THE OXIDATION OF DITERPENOID ALKALOIDS[1]

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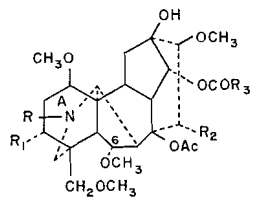
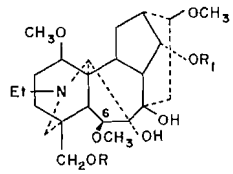
ABSTRACT

The highly oxygenated diterpenoid alkaloids possessing the same C—N ring structure fall into two groups: group A containing the aconitine-like bases in which the C-6 methoxyl is α-oriented, and group B containing the lycoctonine-like bases in which the C-6 methoxyl is β-oriented. The alkaloids of both groups are oxidized rapidly at room temperature by neutral potassium permanganate. The oxidation dealkylates the amino group in the bases of group A giving rise to secondary bases while it converts the bases of group B to the corresponding lactams. The different course of the oxidation from one group to the other is due to the different orientation of the C-6 methoxyl, and can be used to determine the stereochemistry at C-6.

The highly oxygenated diterpenoid alkaloids can be classified into two groups: group A containing the aconitine-like alkaloids I and group B or the lycoctonine-like bases II. The latter contain a ditertiary vicinal glycol and the former do not. More particularly in I the C-6 methoxyl is α whereas in II it is β.



I



II

There has been no method reported of determining the orientation of this group except X-ray crystallography. We now wish to report a method of ascertaining the stereochemistry at C-6 through an oxidation of the bases.

Oxidation of these alkaloids involving the attack of the reagent on the nitrogen is complicated and gives variable results depending on reaction conditions and the structure of the alkaloids. Of the various oxidizing agents tried, potassium permanganate proved the most promising. In the presence of acid, however, the oxidation gave rise to mixtures. The oxidation of aconitine with potassium permanganate in acetone containing acetic acid produced several neutral compounds and from the mixture oxonitine was isolated in 20% yield. Although oxonitine is N-formyl-N-deethylaconitine (1) it was not possible to find N-deethylaconitine among the reaction products. Under identical conditions mesaconitine I (R = Me, $R_1 = R_2 = OH$, $R_3 = C_6H_5$) is oxidized to oxonitine, and delphinine to α-oxodelphinine, which is N-formyl-N-demethyldelphinine I (R = CHO, $R_1 = R_2 = H$, $R_3 = C_6H_5$) and β-oxodelphinine claimed to be delphinine lactam (2).

In contrast, lycoctonine II (R = H; $R_1 = CH_3$) is oxidized under the same acidic

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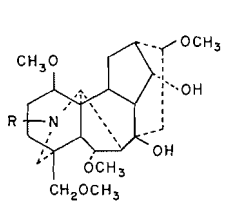
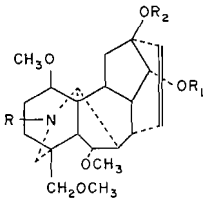
conditions to a mixture of the lactam oxolycoctonine, deoxymethylene oxolycoctonine, and lycoctonamic acid (3). Similarly delpheline and acetylbrowniine are oxidized to oxodelpheline (4) and acetyloxobrowniine (5) respectively. In neither group of alkaloids was the formation of a secondary base observed.

In the absence of acid, however, the course of the oxidation with potassium permanganate was quite different and straightforward. In the course of the work that led to the determination of the structure of chasmanine, $C_{25}H_{41}O_6N$, III (R = Et), it was found that the alkaloid could be smoothly dealkylated when treated at room temperature for



III



IV

5 min with potassium permanganate in acetone–water solution (6). The product no longer showed the signal characteristic of the ethyl group in the n.m.r. spectrum and hence the product is III (R = H). That dealkylation was the only change brought about by the oxidation was shown by reconversion of the product (N-deethylchasmanine) to chasmanine with the aid of ethyl iodide and to the lower homologue, N-methyl-N-deethylchasmanine $C_{24}H_{39}O_6N$, III (R = CH_3) by treatment with methyl iodide.

