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# The Chemistry of Certain Imines Related to the Diterpene Alkaloids[1]

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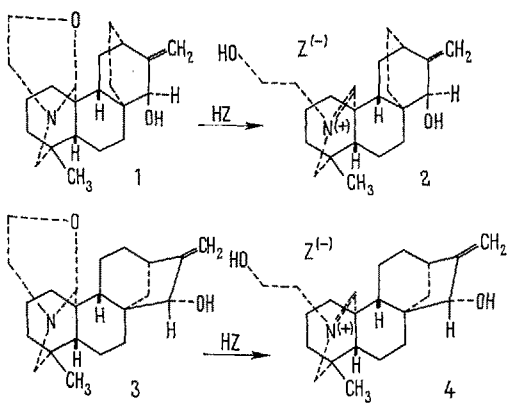
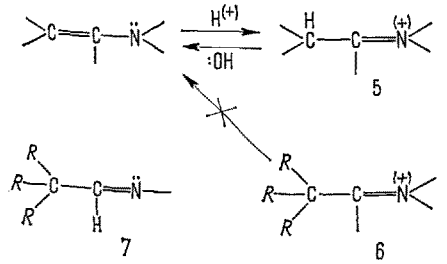
The high degree of bridging in the polycyclic skeleta of the *Aconitum* and *Delphinium* Alkaloids leads in many instances to unusual chemical properties. This paper surveys some of these reactions—and in particular those of the imines and ternary iminium salts derived from diterpene alkaloids of the atisine and veatchine type.

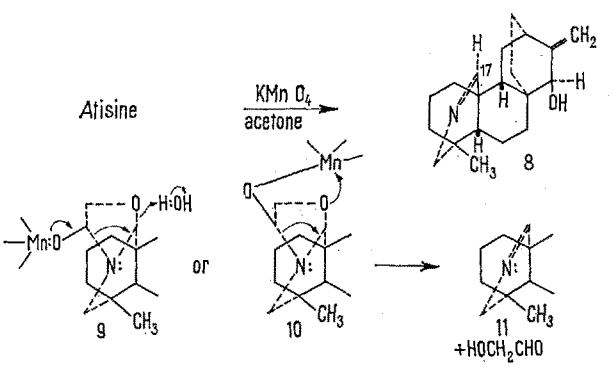
Several unusual reactions and properties of the diterpene alkaloids of the atisine (1)[2] and veatchine (3) type[3–6] are explainable in terms of the ternary iminium salts (formulas 2 and 4) in which these compounds exist in hydroxylic solvents. These forms correspond to the ternary iminium salts (5) which are formed reversibly during protonation of enamines.



Since the alkaloids are fully substituted in the position $\beta$ to the nitrogen, their ternary iminium salts (6) are incapable of isomerization to the enamine forms and hence undergo reactions exclusively in the iminium form. A few reactions of the unalkylated imines, represented by the azomethine formulation (7) will also be discussed.



The first diterpene alkaloid imine (8) of the type in formula 7 was isolated in low yield as a by-product of the oxidation of atisine (1) with potassium permanganate in acetone[7]. The mechanism of formation probably follows some such pathway as illustrated below (9 or 10 → 11) and involves hydroxylation at an unhindered position adjacent to the nitrogen atom, followed by ester formation and subsequent elimination. More recently it has been possible to prepare the O-acetate of this same imine in 70% yield from atisinium diacetate chloride[8]. We had earlier found[9] that treatment of an aqueous solution of the diacetate chloride (12) with



[1] Parts of this paper were presented before the Symposium on Enamine Chemistry at the American Chemical Society meeting in Chicago, September 6 (1961), and at the International Phytochemistry Symposium held during the Golden Jubilee Congress of the University of Hong Kong on September 12 (1961).

[2] For the most part the structures used in this paper indicate the correct absolute configuration. Occasionally, however, because of ease in representation or where the configuration is incidental to the point under consideration, the structures are drawn without regard to absolute configuration.

[3] K. WIESNER and Z. VALENTA, *Progress in the Chemistry of Organic Natural Products* (Springer-Verlag, Wien 1958), vol. 16, p. 26.

[4] S. W. PELLETIER, Tetrahedron *14*, 76 (1961).

[5] S. W. PELLETIER, J. Amer. chem. Soc. *82*, 2398 (1960).

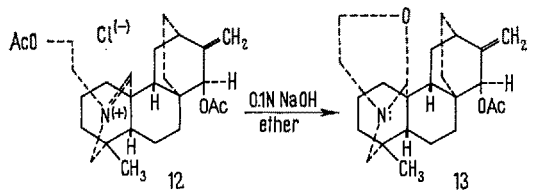
[6] H. VORBRUEGGEN and C. DJERASSI, J. Amer. chem. Soc. *84*, 2990 (1962).

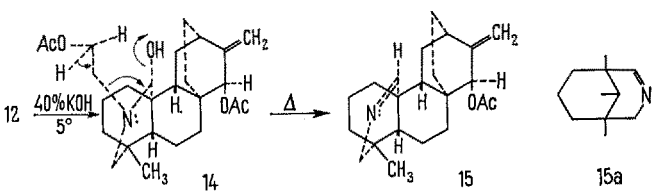
[7] S. W. PELLETIER and W. A. JACOBS, J. Amer. chem. Soc. *78*, 4139 (1956).

[8] D. DVORNIK and O. E. EDWARDS, Canad. J. Chem. *35*, 860 (1957).

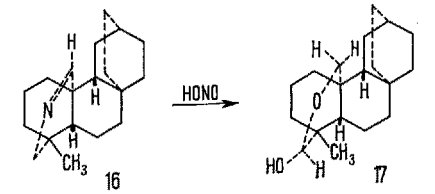
[9] S. W. PELLETIER and W. A. JACOBS, Chem. and Ind. *1955*, 1385.

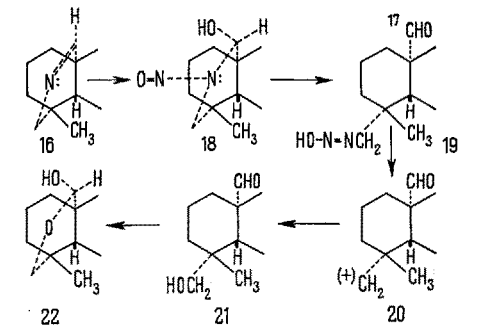
cold, 0.1 *N* sodium hydroxide, followed by rapid extraction with ether gave a monoacetate (13). The reaction apparently proceeds by saponification of the primary hydroxyl followed by cyclization on the ternary double bond. By contrast, treatment of 12 with base under non-hydrolytic conditions leads initially to a diacetoxy carbinol amine (14) which undergoes an internal Hofmann-type elimination when heated briefly in chloroform or carbon tetrachloride to give acetaldehyde and the imine acetate (15)[8].

