CHASMANINE AND ITS STRUCTURE[1]

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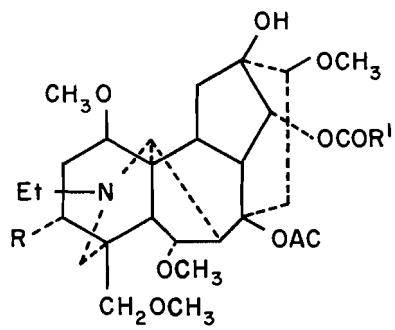
ABSTRACT

The alkaloid chasmanine, $C_{25}H_{41}O_6N$, isolated from *A. chasmanthum* contains four methoxyl and two hydroxyl groups as well as an imino-ethyl. It undergoes the usual pyrolytic reaction and the unsaturated product, pyrochasmanine, $C_{25}H_{39}O_5N$, gives rise to an acid-catalyzed allylic rearrangement product, isopyrochasmanine. Pyrochasmanine, on treatment with lithium aluminium hydride, is demethoxylated. It can be concluded that the base, like bikhaconine, contains the sequence $\rangle C(OH)—CH_2—CH(OCH_3)—$. Chasmanine can be oxidized to a compound containing a cyclopentanone ring so that its second hydroxyl must be secondary and located on a five-membered ring. It is possible to benzoylate the secondary hydroxyl and acetylate the tertiary hydroxyl. The n.m.r. characteristics of the resulting double ester determine the location of these two groups and their stereochemistry. The relative position of two of the remaining methoxyl groups is established via a demethylation reaction resulting in the formation of a cyclic ether. All the chemical reactions studied are in agreement with structure IV (R = R′ = H) for chasmanine. There is, however, no positive proof for the location of the fourth methoxyl and it has been placed in ring A by analogy. An attempted correlation with bikhaconine is described.

Recently the isolation of five alkaloids from the roots of *Aconitum chasmanthum* Stapf has been reported (1). One of these, indaconitine I, the structure of which has already been established (2), had been isolated long ago from this source by Dunstan and Andrews (3). Two others, designated chasmaconitine and chasmanthinine, have been shown to have structures II and III respectively (1).



I, R = OH, R′ = C_6H_5

II, R = H, R′ = C_6H_5

III, R = H, R′ = -CH=CH-C_6H_5

We now wish to report on the fourth alkaloid, previously identified as base B (1), for which the name chasmanine is now suggested. Whereas chasmaconitine and chasmanthinine were isolated from the weak bases, chasmanine was obtained from the fraction containing the strong bases, of which it formed the main component.

Chasmanine (base B), $C_{25}H_{41}O_6N$, was earlier reported to melt at 84–88°. By further purification this has been raised to 90–91°. The base was optically active, $[\alpha]_D^{25}$ +23.6°.

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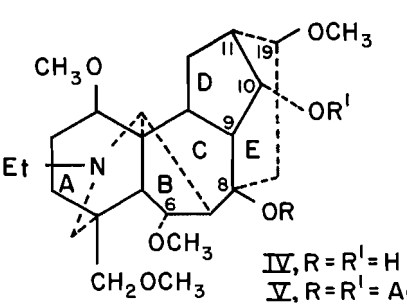
Although it crystallized readily, all attempts to prepare crystalline salts failed. Its infrared spectrum contained a broad absorption band with a small peak at 3 475 and two well-defined peaks at 3 365 and 3 263 cm^{-1} indicative of hydroxyl groups, but contained no carbonyl absorption, so that no ester group is present. The nuclear magnetic resonance (n.m.r.) spectrum revealed the presence of four methoxyl groups (δ 3.31, 3.21 corresponding to three protons each and δ 3.28 corresponding to six protons) and an N-ethyl group (triplet centered at δ 1.03). Acetylation of the base with acetic anhydride and *p*-toluenesulfonic acid produced a readily crystallized diacetate, the n.m.r. spectrum of which confirmed the introduction of two acetyl groups (δ 2.02, 1.97). Oxidation of chasmanine with chromium trioxide in acetone (3) gave rise to a gummy ketone characterized as its crystalline monoacetate. In the infrared the latter showed a band at 1 752 cm^{-1} attributable to a five-membered cyclic ketone, and one at 1 727 cm^{-1} indicative of an acetate carbonyl. In the n.m.r. spectrum only one acetyl group was indicated (δ 1.99). Both the ketone and its acetyl derivative were converted back to chasmanine by reduction with sodium borohydride and lithium aluminium hydride respectively.

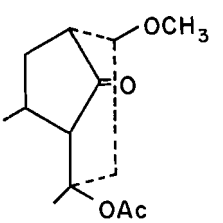
Oxidation of chasmanine with chromium trioxide – pyridine complex (Sarett's reagent) went further than chromium trioxide in acetone and gave two products, one, m.p. 196°, $C_{23}H_{33}O_6N$, that contained a cyclopentanone ring, but had lost the imino-ethyl group and had the properties of an azomethine. It formed an ethiodide convertible into chasmanine by reduction with sodium borohydride. In the n.m.r. spectrum the azomethine showed a singlet at δ 3.72 attributable to the protons of a methylene adjacent to an oxygen (—CH_2—O—), and a singlet at δ 7.51 that can be ascribed to —CH=N—. The infrared spectrum contained bands at 1 655 cm^{-1} attributable to the latter function, and at 1 761 cm^{-1} indicative of a five-membered cyclic ketone. The second oxidation product is neutral, m.p. 206–207° ($C_{25}H_{37}O_7N$). It also contains a cyclopentanone ring, but its imino-ethyl group has been oxidized to an acetyl group. It is converted back into chasmanine by the action of lithium aluminium hydride.

Consequently, of the six oxygens in chasmanine, four are present in methoxyl groups, one is in a tertiary hydroxyl, and the sixth is in a secondary hydroxyl located on a five-membered ring.

Just as with lycoctonine ($C_{25}H_{41}O_7N$) and aconitine ($C_{34}H_{47}O_{11}N$), if all the oxygen-containing substituents in chasmanine are replaced by hydrogen, there is obtained the common empirical formula $C_{21}H_{33}N$. As a working hypothesis, therefore, we have assumed that chasmanine possessed the same carbon–nitrogen skeleton common to lycoctonine and aconitine, and that it could be represented by structure IV. Hence the diacetate would be V and the keto-monoacetate or 10-dehydrochasmanine VI. The oxidation products obtained by the action of Sarett's reagent would be N-deethyl-10-dehydrochasmanine-azomethine and N-acetyl-N-deethyl-10-dehydrochasmanine.



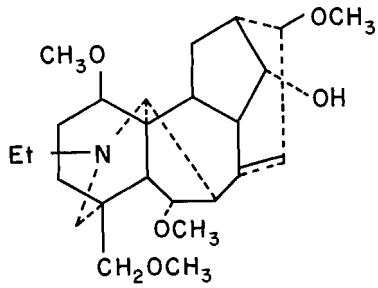
IV, R = R' = H
V, R = R' = Ac



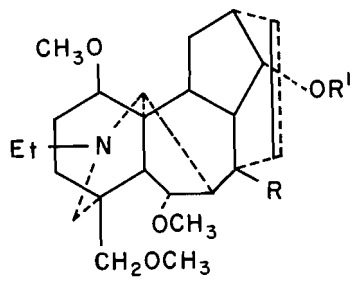
VI

The stereospecific course of the reduction of the ketone and the keto-monoacetate VI indicates the position of the secondary hydroxyl in the five-membered ring. There are two possible positions for a secondary hydroxyl in this ring. Whereas there is free access to the C-12 position, the C-10 position is hindered on one side and would thus account for a stereospecific reduction.

Diacetylchasmanine V when heated *in vacuo* gave rise to three products showing distinct spots in thin layer chromatography. The relative yield of each component varied with the condition of pyrolysis. The combined product was not crystalline and could not be separated by chromatography on alumina, although after saponification it separated readily into three crystalline components that proved to be pyrochasmanine VII, isopyrochasmanine VIII, and demethylisopyrochasmanine IX.