In connection with an attempted correlation of chasmanine with bikhaconine (6) a derivative of the latter, diacetyldemethoxyisopyrobikhaconine IV (R = Et, $R_1 = R_2 = Ac$) (7), was found to undergo ready dealkylation in good yield when oxidized for 5 min with potassium permanganate in aqueous acetone at room temperature. A single product was obtained, m.p. 200–204°, which was the deethyl derivative IV (R = H, $R_1 = R_2 = Ac$). It still showed signals from the olefinic protons in the n.m.r. spectrum but no longer showed the N-Et signal. On acetylation, the product gave the neutral N-acetyl derivative IV (R = $R_1 = R_2 = Ac$), which, when treated with lithium aluminium hydride, produced demethoxyisopyrobikhaconine IV (R = Et, $R_1 = R_2 = H$). Direct ethylation of the oxidation product gave back the starting material IV (R = Et, $R_1 = R_2 = Ac$). The triacetyl derivative IV (R = $R_1 = R_2 = Ac$), when hydrogenated catalytically and subsequently saponified with methanolic sodium hydroxide, was converted to N-acetyl-N-deethyldihydrodemethoxyisopyrobikhaconine $C_{24}H_{35}O_6N$, showing an N-acetylcarbonyl band at 1 600 cm^{-1} in the infrared. Hence oxidation under the conditions described does not affect any part of the molecule besides removing the N-alkyl group. This interesting result prompted us to examine systematically the diterpenoid alkaloids of group A and group B.

First we studied the effect of the reaction on the alkaloids of group A, related structurally to aconitine and, like chasmanine, bearing an α-methoxyl group at C-6. With these ester alkaloids the reaction was slower and was allowed to proceed for a somewhat longer time. In spite of this the oxidation was not complete and for all except bikhaconitine an appreciable quantity of unchanged starting material was recovered. The predominant product was the N-dealkyl ester alkaloid accompanied by a small quantity of the neutral

TABLE I

Oxidation of ester alkaloids

Alkaloid	mg	Time, min	N-dealkyl base mg	N-dealkyl base %	Recovered starting base mg	Recovered starting base %	Net yield	Neutral compound mg	Neutral compound %	Structural formula of alkaloid
Aconitine	664	10	135	20	450	68	63	78	10	R = Et; $R_1 = R_2 = OH$; $R_3 = C_6H_5$
Aconitine	1950	20	578	30	522	27	40	600	31	
Deoxyaconitine	161	10	75	47	77	48	90	—	—	I, R = Et; $R_1 = H$; $R_2 = OH$; $R_3 = C_6H_5$
Deoxyindaconitine	248	10	92	37	111	45	67	17	7	I, R = Et; $R_1 = R_2 = H$; $R_3 = C_6H_5$
Pseudaconitine	464	10	246	53	136	30	75	32	7	I, R = Et; $R_1 = OH$; $R_2 = H$; $R_3 = C_6H_3(OCH_3)_2$
Indaconitine	430	10	177	41	207	48	80	21	5	I, R = Et; $R_1 = OH$; $R_2 = H$; $R_3 = C_6H_5$
Bikhaconitine	183	10	65	35	101	55	80	2	1	I, R = Et; $R_1 = R_2 = H$; $R_3 = C_6H_3(OCH_3)_2$
Bikhaconitine	540	50	479	89	12	2	91	32	6	
Delphinine	679	10	171	25	351	52	52	24	4	I, R = Me; $R_1 = R_2 = H$; $R_3 = C_6H_5$
Anhydropseudaconitine	568	10	134	24	224	40	40	—	—	

N-dealkyl oxobase (Table I). All the N-dealkyl ester bases prepared except N-demethyldelphinine (identical with N-deethyldeoxyindaconitine, I, R = R_1 = R_2 = H; R_3 = C_6H_5)[3] were amorphous. The lowest yield of N-dealkyl ester base obtained was 40% and the highest was 91%, calculated after subtraction of the recovered unchanged starting material.

The neutral product in each case was the N-deethyl-oxobase. Those obtained in the oxidation of the various ester alkaloids are listed in Table IV (see experimental). The N-deethyl-ester alkaloids obtained in each case as the main product were all smoothly methylated to the corresponding N-methyl derivatives. Thus the N-deethyl derivatives of aconitine (I, R = H; R_1 = R_2 = OH; R_3 = C_6H_5), deoxyaconitine (I, R = R_1 = H; R_2 = OH; R_3 = C_6H_5), and deoxyindaconitine (I, R = R_1 = R_2 = H; R_3 = C_6H_5) yielded respectively mesaconitine, hypaconitine, and delphinine, while the N-deethyl derivatives of pseudaconitine, indaconitine, and bikhaconitine yielded lower homologues which have not yet been reported as occurring in nature (see Table III). The N-methyl bases having properties very similar to those of the corresponding N-ethyl alkaloids are not separable from the latter in thin-layer chromatography, and to obtain them pure it is essential to purify the secondary base before methylation.

