NEW SYNTHETIC DERIVATIVES OF ACONITINE, DELPHONINE AND *N*-DEACETYL-LAPPACONITINE

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*Abstract – This paper reports the synthesis and spectral data for 3,13-diacetylaconitine (**3**), 3,13,15-triacetylaconitine (**4**), 3,13-diacetyl-14-benzoylaconine (**7**), aconine pentaacetate (**10**), delphonine methiodide (**11**), 8,9-diacetyllappaconitine (**12**), N-deacetyl-N-methyllappaconitine (**13**), N-deacetyl-N-N-dimethyllappaconitine (**14**), N-deacetyl-N-benzoyllappaconitine (**15**), N-deacetyl-N-o-anisoyllappaconitine (**16**), N-deacetyl-N-p-anisoyllappaconitine (**17**), N-deacetyl-N-(3,4,5,-trimethoxybenzoyl)lappaconitine (**18**), N-deacetyl-N-p-nitrobenzoyllappaconitine (**19**), N-deacetyl-N-triphenylmethyllappaconitine (**20**), and N-deacetyl-N-(3,3-dimethylacryloyl)lappaconitine (**21**).*

Of all the diterpenoid alkaloids, most attention has been given to aconitine (**1**), a reflection of its extremely high toxicity toward mammalian organisms.[1] Dunstan and Carr[2] reported that the diacetylaconitine (the structure was not assigned) was less toxic (by a factor of 40–50) than aconitine. Tulyaganov *et al.*[3] have indicated that aconitine triacetate (structure not assigned) was relatively inactive. Cash and Dunstan[4] reported that the most notable difference in activity of benzoaconine (14-benzoylaconine) compared with aconitine, was a drastic reduction of acute toxicity by a factor of about 300. Diacetylbenzoylaconine and triacetylbenzoylaconine (structures not assigned) were described by Dunstan and Carr[2] as apparently nontoxic in small doses and lacking the ability to produce any tingling of the tongue. Aconine[4] was found to be less toxic than benzoaconine by factor of five to ten. In view of the above results, it seemed worthwhile to synthesize and determine the structures of the various acetates of aconitine and benzoaconine. The following derivatives were prepared: 3-acetylaconitine (**2**), 3,13-diacetylaconitine (**3**), 3,13,15-triacetylaconitine (**4**), 3-acetyl-14-benzoylaconine (**5**), 3,13-diacetyl-14-benzoylaconine (**7**), 15-acetyl-14-benzoylaconine (**8**), 3,15-diacetyl-14-benzoylaconine (**9**), and aconine pentaacetate (**10**).

Recently Jennings *et al.*[5] reported that methyllycaconitine, an ester of lycoctonine, is a far more potent postsynaptic cholinergic agent than aconitine or lycoctonine in an isolated insect nerve system. As an inhibitor of α-bungarotoxin binding to housefly heads, methyllycaconitine showed K_{inh} = 2.5 x 10^{-10}M, whereas aconitine showed K_{inh} = 2.7 x 10^{-4}M and lycoctonine K_{inh} = 3.8 x 10^{-7}M. To study insect mortality and housefly nicotinic receptor activity of analogs and related compounds a series

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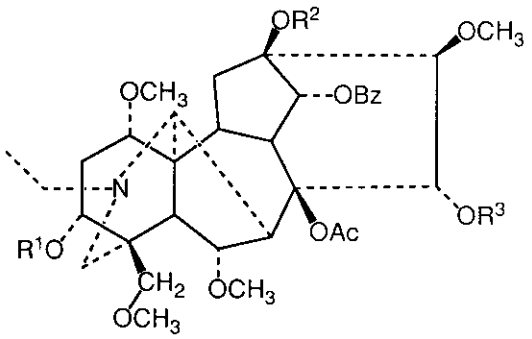
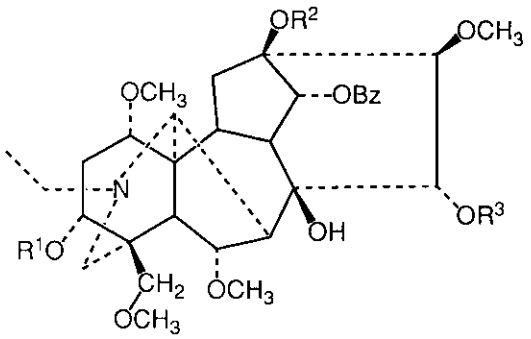
of synthetic derivatives of *N*-deacetyllappaconitine and delphonine was required. In previous publications,[6,7] we reported the physical and spectral properties of twenty-seven new synthetic esters and ethers of delphisine, neoline, delphinine and lycoctonine. This paper records the synthesis and spectral properties of fifteen new derivatives of aconitine, delphonine and *N*-deacetyllappaconitine.