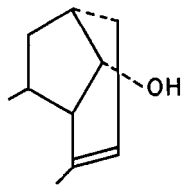
VII



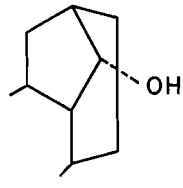
VIII, R = OCH_3, R' = H
IX, R = OH, R' = H
X, R = OAC, R' = AC
XIV, R = R' = H

Pyrochasmanine VII, the compound of intermediate mobility showed in the infrared an absorption band at 3 430 cm^{-1} attributable to a hydroxyl and one at 1 634 cm^{-1} characteristic of a double bond. Its n.m.r. spectrum contained signals for one olefinic proton (δ 5.43, J = 6 c.p.s.), for four methoxyl groups (δ 3.14, 3.28, 3.24, 3.21) and an imino-ethyl (triplet at δ 1.04). When pyrochasmanine was heated with methanolic perchloric acid, it was converted quantitatively to isopyrochasmanine VIII identical with the most mobile component of the hydrolyzed pyrolytic product. Isopyrochasmanine in its n.m.r. spectrum still showed the presence of four methoxyl groups and an imino-ethyl, but in the olefinic region the spectrum contained the signals of two protons (multiplet at δ 5.75–6.12). The acid-catalyzed allylic rearrangement involved in the conversion of pyrochasmanine to isopyrochasmanine has been observed in several highly oxygenated diterpenoid alkaloids (4–7).

The structure of the third compound, demethylisopyrochasmanine IX isolated from the hydrolyzed product of pyrolysis was verified as follows. The n.m.r. spectrum of the compound revealed the presence of three methoxyls only (δ 3.21, 3.30, 3.32), an imino-ethyl (triplet centered at δ 1.02), and two olefinic protons (multiplet at δ 5.67–5.91). The two olefinic protons indicate that the allylic shift has taken place and therefore that the new hydroxyl is at C-8. The presence of a double bond was confirmed by the formation of a dihydro derivative on catalytic hydrogenation. The low chromatographic mobility of IX suggested the presence of an additional hydroxyl, and this was confirmed by the preparation of a diacetyl derivative X (n.m.r. δ 1.93, 1.99) that could be hydrogenated



XII



XIII

to a dihydrodiacetyl derivative XI also obtainable by acetylation of the dihydro derivative obtained from IX.

The dihydrodiacetyldemethylisopyrochasmanine XI was pyrolyzed *in vacuo* at 180–190° for 5 min. The crude pyrolytic product (single spot in thin layer chromatography) showed in the n.m.r. spectrum a single acetyl group (δ 2.02) and one olefinic proton (multiplet at δ 4.98–5.28). It could not be crystallized, but after hydrolysis was characterized as its crystalline perchlorate XII; catalytic hydrogenation of this salt produced a dihydro derivative XIII also characterized as its crystalline perchlorate. Since compound XI undergoes pyrolytic elimination of an *O*-acetyl group, it follows that the additional hydroxyl in IX must be located at C-8 as mentioned above.

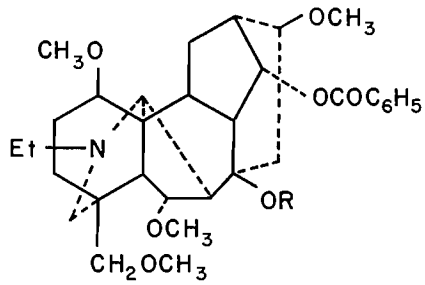
Pyrochasmanine VII treated with lithium aluminium hydride in tetrahydrofurane at room temperature underwent the allylic shift and demethoxylation, giving rise to demethoxyisopyrochasmanine XIV ($C_{24}H_{37}O_4N$). The n.m.r. spectrum of XIV contained signals characteristic of an imino-ethyl (triplet centered at δ 1.02), of two olefinic protons (multiplet at δ 6.03–5.78), and of three methoxyl groups (δ 3.29, 3.28, 3.22), thus confirming the loss of one methoxyl as well as the shift in double bond in the course of the reaction. Catalytic hydrogenation of the perchlorate of XIV gave the corresponding dihydro derivative, isolated as the perchlorate. This salt was identical in every respect (melting point, that of the mixture, infrared spectra, X-ray powder patterns) with the perchlorate of the dihydro derivative XIII.

The above described formation of pyrochasmanine and its transformation products are characteristic of diterpenoid alkaloids containing the sequence $\rangle$C(OH)—CH_2—CH-(OCH_3)— in ring E as was well established in connection with delphinine (8), pseudaconitine (5), and bikhaconitine (7). What is unusual with these reactions in chasmanine is the formation of isopyrochasmanine and its demethyl derivative in the initial pyrolytic reaction. For instance, the pyrolysis of pseudaconitine produced pyropseudaconitine as the only identified base, while isopyropseudaconine was produced by an acid-catalyzed rearrangement of pyropseudaconine (5). As mentioned already, the relative proportions of the three compounds produced by the pyrolysis of chasmanine were dependent on the conditions of the experiment. Heating for less than 5 min at 170–180° favored the formation of pyrochasmanine VII while heating for a longer time (10 min) at higher temperatures (190–200°) produced mainly isopyrochasmanine VIII and demethylisopyrochasmanine IX. The production of a demethylisopyro compound as a direct product of pyrolysis had not been observed before in other diterpenoid alkaloids.

The product of the already described pyrolysis of diacetylchasmanine can also be worked up in a different way. When the crude pyrolyzed product was treated with lithium aluminium hydride in tetrahydrofurane, three compounds were obtained, i.e., isopyrochasmanine VIII, demethylisopyrochasmanine IX, and demethoxyisopyrochasmanine XIV. These compounds were separated readily by chromatography on alumina. In this

experiment, the yield of demethylisopyrochasmanine was higher than when the isolation was carried out after hydrolysis of the product. Surprisingly it was found that demethylisopyrochasmanine could be obtained in 30% yield by treatment of isopyrochasmanine with lithium aluminium hydride in tetrahydrofurane.

Treatment of chasmanine with benzoyl chloride in pyridine at room temperature gave a high yield of monobenzoylchasmanine XV; it was amorphous, but formed a crystalline hydrochloride. The benzoylated product in turn, when acetylated gave rise to crystalline acetylbenzoylchasmanine XVI. The n.m.r. spectrum of this diester showed, in addition

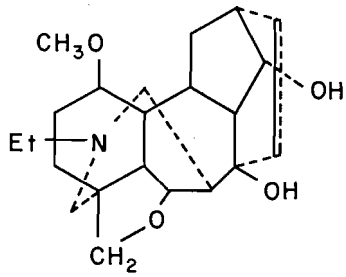


XV, R = H

XVI, R = Ac

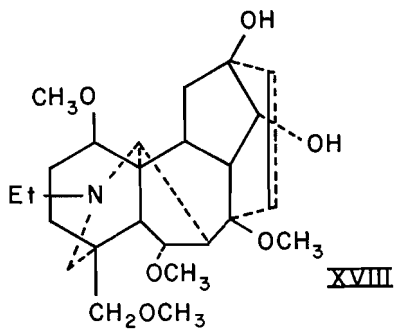
to the main features already present in the spectrum of chasmanine, five aromatic protons (multiplet at δ 8.23–7.20) and a triplet centered at δ 5.07 that may be attributed to the C-10 hydrogen. That this signal is not a doublet as in the case of the other esterified aconite-type alkaloids examined (9) indicates that the C-10 proton must be flanked not by one but by two other protons. Consequently, the substituent at the bridgehead position C-11 must be a hydrogen and not a hydroxyl as in aconitine, pseudaconitine, etc. The signal for the acetyl group protons was at quite high field (δ 1.36). As pointed out previously (9) this shift to high field in esterified oxygenated diterpenoid alkaloids is due to the anisotropic effect of the benzene ring of the aromatic acid, and indicates the location and orientation of the benzoyl ester group. Hence the secondary hydroxyl present on a five-membered ring in chasmanine is the one that was esterified by the action of benzoyl chloride and must be located at C-10. Consequently, the substituents on rings D and E are located as required by structure IV and the stereochemistry of the hydroxyl at C-10 must be the same as that of the benzoyloxy group in aconitine.