The C-3 hydroxyl in ring A seems to have no effect on the course of the oxidation nor on the yield of deethyl base produced. The presence of a double bond in ring A, however, probably because of the half-chair conformation assumed by the ring, complicated the reaction. Oxidation of anhydropseudaconitine, for instance, gave only 64% yield of combined N-deethyl compound and unreacted starting base, while no oxoderivative was present.

TABLE II

Oxidation of alkamines

Alkamine	Wt., mg	Time, min	N-dealkyl base		Recovered starting base		Net yield, %	Neutral product
			mg	%	mg	%		
Chasmanine	245	5	215	94	—	—	94	
Bikhaconine	312	5	208	69	80	25	90	Trace
Pseudaconine	150	5	95	65	45	30	95	Trace
Diacetyl-demethoxy-isopyrobikhaconine	396	5	320	90	Trace	Trace	90	—
Monoacetyl-demethoxy-isopyrobikhaconine	113	5	101	95	—	—	95	Trace

Naturally occurring alkamines of group A and those obtained by saponification of the corresponding ester alkaloids underwent oxidation to the dealkyl base under the same conditions not only more rapidly but more completely in better yield and without the accompanying formation of the oxoderivative (Table II). Owing to their higher solubility in water, however, the products were more difficult to isolate. The dealkyl alkamines also were methylated smoothly to the corresponding N-methyl compounds. In most cases the product was acetylated. Thus bikhaconine gave triacetyldelphonine, and pseudaconine was converted into the new N-methyl-N-deethyl-pseudaconine tetraacetate ($C_{32}H_{47}O_{12}N$).

The bases of group B, which contain a β-C-6 methoxyl were rapidly oxidized by potassium permanganate in aqueous acetone, but with quite different results. With the

[3]*N-Deethyldeoxyindaconitine crystallized readily from ether, although when prepared previously by a different method it could not be induced to crystallize (8).*

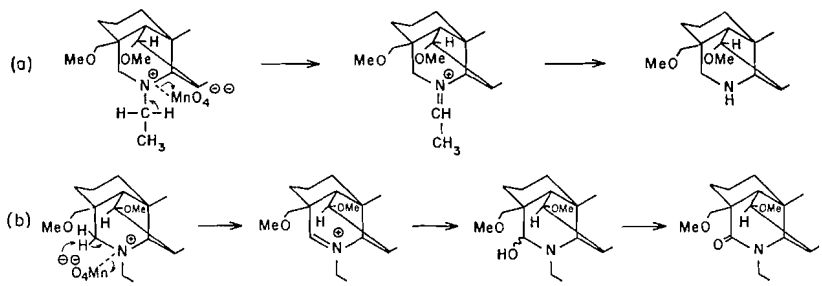
three bases of this group that were oxidized, the main product was the oxoderivative. Lycoctonine (II, R = H; $R_1 = CH_3$) produced oxolycoctonine exclusively. Browniine (II, R = CH_3; R_1 = H) gave mostly oxobrowniine accompanied by 7.5% of deethylbrowniine. Delcosine produced mainly anhydrohydroxydelcosine, a carbinolamine ether, accompanied by 15% of deethyldelcosine. As described already (9) delcosine carries a hydroxyl at C-1 of ring A oriented on the same side of ring A as the nitrogen ring, and readily forms a carbinolamine ether by condensation of this hydroxyl with the carbinolamine hydroxyl initially produced in the oxidation. Hence in the oxidation now described, the formation of anhydrohydroxydelcosine is equivalent to the formation of a lactam, but the reaction is stopped half way by the formation of the stable ether.

The characteristic difference between the alkaloids of group A and those of group B is that the C-6 methoxyl is α in the former and β in the latter. Without exception it has been found that the oxidation product of the group A alkaloids is predominantly the N-dealkyl derivative with the oxoderivative as a minor product, whereas the oxidation product of the group B alkaloids is predominantly the oxoderivative with the dealkyl base as a minor product.

The results obtained show that the ease of oxidation of a highly oxygenated diterpenoid alkaloid possessing the C—N-skeleton I or II to either a dealkyl derivative or to the oxo-base can be taken as an indication of the orientation of the C-6 methoxyl, which must be α in the first case and β when the product is mostly the lactam.