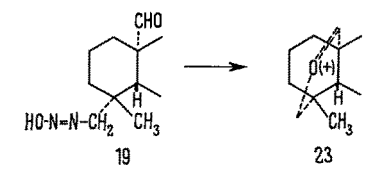


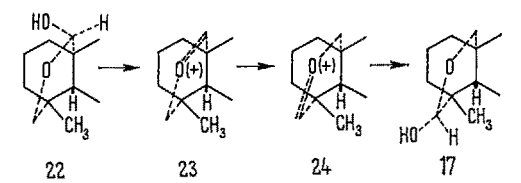




The imine linkage in the atisine derivative (8) is remarkably resistant to the hydrolytic action of acids and bases; e.g. it is unaffected by conditions as drastic as the Wolf-Kishner reduction[10] or boiling 10% hydrochloric acid[11]. In contrast, simple imines are readily hydrolysed to the parent amine and carbonyl derivatives. This behavior of the alkaloid imines is probably due to the special geometry of the system. The strong steric compression between the nitrogen and the C-17 atom would be expected to maintain the integrity of the >C=N-linkage, thereby effectively suppressing reactions which normally would be expected from the aldehyde form. In this connection it would be of interest to see whether an imine of type 15a is hydrolytically stable. Recent work has shown that under proper conditions, the imine linkage may be opened. Thus imine 16 has been deaminated by treatment with nitrous acid in aqueous dioxane buffered with sodium acetate[12]. The hemiacetal (17) was obtained in yields of up to 78%. Since the structure of this product is now secure, the question of the mechanism of the reaction arises. The expected pathway *via* the N-nitroso-carbinol amine (18 → → 22) would lead to a hemiacetal (22) derived from a C-17 aldehyde. Since no appreciable amount of aldehyde acetate could be found in the reaction mixture, it is clear that the aldehyde oxygen participates in the deamination to provide a cyclic oxonium ion (23) as the primary product[12]. Several arguments lead the Canadian workers[12] to believe that dismutation occurs between the hemiacetals, with 22 going to 17 *via* oxonium ions 23 and 24. A parallel series of reactions in the Garrya series leads to a hemiacetal analogous to 17[6,13].



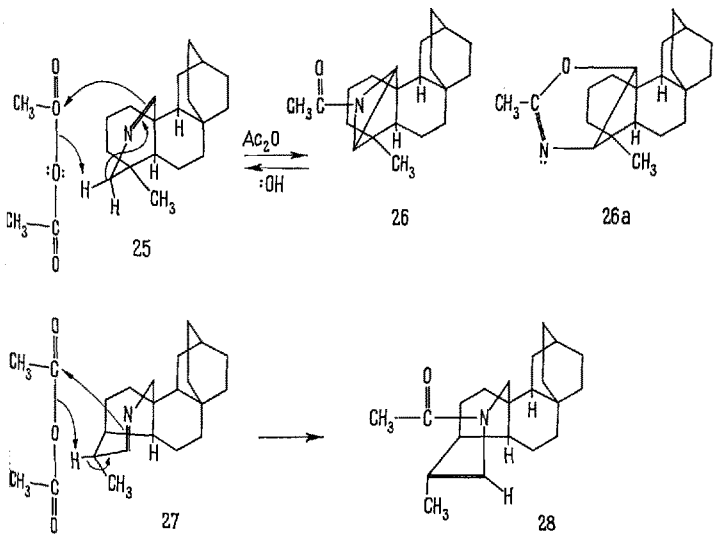




An even more surprising reaction of the imine grouping was encountered during attempts to open the hetero ring of compound 25[14]. Prolonged refluxing of 25 with acetic acid–acetic anhydride mixture gave a neutral product to which an aziridine structure (26) has been assigned on the basis of the analysis and NMR spectrum[15]. An analogous compound (29) of type

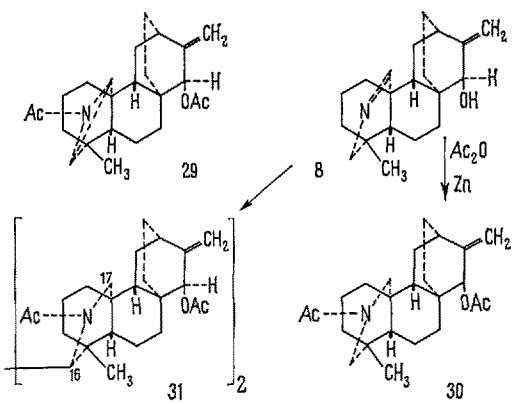
[10] D. DVORNIK and O. E. EDWARDS, Chem. and Ind. *1957*, 952.
[11] S. W. PELLETIER, unpublished work.
[12] J. W. AP SIMON, O. E. EDWARDS, and R. HOWE, Canad. J. Chem. *40*, 630 (1962).
[13] H. VORBRUEGGEN and C. DJERASSI, Tetrahedron Letters, No. 3 119 (1961).
[14] The absolute configuration of these compounds is the mirror image of that represented.
[15] O. E. EDWARDS, Chem. in Canad., Jan. (1961), p. 38.

26 has also been prepared in the atisine series from imine 8[16].

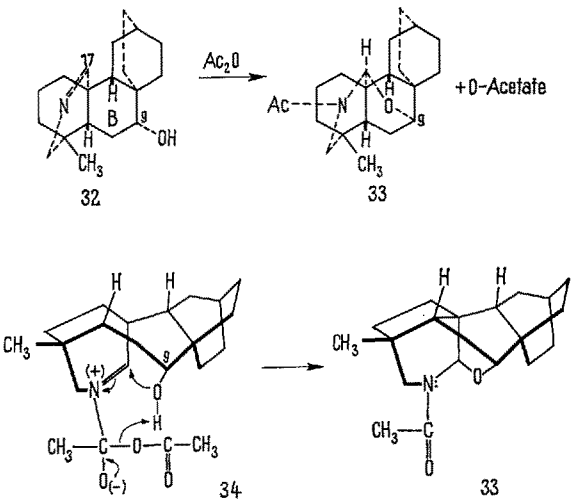
Initially the reaction was interpreted in terms of a new structure for atisine, the imine being 27 and the product 28[15]. However, since the NMR spectrum of the product displays no vinyl hydrogen and the methyl signal is still at high field, structure 28 is clearly eliminated. It is interesting to note that vigorous alkaline hydrolysis of 26 regenerates the imine (25)[15].




The azomethine (8) derived from atisine undergoes a reaction of further interest when refluxed with zinc dust in acetic anhydride. The major product is the O,N-diacetate (30) together with 5–10% of a bimolecular product to which structure 31 is assigned[16a]. The linkage between halves is believed to be at C-16, because of the severely hindered environment about C-17. It is interesting to note that the aziridine (29) bearing the allylic alcohol grouping in ring D is stable to the zinc–acetic anhydride reduction[16a].




