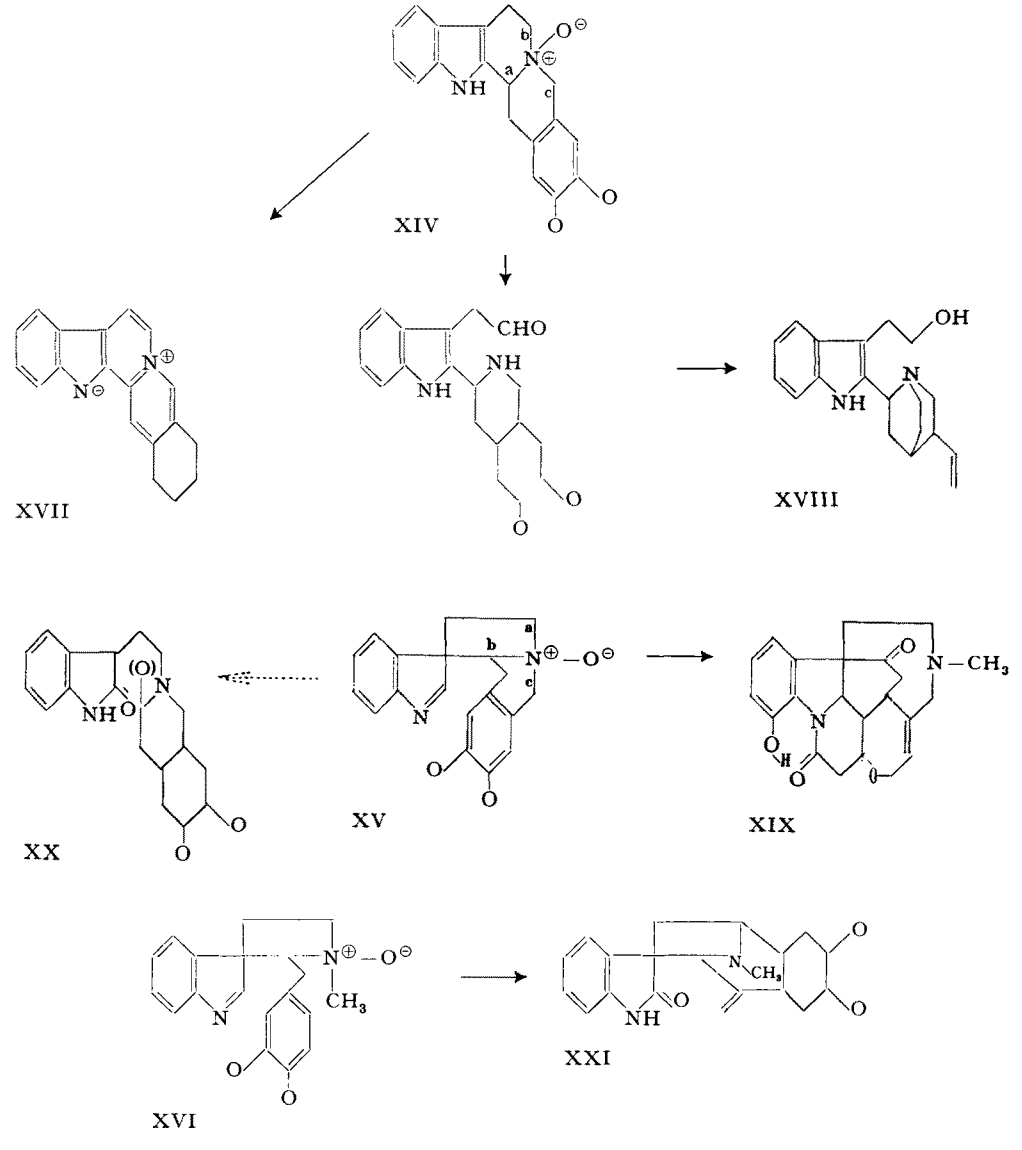
[1] G. K. HUGHES and E. RITCHIE, Rev. pure App. Chem. *2*, 125 (1952). – R. B. TURNER and R. B. WOODWARD, in R. H. F. MANSKE and H. L. HOLMES, *The Alkaloids*, Vol. III (Academic Press, Inc., Publishers, New York, 1953), p. 54.