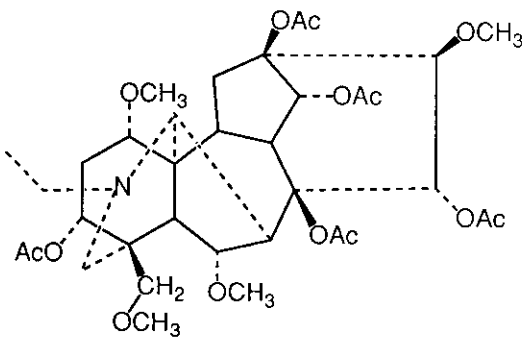
1 $R^1 = R^2 = R^3 = H$
2 $R^1 = Ac$; $R^2 = R^3 = H$
3 $R^1 = R^2 = Ac$; $R^3 = H$
4 $R^1 = R^2 = R^3 = Ac$



5 $R^1 = R^2 = R^3 = H$
6 $R^1 = Ac$; $R^2 = R^3 = H$
7 $R^1 = R^2 = Ac$; $R^3 = H$
8 $R^1 = R^2 = H$; $R^3 = Ac$
9 $R^1 = R^3 = Ac$; $R^2 = H$

Acetylation of aconitine (**1**) with acetic anhydride and pyridine affords 3-acetylaconitine (**2**) [90% yield],[8] while acetylation of **1** with acetyl chloride at room temperature yields 3,13-diacetylaconitine (**3**) [74% yield] and 3,13,15-triacetylaconitine (**4**) [27% yield]. Separately heating **2** and **3** under reflux for 1 h with dioxane and water yields 3-acetyl-14-benzoylaconine (**6**) [89.1% yield] and 3,13-diacetyl-14-benzoylaconine (**7**) [86.7% yield], respectivley.

Acetylation of 14-benzoylaconine (**5**) with acetic anhydride at room temperature for 6 h yields 15-acetyl-14-benzoylaconine (**8**) [74.5 % yield],[9] whereas acetylation for 24 h furnishes 3,15-diacetyl-14-benzoylaconine (**9**) [83.5% yield]. Aconine pentaacetate (**10**) was prepared by direct acetylation of aconine with acetyl chloride.



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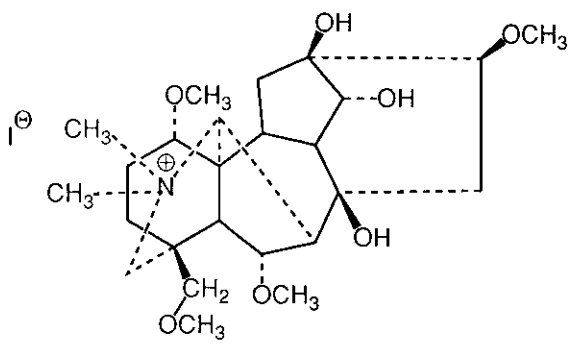

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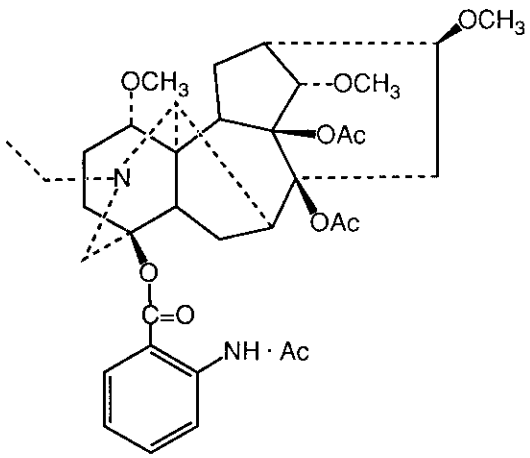
Delphonine methiodide (**11**) was prepared by heating delphonine with CH_3I in a sealed tube at 100°C for 3 h [91.7% yield]. Repeating the same process on *N*-deacetyllappaconitine, instead of giving the corresponding methiodide, afforded *N*-deacetyl-*N*-methyllappaconitine (**13**) [28.1% yield] and *N*-deacetyl-*N,N*-dimethyllappaconitine (**14**) [65.6% yield].

The esters of *N*-deacetyllappacontine were prepared by treatment of *N*-deacetyllappaconitine with the appropriate acid chloride.



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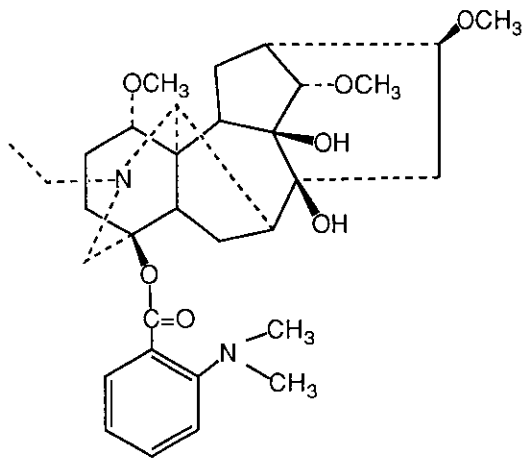

