30 s and did not return. One case of *status epilepticus*, following partial removal of the left temporal lobe, did not respond to large doses of barbiturates. However, during the continuous intravenous administration of 0·7 mg Xylocain per kg per hour during 12 h, the attacks successively diminished. After this treatment, the patient could talk which she had not been able to do since the attacks started 3 days after the operation. Finally in one other patient with frequent (4–6 min intervals) fits of short duration (5–20 s), the fits were temporarily abolished. The duration of the Xylocain effect corresponded to the results from the animal experiments.

Further experiments are carried out in order to elucidate the central effects of Xylocain and related compounds; and it should be pointed out that intravenous injections, in connection with convulsions or other motor disorders, must be made with great care until more is known about the central effects of the drug.

C. G. BERNHARD and E. BOHM

Physiological Department II, Karolinska Institutet and Neurotraumatological Clinic, Serafimerlasarettet, Stockholm, May 26, 1954.

Zusammenfassung

Es hat sich gezeigt, dass kleine intravenöse Dosen von Xylocain im Versuch an der Katze die zentralen epileptiformen Nachentladungen und die poststimulatorischen Krämpfe blockieren können, und in Analogie hierzu zeigte eine preliminäre Untersuchung am Menschen, dass epileptische Anfälle durch intravenöse Injektionen von Xylocain abgebrochen werden können.

Informations - Informationen - Informazioni - Notes

STUDIORUM PROGRESSUS

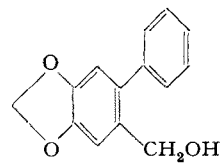
The Structure of Tazettine

By E. WENKERT[1], Ames, Iowa

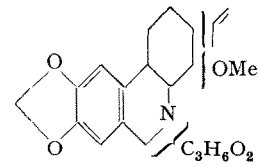
The chemistry of tazettine, a minor alkaloid of the *Amaryllidaceae*, was investigated first by SPÄTH[2], who had isolated the natural product from the bulbs of *Narcissus tazetta L.* The compound was found to contain a tertiary nitrogen, a methylenedioxy, a hydroxy, and one methoxy functions. Zinc dust distillation yielded phenanthridine, while permanganate oxidation produced hydrastic and oxalic acids. HOFFMAN degradation led to an oily methine base, with an apparent loss of the methoxy group, which could be oxidized with permanganate to a mixture of benzoic and oxalic acids. A two-stage HOFFMAN degradation, however, yielded a crystalline non-nitrogenous compound which was identical with synthetic 6-phenylpiperonyl alcohol (I). On the basis of mainly these experimental results SPÄTH suggested part structure II for tazettine.

In 1936 a direct comparison of tazettine with KONDO's "base VIII"[3], one of the minor alkaloids isolated from *Lycoris radiata Herb.*[4], and with ungernine[5], obtained by ORECHOFF from the bulbs of *Ungernia Sewertzowii (Rgl.)* FEDSCH[6], established the identity of the three compounds. ORECHOFF's few experiments[6] supplemented those of SPÄTH. Thus the hydrogenatibility of the alkaloid pointed definitely to the presence of unsaturation in the molecule, while the isolation of compound I both from a single-stage HOFFMAN degradation and from a vigorous base treatment of the alkaloid itself indicated the general lability of the natural product toward alkali.

In a recent series of six papers, KONDO and coworkers described further structure studies on tazettine*. The alkaloid was found to contain a N-methyl but no C-methyl group, and on HOFFMAN degradation, preceded by methylation, yielded a host of mainly non-nitrogenous products (see Table I), including 6-phenylpiperonyl alcohol (I)*[a,b,e]. Whereas none of the structures of these



I



II

"des-N-bases" was known, formulas III and IV were proposed for compounds *A* and *F* respectively*[c,d]. However the synthesis of the methyl ether IV and its non-identity with the hydrogenation product *F* disproved the latter formulation*[d]. Permanganate oxidation of the major "des-N-base" *D* yielded a mixture of the substituted benzaldehyde V and benzoic acid VI which were identical with synthetic specimens*[e]. However a consequent structural assignment VII for the "des-N-base" proved to be also incorrect due to its non-identity with the synthetic product*[f]. Thus while KONDO had previously proposed structure VIII, or its two ketol isomers, for tazettine*[b,c],–a structure which in reality was inadmissible on the basis of the simplest qualitative data, e.g. negative aldehyde and ketone tests,–much of the degradation work appeared to be of little interpretive value.

