The Structures of Condelphine, Isotalatizidine, and Talatizidine

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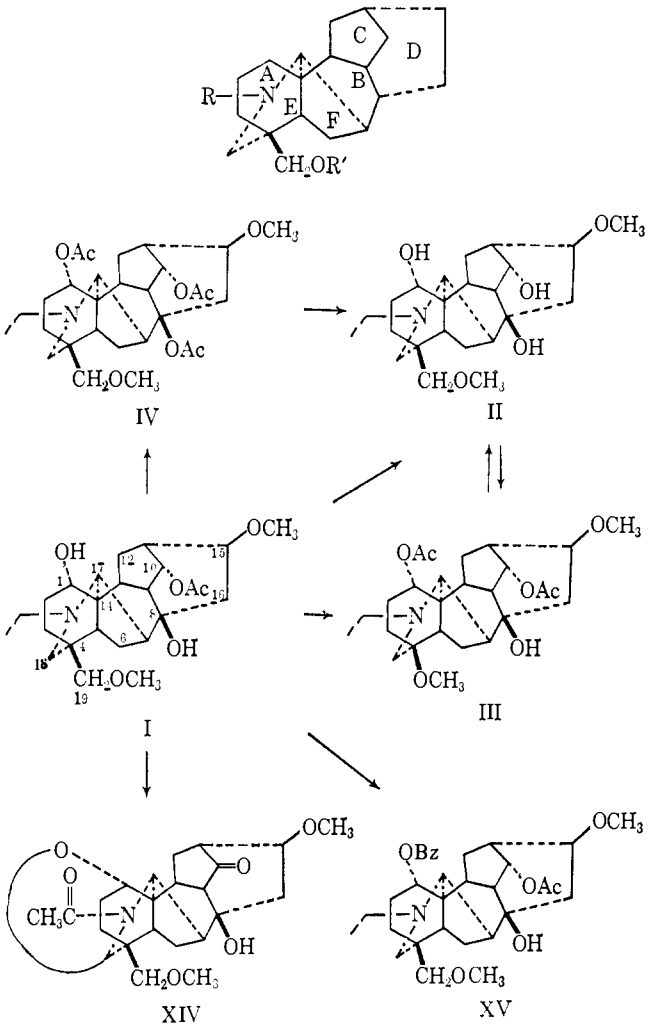
Abstract: Recent reports have described the isolation of two new alkaloids (denudatine and denudatidine) from the roots of *Delphinium denudatum*. An extract of a botanically identified specimen of these same roots has been found to contain none of the described alkaloids but instead two different alkaloids. These were identified as condelphine and isotalatizidine. Conclusive evidence for the determination of the aconitine-type skeleton and the assignment of the N-ethyl, acetate, secondary and tertiary hydroxyls, and one of the methoxyl groups to the previously postulated positions on the skeleton is presented. In addition, the position and configuration of the last methoxyl group, the configuration of the C-10 functional groups, and the configuration of ring A in condelphine and isotalatizidine and their C-1 esters are determined.

Two new alkaloids, denudatine and denudatidine,[2-4] have recently been reported as having been isolated from the roots of *Delphinium denudatum*,[5] a plant native to the high slopes of the Himalayas.[6] In order to carry out a correlation study between denudatine and atisine, 5 kg of the roots were procured[7a] and extracted with ethanol. Two alkaloids were indeed obtained from these roots.[7b] However, their melting points and infrared spectra in no way even remotely resembled those reported for denudatine (lit.[2] mp 248–249°) and denudatidine (lit.[2] mp 273–274°). The major alkaloid I found in our sample of roots melted at 158–159°; the other alkaloid II was found in much smaller amount and melted at 116–117°. The latter was found to be the same as the saponification product of I.

Microanalysis indicated the empirical formula for I to be $C_{26}H_{41}NO_6$ or $C_{25}H_{39}NO_6$. The nmr spectrum showed signals characteristic of one acetate group (3 H singlet at τ 7.98), one ethyl group (3 H triplet at τ 8.90, J = 7 cps), and two methoxyl groups (3 H singlets at τ 6.78 and 6.73). The nmr spectrum of II showed the same signals excluding the acetate signal. The infrared spectrum of I confirmed the presence of the acetate group (1739 and 1229 cm^{-1}) and in addition indicated hydroxyl absorptions (3571 and 3150 cm^{-1}).

The monoacetate derivative III of I was identical with the diacetate derivative of II. The infrared spectrum of III showed two carbonyl absorptions (1748 and 1721 cm^{-1}), and the nmr spectrum showed a signal of six-proton intensity at τ 7.94. Saponification of III gave II, thus demonstrating that I is an O-acetyl derivative of II, the latter having two primary or secondary hydroxyls and the former having only one.

The infrared spectrum of III still contained hydroxyl absorption indicating that there was also a tertiary hydroxyl in these alkaloids. This was confirmed by warming a solution of I in acetyl chloride in a sealed tube for several days to give the fully acetylated derivative IV. In order to ensure that no rearrangements had occurred under these conditions IV was saponified to II, and this was in turn converted to III.



(1) (a) Presented in part at the 4th IUPAC Symposium on Natural Products, Stockholm, Sweden, June 28, 1966. (b) Abstracted from the Ph.D. Dissertation of L. H. Keith, University of Georgia, 1966.

(2) N. Singh, *J. Sci. Ind. Res.* (India), **20B**, 39 (1961).

(3) N. Singh, A. Singh, and M. S. Malik, *Chem. Ind.* (London), 1909 (1961).

(4) N. Singh and K. L. Chopra, *J. Pharm. Pharmacol.*, **14**, 288 (1962).

(5) Identified by S. N. Sobi of the Regional Drug Research Laboratory, Jammu, India, and described as "tuberous roots from the Amritsar crude drug market under the name of Judwar or Nirbishi."

(6) Denudatine was reported as the major alkaloid and was isolated in a yield of 0.05% and classified as a diterpene alkaloid of the atisine group.

(7) (a) They were identified by comparison of the root and the whole plant with authentic specimens of *Delphinium denudatum* at (1) The Indian Botanic Garden, Shibpur, Calcutta, India, (2) The Botanical Survey of India, and (3) The Forest Research Institute, Dehra Dun, India. (b) A small amount of hetisinone was later also isolated from these roots. It has been identified by comparison with an authentic sample.

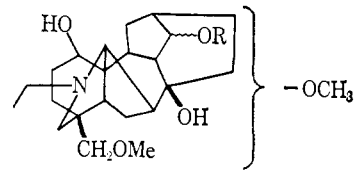
On the basis of these preliminary experiments, the most likely structures were $C_{20}H_{25}N(2OCH_3, C_2H_5, OCOCH_3$, tertiary OH, and primary or secondary OH) or $C_{19}H_{23}N(2OCH_3, C_2H_5, OCOCH_3$, tertiary OH, and primary or secondary OH); the former corresponds to an atisine-type and the latter to a lycoctonine- or aconitine-type skeleton. The mass spectrum of I had a parent peak at *m/e* 449; this molecular weight exactly fits the empirical formula $C_{25}H_{39}NO_6$ which corresponds to a lycoctonine- or aconitine-type skeleton possessing two methoxyls, one acetate, one ethyl, and two hydroxyl groups. Only the alkaloid, condelphine ($C_{25}H_{39}NO_6$),[8,9] appeared to have any possibility of being the same compound as I. It is the O-acetate of a previously isolated alkaloid, isotalatizidine.[10,11] A comparison of the constants of derivatives of I and II with those reported for condelphine and isotalatizidine, respectively (Table I), showed that, whereas there were many similarities, there were also several large discrepancies, *e.g.*, the melting points of the perchlorates and of anhydrous isotalatizidine. Comparison of I with a sample of authentic condelphine, provided by Dr. A. D. Kuzovkov, showed that the melting points, mixture melting points, optical rotation, and infrared and nmr spectra of the two samples were identical. Likewise, the melting points, mixture melting points, and infrared spectra of the perchlorate salts and the saponification products were the same.

Table I

	Mp, °C	ν_{max}, cm^{-1}	Mp, °C	ν_{max}, cm^{-1}
	Condelphine		I	
Alkaloid	156–158		158–159	
Perchlorate	209–210		224–225	
Oxalate	160–162		163–165	
Monoacetyl	112–117	1720, 1734[a]	117–119	1728, 1748[a]
Diacetyl	131–135	1728, 1742	129–132	1725–1750[b]
	Isotalitizidine		II	
Alkaloid	114–117[c] 140–142		116–117	
Didehydro-oxo	182–183.5	3400, 1756 1709, 1644	171–173	3571, 1751 1709, 1644

[a] These spectra were taken in chloroform; all others were taken in Nujol. [b] This carbonyl absorption appeared as a broad band even when the spectrum was taken on the Perkin-Elmer Model 237-B instrument. [c] Contains 1 mole of water of crystallization.

Recent work on the structures of condelphine and isotalatizidine led to the postulation of partial structures V and VI, respectively.[8] A third alkaloid, talatizidine, which had been isolated along with VI was found to be epimeric at C-1 with isotalatizidine and thus could be represented as VII. In the Russian work several of the functional groups were assigned positions on the basis of conjecture, and the position of the remaining methoxyl was unassigned. This paper describes independent, conclusive evidence which locates the functional groups as shown in V–VII. In addition, evidence is presented for the assignment of position and configuration of the remaining methoxyl, the configuration of the C-10 functional groups, and the conformation of ring A in condelphine, isotalatizidine, and their C-1 ester derivatives.



V, R = Ac
VI, R = H
VII, R = H β-OH at (1)

Since both the mono- and diacetate derivatives of condelphine were still basic compounds (being soluble in dilute mineral acids and precipitated when the solutions were rendered basic), the ethyl group was tentatively assumed to be located on the nitrogen atom which must be part of a tertiary amine. This was further substantiated by the observation that a downfield shift of 0.30–0.45 ppm occurred in the triplet assigned to CH_3CH_2 in the salt derivatives of condelphine and monoacetylcondelphine.

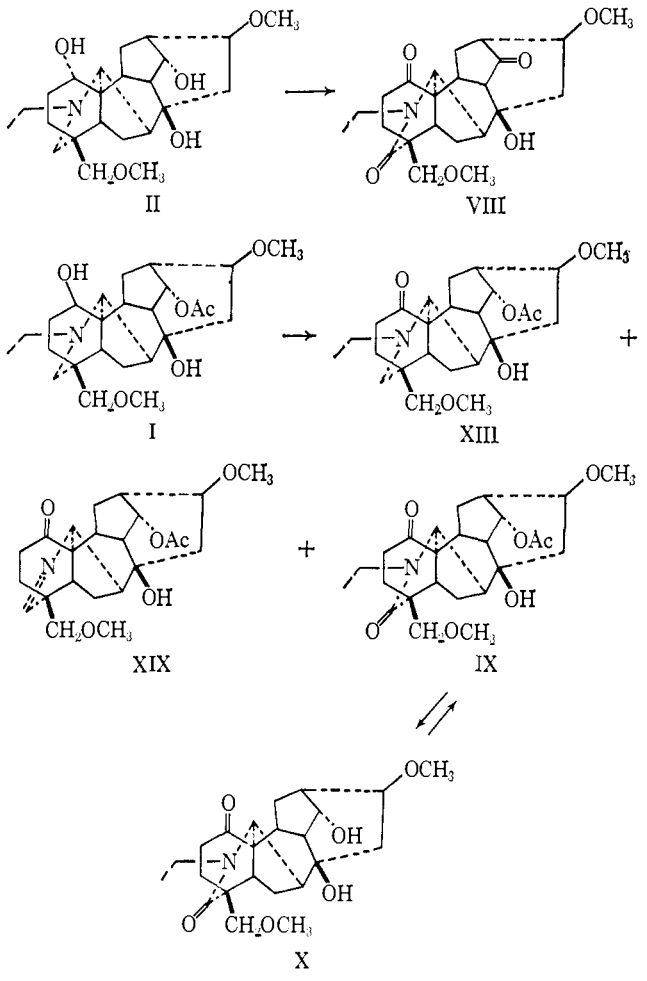
Oxidation of II with Sarett reagent gave a crystalline derivative VIII whose infrared spectrum showed carbonyl absorption for a cyclic five-membered ketone (1748 cm^{-1}), a cyclic six-membered or larger ketone (1712 cm^{-1}), a six-membered tertiary lactam (1642 cm^{-1}), a tertiary hydroxyl (3571 cm^{-1}), and a methylene adjacent to a ketone (1418 cm^{-1}). The latter was confirmed by a positive Zimmerman test. Since the lycoctonine- or aconitine-type skeleton does not contain any available positions for a methylene adjacent to a ketone in a five- or seven-membered ring, the CH_2CO group must occur in ring A or D.