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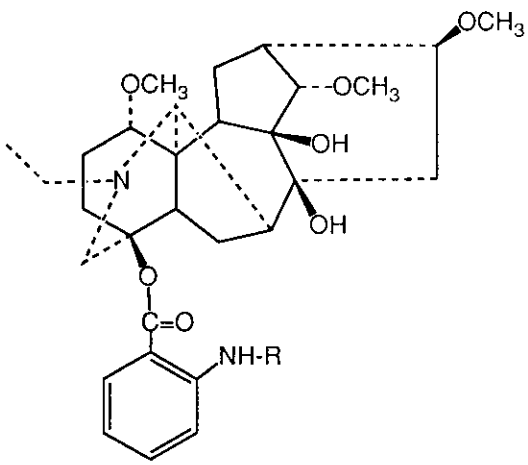


13 R = CH_3
15 R = $CO.C_6H_5$
16 R = $CO.C_6H_4$ -2-OCH_3
17 R = $CO.C_6H_4$ -4-OCH_3
18 R = $CO.C_6H_2$ -3,4,5-$(OCH_3)_3$
19 R = $CO.C_6H_4$-4-NO_2
20 R = $CO.C$-$(C_6H_5)_3$
21 R = $CO.CH{=}C(CH_3)_2$

Table 1. ^{13}C Nmr Chemical Shifts and Assignments for New Aconitine Derivatives

Carbon	3	4	7	10	Carbon	3	4	7	10
1	81.6	81.5	81.5	81.4	1'	56.0	56.1	56.1	56.0
2	31.7	31.8	32.0	31.9	6'	58.2	58.7	58.5	58.7
3	71.4	71.4	71.8	71.3	16'	60.3	61.3	60.8	60.9
4	42.2 s	42.2 s	42.4 s	42.2 s	18'	58.6	58.7	58.7	58.7
5	45.7	45.7	45.8	45.5	CO	172.2 s	172.4 s	170.4 s	170.7 s
6	83.6	83.3	84.1	83.8	CH_3	21.1	21.1	21.2	21.1
7	45.2	45.2	45.5	45.0	CO	170.2 s	172.4 s	170.2 s	170.2 s
8	91.7 s	88.8 s	78.7 s	88.9 s	CH_3	21.1	21.1	21.2	21.1
9	43.1	43.9	44.2	43.7	CO	170.0 s	169.7 s	–	170.2 s
10	41.3	41.3	42.2	41.1	CH_3	21.1	21.1	–	22.0
11	49.7 s	49.9 s	50.2 s	49.8 s	CO	–	168.8	–	169.6 s
12	36.1	35.9	36.6	36.0	CH_3	–	21.1	–	21.1
13	81.0 s	81.1 s	81.8 s	80.8 s	CO	–	–	–	168.4 s
14	79.5	78.9	79.3	81.0	CH_3	–	–	–	21.1
15	79.1	83.7	83.0	78.2	C(14)-O-	C	C	C	–
16	87.1	88.8	87.8	88.2	CO	166.1 s	166.2 s	166.0 s	–
17	60.3	60.4	60.4	60.3	1"	129.7 s	129.6 s	129.8 s	–
18	77.1	76.8	77.5	76.3	2",6"	129.7	130.0	129.9	–
19	47.0	47.1	47.6	47.0	3",5"	128.5	128.7	128.3	–
N-CH_2	48.9	48.9	49.2	48.8	4"	133.2	133.4	133.1	–
CH_3	13.3	13.6	13.4	13.5					

See Table 2 for meaning of C.

EXPERIMENTAL

General – Melting points are corrected. Spectra were recorded on the following instruments: ir: Perkin-Elmer model 1420; ^1H nmr: Bruker WM 300; ^{13}C nmr: JEOL FT model FX-60; and ms: Finnegan Quadrupole model 4023. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter. Chromatographic separations were carried out using vacuum liquid chromatography (VLC)[10] and on a "Chromatotron"[11] with a rotor of 1 mm thickness coated with aluminium oxide (EM 1104-3) or silica gel (EM 7741).

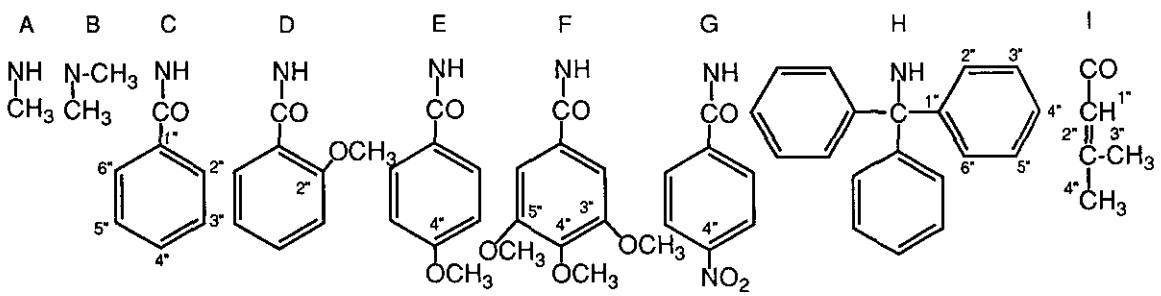
Crystalline Merck "Aconitine" (lot 30619) was chromatographed (VLC) on alumina column to get pure aconitine (**1**) (mp 202.5–204.5°, 87.8% yield).[10] 14-Benzoylaconine (**5**) was prepared by heating aconitine under reflux for 1 h in aqueous dioxane (1:1) (88.7% yield). Delphonine was prepared from delphinine by alkaline hydrolysis with 5% methanolic KOH solution. Delphinine was isolated from the seeds of *Delphinium staphisagria* L.[12,13] *N*-Deacetyllappaconitine was isolated from the roots of *Aconitum septentrionale* Koelle. The 80% ethanol extract of *A. septentrionale* was