The azomethines derived from ajaconine show two special reactions by virtue of the 9-oxygen function. One of these involves the acetylation of imine 32 and provides a dramatic illustration of the effect of a trigonal carbon atom at C-17 in lowering the energy of the boat conformation of ring B[15,17]. Whereas the isolated imine grouping of atisine or veatchine resists the action of acetic anhydride except under prolonged refluxing (see above), compound 32 at room temperature furnishes the N-acetate (33) in 50% yield as well as the normal O-acetate. This is particularly surprising when it is noted that the 9-hydroxyl in this compound is equatorial and readily acetylated. It has been suggested that acetic anhydride coordinates with the unshared pair of electrons on the nitrogen atom and that sufficient molecules of the complexed imine are in the conformation with ring B as a boat (34) so that the reaction giving 33 competes with the O-acetylation reaction[15,17].



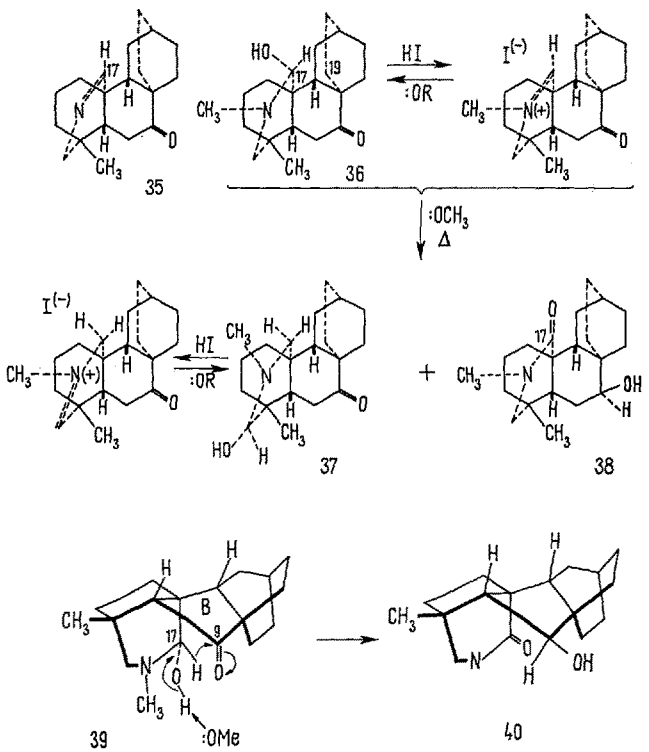

The second unusual reaction of the ajaconine azomethines involves a transannular hydride ion transfer from C-17 to C-9[18]. The keto imine (35) was converted to the methiodide and then to the N-methyl carbinol amine (36). Boiling methanolic potassium hydroxide converted the latter into a mixture of the corresponding iso compound (37) and a hydroxy lactam (38). This lactam is the product of an oxidation-reduction process of the Cannizzaro type[18]. The formation of only one lactam (38) and the fact that the lactam carbonyl is at C-17 establish the intramolecular course of this reaction

[16] (a) S. W. Pelletier and P. C. Parthasarathy, unpublished work. (b) In view of recent work on aziridine rearrangements (see review by H. W. Heine, Angew. Chem. *74*, 772 (1962)) it is interesting to speculate whether the postulated acylaziridine might not readily undergo rearrangement to compound 26a. In fact, it is possible that the product of the reaction in acetic anhydride is actually 26a rather than 26. The NMR data would not necessarily distinguish between the two structures.

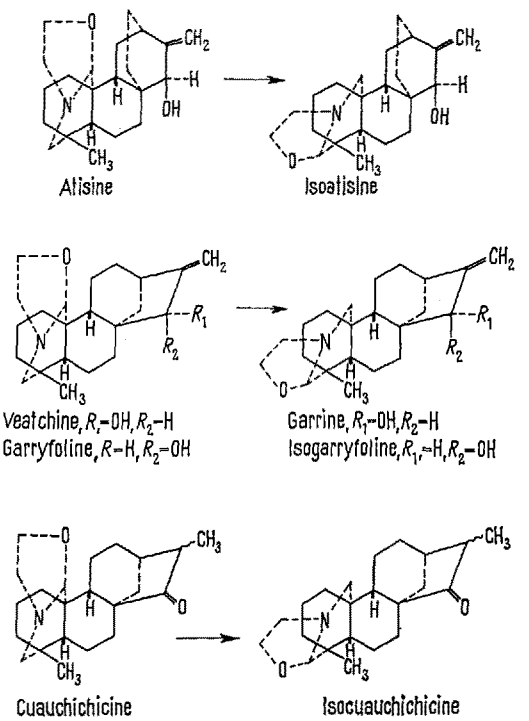
[17] D. Dvornik and O. E. Edwards, Tetrahedron *14*, 54 (1961).

[18] D. Dvornik and O. E. Edwards, Proc. chem. Soc. *1958*, 280.

since an intermolecular process is not possible because of the inaccessibility of the C-17 hydrogen facing C-19. When ring B assumes a boat conformation (39) the geometry is ideal for a transannular hydrogen transfer from C-17 to the 9-carbonyl to give the hydroxy lactam (40). The formation of a boat is assisted by the trigonal state of C-9[18].



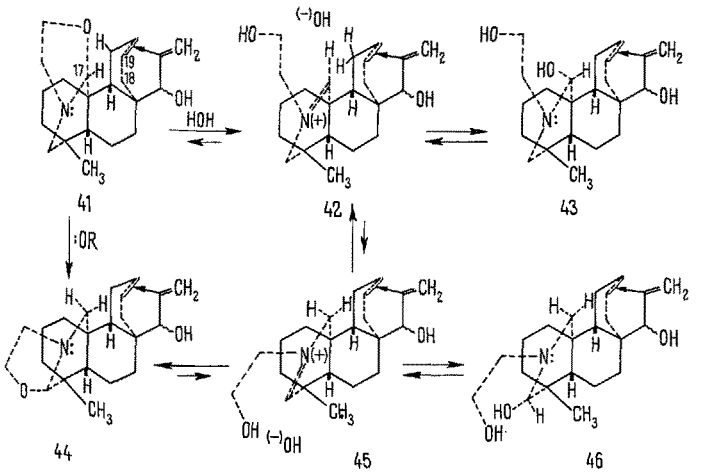
Several novel reactions involving the ternary iminium salts of the atisine alkaloids will now be considered. Early in his studies on the structure of atisine, JACOBS observed that brief treatment with warm alkali was sufficient to isomerize atisine to another base which he named isoatisine[19]. Subsequent work has shown that the related alkaloids veatchine[20], garryfoline[21] and cuauchichicine[21] are similarly isomerized to garryine[20], isogarryfoline[20] and isocuauchichicine[21], respectively. The isomerization is a very facile one and proceeds at room temperature in alcohol without external base, the alkaloid itself promoting the change[21]. For example, in the case of atisine we have followed the isomerization by the change in optical rotation and find that the reaction is essentially complete after 80 min refluxing in methanol or after ten days at room temperature without external base[11]. Another feature worthy of note is that the members of these pairs of isomers manifest a remarkable difference in basic strengths. Thus atisine in 50% methanol shows a pKa' of 12.8 while isoatisine gives a value of 10.35[9]. Similar differences prevail for the veatchine-garryine, garryfoline-isogarryfoline and cuauchichicine-isocuauchichicine pairs[20,21]. The greater basicity of the 'normal' compounds compared with the 'iso' series finds explanation in terms of the equilibria presented below.




