SYNTHETIC ESTERS AND ETHERS OF DELPHININE AND LYCOCTONINE

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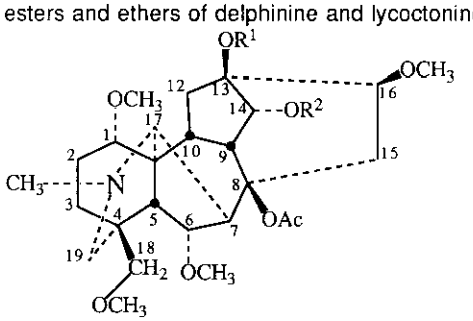
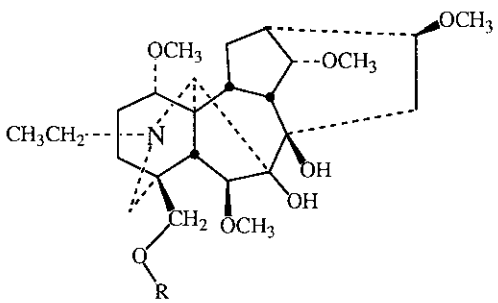
*Abstract – This paper reports the synthesis and spectral data for 8,13,14-triacetyldelphonine (**1**), 13-benzoyldelphinine (**2**), 13-O-methyldelphinine (**3**), 18-p-anisoyllycoctonine (**4**), 18-o-anisoyllycoctonine (**5**), 18-p-nitrobenzoyllycoctonine (**6**), 18-(3,4,5-trimethoxybenzoyl)lycoctonine (**7**), 18-stearoyllycoctonine (**8**), 18-lauroyllycoctonine (**9**), 18-linoleoyllycoctonine (**10**), lycoctonine 18-O-p-phenylbenzyl ether (**11**), and lycoctonine 18-O-ethyl ether (**12**).*

Recently Jennings, Brown and Wright have shown that a principal insecticidal toxin in the seeds a *Delphinium* hybrid, cv "Pacific Giant, King Arthur" is methyllycaconitine.[1] This compound is a very potent inhibitor of α–bungarotoxin binding to housefly heads (K_{inh} = 2.5 x 10^{-10} ± 0.5 x 10^{-10} M). To study insect mortality and housefly nicotinic receptor inhibition activity of analogs and related compounds a series of synthetic esters and ethers of delphisine, neoline, delphinine, and lycoctonine was required. In a previous publication,[2] we reported the physical and spectral properties of fifteen new synthetic esters of delphisine and neoline. This paper records the synthesis and the physical, nmr and mass spectral data of twelve new esters and ethers of delphinine and lycoctonine.



1 $R^1 = R^2 = COCH_3$
2 $R^1 = R^2 = COC_6H_5$
3 $R^1 = CH_3$, $R^2 = COC_6H_5$



4 $R = COC_6H_4$-4-OCH_3
5 $R = COC_6H_4$-2-OCH_3
6 $R = COC_6H_4$-4-NO_2
7 $R = COC_6H_2$-3,4,5-$(OCH_3)_3$
8 $R = CO(CH_2)_{16}$-CH_3
9 $R = CO(CH_2)_{10}$-CH_3
10 $R = CO(CH_2)_7$-CH=(Z)CH-CH_2-CH=(Z)CH-$(CH_2)_4$-CH_3
11 $R = CH_2C_6H_4$-4-C_6H_4
12 $R = CH_2CH_3$

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Table 1. ^{13}C Nmr Chemical Shifts and Assignments for Delphinine Esters and Ethers

Carbon	1	2	3	Carbon	1	2	3
1	84.6	82.4	85.1	13'	-	-	52.3
2	26.4	24.0	26.2	16'	58.1	58.7	58.2
3	35.5	34.9	35.0	18'	59.1	59.0	59.1
4	39.2 s	38.7 s	39.4 s	C(8)-OCO	169.5 s	169.7 s	169.9 s
5	48.2	48.6	48.9	CH_3	21.3	21.3	21.5
6	83.4	82.4	82.9	C(13)-OCO	170.1[a] s	-	-
7	48.0	44.9	48.4	CH_3	21.2[b]	-	-
8	85.7 s	84.7 s	85.3 s	C(14)-OCO	170.9[a] s	-	-
9	41.6	40.5	41.3	CH_3	22.4[b]	-	-
10	43.7	44.1	45.3	C(13)-O-	-	B	-
11	50.5 s	50.7 s	50.4 s	CO	-	169.7 s	-
12	34.7	30.6	34.2	1'	-	129.9 s	-
13	81.7 s	74.7 s	79.9 s	2',6'	-	127.9	-
14	77.1	78.6	76.8	3',5'	-	129.6	-
15	39.2	39.4	38.9	4'	-	131.7	-
16	80.0	82.1	81.6	C(14)-O-	-	B	B
17	63.2	64.5	63.3	CO	-	166.1 s	166.6 s
18	80.2	79.2	80.3	1'	-	129.9 s	130.4 s
19	56.3	56.8	56.4	2',6'	-	128.5	128.4
N-CH_3	42.4	42.7	42.4	3',5'	-	129.8	130.1
1'	56.1	55.7	56.2	4'	-	133.1	133.0
6'	58.1	58.0	57.8				