Table 2. ^{13}C Nmr Chemical Shifts and Assignments for *N*-deacetyllappaconitine Derivatives

Carbon	13	14	15	16	17	18	19	20	21
1	84.4	84.5	84.1	84.2	83.9	84.1	83.9	84.5	84.1
2	26.2	26.2	26.2	26.2	26.2	26.2	26.1	26.2	26.2
3	32.0	31.6	31.8	32.0	31.9	31.7	31.6	31.9	31.4
4	82.8 s	82.8 s	84.7 s	83.9 s	84.5 s	84.9 s	85.1 s	82.8 s	84.4 s
5	49.9	49.8	49.8	49.9	49.8	49.9	49.7	49.8	49.8
6	26.8	26.8	26.8	26.9	26.8	26.8	26.6	26.8	26.8
7	47.6	47.6	47.6	47.6	47.6	47.6	47.6	47.6	47.6
8	75.6 s	75.6 s	75.6 s	75.6 s	75.3 s	75.6 s	75.3 s	75.6 s	75.4 s
9	78.6 s	78.6 s	78.6 s	78.6 s	78.4 s	78.6 s	78.4 s	78.6 s	78.5 s
10	48.8	48.6	48.9	49.0	48.7	48.9	48.7	49.0	48.9
11	50.9 s	50.9 s	51.0 s	50.9 s	50.8 s	50.9 s	50.9 s	50.9 s	50.9 s
12	24.1	24.2	24.1	24.1	24.2	24.1	24.0	24.1	24.0
13	36.4	36.4	36.3	36.4	36.1	36.3	36.1	36.3	36.3
14	90.1	90.2	90.1	90.1	89.9	90.1	89.9	90.1	90.1
15	44.8	44.8	44.7	44.8	44.8	44.8	44.4	44.8	44.6
16	83.0	82.9	82.9	83.0	83.0	82.9	82.7	82.9	82.8
17	61.6	61.7	61.4	61.5	61.2	61.6	61.1	64.0	61.3
18	–	–	–	–	–	–	–	–	–
19	55.7	55.6	55.5	55.7	55.2	55.6	55.3	55.6	55.4
N-CH_2	49.0	49.1	48.6	48.5	48.2	48.6	48.1	48.7	48.5
CH_3	13.5	13.5	13.5	13.5	13.4	13.4	13.4	13.6	13.4
1'	56.5	56.5	56.5	56.5	56.3	56.3	56.3	56.5	56.4
14'	57.9	57.9	57.9	57.9	57.7	57.9	57.6	58.0	57.8
16'	56.1	56.1	56.1	56.1	55.9	56.1	55.9	56.1	56.0
CO	168.1 s	167.1 s	167.7 s	166.6 s	167.6 s	168.1 s	167.6 s	168.0 s	167.4 s
1'	114.3 s	122.3 s	116.3 s	117.7 s	116.0 s	116.0 s	116.2 s	112.6 s	115.7 s
R 2'	152.1 s	152.1 s	141.9 s	141.4 s	142.0 s	142.0 s	141.1 s	149.8 s	142.1 s
3'	110.9	116.7	120.4	120.9	120.1	120.0	120.1	114.9	120.1
4'	134.4	131.8	134.4	133.8	134.2	134.6	134.4	132.7	134.1
5'	110.6	118.5	122.6	122.4	122.1	122.5	123.1	117.0	121.9
6'	131.9	131.1	131.2	131.0	131.0	131.2	131.2	131.5	131.0

R	A	B	C	D	E	F	G	H	I
	29.5	43.6	165.9 s	164.5 s	165.1 s	165.2 s	163.1 s	71.0 s	165.4 s
1"	–	–	134.9 s	122.9 s	127.0 s	130.1 s	140.1 s	145.3 s	119.6
2"	–	–	128.8	157.5 s	129.2	104.8	123.8	129.1	153.5
3"	–	–	127.4	111.2	113.8	153.2 s	128.4	127.9	27.3[a]
4"	–	–	131.8	132.3	162.4 s	141.1 s	149.5 s	126.7	19.9[a]
5"	–	–	127.4	133.1	113.8	153.2 s	128.4	127.9	–
6"	–	–	128.8	121.8	129.2	104.8	123.8	129.1	–
OCH_3	–	–	–	55.4	55.2	56.1	–	–	–

[a] The assignments may be interchanged in any vertical column.



passed over DOWEX 50 W x 8, H^+; then the column was basified with 10% NH_4OH solution and the resin was extracted with CH_2Cl_2. The crude alkaloidal fraction was again purified through an acid-base extraction procedure and fractionated on a VLC column to get *N*-deacetyllappaconitine (mp 122–123°C).

