Reviews

Interpretation of the Formation of Nine "Artifact Indole Alkaloids" in the Ajmaline/Sarpagine Series

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Introduction

Nine "indole alkaloids" of the ajmaline-/sarpagine-type, having a C-19 methyl group α to N_b, are known.[1,2] Five of them are sarpagine derivatives [*O*-acetylpreperakine (**1**),[1,3] macrosalhine (**2**),[1,4] peraksine (vomifoline) (**3**),[1,5] dihydroperaksine (**4**),[1,6] and verticillatine (**5**)[1,7,8]], and four are ajmaline derivatives [perakine (raucaffrine) (**6**),[2,9,10] raucaffrinoline (**7**),[2,11] 10-methoxyperakine (**8**),[2,12] and vincawajine (10-methoxyraucaffrinoline acetate) (**9**)] (Chart 1).[2,12]

Discussion

Overview. Compounds **1**−**4** and **6**, **7** are artifacts formed from *E*-vomilenine (**10**), via *Z*-vomilenine (**11**), during isolation from the respective plant materials. Compound **5** is formed in the same way but from the corresponding 10-hydroxy counterpart, and compounds **8** and **9** are formed from the 10-methoxy counterparts (vide infra). The C-21 hydroxy compounds are in equilibrium with their tautomeric amino aldehydes [ring-opened forms **10** ⇄ **10a**, **11** ⇄ **11a**; *chano* forms), which are interconvertible. This permits *E*-vomilenine (**10**) and *Z*-vomilenine (**11**) in solution to approach the equilibrium position where *E*-vomilenine predominates (Scheme 1).

Under the hydrolytic conditions (acidic or basic) often used during the isolation procedures, the acetyl group of vomilenines (**10** and/or **11**) may be cleaved. In the case of *Z*-vomilenine (**11**) this leads to deacetyl-*Z*-vomilenine (**12**), which is in equilibrium with 16-epi-*Z*-vellosimine (**13**) and *Z*-vellosimine (**14**) (Scheme 2).

A striking general aspect of compounds **1**−**9** is that the C-19 methyl group in all nine is β (when the quinuclidine ring system is considered) (vide supra).[13] Moreover, an interesting point in their formation is that in the recyclization process the attack can take place only from the β-side (vide infra). This would lead in the case of *E*-vomilenine (**10**) (*E*-ethylidene side-chain), via intermediate **10a/10b** (*chano* form), to 19-epi-perakine (**15**) (C-19α-CH_3), which has never been detected (Scheme 3).

In contrast, *Z*-vomilenine (**11**) would lead by a similar procedure (via **11a/11b**; *chano* form) to perakine (**6**) (C-19β-CH_3) (Scheme 4).

It seems evident to us, therefore, that compounds **1**−**9** are formed via the *Z*-ethylidene derivatives, even where only the thermodynamically more favored *E*-derivative has been detected in the plant. This means that the *E*-ethylidene derivatives must isomerize to the corresponding *Z*-ethylidene derivatives, via the corresponding *chano* forms (cf. Scheme 1), prior to the recyclization.

In spite of the fact that compounds **1**−**9** are artifacts, they are generally presented in the chemical literature as naturally occurring compounds (vide infra). To clarify the situation thoroughly, we now propose to look at the formation of the different compounds more closely.

O-Acetylpreperakine (1).[3] *O*-Acetylpreperakine (**1**) can be expected to form from *Z*-vellosimine (**14**) [itself formed from *E*-vomilenine (**10**), via *Z*-vomilenine (**11**); vide supra], which is in equilibrium with its ring-opened form **14a/14b** (*chano* form). Recyclization of **14a/14b** (attack from the β-side) leads to a C-20 equilibrium mixture of two aldehydes (**16** ⇄ **17**). Selective, partial reduction (Cannizzaro reaction) of the aldehyde mixture affords compound **18**, which then is acetylated during the isolation procedure (transesterification) to *O*-acetylpreperakine (**1**) (Scheme 5).

Macrosalhine (2).[3,14] An analogous scheme can be presented for the formation of macrosalhine (**2**) from *Z*-vellosimine (**14**). Recyclization of the ring-opened form (**14a/14b**; *chano* form) (attack from the β-side) leads to the C-20 equilibrium mixture of two aldehydes (**16** ⇄ **17**) (vide supra). Selective, partial reduction of the C-16 aldehyde function (Cannizzaro reaction) leads to intermediate **19**, which then, by intramolecular hemiacetal formation and methylation, affords macrosalhine (**2**) (Scheme 6). It is not quite clear whether the methylation takes place during the last step (as presented) or during an earlier step.