The salts of these alkaloids show bands in the infrared characteristic of the $\overset{\oplus}{N}{=}C$ group and therefore exist in the ternary iminium form[9,22]. In hydroxylic solvents atisine and the other 'normal' type bases (41) exist almost completely as the ternary iminium hydroxide (42) since parallel titrations show that in 50% methanol atisine is about as strong a base as sodium hydroxide. The question arises as to why the 'iso' bases are not as strong bases as atisine since they might also be expected to exist in the ternary iminium form. It is obvious that the difference in position of the double bond in the ternary iminium hydroxide forms of the 'normal' (42) and the 'iso' bases (45), by itself, cannot account for the large difference in the basic strengths. Rather we must assume that in the case of the 'normal' bases a higher proportion of the ternary iminium form (42) is present in an equilibrium between the oxazolidine (41), ternary iminium (42), and pseudo base (43) forms, whereas in the 'iso' bases a high proportion of the oxazolidine (44) or pseudo base forms

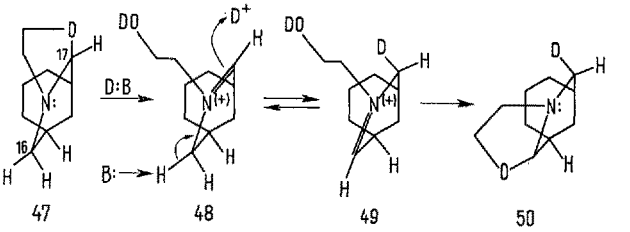
[19] W. A. JACOBS and L. C. CRAIG, J. biol. Chem. *147*, 567 (1943).
[20] K. WIESNER, S. K. FIGDOR, M. F. BARTLETT, and D. R. HENDERSON, Canad. J. Chem. *30*, 608 (1952).
[21] C. DJERASSI, C. R. SMITH, A. E. LIPPMANN, S. K. FIGDOR, and J. HERRAN, J. Amer. chem. Soc. *77*, 4801 (1955).
[22] O. E. EDWARDS and T. SINGH, Canad. J. Chem. *32*, 465 (1954).

(46) is present. The fundamental reason for the preponderance of the ternary iminium hydroxide in the atisine equilibrium has been recognized as the steric interference with substituents on the tetragonal C-17 in the oxazolidine form[3,4,9,21,23]. Thus serious repulsive interactions of the hydrogens on C-17, C-18, and C-19 occur when C-17 is tetrahedral. However, the strain is relieved in the ternary iminium form when C-17 is trigonal. Consequently, in solution atisine and the other 'normal' bases will exist almost completely as ternary iminium hydroxides and show high pKa's, whereas the iso-type bases, in which the steric factor does not operate to the same extent, will exist mostly in the oxazolidine form and show lower pKa's.

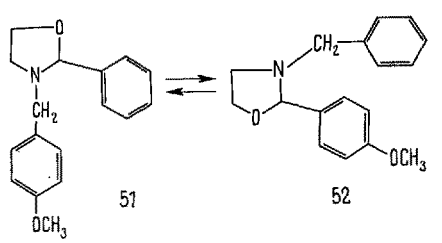


The same explanation accounts for the isomerization of the 'normal' to the 'iso' bases. In solution the isomerization proceeds through the ternary iminium forms 42 and 45 by prototropy. Since steric factors are responsible for the 'iso' bases having a lower free energy than the normal bases (the reasons for this will be discussed subsequently), the equilibrium is shifted toward the sterically more favored 'iso' forms.

The interpretation, outlined above, involving steric factors as the driving force for the isomerizations described, is given support by Leonard's study of the isomerization of a tricyclic oxazolidine model of the AEF-ring system of the diterpene alkaloids[24]. The mechanism[23] which has been postulated for the isomerization involves abstraction of a proton from the methylene carbon at 16 with concommitant addition of a proton at trigonal carbon C-17. The catalyzing base may be either added alkali, solvent or the alkoxide produced by heterolytic fission of the oxazolidine itself. Since the isomerization is accompanied by the loss and gain of a proton, it is subject to study by deuterium exchange (see 47 → 50). It is to be noted that no steric driving force to rearrangement of the oxazolidine ring is present in the model oxazolidine (47).



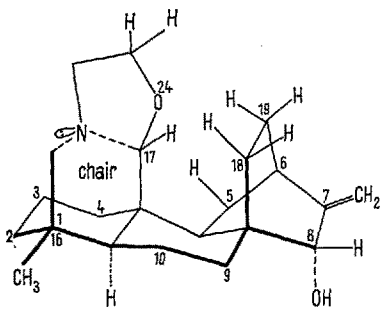
When the tricyclic oxazolidine (47) was heated under reflux with methanol-d for 24 h, conditions sufficient to isomerize atisine, no deuterium was incorporated in the product which was identical with starting material. Refluxing with added NaOD for 3 h resulted in less than 5% incorporation. Refluxing in a mixture of dioxane and deuterium oxide at 85° for 24 h resulted in $< 30\%$ incorporation of one deuterium atom per molecule. Thus it is evident that without the steric driving force which is present in the alkaloid system, strenuous conditions are required to effect isomerization[24]. In another model system of the arylaralkyl oxazolidine type (51 and 52), in which there was no steric differentiation between the two α N-carbons, but in which the protons on these particular carbons were relatively more acidic than in the diterpene alkaloids, isomerization did not occur under conditions which lead to formation of the 'iso' alkaloids. However, when either 51 or 52 was heated at 193° in diethylene glycol monomethyl ether for 24 h, isomerization occurred to give a mixture of the two products in about equal amounts. Though isomerization can be induced, the rate is far lower than that observed for the diterpene alkaloids. These results provide clear evidence that prototropic isomerization of ternary iminium compounds is not a general phenomenon, but is highly dependent upon both the steric environment and the reaction conditions[24].