Preparation of 3,13-diacetylaconitine (**3**) and 3,13,15-triacetylaconitine (**4**): – Ten ml of acetyl chloride was added to 200 mg of aconitine and kept at room temperature for 3 days. Usual work-up and subsequent purification on a Chromatotron (Al_2O_3) furnished 148 mg of **3** (mp 156–158°C, from ether-hexane) and 48 mg of **4** (mp 209.5–211.5°C, from ether) with characteristics as listed below.

3,13-Diacetylaconitine (**3**): – $[\alpha]^{26}$ +13.6° (c, 0.4, $CHCl_3$); ir (nujol): 3500 cm^{-1} (OH), 1740, 1725 cm^{-1} (CO); ^1H nmr ($CDCl_3$): δ 1.11 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 1.36 (3H *s*, C(8)-$OCOCH_3$), 2.05 and 2.07 (3H each, *s*, 2 X $OCOCH_3$), 3.20 (6H, *s*, 2 X OCH_3), 3.24, 3.59 (3H each, *s*, 2 X OCH_3), 5.10 (1H, *d*, J = 4.5 Hz, C(14)-β-*H*), 7.43–8.10 (5H, *m*, aromatic protons); for ^{13}C nmr data see Table 1; mass m/z: 729 (M^+, $C_{38}H_{51}NO_{13}$, 0.2), 714(0.4), 699(22), 671(12.3), 639(43), 610(13), 578(18), 105(65), 77(15), 43(100).

3,13,15-Triacetylaconitine (**4**): – $[\alpha]^{27}$ +6.7° (c, 0.6, $CHCl_3$); ir (nujol): no absorption band for OH groups, 1730, 1715 cm^{-1} (CO); ^1H nmr ($CDCl_3$): δ 1.18 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 1.25 (3H, *s*, C(8)-$OCOCH_3$), 2.07, 2.08, and 2.15 (3H each, *s*, 3 X $OCOCH_3$), 3.2 (6H, *s*, 2 X OCH_3), 3.25, 3.42 (3H each, *s*, 2 X OCH_3), 5.12 (1H, *d*, J = 4.5 Hz, C(14)-β-*H*), 7.43–8.20 (5H, *m*, aromatic protons); for ^{13}C nmr data see Table 1; mass m/z: 771 (M^+, $C_{40}H_{53}NO_{14}$, 0.3), 756(0.5), 741(37), 713(32), 681(13), 105(47), 77(11), 43 (100).

Preparation of 3,13-diacetyl-14-benzoylaconine (**7**): – A mixture of **3** (60 mg), dioxane (2 ml) and water (2 ml) was heated under reflux for 1 h. The solvent was distilled and 20 ml of ice water was added to the residue. The mixture was rendered alkaline with 1% aqueous ammonia (6 ml) and extracted with CH_2Cl_2 (3 x 10 ml each). The CH_2Cl_2 extract was evaporated and the residue (56 mg) was purified on a Chromatotron (Al_2O_3, hexane: ether 60:40 and 50:50) to afford 52 mg of **7**; mp 277–280°C (from $CHCl_3$-hexane); $[\alpha]^{25}$ +4.9° (c, 0.82, $CHCl_3$); ir (nujol): 3480–3440 cm^{-1} (OH), 1740, 1710 cm^{-1} (CO); ^1H nmr ($CDCl_3$): δ 1.11 (3H, *t*, J = 7.1 Hz, *N*-CH_2-CH_3), 2.02 and 2.08 (3H each, *s*, 2 X $OCOCH_3$), 3.23, 3.25, 3.33, 3.56 (3H each, *s*, 4 X OCH_3), 4.91 (1H, *dd*, J = 6.1 and 12.9 Hz, C(3)-*H*), 5.31 (1H, *d*, J = 5.1 Hz, C(14)-β-*H*), 7.43 (2H, *dt*, J = 8 and 1.5 Hz, H-3' and H-5'), 7.55 (1H, *m*, H-4'), 8.05 (2H, *dd*, J = 8 and 1.5 Hz, H-2' and H-6'); for ^{13}C nmr data see Table 1; mass m/z: 687 (M^+, $C_{36}H_{49}NO_{12}$, 0.24), 672 (1.3), 656(13.3), 629(13.8), 596(19.3), 105(59.7), 58(10.6), 45(20.7), 43(100).

Preparation of aconine pentaacetate (**10**): – Three ml of acetyl chloride was added to 90 mg of aconine•HCl and kept at room temperature for two days. Usual work-up and subsequent purification on a Chromatotron (Al_2O_3, hexane:ether 60:40) furnished 64.5 mg of **10**, mp 244–246°C (from ether-hexane) [Lit.,[14] 248–249°C]; $[\alpha]^{28}$ -30.7° (*c*, 0.77, $CHCl_3$) [Lit.,[13] -31.0° ($CHCl_3$)]; ir (nujol): 1760 and 1742 cm^{-1} (CO); ^1H nmr ($CDCl_3$): δ 1.14 (3H, *t*, J = 7.1 Hz, *N*-CH_2-CH_3), 1.94, 2.05, 2.06, 2.13, 2.14 (3H each, *s*, 5 X $OCOCH_3$), 3.19, 3.21, 3.25, 3.33 (3H each, *s*, 4 X OCH_3), 4.88 (2H, *m*, H-

3 and H-14), 5.83 (1H, *d*, J = 6.4 Hz, H-5); for ^{13}C nmr data see Table 1; mass m/z: 709 (M^+, $C_{35}H_{51}NO_{14}$, 0.1), 678(12.9), 651(14.7), 618(4.3), 558(1.8), 43(100).