Oxidation of I with Sarett reagent under similar conditions gave, as the major product of the reaction, a crystalline compound IX whose infrared spectrum retained its tertiary hydroxyl absorption (3610 cm^{-1}) and showed absorption in the carbonyl region for an acetate (1739 cm^{-1}), a six-membered ketone (1701 cm^{-1}), and a six-membered lactam (1637 cm^{-1}). The absorption for the CH_2CO grouping was not clearly distinguishable, but a positive Zimmerman test was obtained which indicated that it was present.

In order to preclude the possibility of having assigned the wrong frequencies to the carbonyl absorptions of the acetate and the six-membered ketone, IX was saponified to the crystalline derivative X, which showed only carbonyl absorption characteristic of the six-membered ketone (1712 cm^{-1}) and the lactam carbonyl (1639 cm^{-1}). In addition, the infrared spectrum showed absorption for the secondary hydroxyl (3636 cm^{-1}), the tertiary hydroxyl (3559 cm^{-1}), and the absorption characteristic of a methylene adjacent to a ketone (1416 cm^{-1}), which was confirmed by a positive Zimmerman test.

From these two oxidations the following conclusions may be drawn. (1) The acetate group in condelphine is located in one of the five-membered rings since oxidation of condelphine produced a six-membered ketone, and oxidation of its saponification product (isotalatizi-

(8) A. D. Kuzovkov and T. F. Platonova, *J. Gen. Chem. USSR*, 1286 (1961).
(9) M. S. Rabinovich and R. A. Konovalova, *Zh. Obshch. Khim.*, **29**, 329 (1942).
(10) R. A. Konovalova and A. P. Orekhov, *ibid.*, **10**, 745 (1940).
(11) Isotalatizidine, along with its epimer, talatizidine, had been isolated from *Aconitum talassicium*, a plant native to the mountainous regions of Talass-Alataou in central Asia.



dine) gave a product containing ketone groups in both six- and five-membered rings. (2) The acetate of condelphine is on a secondary carbon since its saponification product produces a ketone when oxidized; the possible positions are C-6, C-10, and C-12. (3) The hydroxyl of condelphine which is easily acetylated is a secondary hydroxyl since oxidation produces a ketone. (4) The secondary hydroxyl is in either ring A or ring D since it is oxidized to a six-membered ketone which has an adjacent methylene; the possible positions are C-1, C-2, C-3, C-15, and C-16. (5) Since no aldehyde is produced by these oxidations the oxygen function at C-19 in the lycoctonine- or aconitine-type skeleton must be a methoxyl; the same conclusion is reached by elimination of the known functional groups, *i.e.*, the ethyl is attached to the nitrogen, one hydroxyl is tertiary and the other is secondary as is the acetate group. This leaves only the two methoxyl groups, one of which must be at C-19.

In the infrared spectrum of condelphine there is a broad absorption at 3150 cm^{-1} which does not disappear with dilution. This absorption is not present in monoacetyl condelphine (III) and thus strongly suggests intramolecular bonding of the secondary hydroxyl with the nitrogen atom.

The evidence in Table II led to the conclusion that the secondary hydroxyl of condelphine (I) is in the vicinity of the nitrogen atom, hence in ring A. Whereas the infrared spectrum of monoacetylcondelphine (III) showed two carbonyl bands, its perchlorate, picrate, and hydrochloride showed only one. It can be reasoned that in the free base the pair of electrons on the nitrogen might interact with a carbonyl in the near vicinity, but in the acid salt, where the nitrogen is protonated, the possibility of interaction is removed, and the electronic environment of the two acetate carbonyls would be more nearly the same.

Table II

Compound	ν_{max}, cm^{-1}	OAc, τ
Condelphine (I)	3571 (OH), 3150 (intramolecularly bonded OH), 1739 (OAc)	7.98
Condelphine perchlorate (XXXVI)	3650 (OH) 1739 (OAc)	7.92
Condelphine picrate (XI)	1721 (OAc)	7.95
Monoacetylcondelphine (III) (diacetylisotalatizidine)	3636 (OH) 1748 (OAc) 1721 (OAc)	7.98 (6 H)
Monoacetylcondelphine perchlorate	3650 (OH) 1739 (OAc)	...
Monoacetylcondelphine picrate (XII)	1739 (OAc)	8.14 7.93
Monoacetylcondelphine hydrochloride	1739 (OAc)	...
Diacetylcondelphine (IV) (triacetylisotalatizidine)	1725–1750 (OAc)	8.07 8.00 7.97
Diacetylcondelphine hydrochloride (XXXVII)	1727 (OAc)	8.02 7.98 7.62

The acetate signal of condelphine picrate (XI) was shifted downfield by only 0.03 ppm. The nmr spectrum of monoacetylcondelphine picrate (XII) has one acetate which has been shielded by 0.16 ppm and one which has been deshielded by only 0.05 ppm. If one of the acetates is in the vicinity of the nitrogen atom (which, from previous evidence would require it to be in ring A) then it would easily come within reach of the diamagnetic anisotropic effect of the ring current in the aromatic nucleus. The other acetate, being in one of the more remote positions in one of the five-membered rings, would not come under the influence of the diamagnetic circulation of the π electrons in the aromatic ring and hence would be only slightly deshielded as was the acetate of condelphine picrate.

Oxidation of condelphine (I) with Sarett reagent for a short period of time yielded dehydrocondelphine (XIII) and dehydrooxocondelphine (IX). One of the two methoxyl groups had been assigned to the C-19 position on the basis that all known lycoctonine- or aconitine-type skeletons contain an –OR functional group at this position and since there was no aldehyde produced by these oxidations, it is clear that R must be an alkyl group. The C-19 methylene signal appeared as an AB-type doublet of two-proton intensity at τ 6.93 on the 60-Mc instrument, but on a 100-Mc instrument this is resolved into its two one-proton intensity doublets centered at τ 7.02 and 6.85 (J = 9 cps).[12] The large coupling constant is in accord with

(12) (a) A variable-temperature study in $CDCl_3$ (0–55°) and in C_6D_6 (30–75°) showed no change in the coupling constant and demonstrates that the coupling observed is due to the inherent nonequivalence of the two C-19 protons rather than to a steric barrier to rotation. (b) The absolute configuration of condelphine has not been demonstrated by X-ray crystallography or by correlation with an aconitine-type alkaloid of known configuration (although such a correlation study is

geminal H–H coupling. Additional evidence for a C-4–C-19(H_2)–OCH_3 grouping is obtained from comparison of the nmr spectra of dehydrooxocondelphine (IX) and dehydrocondelphine (XIII) with that of condelphine (I). The C-19 methylene signal of the keto-lactam IX is deshielded by 0.43–0.45 ppm from its position in XIII and I and one of the two methoxyl signals of IX is observed to be deshielded by a smaller degree. The exact methoxyl shift is impossible to determine by comparison of the spectra of IX and I. However, a comparison of IX and XIII reveals that one of the methoxyl signals has the same value in both IX and XIII (τ 6.75) and may therefore be assumed to arise from a methoxyl remote from ring A. The second methoxyl signal of IX is then found to be deshielded by 0.15 ppm from its position in XIII. Dreiding models show that the C-3 and C-18 positions are equidistant from C-19 (Figure 1). Thus, spectral evidence supports the C-4–C-19(H_2)–OCH_3 moiety and, further, excludes C-3 as a possible site of the ring A hydroxyl. Chemical confirmation of the latter was obtained by formation of the inner carbinolamine ether XIV.[8]

Treatment of condelphine with benzoyl chloride in pyridine produced benzoylcondelphine (XV). The nmr spectrum of this compound contained a quartet of one-proton intensity at τ 4.80 (J_{AX} = 10 cps, J_{BX} = 7 cps, X proton of an ABX-type quartet). This could only occur with the grouping $CH_2CHOBzC$ where the two methylene protons are nonequivalent and this situation is satisfied if C-1 is substituted by the benzoyloxy group. If the benzoyloxy had been at C-2 the grouping $CH_2CHOBzCH_2$ should have produced a multiplet. This same quartet is partially observable in the 60-Mc spectrum of most of the derivatives which contain an acetate at C-1, but in these cases the quartet signal is always partially overlapped by the signal of the proton which is geminal to the acetate in the five-membered ring. However, two and sometimes three of the quartet peaks have been distinguished and in these instances J_{AX} and J_{BX} have still been observed to be 10 and 7 cps, respectively.

Chemical evidence that the ring A hydroxyl is at C-1 was provided by the preparation of the *p*-toluenesulfonate (XVI) and methanesulfonate (XVII) esters of condelphine. These compounds underwent elimination of their corresponding sulfonic acids to give only one product, Δ^1-condelphine (XVIII). Had the ring A hydroxyl been at C-2, two olefins should have been produced by the elimination reaction. The elimination of both the sulfonate esters was so facile that work-up of the reaction mixture gave a mixture of the olefin and the sulfonate ester, hence neither of the sulfonate esters was isolated in its pure state. Evidence that they were produced was gained from the nmr spectra of the corresponding mixtures. In the case of XVII, the mixture immediately after work-up showed two spots on thin layer chromatography. The nmr spectrum of this mixture showed a singlet for CH_3SO_3R at τ 7.03 in addition to olefinic signals at τ 4.04 and 4.60. After complete elimination was effected, either by refluxing in chloroform for several hours or by allowing the mixture to stand at room temperature in chloroform overnight, the signal at τ 7.03 was replaced by one

under investigation by this laboratory). However, it will be shown that condelphine possesses an aconitine-type skeleton and the absolute configuration is assumed to be the same as that of aconitine.

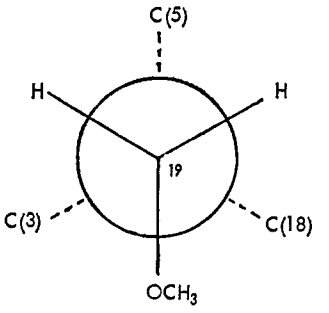
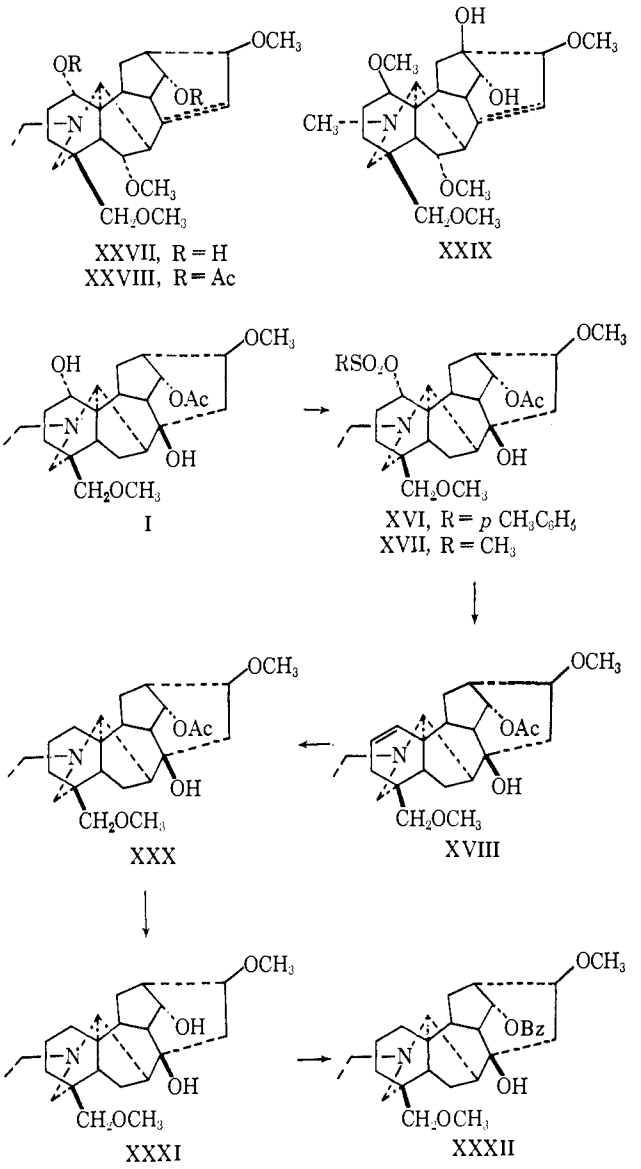


Figure 1.

at τ 7.32 ($CH_3SO_3^-H^+NR_3$). The latter signal disappeared after filtering the solution through a short column of alumina to remove the methanesulfonic acid or after extraction with sodium bicarbonate solution.