Peraksine (Vomifoline) (3)[5] and Dihydroperaksine (4).[6] Peraksine (vomifoline) (**3**) also can be expected to form from *Z*-vellosimine (**14**) (itself formed from *Z*-vomilenine (**11**); vide supra), through a selective partial reduction of the C-20 aldehyde function (Cannizzaro reaction) (**14** ⇄ **14a/14b** → **16** ⇄ **17** → **20**). The alcohol function that is formed, this time at C-21 (compound **20**), then easily cyclizes to an intramolecular hemiacetal, peraksine (**3**). If both aldehyde functions are reduced, dihydroperaksine (**4**) (**16** → **4**) and/or 20-*epi*-dihydroperaksine (**21**) (**20** → **21**) are formed (Scheme 7).

Verticillatine (5).[7,8,14] 10-Hydroxy-*Z*-vellosimine (**22**) leads to a C-20 equilibrium mixture of aldehydes **23** and **24**. Selective, partial reduction of **24** affords intermediate **25**, which, by intramolecular hemiacetal formation and methylation, leads to verticillatine (**5**) (Scheme 8). As in the case of macrosalhine (**2**) (vide supra), the step where the methylation takes placet is not quite clear.

Perakine (6)[9,10] and Raucaffrinoline (7).[11] Perakine (**6**) can be formed from *Z*-vomilenine (**11**) (or a similar compound), which is in equilibrium with its ring-opened form **11a/11b** (vide supra). Recyclization (attack from the β-side) leads to perakine (**6**), which is in equilibrium with 20-epiperakine (**26**). Reduction of perakine (**6**) (Cannizzaro reaction) affords raucraffrinoline (**7**) (Scheme 9).