Isopyrochasmanine VIII when heated for 40 min on the steam bath with 50% sulfuric acid gave a mixture of three products: a component that could not be purified completely (but appeared from its n.m.r. spectrum to contain two methoxyls only), some demethylisopyrochasmanine IX, and tridemethylanhydroisopyrochasmanine XVII, $C_{22}H_{31}O_4N$. If, however, the reaction was carried out for $2\frac{1}{4}$ h, two products only were obtained, i.e., IX and XVII. Jacobs and Sato (10) had found that isopyrooxodelphinine when heated at 40° with zinc chloride and 5% hydrochloric acid underwent a similar demethylation and gave rise to a didemethyl and a tridemethyl cyclic ether. Wiesner *et al.* (11) in a later interpretation of this result provided evidence that the two methyl groups that were removed with the resulting formation of a cyclic ether were located at C-6 and C-17. Consequently, the most probable structure of tridemethylanhydroisopyrochasmanine which contains only one methoxyl—n.m.r. δ 2.50 (3 H)—is XVII and affords strong evidence for the presence of a methoxyl at both C-6 and C-17 positions in the alkaloid (IV). The latter was already indicated by the n.m.r. spectrum of N-deethyl-10-dehydrochasmanine-azomethine (δ 3.72).

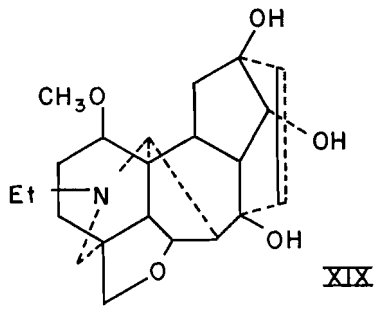


XVII

Neoline undergoes a similar demethylation (6). The structure suggested for neoline (6) differs from that suggested for chasmanine only in that it contains an α-hydroxyl at C-1 in ring A while chasmanine contains a C-1 β-methoxyl. In order to correlate the two through their cyclic ether derivatives, it is necessary to demethylate chasmanine at C-1. Jacobs and Sato (10) in their demethylation experiments had used neutral oxo-derivatives and had observed that by carrying out the reaction at 60° they could obtain a completely demethylated compound. Isopyrochasmanine was therefore oxidized with permanganate in aqueous acetone to remove the imino-ethyl group (12) and the resulting secondary base was acetylated to N-acetyl-N-deethylisopyrochasmanine. This N-acetyl derivative was heated with zinc chloride in 5% hydrochloric acid for 1 h at 70–75° and the crude product (single spot in thin layer chromatography) was reduced with lithium aluminium hydride in tetrahydrofurane. This series of reactions yielded exclusively the tridemethyl cyclic ether XVII already described. The failure of the reaction to remove the last remaining methoxyl, i.e., that in ring A, cannot be considered as militating against the presence of a C-1 methoxyl since an exactly parallel series of reactions carried out with isopyrobikhaconine XVIII gave rise to a product XIX still carrying a methoxyl.



XVIII



XIX

The location of the C-6 methoxyl has been derived from the formation of the cyclic ether. Not only is this position confirmed, but the orientation of the group is also determined by the course of the oxidation of chasmanine with potassium permanganate. It has been established that in the aconite type of diterpenoid alkaloids, in which the C-6 methoxyl is α, potassium permanganate oxidation under neutral (or basic) condition leads mainly to N-deethylation whereas in the lycoctonine type, in which the C-6 methoxyl is β, the same oxidizing agent leads to a lactam (12). The oxidation of chasmanine with permanganate, under these conditions, gives an excellent yield of N-deethylchasmanine, so that the alkaloid must contain a C-6 methoxyl in the α-configuration.

N-Deethylchasmanine when treated with ethyl iodide is converted back to chasmanine.

When treated with methyl iodide instead, it is converted to N-methyl-N-deethyl-chasmanine, $C_{24}H_{39}O_6N$, m.p. 90–92°. This new base, like the acetylated and benzoylated chasmanine described above, has not yet been reported to occur in nature.

Because of the ease with which the allylic rearrangement takes place in pyrochasmanine, it is highly probable that the configuration of the C-19 methoxyl is the same as in the other aconite alkaloids already investigated.

The location of all the substituents in the proposed chasmanine structure IV has been confirmed chemically except for the ring A methoxyl. Concerning the carbon skeleton, it is known that pyrodelphonine shows unexpected absorption in the ultraviolet (λ_{max} 245 mμ, log ϵ 3.8) and that this disappears on acidification. Wiesner *et al.* (6) noticed similar spectroscopic properties in pyroneoline and considered that this similarity indicated an analogy between the neoline and the delphonine structures. The ultraviolet spectra of pyrochasmanine and of pyrobikhaconine show absorption at λ_{max} 244 mμ, log ϵ 3.74 and λ_{max} 249 mμ, log ϵ 3.71 respectively. In both cases the peak disappeared on acidification. This parallel spectroscopic behavior of chasmanine and bikhaconine as well as delphonine and neoline supports the assumption of the same carbon skeleton in all four compounds.

There is a close relation between structure IV suggested for chasmanine and the structure of bikhaconine, the hydrolytic alkamine derived from bikhaconitine (7). The only difference is that bikhaconine contains a C-11 bridgehead hydroxyl that is absent in chasmanine. In an attempt to find a rigorous confirmation of the structure of chasmanine, we sought to correlate the base with bikhaconine. Such a correlation involved removing the C-11 hydroxyl from the latter, either by first opening ring E or by direct attack on the hydroxyl.

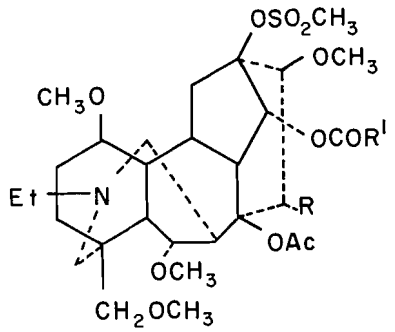
Although the initial opening of ring E prior to removal of the hydroxyl appeared to be the more promising, three different methods of achieving this proved unsuccessful and failed to yield the ultimate expected product.

After several fruitless attempts to remove the C-11 hydroxyl directly it was decided to try a recently described method. Okamoto *et al.* (13) have reported that a bridgehead *O*-mesylate group in a pseudokobusine derivative could be hydrogenolyzed by high pressure hydrogenation over Raney nickel. Although in pseudokobusine the hydroxyl thus removed is a carbinolamine the reaction might work with bikhaconine if it proceeded through radical formation.

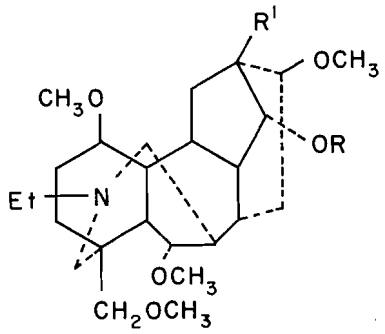
Methanesulfonation of bikhaconitine gave the desired mesylate $C_{37}H_{53}O_{13}NS$ (XX) in a good yield. Deoxyindaconitine and deoxyaconitine were similarly smoothly mesylated to XXI and XXII respectively. The last compound was a monomesylate and it was the bridgehead hydroxyl that reacted; even forced conditions could not mesylate the second ring E hydroxyl. The hydrogenation of bikhaconitine mesylate at 41 atm and 120–130° for 15 h gave two products. The main product separated by chromatography represented a 60% yield; it still contained the mesylate and the veratroyl groups, but lacked the acetoxy group. Its structure has been confirmed by an alternative synthesis. Pyrobikhaconitine was hydrogenated over platinum to the dihydro derivative and this when mesylated gave the same mesylate XXIII previously obtained from XX.