We return now to a consideration of the steric factors which provide the driving force for the isomerization and account for the greater stability of the 'iso' bases compared to normal-type bases. Since both atisine and isoatisine have tetragonal C-17 groups it is necessary

[23] K. Wiesner and J. A. Edwards, Exper. *11*, 255 (1955).
[24] N. J. Leonard, K. Conrow, and R. R. Sauers, J. Amer. chem. Soc. *80*, 5185 (1958).

to invoke factors in addition to the above equilibria to explain the greater stability of isoatisine over atisine. The following two interactions may be observed in models (Dreiding) of the atisine molecule: (1) C-24 oxygen with the C-5 hydrogen and (2) C-17 hydrogen with the C-18 and C-19 hydrogens. The first interaction is of course absent in isoatisine. However, it must be emphasized that while it is present and causes steric strain in rotamer 53[14] of atisine, it is entirely absent in rotamer 54[14]. The latter therefore would be expected

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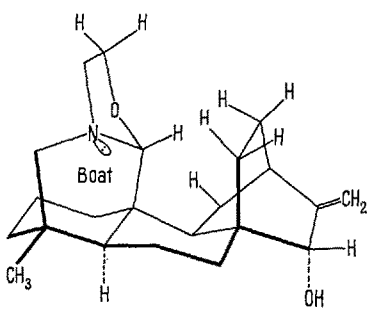


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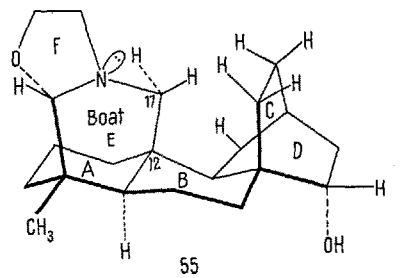
to be the more stable and preferred conformation. It is therefore difficult to accept the suggestion[25] that the C-24 oxygen–C-5 hydrogen interaction alone provides the driving force for the isomerization. If rotamer 54 can be shown to be less stable than 53, this interaction may be a contributing factor, but still is not sufficient by itself to explain the energy difference between atisine and isoatisine[26]. The great importance of the steric compression between the C-17 hydrogen and the C-18 and C-19 hydrogens may not be immediately obvious since this interaction is also present in isoatisine. However, in models of isoatisine (55)[14] the resulting strain can be relieved by a distortion of the ring system involving the bending of the C-12–C-17 bond and rotation of the C-17 hydrogen away from ring C. Since in atisine, C-17 is a part of the oxazolidine ring and is not free to rotate, the repulsive interactions cannot be relieved by rotation and bending of the C-17 group. We proposed, therefore, that the driving force of the atisine–isoatisine isomerization is due largely to the increased steric hindrance in atisine which results from the restriction which ring E imposes upon the rotation of the C-17 group[26]. Recently it has been suggested that the rearrangement of compound 56 and one other N-methyl 17-hydroxy compound to the 16-hydroxy compounds (57) invalidates this explanation of the driving force for the rearrangement of the normal to the iso-type compounds[17]. It is to be noted that the oxygen of the 17-hydroxyl in 56 occupies a position analogous to the oxygen in the oxazolidine ring in atisine, veatchine, garryfoline, or cuauchichicine. In this case the 27-oxygen:5-hydrogen interaction probably is responsible for the driving force for the isomerization, since the oxazolidine ring is not present. However, it is worth comparing the conditions used to isomerize 56 to 57 with those effective in the atisine–isoatisine case. Compound 56 required boiling in about 0.6 *N* KOH in methanol for 3 h, whereas atisine is isomerized by refluxing in methanol for 80 min without external base, or even in alcohol at room temperature[11]. It is thus obvious that in the atisine case a factor, in addition to the 24-oxygen:5-hydrogen interaction, must be present to explain the far greater ease of isomerization.

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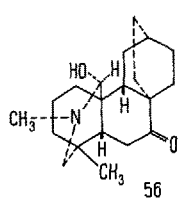

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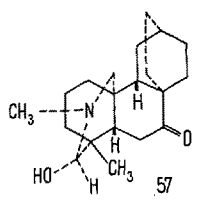

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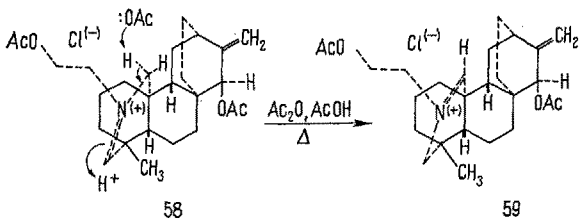
We believe this additional factor which causes atisine, veatchine, garryfoline and cuauchichicine to undergo isomerization with such great ease is the *steric hindrance resulting from the restriction which the oxazolidine ring imposes upon the rotation of the C-17 group*. In summary we may say that while the 27-oxygen:5-hydrogen interaction of Edwards may furnish part of the driving force for the normal to iso-type conversion, the greater part of the driving force must be due to the steric interaction resulting from the rigidity imposed on the system by the oxazolidine ring.

In the case of the salts of the normal and 'iso' bases, the reverse of the situation described for the bases would be expected to obtain. The normal salts have a less bulky trigonal carbon atom in the hindered 17-position and therefore should be more stable than the 'iso' salts which have the more bulky tetragonal carbon at C-17. This reasoning has been substantiated by the demonstration that refluxing isoatisine diacetate chloride (58) in acetic anhydride gives the atisine salt (59)[27]. The isomerization probably proceeds by a mechanism involving a concerted abstraction and re-addition of a

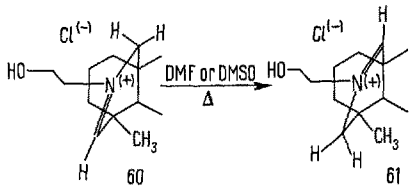
[25] D. DVORNIK and O. E. EDWARDS, Proc. chem. Soc. *1958*, 305.
[26] A. J. SOLO and S. W. PELLETIER, Proc. chem. Soc. *1961*, 14.
[27] O. E. EDWARDS and T. SINGH, Canad. J. Chem. *33*, 448 (1955).

proton by acetate ion and acetic acid, respectively as shown in 58 → 59[9]. A similar reaction in the Garrya



58 59

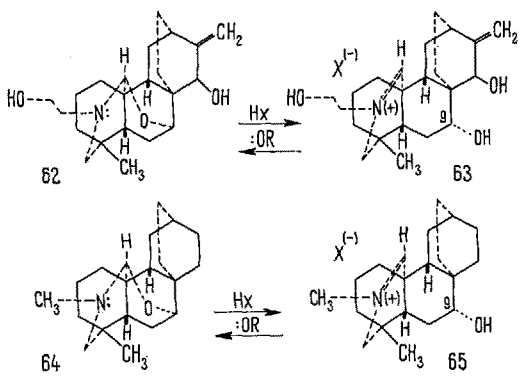
series, resulting in the transformation of garryine diacetate chloride to veatchine diacetate chloride, has also been effected[28]. Moreover, recently we have been able to convert isoatisinium chloride (60) directly to atisinium chloride (61) by simple refluxing in dimethyl



60 61

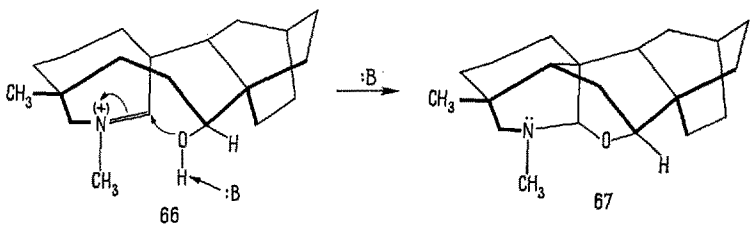
formamide, diethyl formamide, phenol, ethylene glycol or dimethyl sulfoxide[28]. A 9-h reaction time in DMF is necessary to achieve 86% conversion to the 'normal' salt whereas the isomerization is complete in phenol in 1 h and in DMSO in only 30 min. Though the boiling point of ethylene glycol is higher than that of DMSO, isomerization in refluxing ethylene glycol requires two to three times as long as in DMSO. Thus it is evident that the rate of isomerization is not purely temperature dependent. A similar isomerization of garryine chloride to veatchine chloride has also been effected in boiling DMSO or DMF. These results clearly demonstrate that the operation of steric factors makes for the greater stability of the 'normal' type salt which possesses $SP^2$-type bonding at the C-17 atom.