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

[3] The oxindole moiety in mitraphylline, rhyncophylline and formosanine (J. W. COOK, R. M. GAILEY, and J. D. LONDON, Chem. Ind. *1953*, 640) may arise from the oxidation of the indolenine part of XV or from the oxidation and hydration-dehydration of a 3-substituted indole (XXII) [A. EK, H. KISSMAN, J. B. PATRICK, and B. WITKOP, Exper. *8*, 36 (1952)]. See Formulas XXII and XXIII. Whereas the intermediate XXII requires a slightly different biogenetic elaboration of its amino acid precursors than XIV or XV, an analogy can be drawn with intermediates proposed in the formation of some pyrrocoline bases (E. WENKERT, Chem. Ind., *1953*, 1088). Final differentiation between paths XV–XX and XXII–XXIII will have to await total elucidation of structures in the mitragyna series.



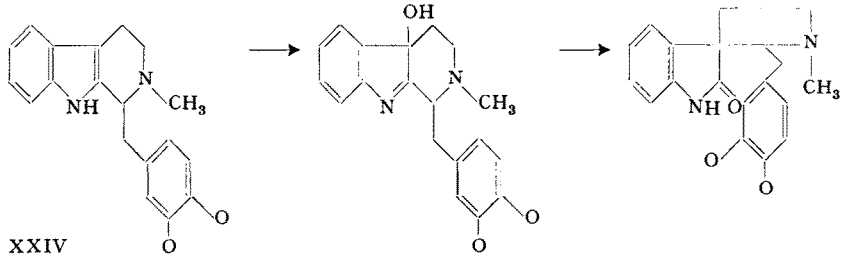
and gelsemine (XXI)[1]. The amine oxide rearrangements would involve each of the following sets of carbon atoms respectively: a-b-c, b, a, a, and b.



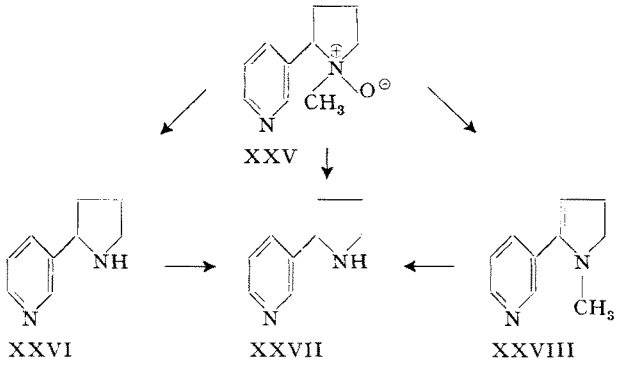
In the realm of the tobacco alkaloids nicotine has been shown definitely to be the precursor of nornicotine (XXVI) in the plant[2]. The removal of the N-methyl group has been ascribed to a process of transmeth-

[1] The introduction of N-oxides as biogenetic intermediates precludes the necessity for the use of unusual processes in the formation of gelsemine. In the original scheme [M. S. GIBSON and R. ROBINSON, Chem. Ind. *1951*, 93. – R. GOUTAREL, M.-M. JANOT, V. PRELOG, R. P. A. SNEEDEN, and W. I. TAYLOR, Helv. chim. Acta *34*, 1139 (1951)] both tryptophan and (oxy-)phenylalanine were assumed to act as aldehydes, a proposal now superceded by the route XVI–XXI. – An alternative suggestion for the origin of the oxindole part of gelsemine, other than the oxidation of the indolenine group in XVI, might be the oxidation and hydration-rearrangement-dehydration of the indole XXIV [*Cf.*: B. WITKOP and A. EK, J. Amer. Chem. Soc. *73*, 5664 (1951). – B. WITKOP and J. B. PATRICK, ibid. *75*, 2572 (1953)].

[2] R. F. DAWSON, Adv. Enzymology *8*, 203 (1948).