Most recently a biogenetic scheme encompassing the alkaloids of the *Amaryllidaceae* has been proposed, wherein the possible origin of the basic carbon-nitrogen skeleton of lycorine (IX), the major alkaloid of this family, was presented[1]. An oxidative variation of this biogenesis[2] would lead to structures such as X, requiring a two-carbon side-chain at C–1 of the phenanthridine nucleus,–a requirement borne out by the structures of lycorenine and lycoramine, two minor alkaloids of this series, but violated by the SPÄTH or KONDO

[1] Department of Chemistry, Iowa State College, Ames, Iowa, U.S.A.

[2] E. SPÄTH and L. KAHOVEC, Ber. dtsch. chem. Ges. *67*, 1501 (1934).

[3] E. SPÄTH, H. KONDO, and F. KUFFNER, Ber. dtsch. chem. Ges. *69*, 1086 (1936).

[4] H. KONDO, K. TOMIMURA, and S. ISHIWATARI, J. pharm. Soc. Japan *52*, 51 (1932).

[5] E. SPÄTH, A. ORECHOFF, and F. KUFFNER, Ber. dtsch. chem. Ges. *69*, 2446 (1936).

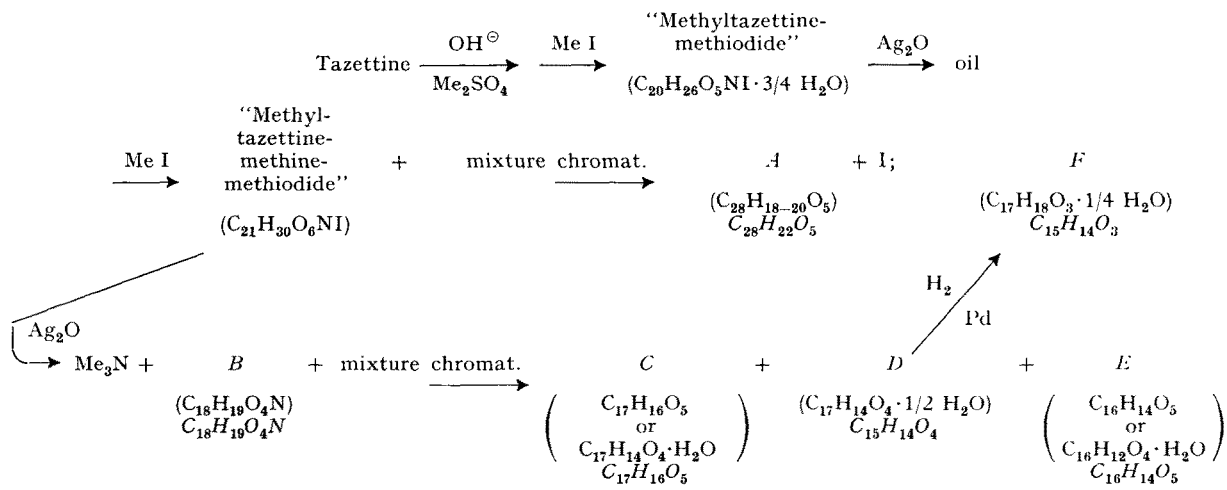
[6] S. NORKINA and A. ORECHOFF, Ber. dtsch. chem. Ges. *69*, 500 (1936).

[a] H. KONDO and T. IKEDA, J. Pharm. Soc. Japan *65*, 9 (1945); [b] H. KONDO, T. IKEDA, and N. OKUDA, Ann. Reports Itsuu Lab. *1*, 21 (1950); [c] H. KONDO and T. IKEDA, ibid. *2*, 18 (1951); [d] H. KONDO, T. IKEDA, and K. TAKEDA, ibid. *3*, 24 (1951); [e] H. KONDO, T. IKEDA, and J. TAGA, ibid. *3*, 30 (1952); [f] H. KONDO, T. IKEDA, and J. TAGA, ibid. *4*, 30 (1953).