The minor product of the hydrogenation over Raney nickel was obtained in 5% yield only. Although it could not be crystallized, its infrared and n.m.r. spectra revealed that it no longer contained the mesylate and acetoxy groups, but still contained an imino-ethyl, four methoxyl, and the veratroyl groups. It was assumed to possess structure XXIV, and was hydrolyzed into the corresponding hydroxy base XXV.

Pyrochasmanine VII prepared as described above was hydrogenated catalytically to



XX, R = H, R' = $C_6H_3(OCH_3)_2$
XXI, R = H, R' = C_6H_5
XXII, R = OH, R' = C_6H_5



XXIII, R = $COC_6H_3(OCH_3)_2$, R' = OSO_2CH_3
XXIV, R = $COC_6H_3(OCH_3)_2$, R' = H
XXV, R = R' = H

its amorphous dihydro derivative. This derivative had exactly the same R_f value as the hydroxy base XXV in thin layer chromatography, thus suggesting their identity. All attempts to crystallize the two products or their salts failed, and the quantities available were too small for further comparison. The correlation work will be repeated but the present results are now reported as they do support the structure of chasmanine although they do not constitute a rigorous proof.

Ochiai, Okamoto, and Sakai (14) have reported the isolation from *Aconitum subcuneatum* Nakai and *Aconitum yesoensis* Nakai (both plants collected in the northern part of Japan) of an alkaloid designated Toroko-base II, m.p. 85–88°, $C_{24}H_{39}O_6N$, $[\alpha_D]$ +43°, containing an imino-methyl. Further purification and investigation by these authors has shown that the base had m.p. 90–91°, $[\alpha]_D$ +25.0° and contained an imino-ethyl instead of an imino-methyl, so that the empirical formula was corrected to $C_{25}H_{41}O_6N$. A direct comparison of chasmanine with Toroko-base II has shown the two to be identical in every respect (melting point, that of the mixture, infrared spectra, and X-ray powder patterns).

Undoubtedly the discovery of the occurrence of the base in *A. subcuneatum* antedates the report of its occurrence in *A. chasmanthum*. Since, however, the designation Toroko-base, meant to be tentative, refers to the place where the plant was collected, it is proposed to abandon it and retain the name chasmanine[3] derived from the specific name of one of the plants in which the base occurs.

EXPERIMENTAL

The infrared spectra were taken in Nujol mulls (unless otherwise mentioned) on a Perkin–Elmer double beam Model 21B spectrometer. The n.m.r. spectra were measured in chloroform solution containing

[3]*Professor E. Ochiai is in agreement with this proposal.*

tetramethylsilane as an internal reference, on a Varian A-60 instrument, and the chemical shifts are given in p.p.m. The ultraviolet spectra were measured on a Cary recording spectrometer Model 11.

The melting points were taken on a Kofler hot stage and were not corrected. For column chromatography Woelm grade IV neutral alumina was used, unless otherwise mentioned, and for thin layer chromatography the adsorbent was Merck silica gel G, and the developing solvent employed was cyclohexane – chloroform – diethyl amine. All extracts were dried and subsequently evaporated under reduced pressure.

Chasmanine

The alkaloid was isolated from the plant extract as previously described (1). After several recrystallizations from *n*-hexane it consisted of fine colorless needles, m.p. 90–91°, $[\alpha]_D^{25}$ +23.6° (*c*, 2.5 in EtOH), pK_a 6.3 (in 80% ethanol).

Anal. Calcd. for $C_{25}H_{41}O_6N$: C, 66.49; H, 9.15; N, 3.10. Found: C, 66.31; H, 9.09; N, 3.14.

ν_{max} 3 460, 3 365, 3 260 cm^{-1} (OH); 1 113, 1 095 cm^{-1} (OCH_3). In the n.m.r. spectrum: singlets at δ 3.31 (3H), 3.28 (6H), 3.21 (3H), triplet centered at δ 1.03 (3H). Chasmanine may be distilled at 150° and 5×10^{-5} mm without decomposition, but the pure crystalline base is somewhat unstable and after several months it contains a considerable amount of impurities ($\sim$10%).

Diacetyl Chasmanine

A mixture of chasmanine (109 mg) and *p*-toluenesulfonic acid (100 mg) in acetic anhydride (3 ml) was heated on a steam bath for 1 h. After cooling, the mixture was poured on ice and made basic with sodium carbonate, and the solution extracted with chloroform. Evaporation of the extract left a gum (128 mg) which was dissolved in *n*-hexane – benzene (1:1) and chromatographed on alumina. The column was eluted with the same solvent mixture and the eluate evaporated to dryness. There was left a residue (93 mg) which crystallized when triturated with *n*-hexane. After several recrystallizations from the same solvent, the diacetyl chasmanine produced consisted of colorless needles, m.p. 139–141°.

Anal. Calcd. for $C_{29}H_{45}O_8N \cdot \frac{1}{2}H_2O$: C, 63.96; H, 8.45; N, 2.57. Found: C, 63.76; H, 8.46; N, 2.79.

ν_{max} 1 725, 1 242 cm^{-1} (acetate). In the n.m.r. spectrum: singlets at δ 2.02 (3H), 1.97 (3H), 3.30 (3H), 3.28 (3H), 3.22 (6H), triplet centered at δ 1.05 (3H), poorly resolved triplet at δ 4.76 (1H).

Oxidation of Chasmanine with Chromic Oxide

(*a*) To a solution of chasmanine (640 mg) in acetone (15 ml) cooled in ice, a solution of chromic oxide (650 mg) in acetone (10 ml) also cooled in ice was added all at once. After having been left 48 h at room temperature, the acetone was evaporated, the residue was suspended in 2 *N* sulfuric acid (60 ml), and sodium sulfite was added until the green color persisted. The liquor was made basic with sodium carbonate and extracted with chloroform. Evaporation of the extract yielded the crude oxidation product (585 mg) which in thin layer chromatography was found to contain minor contaminating substances and some starting material as well. The crude product was therefore acetylated by the usual method. The resulting product was dissolved in benzene, chromatographed on alumina, and eluted with benzene. Fractions 2–7 of the eluate on evaporation left a crystalline acetyl ketone (480 mg), m.p. 151–159°. After several recrystallizations from acetone – *n*-hexane, it consisted of colorless needles, m.p. 158–160°.

Anal. Calcd. for $C_{27}H_{41}O_7N$: C, 65.96; H, 8.41. Found: C, 65.79; H, 8.83.

ν_{max} 1 751, 1 727, 1 242 cm^{-1}. In the n.m.r. spectrum: singlets at δ 1.99 (3H), 3.28 (9H), 3.19 (3H), triplet centered at δ 1.08 (3H).

Hydrolysis of the pure acetyl ketone (V) gave a colorless glass that failed to crystallize. ν_{max} 3 350 cm^{-1} (OH), 1 750 cm^{-1} (cyclic five-membered ketone). An attempt to prepare a crystalline salt also failed.

To a small quantity of the amorphous ketone in methanol, sodium borohydride was added. The reduction product, worked up as usual, was identical in every respect with chasmanine. Reduction of the crystalline monoacetyl ketone with lithium aluminium hydride also produced chasmanine shown by X-ray powder patterns to be identical with the original alkaloid.