In the case of XVI, the mixture immediately after work-up showed two spots on thin layer chromatography, and the nmr spectrum showed signals due to aromatic protons in addition to the olefinic signals at τ 4.04 and 4.60. The more mobile spot, which was

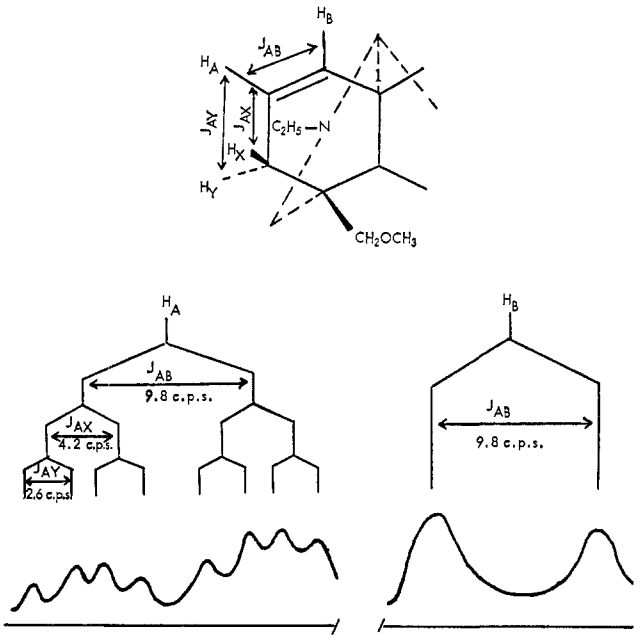


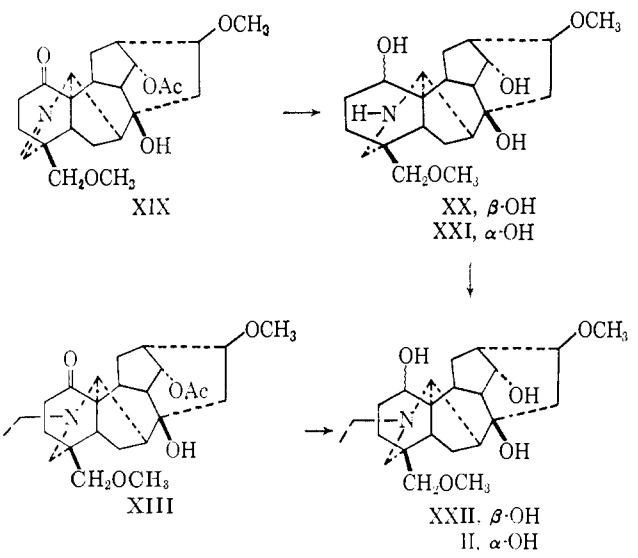
Figure 2.

the sulfonate ester in both cases, gradually diminished in size upon standing in chloroform at room temperature over a period of about 8 hr. The less mobile spot was identified as Δ^1-condelphine by comparison with a sample of the pure material which had been obtained from the elimination reaction with condelphine methanesulfonate (XVII).

The olefinic signals of Δ^1-condelphine were observed to be an octet of one-proton intensity at τ 4.04 (J_{AB} = 9.8 cps, J_{AX} = 4.2 cps, J_{AY} = 2.6 cps, $CH_2CH{=}CHC$) and a doublet of one-proton intensity at τ 4.60 (J = 9.8 cps, $CH{=}CHC$) (Figure 2). Decoupling the H_A proton collapsed the H_B signal to a singlet.

In order to account for the rather large coupling constants (7 and 10 cps) when the C-1 hydroxyl is substituted with an acetate or a benzoate, one of the dihedral angles must be rather large (ϕ calculated for 10 cps = 140–145°, ϕ calculated for 7 cps = 30–35°).[13] The dihedral angles are about 50 and 60° between the C-1 and the C-2 protons in both the α-boat and the β-chair forms. In the α-chair or β-boat the angles are about 50 (equatorial) and 170° (axial). The α-chair and β-boat are clearly the two possibilities which come the closest to the theoretical values of the dihedral angles. However, in the β-boat configuration the hydroxyl would be too far from the nitrogen to explain the intramolecular hydrogen bonding which is observed in the infrared spectrum of condelphine. Also, the formation of the inner carbinolamine ether would have been impossible. It thus appears that the C-1 acetate and benzoate derivatives of condelphine and isotalatizidine exist in the chair conformation and that the C-1 hydroxyl of condelphine and isotalatizidine has the α configuration. Talatizidine, which is the C-1 epimer of isotalatizidine, must then have a β-hydroxyl at this position. Condelphine, however, as well as isotalatizidine, must exist in the α-boat configuration an appreciable amount of its time as indicated by the intramolecular hydrogen bonding which could not occur to any significant degree in the α-chair configuration. One can rationalize that the extra stability gained from the hydrogen bonding would tend to offset the higher energy boat conformation. Actually, condelphine and isotalatizidine most likely exist in a rapid equilibrium between the boat and chair conformations as evidenced by the fact that the nmr spectra always show the C-1 proton as a multiplet when the C-1 hydroxyl is not esterified and this multiplet becomes a triplet (J = 3 cps) in C_6D_6 at 75°.

The presence of an N-ethyl group in condelphine was conclusively demonstrated by reducing N-desethyldidehydrocondelphine (XIX) to a mixture of N-desethyltalatizidine (XX) and N-desethylisotalatizidine (XXI); N-alkylation with ethyl iodide produced the corresponding mixture of talatizidine (XXII) and isotalatizidine (II). This same mixture was produced from the reduction of dehydrocondelphine (XIII) with sodium borohydride. Since the acetate group in condelphine is very labile, in order to be certain that the sodium borohydride reduction was responsible for the hydrolysis of this group in the foregoing reactions, condelphine was subjected to these same conditions and was found to be converted to isotalatizidine.



In the nmr spectra of all of the derivatives of condelphine containing an acetate in the five-membered ring there appeared a triplet of one-proton intensity at τ 5.1–5.2 (J = 4.5 cps). This triplet also appears at τ 4.8–4.9 (J = 4.5 cps) in all the esters with a benzoate at this position and at τ 5.5–5.8 (J = 4.5 cps) in the isotalatizidine derivatives, but it is absent in derivatives with a ketone at this position. Hence, this triplet is assigned to the geminal proton of that position which must be coupled with two equivalent, or nearly equivalent, adjacent protons. This requirement is met with the β-proton on C-10 and possibly, although not very likely since the coupling constant should be about twice that which is observed, with the β-proton on C-12. Position C-6 would be ruled out altogether on this basis since the calculated value for J is about 8–9 cps and the signal should appear as a doublet (ϕ_1 = 15–25°, ϕ_2 = 100–110°, whether the C-6 proton is α or β).

(13) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 51.

Conversion of dehydrooxoisotalatizidine (X) to benzoyldehydrooxoisotalatizidine (XXIII) and subsequent acetylation of the tertiary hydroxyl (XXIV) indicated that the secondary hydroxyl of X was most likely at C-10 and the tertiary hydroxyl at C-8. One is led to this conclusion by the fact that the acetate signal in the nmr spectrum of XXIV appears at an unusually high field (τ 8.62) which is due to the shielding by the diamagnetic circulation of the aromatic π electrons in close proximity. This phenomenon has been observed[14] to be a common feature of several other alkaloids when they are substituted with a C-10 benzoate and a C-8 acetate. Models show that if the benzoate is at C-10 or C-6, in either the α or β configuration, the tertiary acetate of XXIV must be at C-8 in order to be shielded by the aromatic ring. If the benzoate were at C-12 the tertiary acetate could only be at C-17. Pyrolysis of triacetylisotalatizidine (diacetylcondelphine) (IV) gave pyroacetylcondelphine (XXV) which was isomerized to the partially hydrolyzed isopyroacetylisotalatizidine (XXVI). This series of reactions enables not only the assignment of the tertiary acetate to C-8 but also the assignment of position of the remaining methoxyl group and its configuration plus the establishment of an aconitine-type[15] skeleton for condelphine, isotalatizidine, and talatizidine.

The nature of this pyrolysis is well established for aconitine-type alkaloids bearing a C-8 acetyl. A distinguishing characteristic has been noted in the ultraviolet spectra of pyroneoline, diacetylpyroneoline, and pyrodelphonine, all of which are produced by pyrolysis of the corresponding C-8 acetate;[16] these pyro derivatives contain an absorption maximum at about 235–245 mμ which disappears when the solution is made acidic and reappears on neutralization (Table III).

Table III

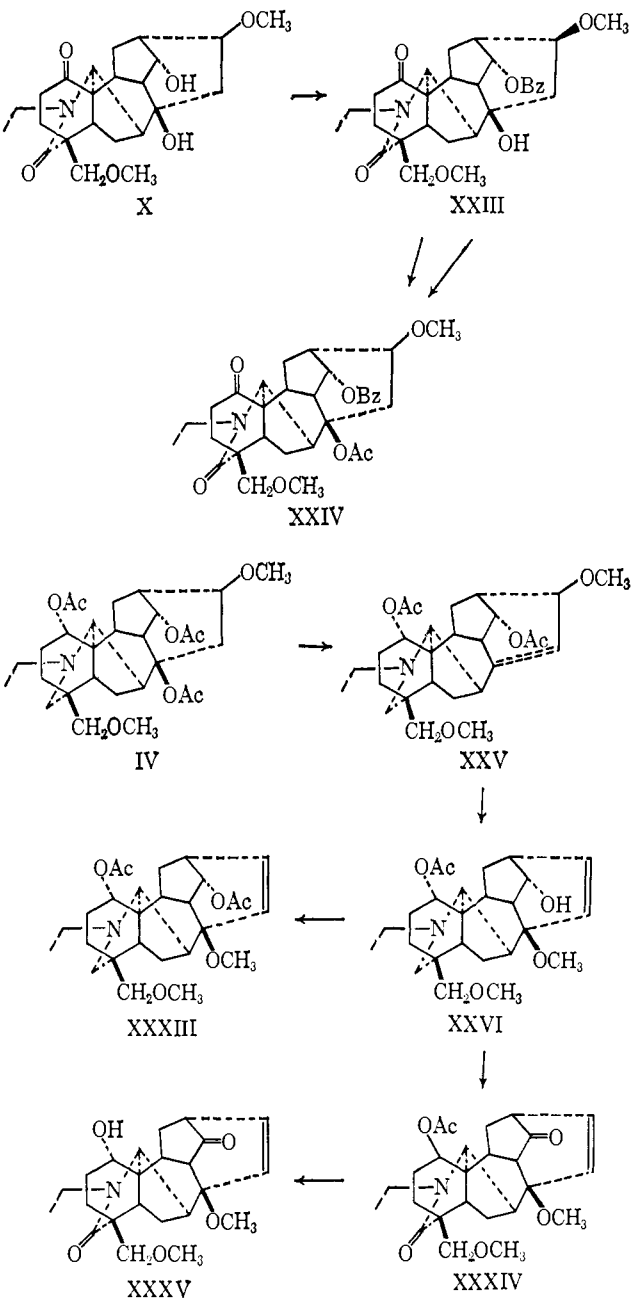
Alkaloid	λ_{max}, mμ	ϵ
Pyroneoline (XXVII)	236	7100
Diacetylpyroneoline (XXVIII)	243	5600
Pyrodelphonine (XXIX)	245	6300
Pyroacetylcondelphine (XXV)	240	6110

This absorption is completely absent in the corresponding isopyro derivatives. Diacetylcondelphine undergoes this same pyrolytic elimination to give a product which shows only two acetate signals and a signal of one-proton intensity for the olefinic proton (τ 4.58). The ultraviolet spectrum shows the characteristic absorption at 240 mμ which disappears when the solution is made acidic, reappears when it is neutralized and which is absent in the isopyro derivatives. Thus, diacetylcondelphine must have the tertiary acetyl at C-8 on an aconitine-type skeleton. C-12 is then eliminated as a possible site of the benzoate in the five-membered ring of XXIV because models show that it is not possible for the tertiary acetate of XXIV to come within the influence of the aromatic ring when the benzoate is at C-12.