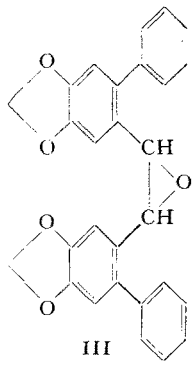
[1] E. WENKERT, Chem. and Ind. *1953*, 1088.

[2] E. WENKERT, Exper. *8*, 346 (1954)

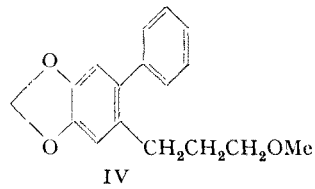
Table I



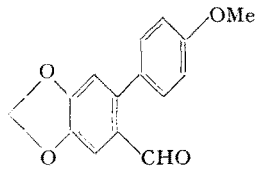
part formulas (II and VIII) of tazettine, whose side-chain appears at C–9. This inconsistency, added to the odd fact that many of KONDO's tazettine degradation products were formulated as fractional hydrates (see the empirical formulas in parentheses in Table I), called for a reevaluation of KONDO's chemical, especially analytical, data.



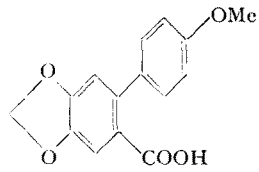
III



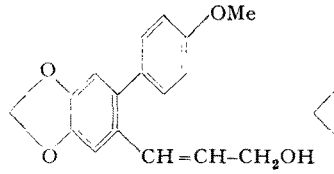
IV



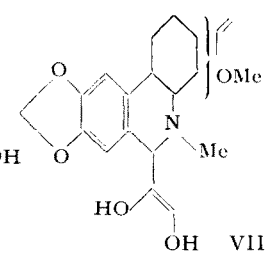
V



VI

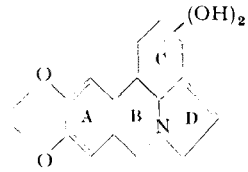


VII

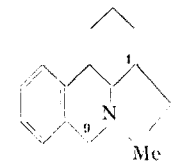


VIII

Recalculation of KONDO's reported analytical values for compound *D*[*b], the major HOFFMAN degradation product, reveals that $C_{15}H_{14}O_4$ is the most acceptable (*non-hydrated*) empirical formula (see italicized formulas in Table I). The fact that this compound was oxidizable to a mixture of aldehyde V and acid VI and was hydrogenatable to *F*, whose corrected empirical structure is $C_{15}H_{14}O_3$, with a concommitant loss of an oxygen atom limits its structural formula to the benzyl alcohol XI and consequently that of its hydrogenolysis product *F* to XII. These formulations are strengthened by the fact the "des-N-base" *D*, now compound XI, had been reported to be acetylable to a product which on alkaline hydrolysis reverted to the starting material. Whereas, $C_{19}H_{18}O_5 \cdot 1/2H_2O$ was the assigned formula for this acetate, a recalculation showed that $C_{17}H_{16}O_5$ fitted the analytical values best and hence established the already-predictable structure XIII for this compound. Coincidentally, the latter also must be the structure of "des-N-base" *C* since its empirical formula as well as its melting point, 87–89°, agree with those of the acetate (m.p. 89–90°). As a final confirmation for the above arguments it must be mentioned that KONDO's ultraviolet absorption spectra*[b] for compounds XI, XII, and XIII are essentially superposable as would be expected for an identical diphenyl chromophoric system in all three degradation products.