(*b*) To a solution of chasmanine (243 mg) in pyridine (1 ml) was added chromium trioxide – pyridine complex, prepared from chromium trioxide (600 mg) and pyridine (9 ml), and the reaction mixture allowed to stand at room temperature for 90 h. The mixture was made basic with dilute ammonia and extracted thoroughly with chloroform. Evaporation of the extract left a brown syrup which was suspended in 5% hydrochloric acid and extracted with chloroform to remove the neutral product (extract A). The aqueous solution was rendered alkaline with sodium carbonate and extracted with chloroform. Evaporation of this previously dried extract left a syrup (112 mg); it was dissolved in chloroform, chromatographed over Florisil, and eluted with the same solvent, the eluate being collected in 10 ml fractions. Evaporation of the eluant left a number of crystalline fractions that were combined and recrystallized in ether from which N-deethyl-10-dehydrochasmanine-azomethine separated as colorless needles, m.p. 196°, wt. 20 mg. ν_{max}^{KBr} 1 761 cm^{-1} CO), 1 655 cm^{-1} (—CH=N—); $\nu_{max}^{CHCl_3}$ 1 756, 1 634 cm^{-1}. In the n.m.r. spectrum: singlet at δ 7.51 (1H, —CH=N—), δ 3.72 (2H, $\rangle$C—CH_2—OCH_3), δ 6.68, 6.74, 6.76 ($4OCH_3$).

Anal. Calcd. for $C_{23}H_{33}O_6N$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.86; H, 7.93; N, 3.37.

The extract A from the acid separation was washed with water, dried, and evaporated. The residual syrup (156 mg) was chromatographed over Florisil exactly as above. The crystalline fractions obtained

from the eluate were combined and recrystallized from *n*-hexane – acetone from which N-acetyl-N-deethyl-10-dehydrochasmanine separated as colorless scales, m.p. 206–207°, wt. 54 mg. ν_{max}^{KBr} 1 755 cm^{-1} (CO), 1 660 cm^{-1} (N—Ac). In the n.m.r. spectrum: signals at δ 6.68, 6.72, 6.75 ($4OCH_3$), singlet at δ 2.19 (N—Ac).

Anal. Calcd. for $C_{25}H_{37}O_7N \cdot H_2O$: C, 62.35; H, 8.16; N, 2.91. Found: C, 62.06; H, 7.89; N, 2.90.

Conversion of N-Deethyl-10-dehydrochasmanine-azomethine to Chasmanine

N-Deethyl-10-dehydrochasmanine-azomethine (23 mg) was dissolved in ethyl iodide (1 ml), the solution kept for 3 h at room temperature and evaporated to dryness under reduced pressure. The residue was crystallized twice from ethanol, m.p. 250–251° (decomp.), wt. 20 mg. ν_{max}^{KBr} 1 762, 1 672 cm^{-1}.

Anal. Calcd. for $C_{23}H_{33}O_6N—C_2H_5I$: C, 52.17; H, 6.66; N, 2.44. Found: C, 52.38; H, 6.71; N, 2.42.

To a solution of the ethiodide (18 mg) in methanol sodium borohydride (18 mg) was added and the solution was allowed to stand at room temperature for 16 h. The reduction product, worked up as usual, was a crystalline mass which after recrystallization from *n*-hexane consisted of colorless needles, m.p. 88–89°, wt. 4 mg. A further crop (8 mg) was obtained from the mother liquor. In admixture with chasmanine the melting point was unaltered, and the infrared spectra of both were superimposable.

Reduction of N-Acetyl-N-deethyl-10-dehydrochasmanine

This product (10 mg) was refluxed for 20 min with lithium aluminium hydride (40 mg) in tetrahydrofurane (5 ml). The reaction mixture, worked up as usual, yielded a crystalline substance (9 mg) which after recrystallization from *n*-hexane had m.p. 85°, wt. 5 mg. It was identical in every respect with chasmanine.

Benzoylchasmanine (XV)

A mixture of chasmanine (47 mg), freshly distilled benzoyl chloride (0.15 ml), and pyridine (1 ml) was kept at room temperature for 1 h. The reaction mixture was poured onto ice and made basic by the addition of potassium carbonate and the solution extracted with chloroform. Evaporation of the extract left the crude product (79 mg) which after chromatography in benzene on alumina afforded benzoylchasmanine (48 mg) which gave only one spot in thin layer chromatography. The product could not be induced to crystallize. It was distilled at 145° and 5×10^{-5} mm, but gave somewhat unsatisfactory analytical figures. ν_{max} 3 350 (OH), 1 710 cm^{-1} (CO). In the n.m.r. spectrum: multiplet at δ 8.10–7.30 (5H), triplets centered at δ 5.17 (1H) and 1.08 (3H), singlets at δ 3.30 (6H), 3.26 (3H), 3.17 (3H). It formed a hydrochloride that crystallized from acetone as colorless prisms, m.p. 248–249°, and gave good analytical results.

Anal. Calcd. for $C_{32}H_{45}O_7N \cdot HCl$: C, 64.86; H, 7.67. Found: C, 64.60; H, 7.76.

Acetylbenzoylchasmanine (XVI)

Benzoylchasmanine (264 mg) was heated on a steam bath for 1 h with *p*-toluenesulfonic acid (150 mg) and acetic anhydride (5 ml). The reaction mixture, worked up as usual, yielded acetylbenzoylchasmanine (260 mg) which solidified when triturated with *n*-hexane. After several crystallizations from the same solvent, it consisted of a microcrystalline solid, m.p. 148–156°.

Anal. Calcd. for $C_{34}H_{47}O_8N$: C, 68.32; H, 7.93. Found: C, 68.34; H, 7.84.

In the n.m.r. spectrum: singlets at δ 3.37 (3H), 3.27 (3H), 3.24 (3H), 3.16 (3H) (OCH_3 groups), 1.36 (OAc), triplets centered at δ 1.07 (3H), 5.07 (1H).

Acetylbenzoylchasmanine readily formed a perchlorate which after two crystallizations from ethanol consisted of colorless needles, m.p. 231–234°. ν_{max} 1 718, 1 600, 1 583 (weak), 719 cm^{-1} (strong).

Anal. Calcd. for $C_{34}H_{47}O_8N \cdot HClO_4$: C, 58.45; H, 6.88. Found: C, 58.24; H, 7.02.

Pyrolysis of Diacetylchasmanine

Diacetylchasmanine (264 mg) was heated under reduced pressure (10 mm) during 6 min at 185–190° (air bath). The product was dissolved in ether, chromatographed on a short column of alumina, and eluted with ether. Evaporation of the elutate left a gum (234 mg) which showed three spots in thin layer chromatography. The mixture could not be separated by column chromatography. It was dissolved in 2% methanolic potassium hydroxide (20 ml) and the solution refluxed for 1 h. The methanolic solution was evaporated to dryness, the residue dissolved in ice-cold water, and the aqueous solution extracted with chloroform. Evaporation of the extract left a gum (219 mg) which was dissolved in *n*-hexane and chromatographed on alumina. It was eluted with *n*-hexane, with benzene, with 50% chloroform–benzene and finally with chloroform, the eluate being collected in 10 ml fractions.

The *n*-hexane eluate (fractions 2–5) yielded isopyrochasmanine VIII (62 mg) which, after several crystallizations from *n*-hexane, was obtained as colorless elongated prisms, m.p. 177–179°. ν_{max} 3 450 (OH), 1 106, 1 087 cm^{-1} (OCH_3). In the n.m.r. spectrum: singlets at δ 3.31 (6H), 3.25 (3H), 3.21 (3H), triplet centered at δ 1.02, multiplet at δ 6.12–5.75.

Anal. Calcd. for $C_{25}H_{39}O_5N$: C, 69.25; H, 9.07. Found: C, 68.98; H, 9.28.