(14) L. Marion and Y. Tsuda, *Can. J. Chem.*, 41, 1634 (1963).

(15) The term "aconitine-type" denotes alkaloids with the aconitine skeleton (with a hydrogen on C-7). "Lycoctonine-type" alkaloids are those bearing a hydroxyl group at C-7.

(16) K. Wiesner, H. W. Brewer, D. L. Simmons, D. R. Babin, and F. Bickelhaupt, *Tetrahedron Letters*, 17 (1960).



The models also show, however, that if the benzoate is at C-6 it would also be able to shield the C-8 tertiary acetate. One would expect the C-19 methoxyl to be shielded if the benzoate were indeed at C-6. The nmr spectra of XXIII and XXIV do not show any significant methoxyl shifts but since the C-19 methylene is deshielded about 0.4 ppm by the lactam carbonyl there is no assurance that a deshielding effect by the lactam carbonyl is not being offset by the shielding of the aromatic ring so that the net result is no apparent shift. In order to eliminate this possibility, Δ^1-condelphine (XVIII) was hydrogenated, and the resulting dihydrodeoxycondelphine (XXX) was saponified to dihydrodeoxyisotalatizidine (XXXI) and then benzoylated. The resulting dihydrodeoxybenzoylisotalatizidine (XXXII) had no shielded methoxyl signal in its nmr spectrum (Table IV). The triplet of one-proton intensity at τ 4.85 (J = 4.5 cps) showed that the secondary hydroxyl in question was the one which had been esterified, This evidence, coupled with the argument that

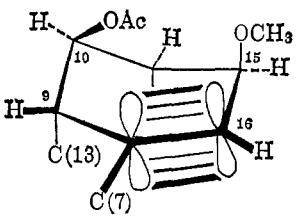


Figure 3.

one of the coupling constants should have been twice as large as the observed coupling constant had it been at C-6 eliminates this position as a possible site of the benzoate.

Table IV

Alkaloid	Methoxyl signals, τ
Condelphine (I)	6.73, 6.78
Dihydrodeoxycondelphine (XXX)	6.71, 6.77
Dihydrodeoxybenzoylisotalatizidine (XXXII)	6.71, 6.78

Having established the position of the C-10 acetate of condelphine, there remains the question of configuration at this position. It is noted that the C-10 proton signal always appears as a triplet with a coupling constant of 4.5 cps and that this same proton in aconitine, indaconitine, psudaconitine, delphinine, and bikhaconitine gives a signal having, without exception, a coupling constant of 4.5 cps.[14] These alkaloids all contain the aconitine-type skeleton with the C-10 ester in the α configuration and thus, by analogy, condelphine, isotalatizidine, and talatizidine should have the C-10 functional group in the α configuration. This is supported by the calculated coupling constants for the C-10 proton in the α and β configuration. Had the C-10 functional group been β, the α-proton should have a coupling constant of 1 cps or less. The calculated value of the coupling constant for the corresponding β-proton (4–6 cps) is in good accord with the observed value.

All that remains is the assignment of position and configuration of the last methoxyl group. The olefinic proton of pyroacetylcondelphine (XXV) is a doublet of one proton intensity at τ 4.58 (J = 6 cps). There are no adjacent protons on C-8; therefore, the coupling has to occur between the C-16 olefinic proton and one proton on C-15. Since there is only one proton on C-15 it must contain a substituent and since all of the other groups have been assigned positions elsewhere in the molecule this substituent must be the remaining methoxyl group.

Models indicate that the dihedral angle between the olefinic proton and the α-proton of C-15 is 30–35° (J (calcd) = 6.5–7.5 cps)[13] while between the olefinic and β-proton of C-15 the dihedral angle is 85–90° (J (calcd) = 0–0.1 cps).[13] Thus, the spectral evidence clearly indicates that the methoxyl must be in the β configuration. This was confirmed by refluxing pyroacetylcondelphine (XXV) in methanol acidified with perchloric acid. The resulting isopyroacetylisotalatizidine (XXVI) contained a multiplet of two-proton intensity at τ 4.05 and a methoxyl signal which was at slightly higher field than usual. This confirmed the rearrangement of the double bond from C-8=C-16 to C-15=C-16 and of the methoxyl from C-15 to C-8. This type of rearrangement is characteristic of aconitine-type alkaloids containing a C-15 β-methoxyl. Rigorous proof that this is an allylic rearrangement rather than just a shift of the double bond has been shown in the case of the alkaloid delphinine.[17] An allylic rearrangement requires that the π electrons of the double bond and the leaving group (methoxyl) be in the same plane. This requirement can be met with the minimum amount of strain if the methoxyl is in the β configuration, but would be impossible to attain if the methoxyl was in the α configuration where it would lie at a right angle to the plane of the π electrons (Figure 3).

The presence of only one acetate signal (three-proton intensity) in XXVI showed that partial hydrolysis had occured and this was further confirmed by obtaining isopyrodiacetylisotalatizidine (isopyroacetylcondelphine) (XXXIII) by acetylation of XXVI with acetic anhydride–pyridine (the nmr of XXXIII shows two acetate signals). The position of hydrolysis in XXVI was determined by oxidation of this compound with Sarett reagent which produced an acetylketolactam (XXXIV). The infrared spectrum of this compound shows a broad carbonyl due to both the ketone and acetate (1736–1770 cm^{-1}) plus the lactam absorption (1637 cm^{-1}). Saponification of XXXIV gave XXXV which contained carbonyl absorptions due only to the lactam (1634 cm^{-1}) and the ketone (1761 cm^{-1}). The high frequency of the ketone absorption unambiguously showed that it was a cyclic five-membered ketone; hence, the partial hydrolysis in XXVI occurred at C-10.

Thus, it has been shown conclusively that the structures of condelphine and isotalatizidine are represented by I and II, respectively, and that talatizidine, which is the C-1 epimer of isotalatizidine, has structure XXII.

Experimental Section

General Experimental Procedures. Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point, and the temperature was raised at a rate of about 4°/min. Rotations were taken in chloroform. Ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer Model 202 spectrometer. Infrared spectra were taken in Nujol mulls (unless otherwise specified) on Perkin-Elmer Model 137 Infracord and Model 237B spectrometers. Nmr spectra were taken on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Certain high-resolution nmr spectra were taken on a Varian HA-100 spectrometer. The removal of solvents *in vacuo* was accomplished with a Craig-type rotating flash evaporator (15–20 mm) and with the water bath usually at 35–55°.

Isolation of Condelphine (I). A Waring blendor was used to grind 4.335 kg of dried *Delphinium denudatum* roots with 15 l. of 95% ethanol. After standing overnight the solution was slowly filtered through glass wool, and the solvent was removed *in vacuo* leaving a dark viscous residue which was dissolved in 2 l. of ether and 400 ml of 5% sulfuric acid. The aqueous layer was separated, and the ether solution was extracted six times with 40-ml portions of 5% sulfuric acid. The combined aqueous solutions were made basic to a pH of about 10 with cold, concentrated ammonium hydroxide and extracted seven times with 300-ml portions of ether. Removal of the ether *in vacuo* left 25 g of a yellow varnish which was dissolved in 50 ml of ether and scratched to induce crystallization of crude condelphine (8.5 g). The mother liquor was concentrated to a varnish, dissolved in 100 ml of 5% sulfuric acid, and extracted twice with 200-ml portions of ether. The ether solu-

(17) K. Wiesner, F. Bickelhaupt, and D. R. Babin, *Experientia*, 15, 93 (1959).

tions were washed with fresh 50-ml portions of 5% sulfuric acid, and all of the aqueous solutions were combined, made basic to a pH of 8 with cold, concentrated ammonium hydroxide, and extracted five times with ether. Evaporation of the ether left 8.5 g of a gum which did not crystallize on addition of ether. The aqueous mother liquor was then made basic to a pH of 10.5 with concentrated ammonium hydroxide and again extracted five times with ether. Evaporation of the left 4.8 g of a gum which was dissolved in 20 ml of ether and scratched to induce crystallization of condelphine (0.665 g).

A second extraction of the roots gave an additional 3 g of crude condelphine and a third and fourth extraction yielded 3.4 and 1.6 g, respectively, bringing the total yield of the crude alkaloid to 17.1 g.

Recrystallization of crude condelphine from ether–methanol gave colorless crystals melting at 158–159° (lit.[8] mp 156–158°); $[\alpha]^{30}D$ +21.3°; ν_{max} 3575 (OH), 3150 (bonded OH), 1739, and 1229 cm^{-1} (OAc); λ_{max} 205 mμ (ε 1090); τ 8.90 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.98 (3 H singlet, $OCOCH_3$), 6.93 (2 H AB-type doublet which is resolved on a 100-Mc instrument into two doublets at 7.02 and 6.85, J = 9 cps, $C\text{-}CH_2OCH_3$), 6.78 (3 H singlet, OCH_3), 6.73 (3 H singlet, OCH_3), 6.28 (1 H multiplet, CHOH), 5.20 (1 H triplet, J = 4.5 cps, CHCHOAcCH), and 3.02 (1 H multiplet which exchanges with deuterium oxide, CHOH).

Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.75; N, 3.12; 2(OCH_3), 13.81. Found: C, 66.83, 66.65; H, 8.80, 8.85; N, 3.20, 3.15; 2(OCH_3), 13.62. Calcd mol wt, 449.57; mass spectrum, *m/e* 449.

Condelphine gave a positive test with silicontungstic acid. Negative tests were obtained for Beilstein halogen, sodium-fusion halogen, sodium-fusion sulfur, and the Zimmerman test for methylene adjacent to a ketone.

Condelphine oxalate showed the following physical properties: mp 163–165° dec (lit.[9] mp 160–162°); ν_{max} 3333 (H^+N), 1739 (OAc), and 1712 cm^{-1} (COOH).

Anal. Calcd for $C_{27}H_{40}NO_{10}$: C, 60.09; H, 7.66. Found: C, 59.98; H, 7.83.

Condelphine perchlorate (XXXVI) showed the following physical properties: mp 224–225° (lit.[9] mp 209–210°); ν_{max} 3650 (OH), 3300 (H^+N), and 1739 cm^{-1} (OAc); (D_2O) τ 8.65 (3 H triplet, J = 7 cps, $N^+CH_2CH_3$), 7.92 (3 H singlet, $OCOCH_3$), 7.05 (2 H AB-type doublet, CCH_2OCH_3), 6.66 (3 H singlet, OCH_3), 6.64 (3 H singlet, OCH_3), 5.85 (1 H multiplet, CHOH). The triplet at 5.2 was not detectable due to the HOD signal.

Anal. Calcd for $C_{25}H_{40}NO_{10}Cl$: C, 54.59; H, 7.33. Found: C, 54.66; H, 7.34.