IX

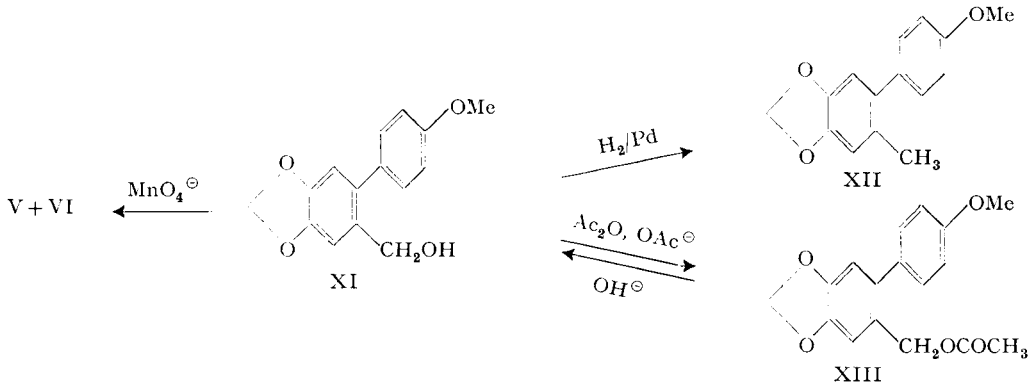


X

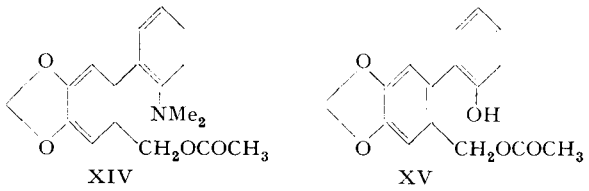
B, the only nitrogenous HOFFMAN product, has been assigned correctly formula $C_{18}H_{19}O_4N$ and has been reported to possess no methoxy group*[b]. The structure of this compound can be envisaged to be XIV mainly on the basis of it having to possess a dimethylamino group in the position of the methylimino function in the original phenanthridine nucleus. The ultraviolet spectra of *B* confirms the presence of a diphenyl system although its absorption characteristics are different than those of the above HOFFMAN degradation products and thus in agreement with a shift of chromophores, i.e. p-methoxy to o-dimethylamino. The oxygen atoms, other than those associated with the ever-recurring methylenedioxy linkage, were assigned their function as acetate for reasons that will become obvious below although one immediate reason for considering only this structure is the fact that their only other logical position, i.e. somewhere in the newly created benzene ring, would most likely affect the chromophore of the system more drastically than the spectra would warrant. Compound *E*, $C_{16}H_{14}O_5$, was

*[b] See footnote pag. 476.

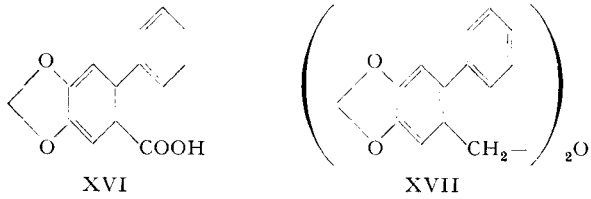
*[b] See footnote pag. 476.



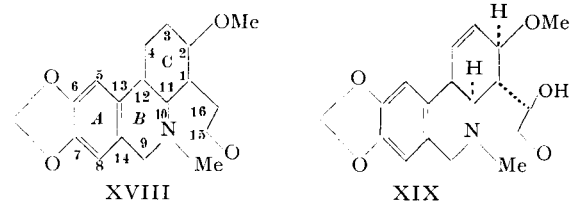
shown to have identical ultraviolet absorption spectra to *B*. Since it also is lacking a methoxyl group and its formula indicates a replacement of a dimethylamino function in *B* by a hydroxyl group, its structure must be XV. It is interesting to note that its polar phenolic hydroxyl group causes it to be the product isolated last (by elution with methanol) in the chromatographic separation of "des-N-bases" *C*, *D*, and *E* (see Table I).