Fractions 6–10 made up the benzene eluate. Fractions 6 and 7 contained mainly pyrochasmanine VII but was contaminated with isopyrochasmanine. Fractions 8 and 9 yielded pure pyrochasmanine (74 mg) while fraction 10 contained mainly pyrochasmanine with an impurity of lower mobility in thin layer chromatography. Fractions 6, 7, and 10 were combined and rechromatographed thus affording a second crop of pure pyrochasmanine (35 mg). Pyrochasmanine, after crystallization from *n*-hexane, consisted of colorless prisms, m.p. 126–129°. ν_{max} 3 430 (OH), 1 634 cm^{-1} (double bond). In the n.m.r. spectrum: singlets at δ 3.14

(3H), 3.28 (3H), 3.24 (3H), 3.21 (3H), doublet at δ 5.43 (1H) (J = 6 c.p.s.), triplet centered at δ 1.04 (3H).

Anal. Calcd. for $C_{25}H_{39}O_5N$: C, 69.25; H, 9.07. Found: C, 69.16; H, 8.78.

The chloroform–benzene and chloroform eluates gave fractions 11–13. They contained demethylisopyrochasmanine IX (36 mg), homogeneous in thin layer chromatography. After several crystallizations from *n*-hexane – acetone, it consisted of colorless needles, m.p. 163–165°. ν_{max} 3 420, 3 418 cm^{-1} (OH), 743 cm^{-1} (double bond). In the n.m.r. spectrum: singlets at δ 3.32 (3H), 3.30 (3H), 3.21 (3H), triplet centered at 1.02 (3H), multiplet at δ 5.91–5.67 (2H). For analysis a sample was sublimed at 150° and 9×10^{-5} mm.

Anal. Calcd. for $C_{24}H_{37}O_5N$: C, 68.70; H, 8.89. Found: C, 68.56; H, 8.86.

Isopyrochasmanine VIII

Pyrochasmanine (20 mg) dissolved in methanol (5 ml) containing 1 drop of 70% perchloric acid was heated under reflux for 30 min. The reaction mixture was evaporated, the residue dissolved in water, and the solution made basic with sodium carbonate and extracted with chloroform. Evaporation of the extract left a residue of isopyrochasmanine that crystallized spontaneously. Recrystallized from *n*-hexane it separated as colorless elongated prisms, m.p. 177–179°, This product was identical with the sample obtained directly from the pyrolysis mixture (melting point, that of the mixture, infrared spectra, mobility in thin layer chromatography).

Demethoxyisopyrochasmanine XIV

A mixture of pyrochasmanine (32 mg) and lithium aluminium hydride (50 mg) in tetrahydrofurane (5 ml) was stirred for 15 h at room temperature. After decomposition of the excess hydride by the addition of wet ether, the mixture was diluted with methylene chloride and filtered. The inorganic material was washed with methylene chloride and the combined filtrate and washings were evaporated to dryness. The residue was dissolved in *n*-hexane and passed through a short column of alumina, and the solution evaporated to dryness. The residue was demethoxyisopyrochasmanine (29 mg) which crystallized when triturated with *n*-pentane. Recrystallized from *n*-hexane, it consisted of colorless fine needles, m.p. 84–88°. ν_{max} 3 410 (OH), 710, 690 cm^{-1} (double bond). In the n.m.r. spectrum: singlets at δ 3.29 (3H), 3.28 (3H), 3.22 (3H), a triplet at δ 1.02 (3H), a multiplet at δ 6.03–5.78.

Anal. Calcd. for $C_{24}H_{37}O_4N$: C, 71.43; H, 9.24. Found: C, 71.41; H, 9.37.

Demethoxyisopyrochasmanine formed a perchlorate which after several crystallizations from isopropanol gave colorless prisms, m.p. 207–210°.

Anal. Calcd. for $C_{24}H_{37}O_4N.HClO_4$: C, 57.14; H, 7.54. Found: C, 56.98; H, 7.66.

Dihydrodemethoxyisopyrochasmanine

The perchlorate of demethoxyisopyrochasmanine (55 mg) was dissolved in ethanol (10 ml) and hydrogenated in the presence of platinum oxide (22 mg). When the absorption of hydrogen had ceased, the catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in water and the solution was made basic with sodium carbonate and extracted with chloroform. Evaporation of the extract left a foam (54 mg) which was dissolved in benzene, chromatographed on alumina, and eluted with benzene. The eluate on evaporation yielded pure dihydrodemethoxyisopyrochasmanine (52 mg) which could not be induced to crystallize. Its n.m.r. spectrum contained no signal attributable to double bond protons. The base was converted to the perchlorate which crystallized from ethanol. After two recrystallizations from the same solvent, it consisted of colorless prisms, m.p. 173–174°.

Anal. Calcd. for $C_{24}H_{39}O_4N.HClO_4$: C, 56.92; H, 7.91. Found: C, 57.32; H, 7.68.

Demethylisopyrochasmanine IX

Isopyrochasmanine (48 mg) and lithium aluminium hydride (50 mg) were stirred overnight in tetrahydrofurane (5 ml) at room temperature. The reaction mixture was worked up as in the similar experiment with pyrochasmanine. Thin layer chromatography showed the presence in the product of starting material and several other substances of lower mobility. The product was dissolved in benzene, chromatographed on alumina, and eluted with benzene. Fractions 3–5 of the benzene eluate contained demethylisopyrochasmanine. The total yield obtained (20 mg) was crystallized twice from *n*-hexane – acetone from which the compound separated as colorless needles, m.p. 158–164°. After sublimation at 145° and 5×10^{-5} mm, it melted at 163–165°, and was identical in melting point, that of the mixture, infrared spectra, and behavior in thin layer chromatography with demethylisopyrochasmanine isolated in the pyrolysis reaction described above.

Reduction of Pyrolysis Product with Lithium Aluminium Hydride

Diacetylchasmanine (1.880 g) was pyrolyzed at 190° (air bath) for 8 min. The crude reaction mixture was dissolved in ether, chromatographed on alumina, and eluted with ether. Evaporation of the eluate left a foam (1.765 g) which was dissolved in tetrahydrofurane (25 ml) and stirred overnight at room temperature with lithium aluminium hydride ($\sim$ 0.5 g). The excess hydride was decomposed by the addition of wet ether and the product was worked up exactly as described above for the reduction of pyrochasmanine. The product (1.532 g) was found by thin layer chromatography to contain three compounds. It was dissolved in benzene and chromatographed on alumina. The column was eluted first with benzene, then with chloroform–benzene (1:4) and chloroform–benzene (1:1), and finally with chloroform and with chloroform containing 3% methanol, the eluate being collected in 50 ml fractions.

Fractions 2–6 (benzene eluate) contained isopyrochasmanine (658 mg) which after two crystallizations from *n*-hexane consisted of colorless needles, m.p. 177–179°.

Fractions 7–9 (chloroform–benzene (1:4)) and fractions 10–13 (chloroform–benzene (1:1)) both yielded demethoxyisopyrochasmanine (439 mg) which was slightly impure and was rechromatographed. The eluted material consisted of the homogeneous compound (407 mg) which crystallized from *n*-hexane as fine needles, m.p. 84–88°. It formed a perchlorate separating from isopropanol as colorless prisms, m.p. 207–210°.

The remaining fractions (14–17) eluted with chloroform and methanol–chloroform, yielded a residue (436 mg) which in thin layer chromatography showed one main spot and a few weaker, less mobile spots. Repeated chromatography in benzene on short alumina columns gave homogeneous demethylisopyrochasmanine (427 mg) which after crystallization from *n*-hexane – acetone melted at 163–165°.

All three products, isopyrochasmanine, demethoxyisopyrochasmanine, and demethylisopyrochasmanine, were identical in every respect with samples obtained in previous experiments described above.

Diacetyldemethylisopyrochasmanine X

Demethylisopyrochasmanine (60 mg) was heated on a steam bath with acetic anhydride (2 ml) and *p*-toluenesulfonic acid (50 mg). The reaction mixture, worked up as usual, yielded the product which was chromatographed on alumina in benzene solution and eluted with the same solvent. On evaporation, the eluate left the diacetyl compound (53 mg) which crystallized from *n*-hexane as colorless plates, m.p. 121–123°.