Preparation of delphonine methiodide (**11**): – A solution of delphonine (85 mg) in excess methyl iodide (3 ml) was heated in a sealed tube at 100°C for 3 h. A resin of the methiodide separated. After removal of excess methyl iodide, the resin was dissolved in methanol. The iodine was removed from the solution with excess silver oxide. The filtrate was evaporated and the residue (107 mg) was purified twice on a Chromatotron (silica, $CHCl_3$: ethanol 85:15 and 75:25) to afford 78 mg of **11**; $[\alpha]^{25}$ +5.8° (*c*, 0.8, $CHCl_3$); ir (nujol): 3300–3500 cm^{-1} (OH); ^1H nmr ($CDCl_3$); δ 3.22, 3.28, 3.35, 3.42 (3H each, *s*, 4 X OCH_3), 3.53 and 4.00 (3H each, *s*, two methyl groups attached to quaternary nitrogen); mass m/z: 454(2.4), 452(2.5), 438(2.4), 436(4.3), 424(4.7), 423(100), 142(37.6), 127(20.6), 85(18.6), 82(21.9), 71(30.1), 45(98.7); ^{13}C nmr ($CDCl_3$): 82.9(C-1), 24.2(C-2), 34.0(C-3), 40.7 s (C-4), 48.5(C-5), 79.9(C-6), 50.8(C-7), 71.5(C-8), 50.4(C-9), 39.0(C-10), 50.8 s (C-11), 34.3(C-12), 76.1 s (C-13), 77.1(C-14), 38.7(C-15), 80.6(C-16), 61.2(C-17), 77.3(C-18), 54.3(C-19), 56.2 (OCH_3 at C-1), 58.0 (OCH_3 at C-6), 57.2 (OCH_3 at C-16), 59.1 (OCH_3 at C-18), 45.9 and 46.8 ($N\text{-}(CH_3)_2$).

Preparation of 8,9-diacetyllappaconitine (**12**): – Five ml of acetyl chloride was added to 100 mg of lappaconitine and the mixture was kept at room temperature for 3 days. Usual work-up and subsequent purification on a Chromatotron (Al_2O_3, hexane:ether 60:40) furnished 96 mg of **12**; $[\alpha]^{26}$ +30.5° (*c*, 0.55, $CHCl_3$); ir (nujol): 1740, 1736, 1705, 1682 cm^{-1} (CO), 1600, 1588, 1520, 1505 cm^{-1} (C=C); ^1H nmr ($CDCl_3$): δ 1.11 (3H, *t*, J = 7 Hz, $N\text{-}CH_2\text{-}CH_3$), 2.01, 2.11, 2.20 (3H each, *s*, 3 X $OCOCH_3$), 3.26, 3.30, 3.39 (3H each, *s*, 3 X OCH_3), 7.04 and 7.50 (1H each, *dt*, J = 8 and 1.3 Hz, Ar-$H_{4'}$ and $H_{5'}$), 7.84 and 8.65 (1H each, *dd*, J = 8 and 1.3 Hz, Ar- $H_{3'}$ and $H_{6'}$), 11.02 (1H, *s*, NH); mass m/z 668 (M^+, $C_{36}H_{48}N_2O_{10}$, 0.02), 638(1.1), 609(0.23), 491(14.7), 489(14.1), 474(4.3), 178(8), 162(5), 120(6.5), 71(15.6), 43(100); ^{13}C nmr ($CDCl_3$); 83.5(C-1), 26.1(C-2), 31.8(C-3), 84.7 s (C-4), 47.6(C-5), 26.7(C-6), 43.0(C-7), 84.5 s (C-8), 88.9 s (C-9), 37.6(C-10), 50.5 s (C-11), 22.9(C-12), 45.7(C-13), 82.1(C-14), 40.2(C-15), 81.1(C-16), 60.4(C-17), 55.4(C-19), 48.7 and 13.3 ($N\text{-}CH_2\text{-}CH_3$), 56.3 ($OCH_3$ at C-1), 57.4 (OCH_3 at C-14), 56.3 (OCH_3 at C-16), 170.1 s and 23.4 ($CO\text{-}CH_3$), 168.8 s and 22.4 ($CO\text{-}CH_3$), 167.1 s (CO), 115.7 s (C-1'), 141.6 s (C-2'), 120.3 (C-3'), 134.3 (C-4'), 122.2 (C-5'), 130.6 (C-6'), 169.2 and 25.3 ($NH\text{-}CO\text{-}CH_3$).