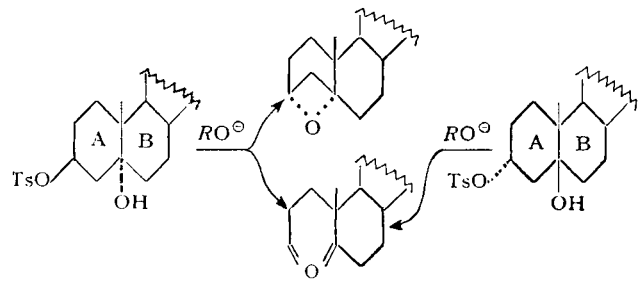
Finally, compound *A*, which was isolated along with 6-phenylpiperonyl alcohol (I) after only a single HOFFMAN treatment, has been reported by KONDO*b,e to be lacking a methoxy function, to possess a high molecular weight (440) but a low oxygen content and to be oxidizable by permanganate to 6-phenylpiperonylic acid (XVI). This data along with the critically reviewed carbon-and-hydrogen analysis ($C_{28}H_{18-20}O_5$ formula having had to be changed to $C_{28}H_{22}O_5$) makes it possible to assign structure XVII to this compound.



With the elucidation of the constitution of the products of alkaline degradation completed, the structural formulation of tazettine itself may be attempted. If for afore-mentioned biogenetic reasons the alkaloid is assumed to have the basic carbon-nitrogen skeleton in X, the latter can now be expanded to XVIII, to incorporate the constantly recurring 6,7-methylenedioxy group, the often appearing 2-methoxy function and an as yet undefined $C_{(15)}$–O linkage (to prevent the presence of a C-methyl group). The positions of the still-missing hydroxyl group, double bond and ether linkage, however, are indeterminable unless a reason can be found for the consistent extrusion of the two-carbon side-chain with a simultaneous loss of the methoxy and/or the methylimino groups during alkaline degradation. Part of this phenomenon, i.e. the cleavage of the $C_{(1)}$–$C_{(16)}$ linkage, is immediately explicable if the prior assumption be made that the $C_{(1)}$–$C_{(16)}$ bond in tazettine is trans to both the $C_{(11)}$–N and $C_{(2)}$–O bonds and that $C_{(16)}$ holds a group (e.g. a hydroxyl group) which in the alkali-induced reactions can function as an internal base for ionic elimination of either the methoxy or methylimino groups.



This condition (as portrayed in formula XIX) has been shown most recently to be responsible for a similar elimination of a 1,3-glycol system in a steroid case[1]:



Because of the participation of carbon atoms 16, 1, 2, and 11 in the above elimination reactions, only positions 3–4 or 4–12 remain for the location of a double bond in ring C. These two sites are distinguishable from each other in as much as the latter places the double bond into conjugation with the aromatic ring A. This is an impossible condition since the ultraviolet absorption spectra of tazettine is identical with that of lycorine (IX)[2], whose methylenedioxyphenyl group is unconjugated with any other site of unsaturation in the molecule[3]. Hence the double bond in tazettine must be located at $C_{(3)}$–$C_{(4)}$. The remaining oxygen atom, already associated with $C_{(15)}$ must link this carbon atom with $C_{(12)}$ in an ether linkage since cross-bonding with any other center in the molecule again would interfer with sites of the base-catalyzed degradative reactions[4]. Thus the complete structure of the alkaloid is represented in formula XX:

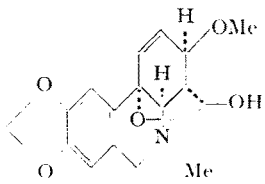
*b,e See footnote pag. 476.

[1] R. B. CLAYTON and H. B. HENBEST, Chem. a. Ind. *1953*, 1315.

[2] H. KONDO, T. IKEDA, and N. OKUDA, Ann. Reports Itsuu Lab. *1*, 21 (1950). – H. KONDO and H. KATSURA, Ber. dtsch. chem. Ges. *73*, 1424 (1940).

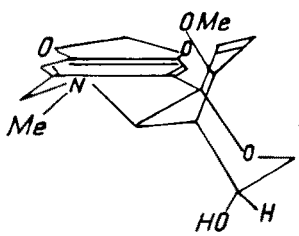
[3] R. B. KELLY, W. I. TAYLOR, and K. WIESNER, J. Chem. Soc. *1953*, 2094.