Anal. Calcd. for $C_{28}H_{41}O_7N$: C, 66.77; H, 8.21. Found: C, 66.57; H, 8.19.

ν_{max} 1728, 1716 (CO), 705 cm^{-1} (double bond). In the n.m.r. spectrum: triplet centered at δ 1.02 (3H), singlets at δ 1.93 (3H), 1.99 (3H), 3.29 (3H), 3.21 (6H), multiplet, at δ 6.60–5.83 (2H). Hydrogenation under the usual conditions gave the dihydrodiacetyl derivative (see below).

Dihydrodemethylisopyrochasmanine

Demethylisopyrochasmanine (213 mg) dissolved in ethanol (20 ml) containing a few drops of 70% perchloric acid was hydrogenated in contact with platinum oxide (57 mg). The reaction product, worked up as usual (see above hydrogenation of demethoxy compound), consisted of a gum (212 mg) which crystallized on contact with ether. After several recrystallizations from ether – *n*-hexane, dihydrodemethylisopyrochasmanine formed colorless prisms, m.p. 124–127°.

Anal. Calcd. for $C_{24}H_{39}O_5N.\frac{1}{2}H_2O$: C, 66.97; H, 9.37. Found: C, 67.34; H, 9.66.

Diacetyldihydrodemethylisopyrochasmanine XI

A mixture of dihydrodemethylisopyrochasmanine (200 mg) and *p*-toluenesulfonic acid (100 mg) was heated with acetic anhydride (5 ml) for 1 h on the steam bath. The diacetyl product (188 mg), isolated as usual from the reaction mixture, was crystallized from *n*-hexane from which it separated as colorless prisms, m.p. 123–125°.

Anal. Calcd. for $C_{28}H_{43}O_7N$: C, 66.51; H, 8.57. Found: C, 66.68, H, 8.73.

ν_{max} 1 730, 1 720 cm^{-1} (CO). The product was identical with that obtained by the catalytic hydrogenation of diacetyldemethylisopyrochasmanine.

Demethoxypyrochasmanine

Diacetyldihydrodemethylisopyrochasmanine (109 mg) was heated under reduced pressure (15 mm) for 5 min at 190° (air bath). The product was dissolved in benzene, chromatographed on alumina, and eluted with the same solvent. Evaporation of the eluate left a gum (80 mg) which gave a single spot in thin layer chromatography. ν_{max} 1 727 cm^{-1} (CO).

The gummy product (80 mg) thus obtained was refluxed with 3% methanolic potassium hydroxide (5 ml) for 30 min. The solvent was evaporated, water and ice were added, and the solution extracted with chloroform. Evaporation of the extract left a residue which was dissolved in *n*-hexane – benzene (1:1), chromatographed on alumina, and eluted with the same solvent. The eluate yielded homogeneous demethoxypyrochasmanine (61 mg) which failed to crystallize. It was converted to the perchlorate which crystallized from isopropanol as prisms with a slight yellowish cast, m.p. 198–202°. ν_{max} 3 475 cm^{-1} (OH).

Anal. Calcd. for $C_{24}H_{37}O_4N.HClO_4.\frac{1}{2}H_2O$: C, 56.21; H, 7.60. Found: C, 56.22; H, 7.60.

Dihydrodemethoxypyrochasmanine

Demethoxypyrochasmanine perchlorate (39 mg) was dissolved in ethanol (10 ml) and hydrogenated in contact with platinum oxide (25 mg). When hydrogen absorption had ceased, the catalyst was filtered off and the filtrate evaporated to dryness. The residue was dissolved in water, and the solution made basic with sodium carbonate and extracted with chloroform. Evaporation of the extract left a gum which was converted into the perchlorate. The salt crystallized from ethanol as colorless prisms, m.p. 173–174°. It was identical in melting point, that of the mixture, mobility in thin layer chromatography, infrared spectra, and X-ray powder patterns with the salt derived earlier from pyrochasmanine and designated dihydrodemethoxyisopyrochasmanine perchlorate (see above).

Demethylation of Isopyrochasmanine

Experiment 1

Isopyrochasmanine (141 mg) was dissolved in 50% sulfuric acid (5 ml) and heated on the steam bath for 40 min. The cooled solution was diluted by the addition of ice and alkalized with sodium carbonate. It

was extracted six times with chloroform and the combined extract evaporated to dryness. There was left a residue (121 mg) which gave three spots in thin layer chromatography. The residue was dissolved in benzene, chromatographed on alumina, and eluted first with benzene, then with benzene–chloroform (1:1), with chloroform, and finally with chloroform containing 2% methanol, the eluate being collected in fractions of 30 ml.

Fractions 1–3 (benzene eluate) afforded a compound (32 mg) which after crystallization from ether consisted of colorless needles, m.p. 164–167°. In the n.m.r. spectrum: singlet at δ 3.29 (6H), triplet centered at δ 1.02 (3H), multiplet at δ 5.90–5.62 (2H). For analysis a sample was sublimed at 145° and 10^{-4} mm.

Anal. Calcd. for $C_{23}H_{33}O_4N$: C, 71.29; H, 8.58. Found: C, 74.22; 9.18.

The analytical figures are unsatisfactory and indicate either the presence of an impurity or partial solvation with benzene even after sublimation (calcd. for $C_{23}H_{33}O_4N.C_6H_6$: C, 74.80; H, 8.44).

Fractions 4–6 eluted with benzene–chloroform (1:1) gave demethylisopyrochasmanine (35 mg) which, after crystallization from ether and sublimation, melted at 163–165°, undepressed by admixture with the product obtained in the pyrolysis. The infrared spectra of the two compounds were identical and so was their behavior in thin layer chromatography.

Fractions 7–10 eluted with chloroform and with chloroform containing 2% methanol yielded tridemethylanhydroisopyrochasmanine XVII (45 mg) which formed colorless prismatic crystals from methanol, m.p. 245–248° (decomp.). For analysis a sample was sublimed at 170° and 5×10^{-5} mm.

Anal. Calcd. for $C_{22}H_{31}O_4N$: C, 70.75; H, 8.27; N, 3.75. Found: C, 70.66; H, 8.27; N, 3.81.

Because of the low solubility of the product, its n.m.r. spectrum was obtained in pyridine solution, and for comparison the spectrum of isopyrochasmanine was taken in the same solvent. Compound XVII: singlet at δ 2.50 (3H), triplet centered at 0.25 (3H). Isopyrochasmanine: singlets at δ 2.63 (3H), 2.59 (3H), 2.49 (3H), 2.31 (3H), triplet centered at δ 0.30 (3H).

Experiment 2

Isopyrochasmanine (41 mg) dissolved in 50% sulfuric acid (2 ml) was heated on the steam bath for 2¼ h. The reaction mixture worked up as in Experiment 1 gave a product (27 mg) which crystallized spontaneously and in thin layer chromatography showed two spots: a more mobile one (weak) corresponding to demethylisopyrochasmanine, and a less mobile one (strong) corresponding to tridemethylanhydroisopyrochasmanine (XVII). The last compound was obtained in a pure condition by crystallization of the crude product from methanol, m.p. 245–248°.

Experiment 3

Tridemethylanhydroisopyrochasmanine was treated under the conditions described in Experiment 2. It was recovered unchanged in 70% yield.