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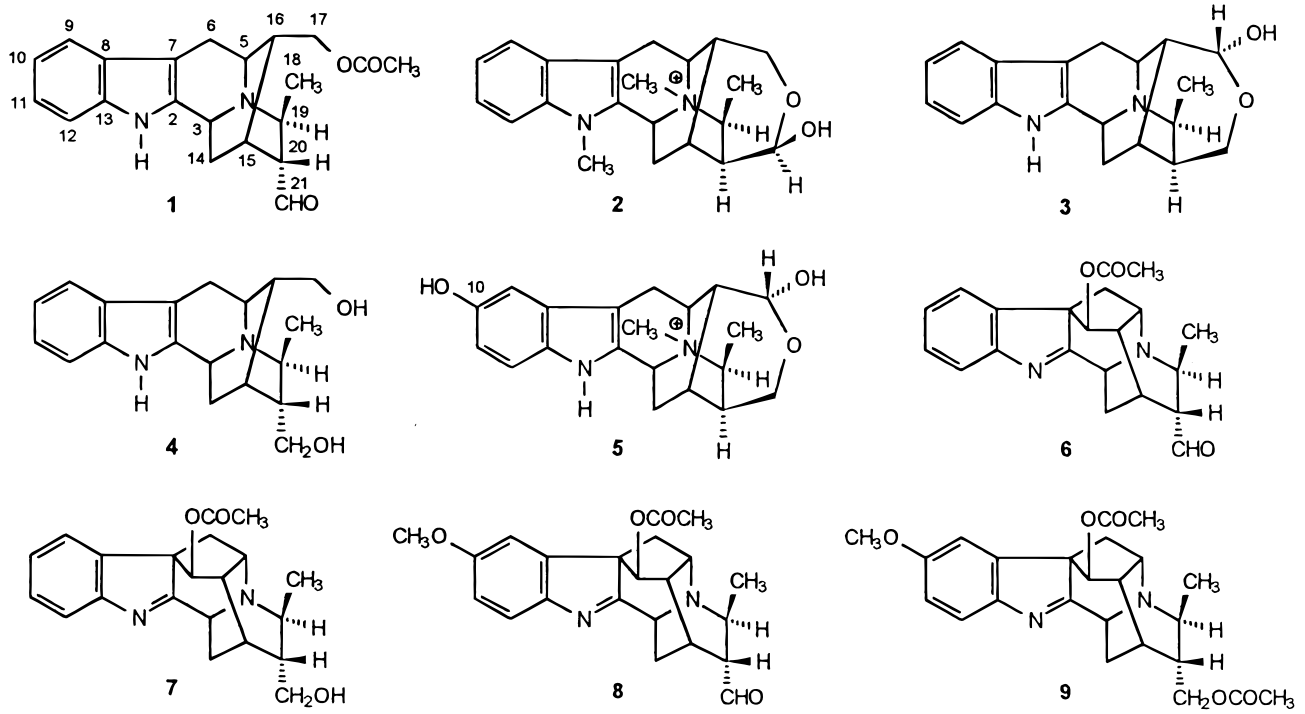
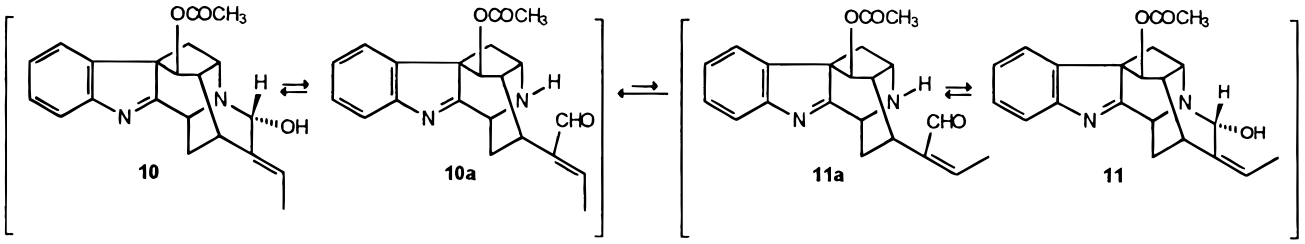
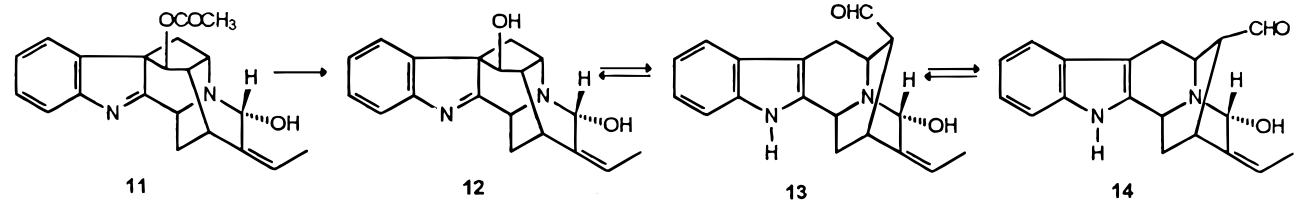
Chart 1



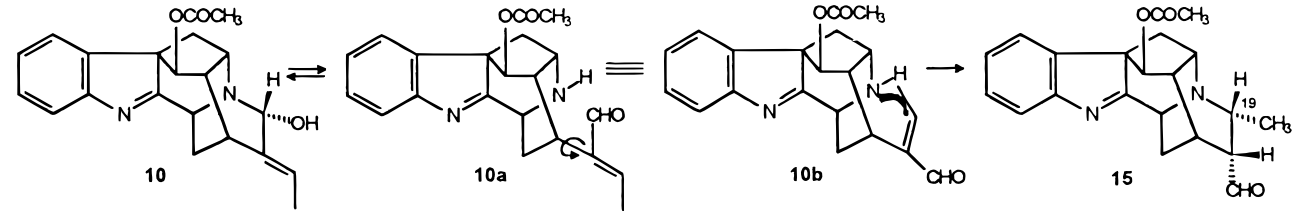
Scheme 1. Equilibrium between *E*-Vomilenine (**10**) and *Z*-Vomilenine (**11**) via Their Ring-Opened Forms **10a** and **11a** (*Chano* Forms)