[4] The presence of ether linkages in tazettine had been indicated already by CLEMO through the infrared spectrum of the alkaloid (G. R. CLEMO and D. G. I. FELTON, Chem. a. Ind. *1952*, 801).

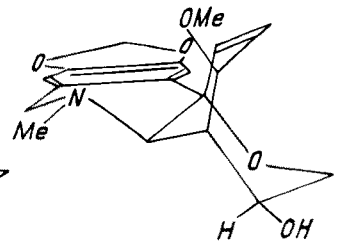


XX

The cited experimental data on tazettine permits even the exact steric assignment of the $C_{(16)}$ hydroxyl group. Both SPÄTH's and ORECHOFF's HOFFMAN degradation procedures (carried out by refluxing crystalline tazettine methiodide with a silver oxide suspension) yielded demethoxylated products only, – indicative of the fact that in the primary elimination reaction (see path A in Diagram I) the hydroxyl group must have been oriented in such a direction as to be coplanar with carbon atoms 16, 1, 2 and the methoxyl group. An inspection of a model of tazettine indicates that such five-center coplanarity is achieved only if the hydroxyl function exists in an axial conformation in its pyran ring. KONDO's degradative experiments yielded both demethoxylated and methoxy-containing compounds, as his HOFFMAN reaction was preceded by a mild *alkaline* "methylation" reaction. The last process would be expected to establish an equilibrium between the axial hydroxyl group and its more stable equatorial isomer which after methiodide formation can be envisaged to undergo HOFFMAN elimination by a break-up of the five-center coplanar betaine (see path B in Diagram I), involving the equatorial hydroxyl group, carbon atoms 16, 1, 11 and the dimethylammonium group[1]. These mechanistic arguments would suggest that tazettine possesses an axial hydroxyl function (vide XXI) which in KONDO's experiments is isomerized to a great extent to its equatorial counterpart (vide XXII).



XXI



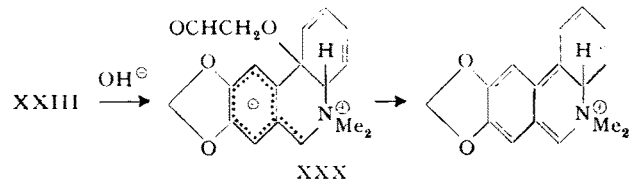
XXII

[1] KONDO's "methyltazettine methiodide" (see Table I) thus must be either a mixture of the methiodides of tazettine and isotazettine or exclusively the latter. Whereas it is impossible to ascertain the correct empirical formula for this "compound", because of insufficient analytical data in this case as well as in the case of all of KONDO's nitrogen-or iodine-containing degradation products (except compound XIV), the C-and-H data alone agree well with $C_{19}H_{24}O_5NI$ for isotazettine methiodide. The inability of tazettine or its isomer to undergo O-methylation is in consonance with the reported similar lack of reactivity of the hydroxyl groups of lycoramine, another amaryllidaceous alkaloid [H. KONDO and S. ISHIWATA, Ber. dtsch. chem. Ges. *70*, 2427 (1937)].

The above elimination reactions, which are the obvious primary steps in the alkaline decomposition of tazettine, now make it possible to correlate the multitude of HOFFMAN degradation products with the structure of the alkaloid. Thus an elimination via *Path A* (vide supra) with a consequent loss of the methoxy group[2] leads to the dihydroaromatic compound XXIII which is unable to aromatize by a concerted elimination of glycolaldehyde because of the cis relationship of the two vicinal groups involved. Hence the aromatization of ring C must proceed by other routes of which there are three theoretically possible all of which lead to different degradation products. Firstly, the coplanar trans relationship of the axial glycolaldehyde sidechain and of the axial dimethylammonium group in the intermediate XXIII suggest a disproportionation of its alkali-produced betaine (XXIV) via another five-center coplanar transition state into glyoxal and the aromatic nucleus and dimethylamino grouping of compound XXV. Secondly, the elimination of glycolaldehyde from XXIII is possible if the reaction is envisaged to occur stepwise, with formation of a discreet carbanion, i.e. the well-stabilized ylid XXVI, prior to extrusion of the aldehyde. Such elimination would produce the phenanthridinium ion XXVII[3]. Finally, the doubly allylic ammonium ion