Condelphine picrate (XI) showed the following physical properties: mp 195.5–196.5°; ν_{max} 3311 (N^+H) and 1721 cm^{-1} (OAc); τ 8.57 (3 H triplet, J = 7 cps, $N^+CH_2CH_3$), 7.95 (3 H singlet, $OCOCH_3$), 6.83 (3 H singlet, OCH_3), 6.66 (3 H singlet, OCH_3), 6.42 (2 H AB-type doublet, CCH_2OCH_3), 5.70 (1 H multiplet, CHOH), 5.10 (1 H triplet, J = 4.5 cps, CHCHOAcCH), 1.17 (2 H singlet, aromatic), and −0.47 (1 H broad multiplet, H^+N).

Anal. Calcd for $C_{31}H_{42}N_4O_{13}$: C, 54.86; H, 6.24. Found: C, 55.05; H, 6.11.

A solution of 10 mg of condelphine picrate in chloroform was filtered through a short column of Woelm neutral alumina and 6 mg of a gum was obtained which crystallized from ether to give 5 mg of colorless crystals. This material had an identical infrared spectrum with condelphine and exhibited no depression of melting point when mixed with condelphine.

Isotalatizidine (II). To 10 ml of a 5% methanolic sodium hydroxide solution was added 450 mg of condelphine, and the solution was allowed to stand at room temperature overnight. After removal of the solvent *in vacuo* the residue was dissolved in 15 ml of water and extracted eight times with 15-ml portions of methylene chloride. The extracts were combined and dried over sodium sulfate, and the solvent was removed *in vacuo* leaving a clear varnish. The latter was dissolved in ether and concentrated to about 2 ml. Scratching induced crystallization of isotalatizidine as colorless needles (402 mg). A sample was recrystallized from ether–hexane solution to give crystals which melted at 116–117° (lit.[10] mp 114–117° with water of crystallization and 140–142° after drying *in vacuo*). The melting point of II could not be raised above 117° even after heating the crystals *in vacuo*, and the microanalysis data indicated that there was no water of crystallization in these crystals; ν_{max} 3636 (OH) and 3378 cm^{-1} (OH); λ_{max} 205.5 mμ (ε 995); τ 8.90 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.04 and 6.84 (1 H doublets, J = 9 cps, CCH_2OCH_3), 6.70 (3 H singlet, OCH_3), 6.68 (3 H singlet, OCH_3), 6.30 (1 H multiplet, CHOH), 5.82 (1 H triplet, J = 4.5 cps, CHCHOHCH).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 68.10, 68.05; H, 9.19, 9.36; N, 3.21, 3.17.

Comparison of Condelphine Isolated from *Delphinium denudatum* with Condelphine Isolated from *Delphinium confusum*.[18] A sample of condelphine from *Delphinium confusum* was recrystallized by dissolving a small amount of the material in the minimum amount of methanol and adding about five times this volume of ether to the solution. This solution was concentrated to about one-half its volume and seeded with a crystal of condelphine obtained from *Delphinium denudatum*. The colorless crystals which were obtained melted at 156.5–157.5°; mixture melting point with I, 156–159°; $[\alpha]^{30}D$ +20.9°. The infrared spectra of the two samples were identical in all respects.

To 68 mg of condelphine (from *Delphinium confusum*) was added 0.5 ml of methanol and two drops of 60% perchloric acid. After 3 min anhydrous ether was added and the product precipitated as a gum. Crystallization from absolute ethanol gave 55 mg of the perchlorate as colorless needles melting at 222–226°; mixture melting point with XXXVI, 222–225°. The infrared spectrum of these crystals was identical with the infrared spectrum of XXXVI.

To 74 mg of condelphine (from *Delphinium confusum*) was added 3 ml of methanol, 1 ml of water, and one pellet (about 150 mg) of potassium hydroxide. After standing at room temperature for 4.5 hr the solvent was removed *in vacuo*, and the residue was dissolved in 8 ml of water and extracted well with methylene chloride. The extracts were combined and dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in a few milliliters of ether, an equal volume of hexane was added, and the volume was concentrated to about 2 ml and seeded with a crystal of isotalatizidine from *D. denudatum*. A yield of 51 mg of isotalatizidine was obtained as colorless crystals which melted at 114–116°; mixture melting point with II, 114–117°. The infrared spectrum of this material was identical with the infrared spectrum of II.

Monoacetylcondelphine (Diacetylisotalatizidine) (III). A solution of 125 mg of condelphine in 1.5 ml of acetic anhydride and 1.5 ml of pyridine was allowed to stand at room temperature for 21 hr. The excess solvent was removed *in vacuo*, and the residue was dissolved in 15 ml of ether, extracted once with 3 ml of dilute ammonium hydroxide, and washed once with 5 ml of water. After drying over sodium sulfate the ether solution was concentrated, petroleum ether (bp 30–60°) was added, and the solution was chilled and scratched to induce crystallization. A yield of 102 mg of colorless crystals was obtained melting at 111–113°. Recrystallization produced an analytical sample which melted at 114.5–117° (lit.[8] mp 112–117°); ν_{max} 3636 (OH), 1748 (OAc), and 1721 cm^{-1} (OAc); λ_{max} 207.5 mμ (ε 2160); τ 8.92 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.98 (6 H singlet, 2 $OCOCH_3$), 6.97 (2 H singlet, $C\text{-}CH_2\text{-}OCH_3$), 6.78 (3 H singlet, OCH_3), 6.73 (3 H singlet, OCH_3), 5.18 (2 H multiplet consisting of the X proton of an ABX-type quartet centered at 5.12, J_{AX} = 10 cps, J_{BX} = 7 cps, $CH_2CHOAcC$), and the 1 H triplet centered at 5.24 (J = 4.5 cps, CHCHOAcCH).

Anal. Calcd for $C_{27}H_{41}NO_7$: C, 65.96; H, 8.41; N, 2.85. Found: C, 65.96, 66.06; H, 8.41, 8.40; N, 2.80, 2.76.

Monoacetylcondelphine perchlorate had a melting point of 226–228°; ν_{max} 3650 (OH), 3300 (H^+N), and 1739 cm^{-1} (OAc).

Anal. Calcd for $C_{27}H_{42}NO_{11}Cl$: C, 54.77; H, 7.15. Found: C, 54.48; H, 7.17.

Monoacetylcondelphine picrate (XII), mp 99–101°, produced the following spectra: ν_{max} 3247 (H^+N) and 1739 cm^{-1} (OAc); τ 8.51 (3 H triplet, J = 7 cps, $N^+CH_2CH_3$), 8.14 (3 H singlet, $OCOCH_3$), 7.93 (3 H singlet, $OCOCH_3$), 6.48 (2 H singlet, CCH_2OCH_3), 6.71 (3 H singlet, OCH_3), 6.66 (3 H singlet, OCH_3), 2 H multiplet at 5.1 of which only the 1 H triplet centered at 5.16 (J = 4.5 cps, CHCH-OAcCH) is distinguishable.

Monoacetylcondelphine Hydrochloride. Anhydrous hydrogen chloride was bubbled through a chilled solution of 22 mg of monoacetylcondelphine dissolved in 4 ml of anhydrous ether. A white precipitate immediately formed and then rapidly dissolved again. The ether was evaporated with nitrogen, and the residue was then dissolved in an acetone–benzene solution and azeotroped to dryness. Addition of anhydrous ether to the residue caused crystallization of the crude product, but due to its extremely hygroscopic nature no solvents or solvent pairs suitable for recrystallization were found. After decanting the ether and drying the crystalline solid, a yield of 24.5 mg of the crude hydrochloride was obtained; ν_{max} 3436 (H^+N) and 1739 cm^{-1} (OAc); mp 126–128°.

(18) We thank Dr. A. D. Kuzovkov for a generous sample of condelphine isolated from *Delphinium confusum*.

Anal. Calcd for $C_{27}H_{42}NO_3Cl$: C, 59.60; H, 7.78. Found: C, 59.45; H, 7.52.

Interconversion of Isotalatizidine and Monoacetylcondelphine. A solution of 50 mg of isotalatizidine (II) in 1.5 ml of acetic anhydride and 1.5 ml of dry pyridine was stoppered and allowed to stand at room temperature for 19 hr. The solvent was removed *in vacuo*, and the residue was dissolved in ether, extracted once with dilute ammonium hydroxide, and dried over sodium sulfate. An equal volume of hexane was added to the ether solution and, after concentrating to about 4 ml, scratched to induce crystallization of monoacetylcondelphine (24 mg) which melted at 113–115°; mixture melting point with III, 114.5–116.5°. The infrared spectrum of monoacetylcondelphine prepared from II is the same as that of III.

To 20 mg of monoacetylcondelphine (III) was added 1 ml of 5% sodium hydroxide in methanol, and the solution was allowed to stand at room temperature for 20 hr. After removal of the solvent *in vacuo*, 10 ml of water was added, and the solution was extracted well with chloroform. The chloroform extract was washed once with water and dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was then dissolved in ether, an equal volume of hexane was added, and the solution was concentrated to about 1 ml and scratched to induce crystallization of isotalatizidine (10 mg) which melted at 111–113°; mixture melting point with II, 114–117°. The infrared spectrum of isotalatizidine prepared from monoacetylcondelphine is identical with that of II.

Unreactivity of Condelphine to Catalytic Hydrogenation with Palladium. To 50 mg of condelphine and 50 mg of 10% Pd–C was added 20 ml of 95% ethanol, and the mixture was shaken in a Parr apparatus under 35 psi of hydrogen at room temperature for 18 hr. The solution was filtered, and the solvent was removed *in vacuo*. The residue was crystallized from an ether–hexane solution to give 33 mg of unchanged condelphine; mp 157–159°; mixture melting point with I, 157–159°.

Unreactivity of Condelphine to Catalytic Hydrogenation with Platinum. To 50 mg of condelphine and 50 mg of platinum dioxide was added 5 ml of 95% ethanol, and the mixture was stirred under 1 atm pressure of hydrogen for 2 hr. The mixture was filtered, and the solvent was removed *in vacuo*. Thin layer chromatography showed only unreacted condelphine to be present, and the nmr spectrum of the residue was identical with that of I.

Reaction of Condelphine with Sodium Borohydride. To 40 mg of condelphine in 4 ml of methanol was added four drops of water and 30 mg of sodium borohydride, and the solution was allowed to stand at room temperature for 3 hr. The solvent was removed *in vacuo*, and the residue was dissolved in 5 ml of water and extracted with ether. The combined extracts were dried over sodium sulfate, concentrated, and scratched to induce crystallization of crude isotalatizidine which melted at 105–110°. The infrared spectrum of this material was identical with that of II.

Didehydrooxoisotalatizidine (VIII). To 5 ml of 5% sodium hydroxide in methanol was added 235 mg of condelphine, and the solution was allowed to stand at room temperature overnight. The solvent was removed *in vacuo*, and the crude isotalatizidine (II) was dissolved in 2 ml of dry pyridine and cooled to 0°. This solution was added to Sarett reagent (prepared from 370 mg of chromic anhydride (CrO_3) in 2 ml of dry pyridine at 0°) and left overnight in the freezing compartment of the refrigerator. After removal of the solvent *in vacuo*, 4 ml of 5% sulfuric acid was added to the residue, and this solution was cooled to 5° and saturated with sulfur dioxide to destroy the excess chromic anhydride. The aqueous solution was extracted with chloroform; the extracts were washed once with water, and the solvent was removed *in vacuo*. The residue was dissolved in a minimum amount of benzene and chromatographed on a column of Woelm neutral alumina, eluting with benzene–1% methanol solution. Removal of the solvent *in vacuo* left a solid which was crystallized from an ether–methanol solution to yield 78 mg of colorless crystals melting at 172–174° (lit.[8] mp 182–183.5°). A positive Zimmerman test was obtained; ν_{max} 3571 (OH), 1748 (saturated cyclic five-membered ketone), 1712 (saturated cyclic six-membered ketone), 1642 (lactam), and 1418 cm^{-1} (CH_2CO).

Anal. Calcd for $C_{28}H_{31}NO_6$: C, 66.16; H, 7.48. Found: C, 66.80, H, 7.59.