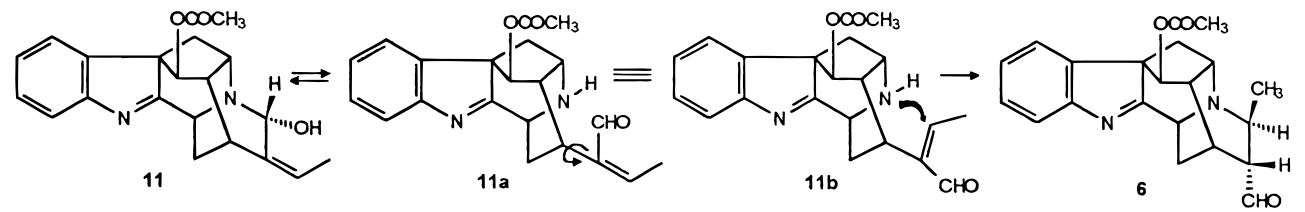
Scheme 2. Transformation of *Z*-Vomilenine (**11**), via Deacetyl-*Z*-vomilenine (**12**), to 16-*epi*-*Z*-Vellosimine (**13**) and *Z*-Vellosimine (**14**)



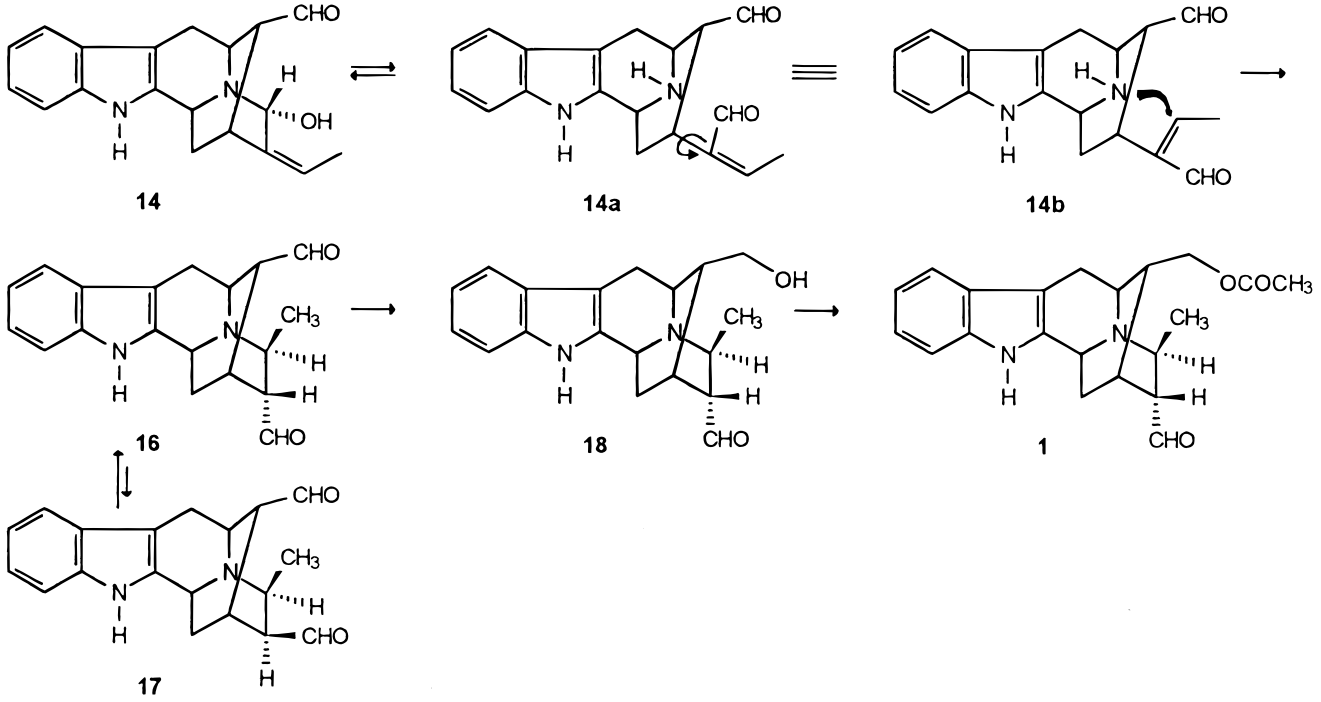
Scheme 3. Hypothetical Transformation of *E*-Vomilenine (**10**) (via Intermediate **10a/10b**) to 19-*epi*-Perakine (**15**) (C-19α-CH_3)