An examination of models shows that when the C-6 methoxyl is α it sterically hinders the vulnerable C-16 methylene group and prevents or restricts its oxidation to a lactamic carbonyl, thus favoring the attack on the imino-ethyl group. In contrast the β-oriented C-6 methoxyl in the alkaloids of group B does not interfere with the C-16 methylene, which is normally oxidized to a lactam carbonyl.

A possible mechanism of the oxidation reaction involves an initial complexing of MnO_4^- with the free pair of electrons on the nitrogen. The presence or absence of steric hindrance then determines the observed specificity of the reaction.



The ring methylene being more reactive is the favored point of attack, but if it is sterically hindered by the α-oriented C-6 methoxyl, as in the alkaloids of group A, the attack is on the ethyl group as in scheme *a* with the resulting elimination of that group. If there is no steric hindrance as in the group B alkaloids in which the C-6 methoxyl is β-oriented, the attack occurs as in scheme *b* and results in the production of the lactam. In the latter case there is a *trans* proton elimination with formation of an anhydronium intermediate which, in the basic medium, is rapidly oxidized, probably via the carbinolamine, to the lactam.

EXPERIMENTAL

Unless otherwise stated Analar acetone was used as a solvent in the oxidations, grade IV Woelm neutral alumina for column chromatography, and Merck's silica gel G as adsorbent and cyclohexane–chloroform–diethylamine as developing solvent for thin-layer chromatography. Infrared spectra were measured in nujol mulls for crystalline substances and in chloroform solution for amorphous compounds. The n.m.r. spectra were all measured on an A-60 instrument in $CDCl_3$ solution with tetramethylsilane as an internal standard. All melting points have been taken on a Kofler hot stage and are uncorrected.

Oxidation of Group A Alkaloids (General Procedure)

Oxidation of Bikhaconitine

Bikhaconitine (I, R = Et; $R_1 = R_2 = H$; $R_3 = C_6H_3(OCH_3)_2$) (183 mg) was dissolved in 80% acetone–water (50 ml) and potassium permanganate (160 mg) in 50% acetone–water (70 ml) was added all at once. The mixture was stirred for 10 min at room temperature and the excess permanganate reduced with sulfurous acid. The acetone was evaporated under reduced pressure and the residual aqueous solution after addition of sodium carbonate was extracted with chloroform. The dried chloroform extract on evaporation left a residue (192 mg) that was dissolved in 1% sulfuric acid (10 ml) and extracted with benzene to remove neutral substances. The aqueous solution was made basic with sodium carbonate and extracted with chloroform. Evaporation of the dried chloroform extract left a foam (180 mg) that was dissolved in benzene and chromatographed on alumina. The chromatogram was eluted first with benzene and then with 50% chloroform benzene. The benzene eluate gave unchanged bikhaconitine (101 mg) while the chloroform–benzene eluate yielded N-deethylbikhaconitine (65 mg), both homogeneous in thin-layer chromatography. The n.m.r. spectrum of the product no longer contained the triplet characteristic of the N-ethyl group. For analyses of N-methyl derivatives, see Table III.

The benzene extract containing the neutral fraction left, on evaporation, a residue that crystallized on contact with ethanol, m.p. 220–222°, wt. 2 mg. This product proved to be N-deethyloxobikhaconitine (cf. Table IV). This lactam becomes the main product of oxidation when the time of reaction is prolonged to 50 min.

Oxidation of Aconitine

Aconitine (1.950 g) in acetone (200 ml) was oxidized at room temperature with potassium permanganate (2.0 g) dissolved in 50% acetone–water (400 ml) for 20 min. The product was treated with 1% sulfuric acid and separated as above into a neutral and a basic fraction. The neutral fraction yielded N-deethyloxoaconitine (600 mg, see below) and the basic fraction gave N-deethylaconitine (578 mg) and unchanged aconitine (522 mg), which were separated by chromatography on alumina.