Oxidation of Condelphine (I) with Sarett Reagent. Dehydrocondelphine (XIII), Dehydrooxocondelphine (IX), and N-Desethyldidehydrocondelphine (XIX). A. A solution of 700 mg of condelphine in 7 ml of dry pyridine at 5° was added to Sarett reagent prepared from 900 mg of chromic anhydride in 10 ml of anhydrous pyridine at 5°. The reaction mixture was stirred in an ice bath for 4 hr and then left overnight in the refrigerator freezer compartment. The solution was then allowed to stand at room temperature for 5 hr, and the solvent was removed *in vacuo*. The residue was dissolved in 25 ml of cold 5% sulfuric acid and saturated with sulfur dioxide to destroy the excess chromic anhydride. The aqueous solution was extracted well with methylene chloride; the combined extracts were washed once with water and dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in the minimum amount of benzene and chromatographed on Woelm neutral alumina, eluting with benzene–1% methanol in three fractions. Addition of ether to the residue of the first two fractions induced crystallization of 245 mg (mp 160–165°) and 32 mg (150–152°) of dehydrooxocondelphine (IX), respectively. Evaporation of the solvent from the third fraction left 104 mg of a gum. Recrystallization of dehydrooxocondelphine from methanol–ether solution gave an analytical sample melting at 162–163°. This compound gives a positive Zimmerman test; ν_{max} 3610 (OH), 1739 (OAc), 1701 (saturated cyclic six-membered ketone), and 1637 cm^{-1} (six-membered lactam); τ 8.92 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.97 (3 H singlet, $OCOCH_3$), 6.75 (3 H singlet, OCH_3), 6.67 (3 H singlet, OCH_3), 6.50 (2 H singlet, CCH_2OCH_3), and 5.12 (1 H triplet, J = 4.5 cps, $CHCHOAcCH$).

Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.05; H, 7.64. Found: C, 65.11; H, 7.83.

The aqueous mother liquor from the reaction mixture was then made basic with concentrated ammonium hydroxide and extracted well with methylene chloride. The extract was washed with water and dried over sodium sulfate, and the solvent was removed *in vacuo* leaving a pale yellow gum from which 89 mg of crude crystalline N-desethyldidehydrocondelphine (XIX) was obtained by adding ether; mp 192–214°. After two recrystallizations from acetone, 40 mg of XIX was obtained as pale yellow flakes; mp 213–216°. This compound gave a positive Zimmerman test; ν_{max} 3390 (OH), 1739 (OAc), 1715 (saturated cyclic six-membered ketone), and 1634 cm^{-1} (N=C); τ 7.95 (3 H singlet, $OCOCH_3$), 6.75 (3 H singlet, OCH_3), 6.62 (3 H singlet, OCH_3), 6.55 (2 H singlet, CCH_2OCH_3), 6.02 (1 H broad singlet, CCH=N), and 5.08 (1 H triplet, J = 4.5 cps, $CHCHOAcCH$).

Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.16; H, 7.48; N, 3.36. Found: C, 66.18; H, 7.62; N, 3.64.

B. A solution of 450 mg of condelphine in 4 ml of dry pyridine at 0° was added to Sarett reagent prepared by rapidly stirring 460 mg of chromic anhydride in 5 ml of dry pyridine at 0° for 2 hr. The reaction mixture was stirred slowly at 0° for 4 hr and then at room temperature for 30 min. The solvent was removed *in vacuo*, and the residue was flashed with benzene once, dissolved in 10 ml of cold 2% sulfuric acid, and saturated with sulfur dioxide to destroy the excess chromic anhydride. The aqueous solution was extracted well with methylene chloride; the combined extracts were dried over sodium sulfate, and the solvent was removed *in vacuo* to give a gum. The latter was dissolved in a small amount of ether and seeded with IX to induce crystallization of 60 mg of dehydrooxocondelphine. Evaporation of the mother liquor left 70 mg of gum which was placed on a 200 × 200 mm plate of alumina G and eluted with benzene–3% methanol solution. After a brief development of the whole plate in iodine vapor the alumina was scraped off, extracted with 1:1 chloroform–methanol solution and filtered. Evaporation of the filtrate gave another 14 mg of dehydrooxocondelphine (IX).

The aqueous mother liquor from the reaction mixture was then made basic with concentrated ammonium hydroxide and extracted with five 20-ml portions of ether; the solution was dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was placed on a 200 × 400 mm plate of alumina G and eluted with chloroform. The alumina just below the solvent front was scraped off and extracted with 1:1 chloroform–methanol solution and filtered, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a short column of Woelm neutral alumina (grade 1), eluting with chloroform. Evaporation of the eluent left 76 mg of a pale yellow gum which was dissolved first in ether and then in hexane to remove about 6 mg of an insoluble yellow impurity. After removal of the hexane *in vacuo*, 65 mg of a colorless glass was left. It was dissolved in a small amount of ether and slowly crystallized overnight. Two recrystallizations from ether gave 35 mg of pure dehydrocondelphine (XIII); mp 120.5–122.5°; picrate, mp 105.5–107.5°; ν_{max} 1739 (OAc) and 1718 (ketone) cm^{-1}. The base did not give a positive Zimmerman test; ν_{max} 3717 (OH), 1748 (OAc), 1686 (ketone), and 1408 cm^{-1} ($-CH_2CO-$); τ 8.93 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.98 (3 H singlet, $OCOCH_3$), 6.95 (2 H singlet, CCH_2OCH_3), 6.82 (3 H singlet, OCH_3),

6.75 (3 H singlet, OCH_3), and 5.20 (1 H triplet, J = 4.5 cps CHC*H*OAcCH); ORD: (in chloroform) 276 mμ [α] 1217°, 321 mμ [α] −630°; (in acetic acid) 274.5 mμ [α] −1126°, 319 mμ [α] 943°.[19]

Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; mol wt, 447.2621. Found: C, 67.27; H, 8.08; mol wt (*m/e* parent peak of mass spectrum), 447.2610.

Dehydrooxoisotalatizidine (X). To 130 mg of dehydrooxocondelphine in 5 ml of methanol was added 65 mg of potassium hydroxide in 2 ml of water. After standing at room temperature for 4 hr, the solvent was removed *in vacuo;* the residue was dissolved in 5 ml of water and extracted well with methylene chloride. After drying the combined extracts over sodium sulfate, the solvent was removed *in vacuo*, and the colorless gum was triturated with ether to induce crystallization. A yield of 110 mg of the crude product was obtained. Recrystallization from a 1:3 acetone–hexane solution afforded an analytical sample which melted at 198–199° and which gave a positive Zimmerman test; ν_{max} 3636 (OH), 3559 (OH), 1712 (ketone), 1639 (lactam), and 1416 cm^{-1} (CH_2CO); τ 8.93 (3 H triplet, J = 7 cps, NCH_2CH_3), 6.63 (6 H singlet, 2-OCH_3), 6.47 (2 H singlet, CCH_2OCH_3), 6.37 (1 H singlet, OH, exchanges with D_2O), 5.78 (1 H multiplet, $CHCHOCH_3CH_2$), and 5.48 (1 H triplet, J = 4.5 cps, CHCHOHCH).

Anal. Calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93. Found: C, 65.67; H, 8.02.

Interconversion of Dehydrooxocondelphine (IX) and Dehydrooxoisotalatizidine (XV). A solution of 62 mg of dehydrooxoisotalatizidine in 1 ml of anhydrous pyridine and 1 ml of acetic anhydride was left at room temperature overnight. The solvent was removed *in vacuo*, and the residue was dissolved in ether, extracted once with dilute ammonium hydroxide, dried over sodium sulfate, and concentrated. Scratching induced crystallization of 55 mg of dehydrooxocondelphine; mp 160–162°; mixture melting point with IX, 160.5–162°. The infrared spectrum of dehydrooxocondelphine prepared from X was identical with that of IX.

To 51 mg of the dehydrooxocondelphine prepared above was added to solution of one pellet of potassium hydroxide dissolved in 3 ml of methanol and 1 ml of water. After standing overnight at room temperature, the solvent was removed *in vacuo*, and the residue was dissolved in 8 ml of water and extracted well with methylene chloride. The combined extracts were dried over sodium sulfate, and the solvent was removed *in vacuo*. Addition of ether to the residue induced crystallization of 33 mg of dehydrooxoisotalatizidine; mp 198–200°; mixture melting point with X, 198–200°. The infrared spectrum of this material was identical with that of X.

Benzoyldehydrooxoisotalatizidine (XXIII). To 97 mg of dehydrooxoisotalatizidine (X) was added 1 ml of pyridine and five drops of benzoyl chloride, and the solution was allowed to stand at room temperature for 2 days. The solvent was removed *in vacuo*, and the residue was flashed once with benzene and then dissolved in water, made basic with dilute ammonium hydroxide, and extracted well with methylene chloride. The extracts were washed once with 5% sulfuric acid and then with water, dried over sodium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in a small amount of ether and, upon standing, 95 mg of the product crystallized from solution; mp 183–185°. Recrystallization of a sample from acetone–ether gave long colorless needles of benzoyldehydrooxoisotalatizidine, mp 183–185°, and which gave a positive Zimmerman test; $[\alpha]^{28}D$ +54.0°; ν_{max} 3546 (OH), 1712 (ketone), 1613 (lactam and phenyl), 1408 (CH_2CO), and 723 cm^{-1} (phenyl); τ 8.92 (3 H triplet, J = 7 cps, NCH_3CH_3), 6.77 (3 H singlet, OCH_3), 6.67 (3 H singlet, OCH_3), 6.50 (2 H singlet, CCH_2OCH_3), 4.79 (1 H triplet, J = 4.5 cps, CHC*H*OBzCH), and 2.0 and 2.5 (5 H multiplet, C_6H_5COO).

Anal. Calcd for $C_{30}H_{37}NO_7$: C, 68.81; H, 7.12. Found: C, 68.57; H, 7.20.

8-Acetyl-10-benzoyldehydrooxoisotalatizidine (XXIV). A solution of 35 mg of benzoyldehydrooxoisotalatizidine (XXIII) in 1 ml of acetyl chloride was sealed in a Pyrex tube and kept at 42° for 40 hr. The excess solvent was removed *in vacuo*, and the residue was flashed with benzene, then dissolved in dilute ammonium hydroxide, and extracted well with ether. After washing the ether extracts once with water and drying over sodium sulfate, the solvent was concentrated and scratched to induce crystallization of XXIV (25 mg). Recrystallization from ether–acetone gave an analytical sample melting at 168–170°. A positive Zimmerman test was observed; ν_{max} 1720–1740 (ketone, OAc, and OBz), 1645 (lactam), 1625, 1635, and 718 cm^{-1} (phenyl); τ 8.90 (3 H triplet, J = 7 cps, NCH_2CH_3), 8.62 (3 H singlet, $OCOCH_3$), 6.65 (3 H singlet, OCH_3), 6.60 (3 H singlet, OCH_3), 6.52 (2 H singlet, CCH_2OCH_3), 4.87 (1 H triplet, J = 4.5 cps, CHC*H*OBzCH), and 2.5 and 2.0 (5 H multiplet, C_6H_5COO).

Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.94; H, 6.95. Found: C, 67.58, 67.66; H, 7.06, 7.06.

Diacetylcondelphine (Triacetylisotalatizidine) (IV) and Diacetylcondelphine Hydrochloride (XXXVII). A solution of 800 mg of condelphine in 20 ml of freshly distilled acetyl chloride was sealed in a Pyrex tube and maintained at 40° for 22 hr. The solvent was removed *in vacuo*, and the residue was flashed once with benzene. Addition of ether spontaneously induced crystallization of 1.08 g of the crude hydrochloride (XXXVII).