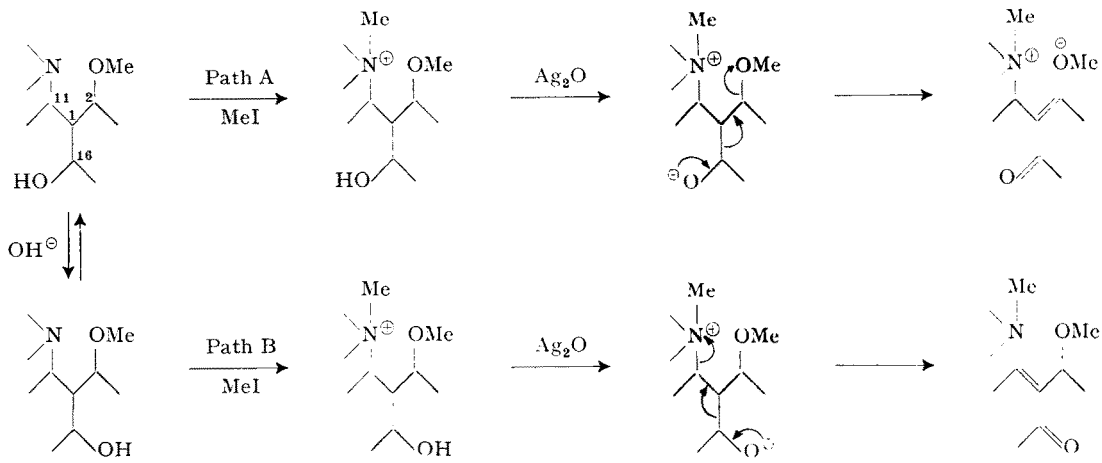
[2] While base-catalyzed E_2-type elimination reactions of ethers are rare and high-energy processes mainly because of the poor nature of the alkoxide ion as a leaving group, the energy of the transition state in the above case is lowered greatly because of the coplanarity of all atoms involved and because of the stabilization of the incipient double bond in the transition state by π-bond overlap with the adjacent A^{3-4} linkage.

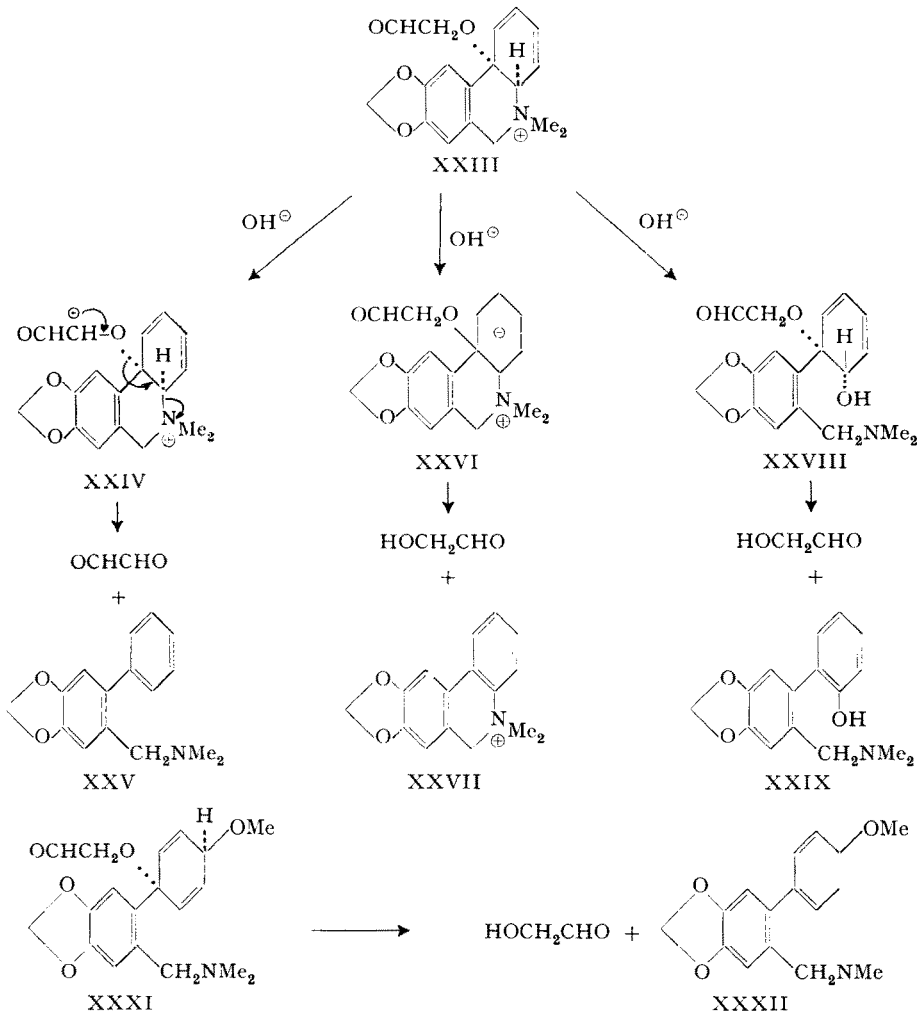
[3] The formation of the phenanthridinium ion could also be visualized to occur via the production of ylid XXX, extrusion of