Experiment 4

Isopyrochasmanine (210 mg) was dissolved in acetone (40 ml) and potassium permanganate (150 mg) in 50% acetone–water (40 ml) was added all at once. The mixture was stirred for 5 min at room temperature and the excess permanganate decomposed with sulfurous acid (sodium sulfite and dilute sulfuric acid). After evaporation of the acetone the remaining aqueous solution was made basic by the addition of aqueous sodium carbonate and extracted with chloroform. The extract was evaporated to dryness and the residue, which was homogeneous in thin layer chromatography, was heated on the steam bath for 90 min with acetic anhydride (2.5 ml) and pyridine (2.5 ml). The reaction mixture, worked up as usual, was dissolved in benzene, chromatographed on alumina, and eluted with benzene. Evaporation of the eluate left the residual gummy N,O-diacetyl-N-deethylisopyrochasmanine (250 mg) which gave a single spot in thin layer chromatography. Its infrared absorption spectrum indicated the presence of an N—Ac group (1 610 cm^{-1}) and an O—Ac group (1 715, 1 245 cm^{-1}). The compound was heated in a water bath (60–65°) for 1 h with zinc chloride (10 g) in 5% hydrochloric acid (3.5 ml). The solution, after cooling, was diluted with water (25 ml) and extracted continuously with chloroform for 50 h. The chloroform extract, on evaporation to dryness, left a gum (167 mg) which was dissolved in tetrahydrofurane (10 ml) and heated with lithium aluminium hydride under reflux for 2 h. The excess hydride was decomposed with wet ether and the solution diluted with chloroform and filtered. The inorganic filtered salt was washed with chloroform and the combined filtrate and washings were evaporated to dryness. There was left a residue (142 mg) which in thin layer chromatography produced only one spot identical in mobility with that produced by tridemethylanhydroisopyrochasmanine XVII. The product was dissolved in chloroform, chromatographed on alumina, and eluted with chloroform. The residue left after evaporation of the eluate was crystallized twice from methanol from which it separated as colorless prisms, m.p. 244–247° (decomp.). Its n.m.r. spectrum in pyridine solution showed a signal at δ 2.50 corresponding to three protons, identical with that of compound XVII.

Demethylanhydroisopyrobikhaconine

Isopyrobikhaconine (XVIII) (130 mg) after the same sequence of reactions as described in Experiment 4 above, yielded demethylanhydroisopyrobikhaconine (XIX) (112 mg) which after crystallization from ethanol was obtained as colorless prisms, m.p. 242–243°. For analysis it was sublimed at 190° and 6×10^{-5} mm. In the n.m.r. spectrum in pyridine solution it showed signals at δ 2.50 (3H) and a triplet centered at δ 0.25 (3H).

Anal. Calcd. for $C_{22}H_{31}O_5N$: C, 68.01; H, 7.96. Found: C, 68.24, H, 8.26.

N-Deethylchasmanine

To chasmanine (243 mg) in acetone (40 ml) potassium permanganate (152 mg) in 50% acetone–water (40 ml) was added all at once. After the mixture had been stored for 5 min at room temperature, the excess permanganate was reduced by the addition of sodium sulfite and dilute sulfuric acid. The liquor was concentrated until the acetone had evaporated, was made basic with sodium carbonate, and extracted with chloroform. The extract was evaporated to dryness, the residue dissolved in benzene, chromatographed on alumina, and eluted with the same solvent. Evaporation of the eluate left a residue which solidified when triturated with ether, and crystallized from benzene (152 mg). The mother liquor, when chromatographed on alumina, yielded a further crop of N-deethylchasmanine (60 mg). The product after two crystallizations from benzene, consisted of colorless needles, m.p. 232–234°. Its n.m.r. spectrum did not contain a triplet at $\delta \sim 1.0$.

Anal. Calcd. for $C_{23}H_{37}O_6N$: C, 65.22; H, 8.81. Found: C, 65.02; H, 8.82.

N-Methyl-N-deethylchasmanine

N-Deethylchasmanine (83 mg) in 50% ether–methanol (6 ml) was heated under reflux for 30 min with methyl iodide (1 ml) and powdered potassium carbonate (100 mg). The solvent was evaporated and the residue dissolved in water and extracted with methylene chloride. The extract was evaporated and the residue dissolved in *n*-hexane – benzene (1:1), chromatographed on alumina, and eluted with the same solvent. Evaporation of the eluate left a residue (78 mg) which crystallized spontaneously. After several crystallizations from *n*-hexane, N-methyl-N-deethylchasmanine formed fine colorless needles, m.p. 90–92°. In the n.m.r. spectrum: singlets at δ 3.31 (3H), 3.28 (6H), 3.23 (3H), and 2.29 (3H).

Anal. Calcd. for $C_{24}H_{39}O_6N$: C, 65.87; H, 8.98; N, 3.20. Found: C, 65.64; H, 9.10; N, 3.19.

When N-deethylchasmanine was treated similarly with ethyl iodide, it was converted back to chasmanine.

Bikhaconitine Methanesulfonate (XX)

Bikhaconitine perchlorate (1.2 g) with pyridine (10 ml) and methanesulfonyl chloride (2 ml) was kept at room temperature overnight. The resulting brown mixture was poured into ice water, made basic with potassium carbonate, and extracted with chloroform. The extract, after drying over magnesium sulfate, was evaporated to dryness. It left a brown gum that was dissolved in benzene, chromatographed on alumina, and eluted with benzene. Evaporation of the eluate left a residue that crystallized when triturated in the presence of ether. Recrystallized from methanol, it consisted of colorless prisms, m.p. 188–190°, yield, 0.9 g.

Anal. Calcd. for $C_{37}H_{53}O_{13}NS$: C, 59.10; H, 7.11. Found: C, 59.01; H, 7.16.

Deoxyaconitine methanesulfonate was also prepared exactly as above. It formed colorless prisms from methanol, m.p. 194–195°.

Anal. Calcd. for $C_{35}H_{49}O_{12}NS$: C, 59.39; H, 6.98. Found: C, 59.22; H, 7.00.

Further treatment with methanesulfonyl chloride failed to introduce a second group.

Hydrogenolysis of Bikhaconitine Mesylate

Bikhaconitine mesylate (900 mg) dissolved in dioxane (100 ml) was hydrogenated over Raney nickel at 120–130° and 41 atm for 15 h. The product, isolated as usual, was dissolved in benzene and extracted with 5% hydrochloric acid. The aqueous solution was alkalized with potassium carbonate and extracted with chloroform. The gummy residue (500 mg) left after evaporation of the extract showed two spots in thin layer chromatography; it was dissolved in benzene–hexane (1:1) and chromatographed on grade III alumina. Elution was done first with the same solvent mixture, then with benzene, with benzene–chloroform, and finally with chloroform. The first eluate yielded 290 mg of a mixture of components A and B while the benzene and benzene–chloroform eluates yielded pure B. Rechromatography of the first eluate gave pure A and pure B. Component B, recrystallized from ether, consisted of colorless prisms, m.p. 190–193°.

Anal. Calcd. for $C_{35}H_{51}O_{11}NS$: C, 60.60; 7.36. Found: C, 61.11; H, 7.45.

That this component is correctly designated by formula XXIII has been shown by its alternative preparation from pyrobikhaconitine (7). This compound was hydrogenated catalytically by the usual procedure over platinum oxide to dihydropyrobikhaconitine, colorless needles from ether, m.p. 181–183°.

Anal. Calcd. for $C_{34}H_{47}O_9N \cdot \frac{1}{2}H_2O$: C, 65.57; H, 7.47. Found: C, 65.71; H, 7.98.

Treatment with methanesulfonyl chloride as described above gave the *O*-mesylate, m.p. 191–194°, identical in every respect (mixture melting point, infrared, thin layer chromatography) with the hydrogenolysis component.

The minor component A separated by chromatography from the product of hydrogenolysis could not be obtained very pure because of paucity of material, and because it failed to crystallize. The infrared and n.m.r. spectra showed that it no longer contained the mesylate nor the acetoxy groups, but still contained an imino-ethyl, four methoxyls, and the two veratroyl methoxyls. It was assumed to have structure XXIV and it was hydrolyzed to the corresponding alkamine XXV.

Pyrochasmanine was hydrogenated catalytically to dihydrochasmanine. The product could not be induced to crystallize; it had the same behavior in thin layer chromatography as compound XXV. All attempts to prepare crystalline salts from the two products failed. It is probable that the two compounds were identical but there was insufficient material for further comparison.

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