A 150-mg portion of XXXVII was recrystallized from an acetone–ether solution, and the crystals obtained melted at 159–164°. After a second recrystallization and drying for 2 hr at 80° *in vacuo*, the melting point was sharper but lower (mp 146–148°), although there was no apparent change in the infrared spectrum of the dried sample. Diacetylcondelphine hydrochloride gave a positive Beilstein halogen test; ν_{max} 3704, 3497, 2747 (H^+N), 2653, 1727 (OAc), and 1642 cm^{-1}; τ 8.43 (3 H triplet, J = 7 cps, $N^+CH_2CH_3$), 8.02 (3 H singlet, $OCOCH_3$), 7.98 (3 H singlet, $OCOCH_3$), 7.62 (3 H singlet, $OCOCH_3$), 6.90 (2 H singlet, CCH_2OCH_3), 6.72 (3 H singlet, OCH_3), 6.68 (3 H singlet, OCH_3), 5.12 (2 H multiplet consisting of the X proton of an ABX type quartet centered at 5.02, J_{AX} = 5.5 cps, J_{BX} = 4 cps, $CH_2CHOAcC$), and the 1 H triplet centered at 5.20 (J = 4.5 cps, CHC*H*OAcCH).

The remaining 0.9 g of XXXVII was dissolved in 30 ml of water, made basic with ammonium hydroxide, and extracted well with ether. The combined extracts were dried over sodium sulfate and then concentrated to 5 ml followed by the addition of 25 ml of hexane. This solution was concentrated to 7 ml and scratched to induce crystallization of diacetylcondelphine (0.65 g, IV) melting at 128.5–132.5°. Recrystallization from hexane gave an analytical sample which melted at 129–132° (lit.[8] mp 131–135°) and which gave a negative Beilstein halogen test; $[\alpha]^{28}D$ −24.1°; ν_{max} 1730 cm^{-1} (OAc); λ_{max} 207.5 mμ (ε 2360); τ 8.92 (3 H triplet, J = 7 cps, NCH_2CH_3), 8.07 (3 H singlet, $OCOCH_3$), 8.00 (3 H singlet, $OCOCH_3$), 7.97 (3 H singlet, $OCOCH_3$), 7.00 (2 H singlet, CCH_2OCH_3), 6.75 (3 H singlet, OCH_3), 6.72 (3 H singlet, OCH_3), 5.18 (2 H multiplet consisting of the X proton of an ABX type quartet centered at 5.12, J_{AX} = 10 cps, J_{BX} = 7 cps, $CH_2CHOAcC$–), and the 1 H triplet centered at 5.24 (J = 4.5 cps, CHC*H*OAcCH).

Anal. Calcd for $C_{29}H_{43}NO_8$: C, 65.27; H, 8.12. Found: C, 65.53; H, 8.13.

Anhydrous hydrogen chloride was bubbled into a solution of 20 mg of diacetylcondelphine (IV) in 5 ml of anhydrous ether. A white precipitate formed and then rapidly dissolved again. Removal of the ether left a white crystalline solid which was recrystallized from acetone–ether solution to give 12 mg of diacetylcondelphine hydrochloride melting at 151–155°. The infrared spectrum of diacetylcondelphine hydrochloride prepared from diacetylcondelphine (IV) was identical with that of XXXVII.

Conversion of Diacetylcondelphine (IV) to Isotalatizidine (II) and Monoacetylcondelphine (Diacetylisotalatizidine) (III). To a solution of one pellet (about 150 mg) of potassium hydroxide dissolved in 1 ml of water and 3 ml of methanol was added 70 mg of diacetylcondelphine. The solution was stoppered and allowed to stand at room temperature overnight. The solvent was removed *in vacuo;* the residue was dissolved in water and extracted with methylene chloride. After the combined extracts were dried over sodium sulfate and the solvent was removed *in vacuo*, the residue was dissolved in ether, hexane was added, and the solution was concentrated and seeded with II to induce crystallization of 8 mg of isotalatizidine melting at 111–114°; mixture melting point with II, 111–114.5°.

The residue from the mother liquor still contained strong carbonyl absorption in its infrared spectrum and so was again dissolved in a 3:1 methanol–water solution containing one pellet of potassium hydroxide. The solution was heated at 50° for 5 hr and then left at room temperature for 3 days. Following the same work-up as just described an additional 13 mg of isotalatizidine was obtained, mp 108.5–115°. Although there was no depression in the mixture melting points, there were some slight discrepancies in the fingerprint region of the infrared spectra of these samples of

(19) Comparison of the ORD spectrum of dehydrocondelphine with the spectra of 1-keto derivatives containing an aconitine-type skeleton was not conclusive in showing that the ketone of dehydrocondelphine was at C-1 since only the longer wavelength half of the ORD curves had been reported.[16]

isotalatizidine which can be attributed to different crystalline structures.

To 14.5 mg of the crude isotalatizidine prepared above was added 0.5 ml of anhydrous pyridine and 0.5 ml of acetic anhydride. The solution was stoppered and allowed to stand at room temperature overnight. The solvent was then removed, and the residue was flashed once with benzene, dissolved in ether, and extracted once with 4 ml of dilute ammonium hydroxide. After drying the ether solution over sodium sulfate it was concentrated, hexane was added, and the solution was further concentrated to 0.5 ml. Seeding with III induced crystallization of 8 mg of monoacetylcondelphine melting at 114.5–117.5°; mixture melting point with III, 114.5–117°. The infrared spectra of the two samples were identical in all respects.

Thermal Stability of Condelphine in Refluxing Ethanol. A solution of 30 mg of condelphine in 25 ml of 95% ethanol was refluxed for 18 hr. The solvent was removed *in vacuo*, and the residue was dissolved in ether, concentrated, and scratched to induce crystallization of 28 mg of unchanged condelphine; mp 157–159°; mixture melting point with I, 156–159°. The infrared spectrum of this sample was identical with that of I.

Thermal Stability of Condelphine under Pyrolytic Conditions. A mixture of 15 mg of condelphine and 200 mg of purified powdered copper was heated at 220–235° (0.05 mm) for 2 hr. The mixture was extracted with chloroform and filtered. Thin layer chromatography showed the presence of only unchanged condelphine.

Pyroacetylcondelphine (XXV). Seven 100-mg batches of diacetylcondelphine (IV) were pyrolized *in vacuo* at 210–220° (0.03–0.05 mm) for 6 min. The products were dissolved in ether, combined, and chromatographed on a 1.5-cm diameter column of 30 g of Woelm neutral alumina (grade 1) cutting 20-ml fractions and monitoring them by tlc. Fractions 4–9 (eluting with 1:1 benzene–ether) and fractions 10–15 (eluting with ether) showed only one spot on tlc and were combined to give 152 mg of pyroacetylcondelphine as an amorphous solid. Eluting with ether–1% methanol gave 426 mg of a mixture which, after chromatographing three times, yielded another 150 mg of pyroacetylcondelphine; ν_{max} ($CHCl_3$) 1730 (OAc) and 1637 cm^{-1} (C=C); λ_{max} (neutral solution) 240 mμ (ε 6110) and 211 mμ (ε 6400), (acidic solution) 213 mμ (ε 6750); τ 8.93 (3 H triplet, J = 7 cps, NCH_2CH_3), 8.03 (3 H singlet, $OCOCH_3$), 8.02 (3 H singlet, $OCOCH_3$), 6.95 (2 H singlet, CCH_2OCH_3), 6.72 (6 H singlet, $2OCH_3$), 5.25 (2 H multiplet consisting of the X proton of an ABX-type quartet centered at 5.17, J_{AX} = 10 cps, J_{BX} = 7 cps, $CH_2CHOAcC$), and the 1 H triplet centered at 5.38 (J = 4.5 cps, $CHCHOAcCH$), and 4.58 (1 H doublet, J = 6 cps, $CCH{=}CHOCH_3$). This material is amorphous and was characterized by microanalysis of the crystalline isopyroacetylcondelphine (XXXIII).

Isopyroacetylisotalatizidine (XXVI). To 50 mg of pyrocondelphine in 5 ml of methanol was added five drops of 60% perchloric acid, and the solution was refluxed for 2 hr. The solvent was removed *in vacuo*, and the residue was dissolved in 10 ml of water, made basic with ammonium hydroxide, and extracted well with ether. After drying over sodium sulfate the ether was removed *in vacuo* leaving 43 mg of a colorless gum which showed one main spot by thin layer chromatography. Column chromatography on Woelm neutral alumina (grade 1) with ether–0.5% methanol as the eluent gave 22 mg of pure isopyroacetylisotalatizidine. This compound is an amorphous solid; ν_{max} ($CHCl_3$) 3584 (OH) and 1724 cm^{-1} (OAc); λ_{max} (neutral) 208 mμ (ε 3780), (acidic) 206 mμ (ε 2400); τ 8.95 (3 H triplet, J = 7 cps, NCH_2CH_3), 8.02 (3 H singlet, $OCOCH_3$), 6.93 (2 H singlet, CCH_2OCH_3), 6.81 (3 H singlet, OCH_3), 6.70 (3 H singlet, OCH_3), 5.10 (2 H multiplet, $CHCHOHCH$ and $CH_2CHOAcC$), and 4.05 (2 H multiplet, CH=CH). This material is amorphous and was characterized by microanalysis of its crystalline monoacetyl derivative XXXIII.

Dehydrooxoisopyroacetylisotalatizidine (XXXIV). A solution of 22 mg of isopyroacetylisotalatizidine (XXVI) in 0.5 ml of dry pyridine at 0° was added to Sarett reagent prepared from 100 mg of chromic anhydride in 1 ml of dry pyridine at 0°. The mixture was stoppered and placed in the refrigerator freezer for 1.5 days. The solvent was then removed *in vacuo*, and the residue was flashed with benzene, dissolved in 4 ml of 2% sulfuric acid, and saturated with sulfur dioxide. The green solution was extracted well with ether; the combined extracts were dried over sodium sulfate, and the solvent was removed *in vacuo* leaving 5 mg of dehydrooxoisopyroacetylisotalatizidine as an amorphous solid; ν_{max} ($CHCl_3$) 1770–1736 (ketone and OAc) and 1637 cm^{-1} (lactam).

Dehydrooxoisopyroisotalatizidine (XXXV). To 5 mg of dehydrooxoisopyroacetylisotalatizidine (XXXIV) was added ten drops of a 5% solution of sodium hydroxide in methanol, and the solution was stoppered and allowed to stand at room temperature for 2 hr. The solvent was evaporated with a jet of nitrogen, and the residue was triturated with anhydrous ether and filtered. Evaporation of the filtrate left 3 mg of XXXV as an amorphous solid; ν_{max} ($CHCl_3$) 3559 (OH), 1761 (cyclic five-membered ketone), and 1634 cm^{-1} (lactam).

Isopyroacetylcondelphine (XXXIII). To 79 mg of crude isopyroacetylisotalatizidine (XXVI) was added 5 ml of dry pyridine and 5 ml of acetic anhydride, and the solution was stopped and allowed to stand at room temperature for 2 days. The solvent was removed *in vacuo*, and the residue was flashed with benzene until the odor of pyridine was no longer detectable. The residue was dissolved in ether and chromatographed on a column of Woelm neutral alumina (grade 1) eluting with ether and monitoring the fractions by tlc. The fractions which showed only one mobile spot on the tlc plates were combined, and the solvent was removed *in vacuo* yielding 27 mg of a gum which slowly crystallized after standing neat for several days. Recrystallization from petroleum ether gave crystals melting at 106–107°. Isopyroacetylcondelphine decolorized a permanganate solution and produced a yellow color with tetranitromethane; ν_{max} 1730 cm^{-1} (OAc); λ_{max} (neutral solution) 225 mμ (ε 1330), (acidic solution) 210 mμ (ε 800); τ 8.97 (3 H triplet, J = 7 cps, NCH_2CH_3), 8.05 (3 H singlet, $OCOCH_3$), 8.02 (3 H singlet, $OCOCH_3$), 6.93 (2 H singlet, CCH_2OCH_3), 6.85 (3 H singlet, OCH_3), 6.71 (3 H singlet, OCH_3), 5.2 (2 H multiplet, $2CHOAc$), and 4.1 (2 H multiplet, CH=CH).

Anal. Calcd for $C_{27}H_{39}NO_6$: C, 68.47; H, 8.30. Found: C, 69.42, 69.18; H, 8.25, 8.09.