Conversion of *N*-deacetyllappaconitine to *N*-deacetyl-*N*-benzoyllappaconitine (**15**), *N*-deacetyl-*N*-*o*-anisoyllappaconitine (**16**), *N*-deacetyl-*N*-*p*-anisoyllappaconitine (**17**), *N*-deacetyl-*N*-(3,4,5-trimethoxybenzoyl)lappaconitine (**18**), *N*-deacetyl-*N*-*p*-nitrobenzoyllappaconitine (**19**), *N*-deacetyl-*N*-triphenylmethyllappaconitine (**20**) and *N*-deacetyl-*N*-(3,3-dimethylacryloyl)lappaconitine (**21**): – To 100 mg of *N*-deacetyllappaconitine in 10 ml of dry benzene was added 1 ml of *o*-anisoyl chloride and 0.5 ml of pyridine and the solution was kept at room temperature for 20 h. Ice water (20 ml) was added and the reaction was rendered alkaline with solid $NaHCO_3$. The mixture was extracted with 3 x 30 ml of $CHCl_3$. The $CHCl_3$ extracts were evaporated and the residue was purified on an alumina rotor of a Chromatotron (hexene:ether 50:50) to afford 122 mg of **16**; mp 182–184°C (from ether); $[\alpha]^{26}$ +19.7° (*c*, 0.42, $CHCl_3$); ir (nujol): 3450 cm^{-1} (OH), 1710, 1700, 1660 cm^{-1} (CO), 1600,

1580, 1515, 1505 cm^{-1} (C=C); ^{1}H nmr ($CDCl_3$): δ 1.11 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 3.30, 3.31, 3.41, 4.04 (3H each, *s*, 4 X OCH_3), 7.00–8.93 (8H, *m*, aromatic protons), 11.51 (1H, *s*, NH); for ^{13}C nmr data see Table 2; mass m/z: 676 (M^+, $C_{38}H_{48}N_2O_9$, 0.01), 645(0.5), 406(6.6), 405(35), 390(32), 374(18.1), 360(10.8), 345(32.6), 178(8.3), 135(100), 120(6.9), 108(6), 92(10.4), 77(28), 71(18.2), 43(27).

The above procedure using the corresponding acid chloride in each case was used to prepare **15** (122 mg), **17** (121 mg), **18** (82.5 mg), **19** (107 mg), **20** (82 mg), and **21** (74 mg) with characteristics as listed below.

N-Deacetyl-*N*-benzoyllappaconitine (**15**): – $[\alpha]^{26}$ +14.6° (c, 0.82, $CHCl_3$); ir (nujol): 1673, 1660 cm^{-1} (CO), 1605, 1585, 1530, 1520 cm^{-1} (C=C); ^{1}H nmr ($CDCl_3$): δ 1.12 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 3.29, 3.30, 3.39 (3H each, *s*, 3 X OCH_3), 7.04–8.99 (9H, *m*, aromatic protons), 11.67 (1H, *s*, NH); for ^{13}C nmr data see Table 2; mass m/z: 646 (M^+, $C_{37}H_{46}N_2O_8$, 0.02), 616(0.22), 615(1.1), 406(3.8), 405(18.7), 390(18.2), 345(17.5), 178(9.4), 105(100), 77(53), 71(22.5), 58(15.7), 41(19.9).

N-Deacetyl-*N*-*p*-anisoyllappaconitine (**17**): – $[\alpha]^{22}$ +13.7° (*c*, 1.57, $CHCl_3$); ir (nujol): 3480, 3300, 3250 cm^{-1} (OH), 1680, 1670 cm^{-1} (CO), 1603, 1585, 1530, 1505 cm^{-1} (C=C); ^{1}H nmr ($CDCl_3$): δ 1.07 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 3.21, 3.23, 3.35, 3.78 (3H each, *s*, 4 X OCH_3), 6.95 and 7.93 (2H each, *d*, J = 9 Hz, four aromatic protons in *p*-anisoyl moiety), 6.97 and 7.47 (1H each, *dt*, J = 1.3 and 8 Hz, Ar-$H_{4'}$ and $H_{5'}$), 7.91 and 8.80 (1H each, *d*, J = 8 Hz, Ar-$H_{3'}$ and $H_{6'}$), 11.82 (1H, *s*, NH); for ^{13}C nmr data see Table 2; mass m/z: 676 (M^+, $C_{38}H_{48}N_2O_9$, 0.01), 646(0.7), 406(4.9), 405(25.1), 390(23.2), 374(13.3), 345(13.3), 176(5.4), 178(8.3), 135(100), 107(10.6), 77(24.7), 41(25).

N-Deacetyl-*N*-(3,4,5-trimethoxybenzoyl)lappaconitine (**18**): – mp 160–162°C (from ether-hexane); $[\alpha]^{26}$ +18.2° (*c*, 0.49, $CHCl_3$); ir (nujol): 1685, 1670 cm^{-1} (CO), 1610, 1588, 1535, 1505 cm^{-1} (C=C); ^{1}H nmr ($CDCl_3$): δ 1.10 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 3.30, 3.31, 3.41, 3.92 (3H each, *s*, 4 X OCH_3), 3.96 (6H, *s*, 2 X OCH_3), 7.10 and 7.57 (1H each, *dt*, J = 1.3 and 8 Hz, Ar-$H_{4'}$ and $H_{5'}$), 7.30 (2H, *s*, ar-$H_{2''}$ and $H_{6''}$), 7.98 and 8.85 (1H each, *dd*, J = 1.3 and 8 Hz, Ar-$H_{3'}$ and $H_{6'}$), 11.59 (1H, *s*, NH); for ^{13}C nmr data see Table 2; mass m/z: 405 (M^+ -HOOC-C_6H_4NH-C_6H_2 $(OCH_3)_2$, 7.9), 390(6.6), 375(1.6), 374(3.7), 345(7.7), 195(40.7), 146(5.1), 71(23.6), 57(29.5), 55(40.5), 45(36.2), 44(100), 43(78.5), 41(70.5).