A type of carbinolamine ether to ternary iminium salt conversion similar to that discussed for atisine, veatchine, garryine, and cauauchichicine has been observed in derivatives of the alkaloid ajaconine (62)[17].



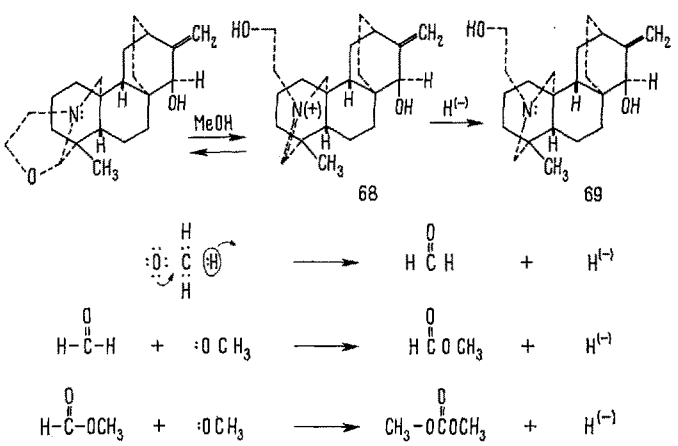
62 63 64 65

In this instance the internal carbinolamine ether (62 and 64) involves the 9-oxygen atom and is not derived from the N-2$\beta$-hydroxyethyl system as in atisine. The salts of the base exist in the ternary iminium forms (63 and 65) and rapidly cyclize to the carbinolamine ethers (62 and 64) in the presence of strong base. The formation of the 9:17 ether is initiated by conversion of ring B to a boat conformation (66) while C-17 is trigonal[17]. Removal of a proton from the hydroxyl gives an anion which undergoes nucleophilic attack at C-17 to close the ring (67).



66 67

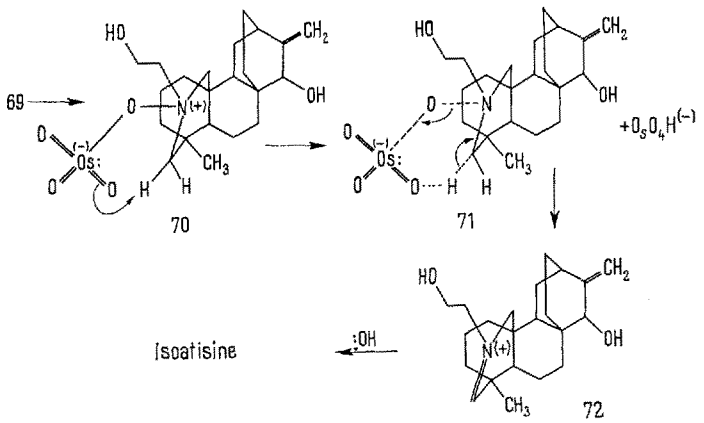
Early in the study of the chemistry of atisine, a rather unusual reduction was observed when isoatisine was heated in a sealed tube with methanolic sodium hydroxide[18]. The product, dihydroatisine (69), which differed from isoatisine by two hydrogen atoms, was formed in 70% yield. A simple disproportionation reaction is thus ruled out. The reaction can be explained by assuming an equilibrium exists between isoatisine and its ternary iminium form (68) and that the latter is reduced by a hydride ion generated as shown from the methoxide ions. Each methoxide can give rise to three hydride ions and thus decomposition of a small amount of methoxide suffices to reduce a large amount of isoatisine. The reaction also proceeds in the presence of ethoxide, though less readily.



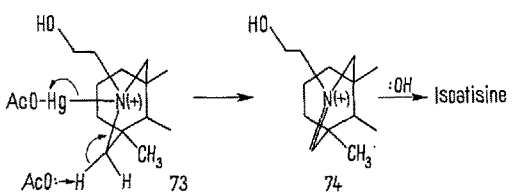
68 69

[28] S. W. Pelletier and K. Kawazu, unpublished work.

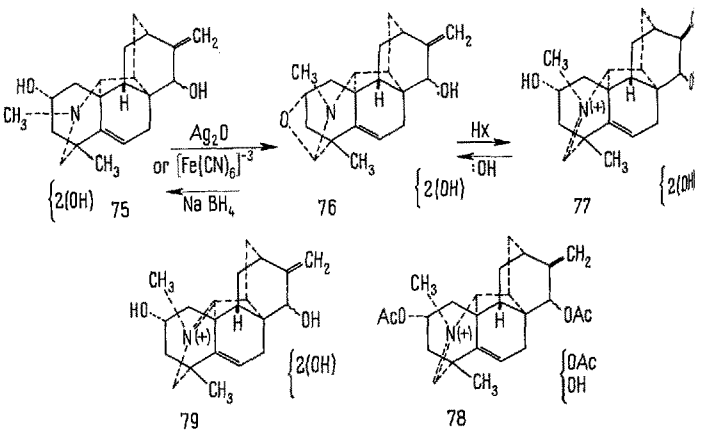
Just the opposite effect, that is the formation of an oxazolidine ring from a β-hydroxyethyl group, can be accomplished by the use of osmium tetroxide[7,29]. We have applied the reaction to dihydroatisine and find that the use of exactly one mole of osmium tetroxide in ether gives a 60–70% yield of isoatisine[7]. A possible mechanism is suggested involving an initial complexing of one equivalent of tetroxide with the unshared pair of electrons on the nitrogen atom (70). The complex can decompose as illustrated by way of a cyclic six membered transition state (71) to give the ternary iminium form of isoatisine (72)[30]. Attack on the hydrogen atom at C-17 is precluded because of the sizable steric requirements of the complex and thus atisine is not formed. It is to be observed that when only one mole of osmium tetroxide is used, the cyclization reaction takes precedent over hydroxylation of the exocyclic methylene group.



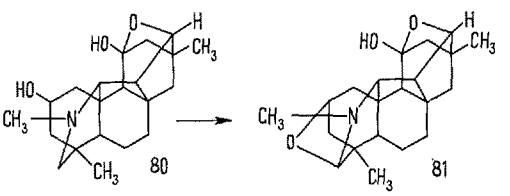

The osmium tetroxide cyclization reaction is reminiscent of the cyclizations which LEONARD[24,31] has shown can be effected nicely with mercuric acetate. Application of the mercuric acetate oxidation to dihydroatisine afforded isoatisine in a yield of 30%[11]. By analogy with the osmium tetroxide oxidation, attack should occur at the C-16 position and atisine should not be a product of the reaction. Careful analysis of the reaction mixture by thin layer chromatography failed to reveal the presence of any atisine[11]. The reaction proceeds presumably as shown in 73 to furnish the quaternary iminium salt of isoatisine (74). The latter is converted to isoatisine by treatment with base.