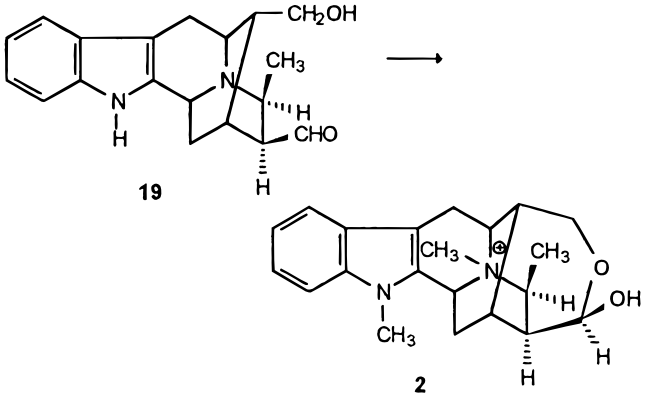
Scheme 4. Transformation of *Z*-Vomilenine (**11**) (via Intermediate **11a/11b**) to Perakine (**6**) (C-19β-CH_3)



Scheme 5. Formation of *O*-Acetylpreperakine (**1**)



Scheme 6. Formation of Macrosalhine (**2**)



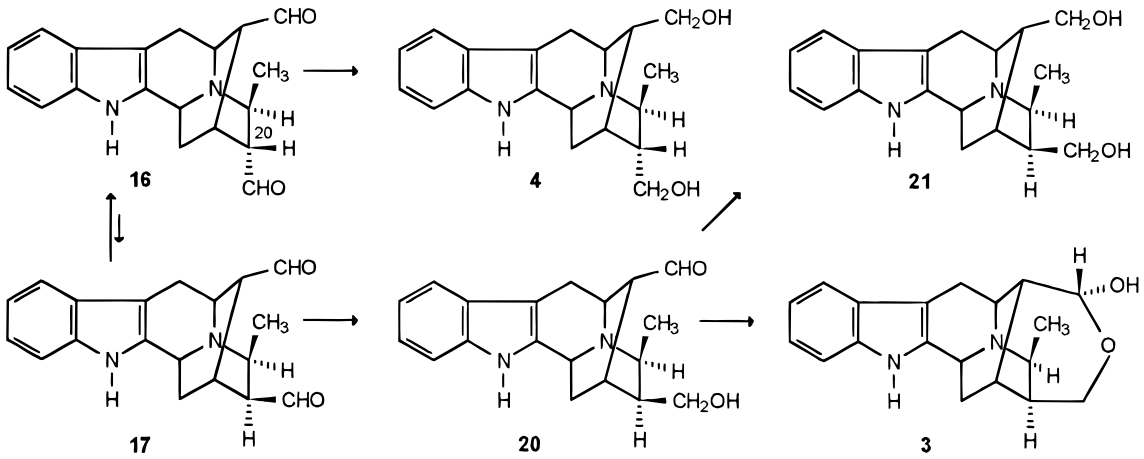
Takayama et al.[15] have shown that both synthetic *E*-vomilenine (**10**) and synthetic *Z*-vomilenine (**11**) are transformed to perakine (**6**), but the latter is transformed much faster and under less drastic conditions. This supports our assumption that perakine (**6**) is "directly" formed from *Z*-vomilenine (**11**) (cf. slow equilibrium between *E*- and *Z*-ethylidene derivatives of C-21−OH compounds; Scheme 1), which is more or less totally "consumed" during the isolation procedure and which thus is difficult to detect as a naturally occurring compound. It seems evident to us that an analogous situation prevails for the other eight cases we consider.

10-Methoxyperakine (8),[12] 10-Methoxyraucaffrinoline (29), and Vincawajine (9).[12] Analogous reasoning can be presented for the formation of 10-methoxyperakine (**8**) from 10-methoxy-*Z*-vomilenine (*Z*-majorinine) (**27**) (or a similar derivative). Reduction of the aldehyde function (**8** ⇄ **28**), due to the Cannizzaro reaction, leads to 10-methoxyraucaffrinoline (**29**). Compound **29** has not yet been isolated because the use of acetic acid (10%) in the applied extraction procedure[10] evidently causes it to transform to the corresponding acetate, vincawajine (**9**) (Scheme 10).