Oxidation of Anhydropseudaconitine

Anhydropseudaconitine (7) (568 mg) was oxidized with potassium permanganate (616 mg) in 50% acetone–water. The product (598 mg) in thin-layer chromatography showed the presence of two main compounds and five minor ones. The two main compounds were unchanged starting material and N-deethylanhydropseudaconitine. The product was chromatographed in benzene solution on alumina. Elution with benzene gave the unchanged starting material (174 mg) and elution with 20% chloroform–benzene gave a mixture (109 mg) of starting material and the N-deethyl base in which the latter predominated. Further elution with the same solvent yielded pure N-deethyl base (26 mg) as a gum. Final elution with chloroform gave material (80 mg) which included the N-deethyl base and the other minor products of low mobility. In the n.m.r. spectrum N-deethylanhydropseudaconitine produced signals at δ 6.20–5.80 (ethylenic protons), δ 3.91, 3.89 (veratroyl methoxyls), δ 3.54, 3.33, 3.30, 3.17 (four methoxyls), δ 1.33 (O-acetyl), but showed no imino ethyl signals.

N-Deethyl Bases

N-Deethylaconitine (I, R = H; $R_1 = R_2 = OH$; $R_3 = C_6H_5$), N-deethyldeoxyaconitine (I, R = R_1 = H; R_2 = OH; $R_3 = C_6H_5$), N-deethylindaconitine (I, R = R_2 = H; R_1 = OH; $R_3 = C_6H_5$), N-deethylanhydropseudaconitine, N-deethylpseudaconitine (I, R = R_2 = H; R_1 = OH; $R_3 = C_6H_3(OCH_3)_2$) and N-deethylbikhaconitine (I, R = $R_1 = R_2$ = H; $R_3 = C_6H_3(OCH_3)_2$) were amorphous. They all lacked the N-ethyl signal in the n.m.r. spectrum. N-Demethyldelphinine, identical with N-deethyldeoxyindaconitine (I, R = $R_1 = R_2$ = H; $R_3 = C_6H_5$) crystallized from ether as fine colorless needles, m.p. 162–164°. The compound obtained from two different sources also lacked the iminoethyl signal in the n.m.r. spectrum. Gilman and Marion (8), who had previously obtained this substance, reported it to be amorphous.

Methylation of N-Deethyl Bases

The N-deethyl base was refluxed in 50% methanol–ether with excess methyl iodide and powdered potassium carbonate for 1 h. In each case the product was purified by chromatography on alumina. Every one of the N-methyl-N-deethyl bases prepared showed an imino-methyl signal at δ 2.30 in the n.m.r. spectrum. They are listed in Table III together with their analytical figures.

N-Dealkyloxo Bases

The neutral fraction of the product of oxidation of the ester alkaloids mentioned above was in each case the N-dealkyloxo-derivative. It was purified by chromatography over alumina. The crystal forms, melting points, and analytical figures are given in Table IV.

Oxidation of Group A Alkamines

Oxidation of Chasmanine

Chasmanine (245 mg) was dissolved in 80% acetone–water (60 ml) and a solution of potassium permanganate (242 mg) in 50% acetone–water (200 ml) was added. The resulting solution was stirred at room temperature for 5 min and the product worked up as usual. It gave N-deethylchasmanine (215 mg), crystallizing as colorless prisms from chloroform–hexane, m.p. 230–231°.

Anal. Calcd. for $C_{23}H_{37}O_6N$: C, 65.22; H, 8.81. Found: C, 64.71; H, 8.67.

On treatment with ethyl iodide by the method described above, the product gave back chasmanine, while treatment with methyl iodide by the same method yielded N-methyl-N-deethylchasmanine, which separated from *n*-hexane as colorless prisms, m.p. 90–92°. In the n.m.r. spectrum: δ 2.29 ($N\text{-}CH_3$) (6).

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.

Oxidation of Diacetyldemethoxyisopyrobikhaconine

To a stirred solution of the compound (7) (396 mg) in acetone (72 ml) and water (8 ml), potassium permanganate (214 mg) dissolved in acetone (40 ml) was added all at once. After 5 min stirring at room temperature, the excess permanganate was decomposed by the addition of sulfurous acid ($Na_2SO_3 + H_2SO_4$) and the acetone evaporated under reduced pressure below 40°. Extraction of the acid liquor with chloroform removed 5 mg of neutral material which was not further investigated. The solution was made basic with sodium carbonate and extracted with chloroform. Evaporation of the dried extract yielded a colorless gum (440 mg) showing in thin-layer chromatography one strong spot (N-deethyl compound) and two weak spots, one of which corresponded to the starting material.

Crystallization of the product from ether gave N-deethyldiacetyldemethoxyisopyrobikhaconine as fine colorless needles (320 mg) m.p. 200–204°. In the n.m.r. spectrum signals at δ 6.20–5.45 (olefinic protons), δ 3.30, 3.29, 3.21 (three OMe), δ 2.05, 2.01 (two acetyl groups).