Recently it has been found that oxidation with silver oxide or alkaline ferricyanide effects cyclization of the 3-hydroxyl group of des-N-methyl hyponavinol (75) to give a carbinolamine ether (76)[32]. The latter is easily reduced by borohydride to the starting material. In the presence of acid the carbinolamine ether opens to give a ternary iminium salt ($>C=\overset{\oplus}{N}<$, 1686–1679 $cm^{-1}$) (77). Acetylation of this salt furnishes the corresponding triacetate (78). It is clear that the double bond must exist between the nitrogen and C-16 since the alternative $>\overset{\oplus}{N}=C<$ $>N=C<$ structure (79) would be severely strained.

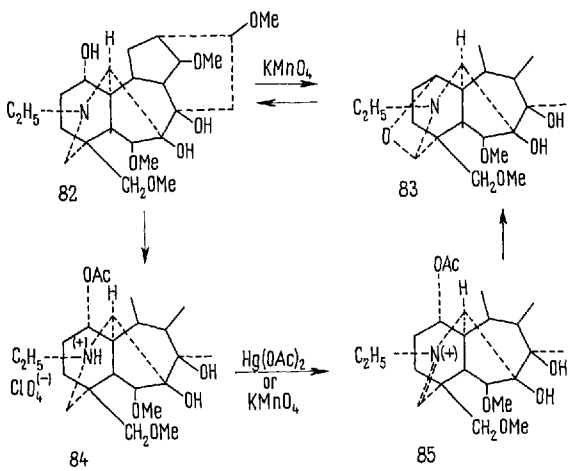



An analogous oxidation in the hetisine series has been effected with permanganate[33]. Dihydrodesmethylhetisine, newly formulated as 80[34], is oxidized to a carbinolamine ether[35] (81)[34] which shows weak hydroxyl absorption, but no carbonyl absorption in the infrared[35]. Reduction of 81 with sodium borohydride regenerates starting material[35].



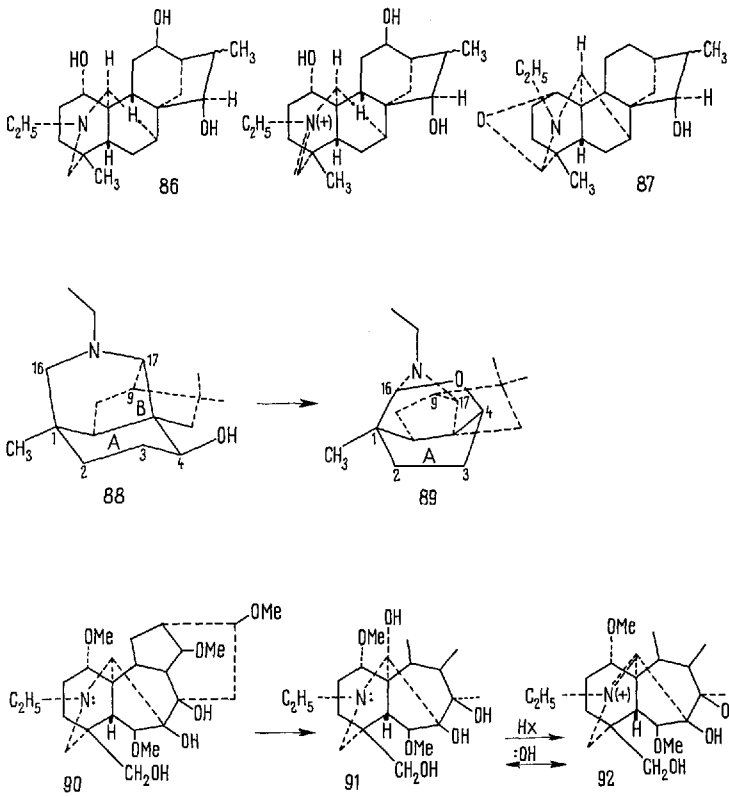

[29] K. WIESNER, W. I. TAYLOR, S. K. FIGDOR, M. F. BARTLETT, J. R. ARMSTRONG, and J. A. EDWARDS, Chem. Ber. *86*, 800 (1953).
[30] Essentially the same mechanism has been proposed independently by DVORNIK and EDWARDS, ref. [17], page 56, footnote 12.
[31] N. J. LEONARD and W. K. MUSKER, J. Amer. chem. Soc. *82*, 5148 (1960).
[32] (a) S. SAKAI, Chem. Pharm. Bull. *6*, 448 (1958); *7*, 55 (1959). (b) The absolute configuration of these compounds is assumed to be the same as that of the other diterpene alkaloids.
[33] W. A. JACOBS and C. F. HUEBNER, J. biol. Chem. *170*, 189 (1947).
[34] K. WIESNER, Z. VALENTA, and L. G. HUMBER, Tetrahedron Letters No. 14, 621 (1962).
[35] A. J. SOLO and S. W. PELLETIER, J. Amer. chem. Soc. *81*, 4439 (1959).

Another example of a similar cyclization, involving this time a 4-equatorial hydroxyl group, is found in the case of the delphinium alkaloid, delsoline (82)[32,36]. This compound undergoes smooth transformation to a carbinolamine ether (83) by the action of permanganate. That the reaction probably proceeds through the ternary iminium form is shown by stepwise conversion to the perchlorate salt (84) and subsequent oxidation with mercuric acetate or permanganate to the iminium chlorate (85). The latter on treatment with base furnishes the carbinolamine ether (83)[36].



It seems that the number of oxidizing agents capable of effecting this kind of change is numerous indeed. On any one compound only one or two reagents have usually been tried. However, from the numerous cases of different compounds undergoing similar reactions, it is clear that a multitude of reagents are capable of effecting the oxidative cyclization. Another example is provided in the work on songorine (napellonine)[37,38]. Oxidation of dihydronapelline (86) proceeds smoothly with silver oxide to give the carbinolamine ether (87)[37]. Initially the compound was assumed to possess a 3-axial hydroxyl. Recently SUGASAWA has shown that actually a 4-equatorial hydroxyl is present[38]. The reaction can be formulated as shown in the conformational drawing 88 → 89.