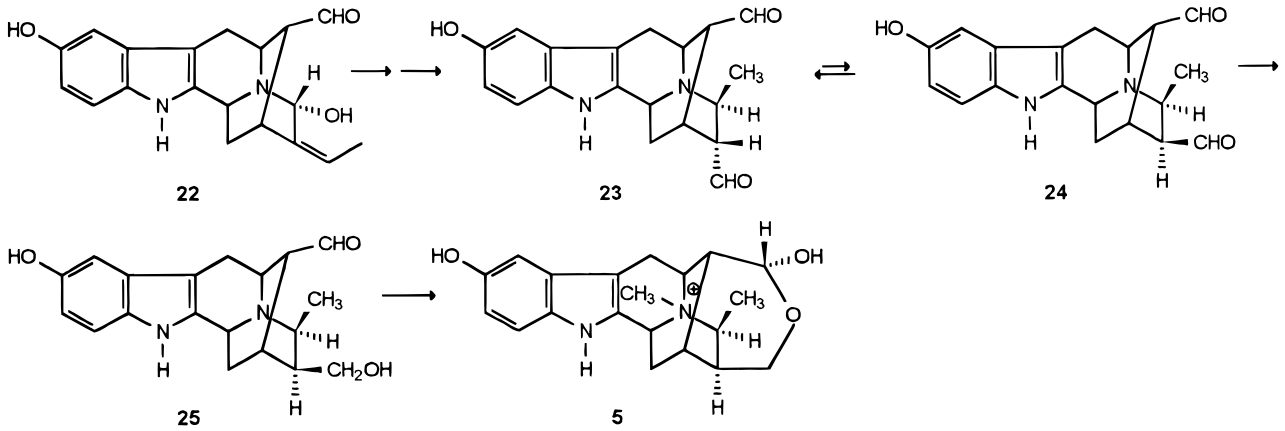
Conclusions

The "artifact character" of perakine (**6**) and 10-methoxyperakine (**8**) is particularly pronounced because of the simultaneous isolation of their presumed "precursors", *E*-vomilenine (vomilenine) (**10**) and *E*-majorinine (majori-

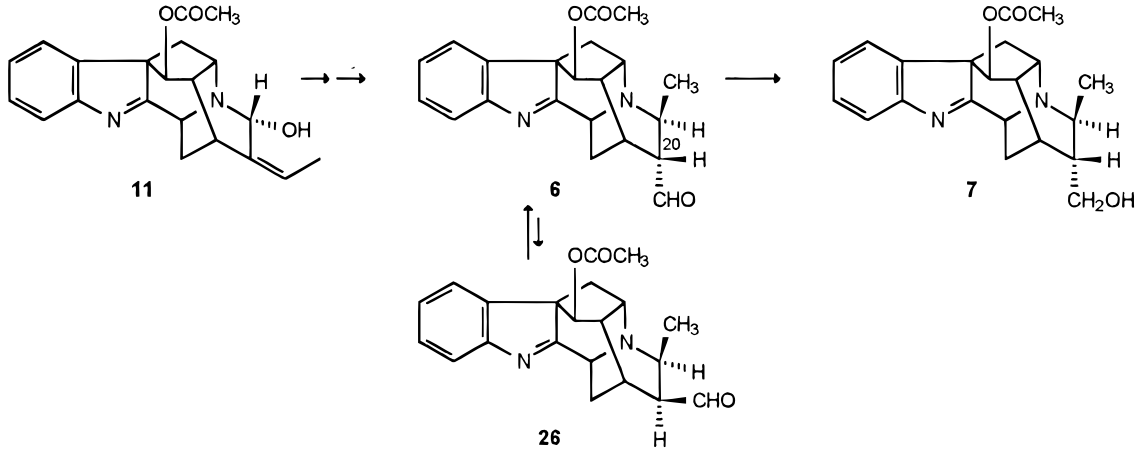
Scheme 7. Formation of Peraksine (Vomifoline) (**3**), Dihydroperaksine (**4**), and/or 20-*epi*-Dihydroperaksine (**21**)