Benzoylcondelphine (XV). To 100 mg of condelphine in 1 ml of dry pyridine was added five drops of freshly distilled benzoyl chloride. The solution was stoppered and allowed to stand at room temperature overnight. The solvent was removed *in vacuo*, and the residue was flashed three times with benzene to remove all traces of pyridine. After dissolving the residue in 4 ml of aqueous sodium carbonate solution it was extracted well with chloroform; the extracts were dried over sodium sulfate, and the solvent was removed *in vacuo*. The orange residue was chromatographed on a 3 × 0.5 in. column of Woelm neutral alumina (grade 1), eluting with 200 ml of chloroform. Removal of the solvent *in vacuo* left 93 mg of benzoylcondelphine as a very pale yellow gum which showed only one spot on tlc with traces of impurities. A highly purified sample of XV was prepared by scraping the spot, which was highly fluorescent on alumina HF in ultraviolet light, off of a 200 × 200 mm tlc plate and extracting the alumina with a 1:1 chloroform–methanol solution. Even in a very pure state the benzoylcondelphine could not be induced to crystallizine; ν_{max} ($CHCl_3$) 3704 (OH), 1742 (OAc), and 1709 cm^{-1} (OBz); τ 8.80 (3 H triplet, J = 7 cps, NCH_2CH_3, perturbed signal), 7.97 (3 H singlet, $OCOCH_3$), 6.90 (2 H singlet, CCH_2OCH_3), 6.86 (3 H singlet, OCH_3), 6.69 (3 H singlet, OCH_3), 5.25 (1 H triplet, J = 4.5 cps, $CHCHOAcCH$), 4.80 (1 H quartet, X proton of an ABX type quartet, J_{AX} = 10 cps, J_{BX} = 7 cps, $CH_2CHOBzC$), and 2.50 and 1.95 (5 H multiplet, C_6H_5COO). Benzoylcondelphine is an unstable gum which slowly decomposes at room temperature. It was characterized by microanalysis of its picrate salt.

Benzoylcondelphine picrate gave the following physical properties: mp 110–111.5°; ν_{max} 1740 (OAc) and 1723 cm^{-1} (OBz); τ 8.58 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.98 (3 H singlet, $OCOCH_3$), 6.80 (3 H singlet, OCH_3), 6.67 (3 H singlet, OCH_3), 6.48 (2 H AB-type doublet, CCH_2OCH_3), 5.2 (1 H unresolved triplet, $CHCHOAcCH$), 4.7 (1 H multiplet, $CH_2CHOBzC$), 2.7 and 2.2 (5 H multiplet, C_6H_5COO), and 1.23 (2 H singlet, $C_6H_2O_7N_3$).

Anal. Calcd for $C_{38}H_{46}N_4O_{14}$: C, 58.30; H, 5.92. Found: C, 57.84; H, 6.30.

Condelphine *p*-Toluenesulfonate (XVI), Condelphine Methanesulfonate (XVII), and Δ^1-Condelphine (XVIII). A. To 50 mg of condelphine (I) in 0.5 ml of pyridine at 0° was added 60 mg of *p*-toluenesulfonyl chloride. The solution was stoppered and left in the refrigerator overnight. The solvent was removed *in vacuo*, and the residue was flashed with benzene, then dissolved in a few milliliters of sodium carbonate solution and extracted well with chloroform. The chloroform extract was washed with water and dried over sodium sulfate and the solvent removed *in vacuo*. The residue was dissolved in ether to separate a red insoluble material and evaporation of the ether left 44 mg of a mixture of XVI and XVIII as indicated by tlc and nmr spectra.

B. To 200 mg of condelphine (I) in 2 ml of pyridine at −10° was added six drops of methanesulfonyl chloride. The solution was stoppered and allowed to stand at −10° for 3.5 hr after which

5 ml of sodium bicarbonate solution was added, and after 10 min the solution was extracted well with chloroform. The extracts were washed once with water, and the washings were in turn extracted with chloroform which was combined with the previous chloroform extracts. After drying over sodium sulfate the chloroform solution, which contained a mixture of XVII and XVIII, was refluxed overnight to complete the elimination of methanesulfonic acid which was then removed by extraction with sodium bicarbonate solution. After drying over sodium sulfate and evaporation of the chloroform *in vacuo*, 194 mg of crude Δ^1-condelphine was obtained. This compound could not be crystallized even after chromatographing on alumina; ν_{max} ($CHCl_3$) 1745 (OAc) and 1653 cm^{-1} (C=C); τ 8.94 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.94 (3 H singlet, $OCOCH_3$), 6.90 (2 H AB-type doublet which is resolved on a 100-Mc instrument into two doublets at 6.97 and 6.83, J = 9 cps, CCH_2OCH_3), 6.75 (3 H singlet, OCH_3), 6.70 (3 H singlet, OCH_3), 5.11 (1 H triplet, J = 4.5 cps, CHCHOAcCH), 4.60 (1 H doublet, J = 9.8 cps, CH=CHC), 4.04 (1 H octet, J_{AB} = 9.8 cps, J_{AX} = 4.2 cps, J_{AY} = 2.6 cps, CH_2CH=CH). Δ^1-Condelphine was characterized by microanalysis of its picrate.

Δ^1-Condelphine picrate, mp 95–98°, showed the following spectrum: ν_{max} 3610 (OH) and 1742 cm^{-1} (OAc).

Anal. Calcd for $C_{31}H_{40}N_4O_{12}$: C, 56.35; H, 6.10. Found: C, 56.45; H, 6.33.

Didehydrodeoxybenzoylisotalatizidine (XXXII). To 50 mg of Δ^1-condelphine (XVIII) in 8 ml of 95% ethanol was added 50 mg of platinum oxide, and the mixture was stirred under 1 atm of hydrogen for 2 hr. The solution was filtered, and the solvent was removed *in vacuo* leaving 50 mg of a gum which slowly crystallized after standing neat for several days. Recrystallization from methanol–ether gave XXX as colorless needles melting at 167.5–170.5° which were saponified without further purification. The infrared spectrum of XXX indicates methanol of crystallization; ν_{max} 3436 (CH_3OH), 1735, and 1745 cm^{-1} (OAc); (in chloroform) 3676 (OH), 3436 (CH_3OH), and 1750 cm^{-1} (OAc); τ 8.87 (3 H triplet, J = 7 cps, NCH_2CH_3), 7.97 (3 H singlet, $OCOCH_3$), 6.95 (2 H singlet, CCH_2OCH_3), 6.77 (3 H singlet, OCH_3), 6.71 (3 H singlet, OCH_3), and 5.15 (1 H triplet, J = 4.5 cps, CHCHOAcCH).

To 181 mg of crude didehydrodeoxycondelphine (XXX) was added 5 ml of methanol and 5 ml of 1 *N* sodium hydroxide solution. After standing at room temperature for 3 hr the solvent was removed *in vacuo*, and the residue was dissolved in 5 ml of water and 5 ml of chloroform. The layers were separated; the aqueous solution was extracted with chloroform, and the combined extracts were washed with water and dried over sodium. The solvent was removed *in vacuo* leaving 161 mg of didehydrodeoxyisotalatizidine (XXXI) as a gum which was benzoylated in its entirely by treating at room temperature with seven drops of benzoyl chloride in 1.5 ml of dry pyridine for 20 hr. The solvent was removed *in vacuo;* the residue was flashed with benzene, then dissolved in ether, and filtered through a short column of neutral alumina. Evaporation of the filtrate left 155 mg of pale yellow foam which was chromatographed on four 200 × 200 mm plates of alumina HF, eluting with ether. The area absorbing strongly under ultraviolet light was divided into thirds, and the alumina was scraped from this area and extracted with 1:1 chloroform–methanol solution. From the uppermost third, 46 mg of pure didehydrodeoxybenzoylisotalatizidine (XXXII) was obtained as a gum which did not crystallize; ν_{max} 3597 (OH) and 1718 cm^{-1} (OBz); τ 8.95 (3 H triplet, J = 7 cps, NCH_2CH_3), 6.93 (2 H singlet, CCH_2OCH_3), 6.78 (3 H singlet, OCH_3), 6.71 (3 H singlet, OCH_3), 4.85 (1 H triplet, J = 4.5 cps, CHCHOBzCH), and 2.7 and 2.2 (5 H multiplet, C_6H_5COO). From the lower two thirds a yield of 67 mg of XXXII was obtained as a gum which was contaminated with 1,10-dibenzoylisotalatizidine.

N-Desethyltalatizidine (XX) and N-Desethylisotalatizidine (XXI). To a solution of 7 mg of N-desethyldidehydrocondelphine (XIX) in 2 ml of methanol and two drops of water was added 50 mg of sodium borohydride. The reaction was allowed to proceed at room temperature for 40 min. The solvent was removed *in vacuo*, and the residue was dissolved in 1 ml of water and extracted with chloroform. The extracts were dried over sodium sulfate and evaporated leaving 6 mg of a mixture of XXXIII and XV as evidenced by tlc and its infrared spectrum.

Talatizidine (XXII) and Isotalatizidine (II) from N-Desethyltalatizidine (XX) and N-Desethylisotalatizidine (XXI). To 5 mg of the mixture of N-desethyltalatizidine (XX) and N-desethylisotalatizidine (XXI) dissolved in 1 ml of ether and 1 ml of methanol was added 30 mg of potassium carbonate and 0.3 ml of ethyl iodide, and the solution was allowed to stir at room temperature for 2 days. The reaction mixture was filtered, and the residue was washed with chloroform which was added to the filtrate. Evaporation of the solvent left 4 mg of a white powder which showed two spots on thin layer chromatography. By comparison of the R_f values of isotalatizidine with those of the mixture in several solvent systems, the more mobile spot was identified as isotalatizidine. The mixture was extracted several times with small portions of cold hexane to dissolve the more soluble isotalatizidine. Two milligrams of the more polar talatizidine (XXII) remained. The crude crystals melted at 209–214° (lit.[8] mp 218–219°).

Talatizidine (XXII) and Isotalatizidine (II) from Dehydrocondelphine. To 8 mg of dehydrocondelphine (XIII) in 1 ml of methanol was added one drop of water and 25 mg of sodium borohydride. After standing overnight at room temperature the solvent was evaporated, and the residue was dissolved in a few drops of water and extracted six times with ether. Evaporation of the ether left 5 mg of a powder which was shown by thin layer chromatography (using benzene–2% methanol, benzene–5% methanol, and benzene–10% ethanol) to be composed of the same mixture of talatizidine and isotalatizidine as was produced by the reaction of XX and XXI with ethyl iodide.

N-Acetate of Dehydroanhydrohydroxydes-N-ethylisotalatizidine (XIV). To 860 mg of isotalatizidine (II) dissolved in 43 ml of acetone was added 2.745 g of potassium permanganate in 305-mg lots over a period of 60 hr. With each addition of permanganate, 3.05 ml of a 10% acetic acid solution in acetone was added. After the reaction was complete, the solution was filtered, and the filtrate was extracted with 5% sulfuric acid. After washing the organic layer with water and drying over sodium sulfate it was evaporated *in vacuo* leaving 481 mg of a white foam. The residue was dissolved in 3–4 ml of acetone and placed in the refrigerator where it crystallized. The 87 mg of crude crystalline material was recrystallized from acetone to yield 51 mg of XIV melting from 107–109°. After two additional recrystallizations from acetone and drying *in vacuo* at 95° for 2 days to remove the acetone of crystallization, 21 mg of an analytical sample was obtained melting at 116–118° (lit.[8] mp 117–119°); ν_{max} 3350, 1757 (five-membered ketone), 1615 (N-Ac), 1005, and 905 (carbinolamine inner ether) (lit.[8] ν_{max} 3360, 1757, 1613, 1000, and 895 cm^{-1}); τ 7.97 (3 H singlet, $NCOCH_3$), 6.74 (2 H singlet, CCH_2OCH_3), 6.66 (6 H singlet, 2 OCH_3), 6.05 (1 H AB-type doublet, CH_2CHOC), and 5.11 (1 H singlet NCHOC).

Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.16; H, 7.48. Found: C, 66.36; H, 7.29.

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