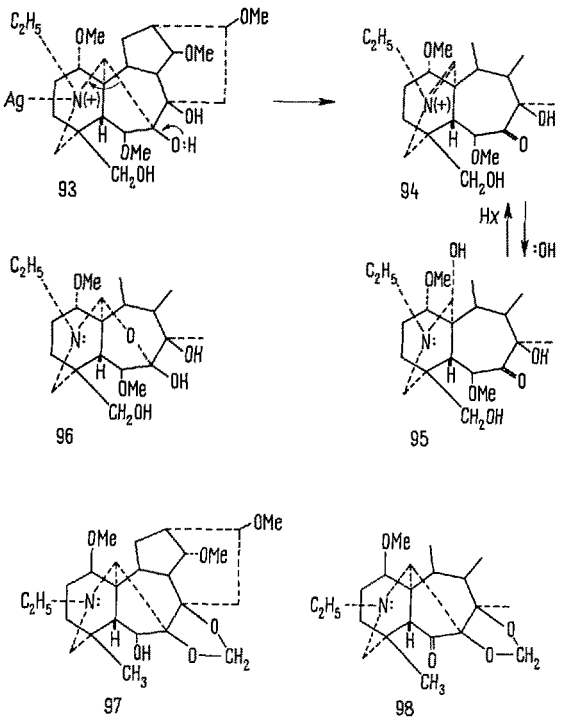
A final reaction to be discussed is the oxidation of lycoctonine (90) to hydroxylycoctonine[39–41]. The structure of the alkaloid determined by X-ray crystallography satisfied most of the observed reactions[42]. A strong objection initially registered against general acceptance of the structure is the behavior of the silver oxide[39] and lead tetraacetate[40,41] oxidation product, hydroxylycoctonine, for which the structure shown (91) was originally proposed by EDWARDS[40]. Since hydroxylycoctonine forms quaternary anhydronium salts from which hydroxylycoctonine can be recovered on basification, it is clear that the presence of a $\rangle N{=}C\langle$ moiety in the anhydronium salt (92) corresponding to 91 involves an impossible strain. Furthermore, although structure 91 contains a vicinal triol system, glycol cleavage reagents cleaved only one diol grouping in the molecule. Other chemical reactions excluded locating the hydroxyl group on one of the other carbon atoms adjacent to the nitrogen atom.



A formulation which explains all the data was first proposed by VALENTA[43]. It is to be noted that the proposed structure (96) can be formed by a plausible pathway involving decomposition of the silver complex (93) to give a ketone salt (94) which is isolated in the hydrated or hemiketal form (95). While hydroxylycoctonine shows no carbonyl absorption in the infrared, the salts (94) show strong absorption at 1710 $cm^{-1}$ and 1660 $cm^{-1}$ corresponding to the $\rangle C{=}O$ and $\rangle \overset{\oplus}{N}{=}C\langle$

[36] F. SPARATORE, R. GREENHALGH, and L. MARION, Tetrahedron *4*, 157 (1958).
[37] K. WIESNER, S. ITO, and Z. VALENTA, Exper. *14*, 167 (1958).
[38] T. SUGASAWA, Chem. and Pharm. Bull. *9*, 897 (1961).
[39] O. E. EDWARDS and L. MARION, Canad. J. Chem. *30*, 627 (1952).
[40] O. E. EDWARDS, L. MARION, and D. K. R. STEWART, Canad. J. Chem. *34*, 1315 (1956).
[41] R. C. COOKSON and M. E. TREVITT, Chem. and Ind. *1956*, 2761.
[42] M. PRZYBYLSKA and L. MARION, Canad. J. Chem. *34*, 185 (1956).
[43] Z. VALENTA, Chem. and Ind. *1959*, 633.

groups. Also the ultraviolet spectrum shows a maximum at 320 mμ (ε 70). Recently, further elegant work has confirmed this interpretation[44].



It is interesting to compare the behavior of the related alkaloid, delpheline (97), in which the necessary hydroxyl is blocked, toward silver oxide. The corresponding hydroxydelpheline is not formed. Instead the secondary alcohol group in ring B is oxidized to a ketone (98)[45].

The foregoing reactions have served to demonstrate the existence in Nature of some very interesting and otherwise rather inaccessible systems which are uniquely fitted for use as substrates for the study of unusual reactions and stereochemical effects[46].

*Zusammenfassung.* Aconitum- und Delphinium-Alkaloide gehen teilweise ungewöhnliche chemische Reaktionen ein, deren Ursache in der polycyclischen Struktur, im besonderen in deren hohem Grad von Brückenbildungen zu suchen ist.

Einige dieser Reaktionen, speziell solche der Imine und Imminiumsalze der Diterpenalkaloide Atisin und Veatchin werden diskutiert.

[44] O. E. EDWARDS, M. LOS, and L. MARION, Canad. J. Chem. *37*, 1996 (1959).—Proc. Chem. Soc. *1959*, 192.

[45] R. C. COOKSON and M. E. TREVETT, J. chem. Soc. *1956*, 2689.

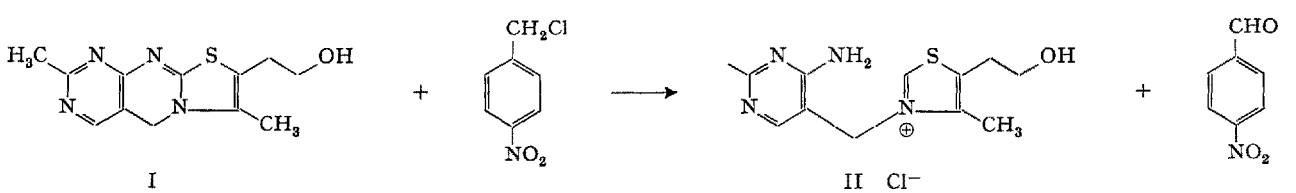
[46] *Acknowledgment.* The author wishes to express appreciation to his colleagues, Drs. R. ANEJA and P. C. PARTHASARATHY for checking the manuscript and making several helpful suggestions. The author's work described herein was supported by Public Health Service Research Grants GM 05807-05 and GM 10921-01.

# Brèves communications – Kurze Mitteilungen – Brevi comunicazioni – Brief Reports



## A Novel Reduction of Thiochrome

In recent years, the chemistry of thiamine and related compounds has been the subject of several investigations[1–4]. The chemistry of thiochrome and other biologically inactive derivatives of thiamine, on the other hand, has not been extensively studied[5,6]. In the course of investigating the reactions of thiochrome, a most interesting reduction was noted. In an attempt to alkylate thiochrome with *p*-nitrobenzyl chloride under mild conditions, it was discovered that thiochrome (I) was reduced to thiamine (II) and the halide was oxidized to *p*-nitrobenzaldehyde. The reaction may be formulated in this manner:



I II $Cl^-$

[1] F. LIPMANN and G. PERLMAN, J. Amer. chem. Soc. *60*, 2574 (1938).

[2] O. ZIMA and R. R. WILLIAMS, Ber. dtsch. chem. Ges. *73*, 941 (1940).

[3] S. MIZUHARA and P. HANDLER, J. Amer. chem. Soc. *76*, 571 (1954).

[4] R. BRESLOW, J. Amer. chem. Soc. *80*, 3719 (1958).

[5] F. BERGEL and A. R. TODD, J. chem. Soc. *1937*, 1504.

[6] J. FINKELSTEIN and R. C. ELDERFIELD, J. org. Chem. *4*, 365 (1939).