Anal. Calcd. for $C_{26}H_{35}O_7N\cdot H_2O$: C, 63.52, H, 7.59. Found: C, 63.83, H, 7.62.

Some of the N-deethyl compound (200 mg) in pyridine (5 ml) and acetic anhydride (2.5 ml) was heated on the steam bath for 4 h. The product of the reaction, a triacetate (200 mg) was a gum that could not be induced to crystallize. In the n.m.r. spectrum signals at δ 6.20–5.40 (olefinic protons), δ 3.29 (6H), 3.19 (3 OMe), δ 2.11, 2.09, 2.03 (three acetyl groups).

Reduction of the triacetate (50 mg) with lithium aluminium hydride in tetrahydrofurane (5 ml) overnight gave a product that was dissolved in benzene and chromatographed on alumina. The chloroform eluate yielded demethoxyisopyrobikhaconine, which crystallized from ether-*n*-hexane as colorless fine needles, m.p. 147–150°, identical with an authentic sample (8).

Some of the triacetate (300 mg) dissolved in ethanol (20 ml) was hydrogenated over platinum oxide (200 mg). The product, worked up as usual, was a colorless gum. It was saponified by refluxing with 3% sodium hydroxide in methanol, the methanol was evaporated, water added, and the solution extracted with chloroform. Evaporation of the extract left N-acetyl-N-deethyldihydrodemethoxyisopyrobikhaconine as a colorless gum (290 mg) which crystallized from methanol–ether as colorless prisms (256 mg), m.p. 242–245°.

Anal. Calcd. for $C_{24}H_{35}O_6N\cdot 0.5H_2O$: C, 65.01; H, 8.13. Found: C, 65.36; H, 8.42.

Oxidation of Bikhaconine

Bikhaconine (312 mg) oxidized with potassium permanganate by the procedure already described gave N-deethylbikhaconine (120 mg) and unchanged starting material (80 mg) separated by chromatography, together with a small quantity of neutral material.

A quantity of N-deethylbikhaconine (90 mg) was methylated with methyl iodide and acetylated. There was obtained a triacetate that crystallized from methanol as colorless prisms (64 mg) m.p. 182–184°.

Anal. Calcd. for $C_{30}H_{45}O_{10}N$: C, 62.16; H, 7.83. Found: C, 61.66, H, 7.41.

The triacetate was identical with triacetyldelphonine, m.p. 182–184°, prepared by hydrolysis and acetylation of delphinine.

Oxidation of Pseudaconine

Pseudaconine (150 mg) was oxidized as above for 5 min and the excess permanganate was reduced with sulfurous acid. After evaporation of the acetone under reduced pressure and extraction with chloroform to remove any neutral product, the solution was made basic with sodium carbonate and extracted for 3 days with chloroform in a liquid–liquid extractor. Evaporation of the extract left N-deethylpseudaconine (140 mg) as a gum. The gummy residue was treated with methyl iodide as described above and the product acetylated. This gave rise to the tetraacetate of N-methyl-N-deethylpseudaconine obtained as colorless prisms from ethanol, m.p. 235°.

Anal. Calcd. for $C_{32}H_{47}O_{12}N$: C, 60.19; H, 7.36. Found: C, 59.61; H, 7.08.

TABLE III

N-Methyl-N-deethyl alkaloids

N-Methyl-N-deethyl derivative of:	Crystal form**	m.p.	Formula	Analysis				Identical with:
				Calcd.		Found		
				% C	% H	% C	% H	
Bikhaconitine*	Needles (*a*)	187–190°	$C_{35}H_{49}O_{11}N$*	63.64	7.43	63.75	7.78	
Bikhaconitine $HClO_4$	Needles (*b*)	200–204°	$B.HClO_4 \cdot H_2O$	53.99	6.69	54.24	6.69	
Aconitine†	Prisms (*c*)	196–198°	$C_{33}H_{45}O_{11}N$†	62.74	7.12	62.50	7.16	Mesaconitine
Deoxyaconitine‡	Prisms (*c*)	184–186°	$C_{33}H_{45}O_{10}N$‡	64.37	7.37	64.57	7.29	Hypaconitine
Indaconitine§	Prisms (*d*)	204–205°	$C_{33}H_{47}O_{10}N$§	64.16	7.67	64.05	7.58	
Pseudaconitine‖	Prisms (*b*)	208–211°	$C_{35}H_{49}O_{12}N.H_2O$	60.61	7.36	60.83	7.41	
Deoxyindaconitine¶	Prisms (*a*)	187–189°	$C_{33}H_{49}O_9N$¶	66.09	7.56	66.30	7.66	Delphinine