XXX

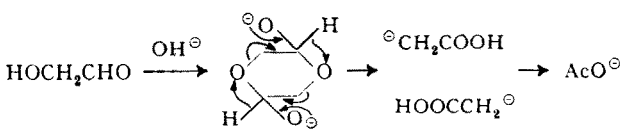
Diagram I





XXIII would be expected to be easily susceptible to hydroxide ion displacement, causing the formation of an equatorial hydroxyl group (vide XXVIII) and an axial hydrogen atom which permit a subsequent concerted elimination of glycolaldehyde.

Displacement reactions by pertinent anions on compounds XXV, XXVII, and XXIX and/or their methiodides yield KONDO's demethoxylated degradation products I and XVII, XIV, and XV respectively. The origin of the acetate group in compounds XIV and XV, and hence the presence of acetate ion in the HOFFMAN reaction medium, can be explained to be due to a rearrangement of the sideproduct glycolaldehyde[1]:



the glycolaldehyde sidechain (or a combination of these two steps in a concerted reaction) and prototropic rearrangement to XXVII. This alternative mechanism would overcome the difficulty in having to formulate a two-step cis elimination. (The author wishes to heartily acknowledge an interesting discussion on this point with Dr. M. F. HAWTHORNE.)

[1] This transformation is in essence a benzilic-acid-type rearrangement but is pictured above to include two molecules of glycolaldehyde because of the known tendency of latter to exist in solution and to react in dimeric form; e.g. the pyridine-catalyzed acetylation of the aldehyde produces 2,5-diacetoxy-1,4-dioxane [H.O.L. FISHER and C. TAUBE, Ber. dtsch. chem. Ges. *60*, 1704 (1927)].

The origin of the methoxy-containing degradation products must be ascribed to the elimination reaction of tazettine methiodide via *Path B* (see Diagram I). The primary product XXXI would be expected to be transformed easily by 1,4-elimination of glycolaldehyde into the amine XXXII, the obvious precursor (through displacement reactions identical with those above) of KONDO's products XI and XIII.

Whereas a correlation of other reported conversion products of tazettine, mainly acetylation products*[c,e], with the here-presented structure of the alkaloid would be highly desirable, insufficient analytical data for these nitrogen-containing compounds prohibits an unambiguous assignment of their structures at this time. Meanwhile the synthesis of all above non-nitrogenous products is being carried out in this laboratory.

Zusammenfassung

KONDOS analytische Resultate der Tazettindegradationsprodukte wurden neu bestimmt, Strukturformeln für diese Substanzen werden vorgeschlagen und die Struktur und Stereochemie des Alkaloids dargestellt.

*[c,e] See footnote pag. 476.