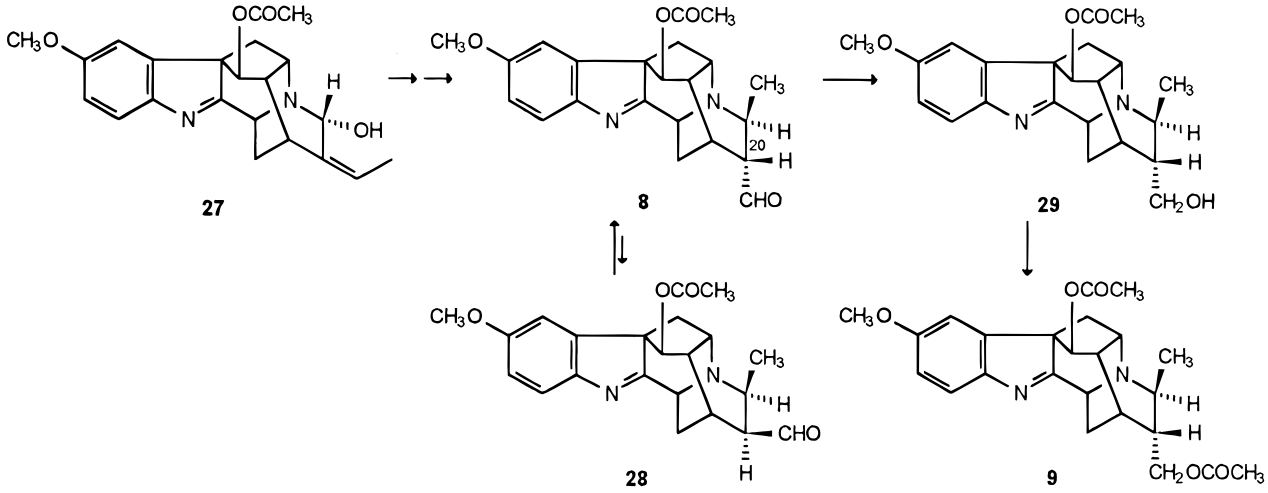
Scheme 8. Formation of Verticillatine (**5**)



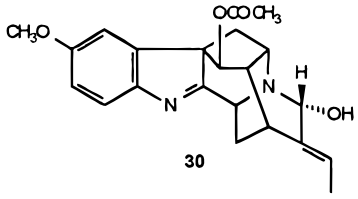
Scheme 9. Formation of Perakine (**6**) and Raucaffrinoline (**7**) (cf. Scheme 4)



Scheme 10. Formation of 10-Methoxyperakine (**8**), 10-Methoxyraucaffrinoline (**29**), and Vincawajine (**9**)



nine) (**30**), respectively, from the same plant (e.g., *Rauvolfia biauriculata*[16] and *Vinca major*,[12,17] respectively).



Finally, simultaneous isolation of large amounts of peraksine (**3**), dihydroperaksine (**4**), perakine (**6**), and raucaffrinoline (**7**), in addition to the presumed "precursor", *E*-vomilenine (**10**), from *Rauvolfia caffra*,[6] is in excellent agreement with the present proposal of "artifact formation" (vide supra).

References and Notes

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(13) The C-19β-CH_3 stereostructure (when the quinuclidine ring system is considered) for macrosalhine (**2**) is based on X-ray analysis[4b] and the stereostructures of peraksine (**3**) and verticillatine (**5**) on our careful examination of published X-ray drawings.[5,7] The stereostructure of dihydroperaksine (**4**) is determined by the chemical transformation of peraksine (**3**) to dihydroperaksine (**4**).[5,6] The C-19β-CH_3 stereostructures of perakine (**6**) and raucaffrinoline (**7**), as well as those of 10-methoxyperakine (**8**) and vincawajine (**9**), are based on NMR measurements.[11,12] The C-19β-CH_3 stereostructure of *O*-acetylpreperakine (**1**) is on a less solid basis. However, the suggested relationship between *O*-acetylpreperakine (**1**) and peraksine (**3**)[3,18] supports C-19β-CH_3 and our proposed theory.
(14) We note that several examples are known[19−21] of tertiary amines reacting under very mild conditions (extraction conditions) with alkyl halides, especially dichloromethane (methylene chloride) and/or chloroform (often containing dichloromethane, bromochloromethane,[22] and eventually other alkyl halides, as impurities), to form quaternary ammonium salts. Since dichloromethane and chloroform are frequently used as solvents in the separation and purification of alkaloid samples, caution is needed when quaternary ammonium derivatives are isolated.
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(18) **Note!** The C-19α-CH_3 stereostructures given for peraksine (vomifoline) (**3**) and dihydroperaksine (**4**) in ref 1 are erroneous and should be C-19β-CH_3.[23] We suggest, moreover, that the isolated dihydroperaksine sample may consist of a mixture of dihydroperaksine (**4**) and its 20-*epi*-isomer (**23**) (cf. Scheme 7).
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