*I, R = CH_3; $R_1 = R_2 = H$; $R_3 = C_6H_3(OCH_3)_2$.
†I, R = CH_3; $R_1 = R_2 = OH$; $R_3 = C_6H_6$.
‡I, R = CH_3; $R_1 = H$; $R_2 = OH$; $R_3 = C_6H_5$.
§I, R = CH_3; $R_1 = OH$; $R_2 = H$; $R_3 = C_6H_5$.
‖I, R = CH_3; $R_1 = OH$; $R_2 = H$; $R_3 = C_6H_3(OCH_3)_2$.
¶I, R = CH_3; $R_1 = R_2 = H$; $R_3 = C_6H_3(OCH_3)_2$.
**Crystallized from (*a*) ether, (*b*) ethanol, (*c*) methanol, (*d*) benzene.

TABLE IV

N-Dealkyloxo alkaloids

Compound	Crystal form*	m.p.	Formula	Analysis			
				Calcd.		Found	
				% C	% H	% C	% H
N-Deethyloxoaconitine	Prisms (*a*)	266–267°	$C_{32}H_{41}O_{12}N$	60.28	6.83	60.84	6.54
N-Deethyloxobikhaconitine	Prisms (*b*)	222–223°	$C_{34}H_{45}O_{12}N$				
N-Demethyloxodelphinine N-Deethyloxodeoxyindaconitine	Needles (*c*)	211–212°	$C_{32}H_{41}O_{10}N$	64.09	6.89	64.43	7.42
N-Deethyloxoindaconitine	Prisms (*b*)	273–280°	$C_{32}H_{41}O_{11}N$	62.44	6.83	62.23	7.34
N-Deethyloxopseudaconitine	Needles (*b*)	256–262°	$C_{34}H_{45}O_{11}N$				

*Crystallized from (*a*) chloroform–acetone, (*b*) ethanol, (*c*) acetone.

Oxidation of Group B Alkaloids

Oxidation of Lycoctonine

Lycoctonine (380 mg) was oxidized with potassium permanganate (380 mg) for 4 min under the conditions described above. It yielded a single product (386 mg) which crystallized on standing, m.p. 93–95°, and proved identical in every respect with an authentic sample of oxolycoctonine (3).

Oxidation of Browniine

Browniine (213 mg) liberated from its perchlorate was oxidized with potassium permanganate (220 mg) for 3 min under the conditions already described. The excess permanganate was decomposed with sulfurous acid. After evaporation of the acetone under reduced pressure, the aqueous solution was extracted with chloroform to remove the neutral fraction (170 mg). The aqueous solution was made basic with sodium carbonate and extracted with chloroform. This second chloroform extract yielded the basic fraction (43 mg). The neutral fraction crystallized immediately and after recrystallization from ether was obtained as colorless needles, m.p. 170–171°, identical by melting point, mixture melting point, and infrared spectra with an authentic sample of oxobrowniine (5).

The basic fraction still contained oxobrowniine. On chromatography in benzene solution on alumina and elution with benzene and then chloroform–benzene (1:1), it yielded a further crop of oxobrowniine (27 mg) and amorphous N-deethylbrowniine (16 mg).

N-Deethylbrowniine (76 mg) was methylated with methyl iodide by the method already described and the resulting amorphous N-methyl-N-deethylbrowniine (28 mg) was characterized as its perchlorate, colorless needles from methanol – ethyl acetate, m.p. 215°.

Anal. Calcd. for $C_{24}H_{39}O_7N \cdot HClO_4$: C, 51.99; H, 7.40. Found: C, 51.89; H, 7.28.

Oxidation of Delcosine

Delcosine (212 mg) was oxidized with potassium permanganate (150 mg) for 7 min under the conditions described and the product worked up as usual. By means of chromatography the product was separated into anhydrohydroxydelcosine (165 mg), m.p. 186–188°, unchanged delcosine (15 mg), and N-deethyldelcosine (30 mg), m.p. 240–241° (decomp.). The identity of these compounds was confirmed by direct comparison with authentic specimens (9).

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