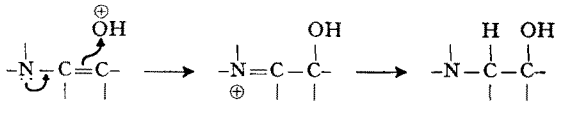
ylation[1], although in view of the lack of direct evidence a biogenetic route via the N-oxide (XXV–XXVI) is still not precluded. The formation of myosmine (XXVII) (from tobacco smoke) must follow a similar route. The amine oxide hypothesis in these cases is strengthened by the recent elucidation of the structures of bacterial degradation products of nicotine[2]. The primary product is nicotine oxide (XXV) which is succeeded by N-methyl myosmine (XXVIII) and further oxidation products.



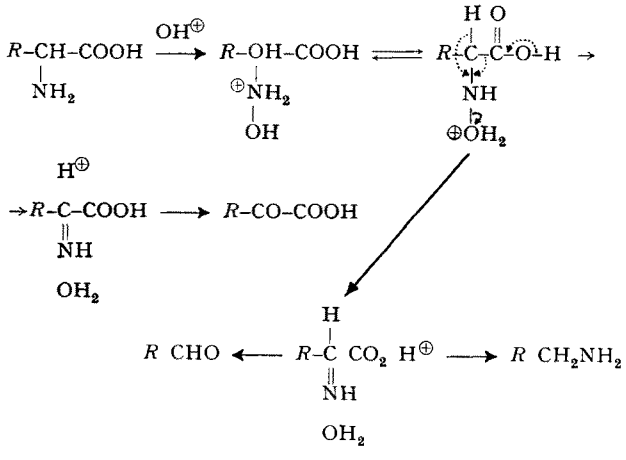
XXV

XXVI XXVII XXVIII

The α-amino alcohol group (or its equivalent) is an oxidized substituent next in prominence to the carbinol amine. It appears frequently in the senecio, tropane, pyrrolidine, pyridine, ephedra, phthalideisoquinoline and other alkaloids. Whereas its origin is quite obscure, most of WITKOP's elegant work on the oxidation of indole derivatives[3] suggests the following biogenetic pathway:



In the fundamental reaction of alkaloid biogenesis[4] amines and aldehydes are considered generally the reacting species. Their actual formation in the plant from amino acid precursors is still extremely vague, if at all real. If their existence, however transient, be valid, a picture (*strictly formal*) of their origin involving spontaneous reactions can be drawn. By an oxidative step, again at the site of a nitrogen, an intermediate is obtained which in effect is a β-hydroxy acid. The latter would be expected to undergo dehydration or dehydration-decarboxylation. Although there is no evidence for this



scheme, it is interesting to note that in principle it is identical with the mechanism proposed for the pyridoxal-induced decarboxylation, deamination, deaminative decarboxylation and other reactions of amino acids prevalent in animal metabolism[1].

Zusammenfassung

Aminoxide werden als intermediäre Oxydationssubstanzen der Alkaloidbiogenese vorgeschlagen. Verschiedene Beispiele in dem Gebiet der Alkaloide werden erwähnt, um die Hypothese zu erklären.

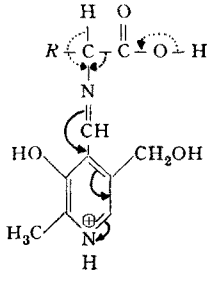
[1] R. F. DAWSON, Adv. Enzymology *8*, 203 (1948).

[2] E. WADA and K. YAMASAKI, Science *117*, 152 (1953).

[3] A. EK, H. KISSMAN, J. B. PATRICK, and B. WITKOP, Exper. *8*, 36 (1952)]: B. WITKOP and A. EK, J. Amer. Chem. Soc. *73*, 5664 (1951). – B. WITKOP and J. B. PATRICK, ibid. *75*, 2572 (1953).

[4] G. K. HUGHES and E. RITCHIE, Rev. pure App. Chem. *2*, 125 (1952).

[1] E. E. SNELL, 2nd Congr. intern. biochim., Chim. biol. V, Symposium metabolisme microbien (Paris) *1952*, 47. – The positive nitrogen atom in the pyridine nucleus of the pyridoxin complex (XXIX) acts in the manner as the positive oxygen in the hydroxy-amino acid complex above.



XXIX