N-Deacetyl-*N*-*p*-nitrobenzoyllappaconitine (**19**): – $[\alpha]^{24}$ +19.7° (*c*, 0.3, $CHCl_3$); ir (nujol): 3500, 3240 cm^{-1} (OH), 1685, 1677 cm^{-1} (CO), 1525 cm^{-1} (N-O); ^{1}H nmr ($CDCl_3$): δ 1.13 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 3.30, 3.31, 3.42 (3H each, *s*, 3 X OCH_3), 7.13 and 7.59 (1H each, *dt*, J = 1.3 and 8 Hz, Ar-$H_{4'}$ and $H_{5'}$), 8.02 and 8.88 (1H each, *dd*, J = 1.3 and 8 Hz, Ar-$H_{3'}$ and $H_{6'}$), 8.21 and 8.40 (2H each, *dd*, J = 1.5 and 9 Hz, four aromatic protons in *p*-nitrobenzoyl moiety); for ^{13}C nmr data see Table 2; mass m/z: 691 (M^+, $C_{37}H_{45}N_3O_{10}$, 0.01), 662(0.4), 660(3.4), 406(6.9), 405(M^+-HOOC-C_6H_4-NH-CO-C_6H_4-NO_2, 35.3), 392(24.2), 390(36.3), 374(24.4), 345(28.8), 178(20.9), 150(100), 120(44.6), 119(69.1), 104(68.4), 92(47.1), 76(61.7), 71(87.1), 58(56.9), 44(80.4), 41(96.2).

N-Deacetyl-*N*-triphenylmethyllappaconitine (**20**): – mp 256–258°C (from ether); $[\alpha]^{22}$ +14.2° (c, 0.33, $CHCl_3$); ir (nujol): 3465, 3330 cm^{-1} (OH), 1775 cm^{-1} (CO), 1577, 1512, 1503 cm^{-1} (C=C); ^1H nmr ($CDCl_3$): δ 1.20 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 3.38, 3.40, 3.50 (3H each, *s*, 3 X OCH_3), 6.22 and 7.88 (1H each, *dd*, J = 1.5 and 8 Hz, Ar-$H_{3'}$ and $H_{6'}$), 6.51 and 6.91 (1H each, *dt*, J = 1.5 and 8 Hz, ar-$H_{4'}$ and $H_{5'}$), 7.29–7.50 (15H, *m*, aromatic protons in triphenylmethyl moiety); for ^{13}C nmr data see Table 2; mass m/z: 541 (M^+ -C-$(C_6H_5)_3$, 0.23), 422(0.78), 406(M^+- $^{\Theta}$OOC-C_6H_4-NH-C-$(C_6H_5)_3$, 11.7), 405 (M^+ -HOOC-C_6H_4-NH-C-$(C_6H_5)_3$, 62.2), 390(46), 374(24.9), 345(42), 244(17.9), 243(100), 165(98.6), 120(40.7), 119(28.4), 92(20), 71(51.6), 58(36.8), 43(48.2), 41(53.7).

N-Deacetyl-*N*-(3,3-dimethylacryloyl)lappaconitine (**21**): – $[\alpha]^{24}$ +16.2° (c, 0.65, $CHCl_3$); ir (nujol): 3500, 3300, 3260 cm^{-1} (OH), 1695, 1680 cm^{-1} (CO), 1640, 1605, 1585 (C=C); ^1H nmr ($CDCl_3$): δ 1.13 (3H, *t*, J = 7 Hz, *N*-CH_2-CH_3), 1.92 and 2.33 (3H each, *s*, CH=C•$(CH_3)_2$), 3.30, 3.31, 3.41 (3H each, *s*, 3 X OCH_3), 5.80 (1H, *s*, CO-CH=C), 7.00 and 7.49 (1H each, *dt*, J = 1.3 and 8 Hz, ar-$H_{4'}$ and $H_{5'}$), 7.92 and 8.77 (1H each, *dd*, J = 1.3 and 8 Hz, Ar-$H_{3'}$ and $H_{6'}$), 10.98 (1H, *s*, NH); for ^{13}C nmr data see Table 2; mass m/z: 623 (M^+ -H, 0.1), 593(0.7), 406(3.7), 405(M^+ -HOOC-C_6H_4-NH-CO-CH=C $(CH_3)_2$, 19.5), 390(17.2), 345(18.3), 178(9.3), 83(100), 71(20.1), 55(51.1), 44(26.1).

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