a and b The assignments may be interchanged in any vertical column.
See Table 2 for meaning of B.

The esters were prepared by treatment of the alkaloid with the appropriate acid chloride, usually in the presence of *p*-dimethylaminopyridine. 13-*O*-Methyldelphinine was prepared by treatment of delphinine with trimethyloxonium tetrafluoroborate in the presence of a proton sponge. The lycoctonine ethers were prepared by treatment of lycoctonine with an appropriate halide in the presence of sodium hydride.

The ^{13}C nmr data of these new synthetic compounds are given in Tables 1 and 2.

EXPERIMENTAL

General: – Melting points are corrected. For chromatographic separations on a Chromatotron[3] silica gel HF-254 + 366 (EM 7744), basic alumina PF-254, type E (EM 1103) and basic alumina PF-254 + 366, type E (EM 1104-3) were used. Tlc was carried out on silica gel 60 H (EM 7736) and alumina 60 H, basic, type E (EM 1085). Delphinine was isolated from the seeds of *Delphinium staphisagria* L.[4-6] Lycoctonine was prepared from methyllycaconitine by alkaline hydrolysis with 5% methanolic KOH solution. Methyllycaconitine was isolated from the seeds of *Delphinium elatum* L.[7]

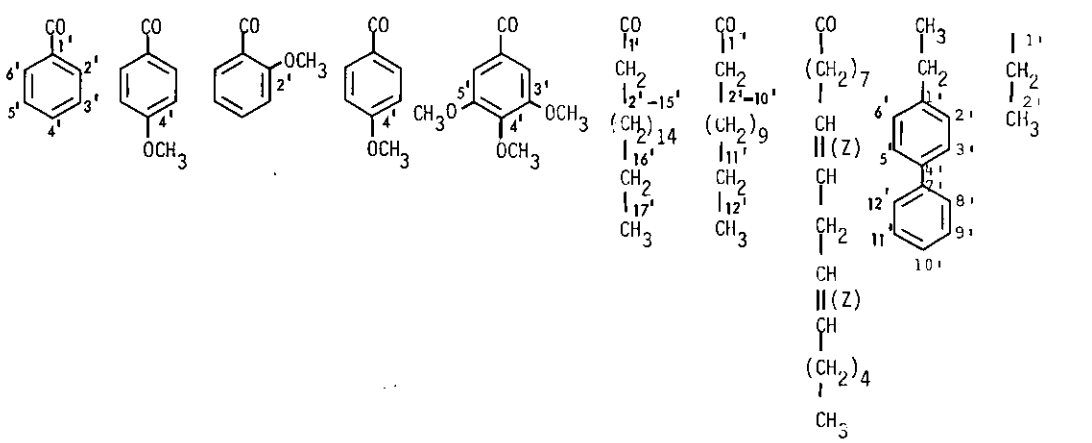
Preparation of Triacetyldelphonine (1): – Five ml of acetyl chloride was added to 40 mg of delphonine (prepared from delphinine by hydrolysis with 5% methanolic KOH solution) and kept at room temperature for 5 days. Usual workup furnished 42 mg of **1**; $[\alpha]^{25}$ - 7.8° (c, 0.45, $CHCl_3$); ir (Nujol): 1740 and 1727 cm^{-1} (CO); ^1H nmr ($CDCl_3$, 90 Mhz): δ 1.94, 202, 2.07 (3H each, s, 3 X $OCOCH_3$), 2.29 (3H, s, N-CH_3), 3.19, 3.21, 3.25, 3.28 (3H each, s, 4 X OCH_3), 4.85 (1H, d, J = 6 Hz, C(14)-β-H); for ^{13}C nmr see Table 1; mass m/z: 579(M^+, $C_{30}H_{45}NO_{10}$, 0.12), 564(0.31), 550(4), 548(22), 520(4), 43(100).

Table 2. ^{13}C Nmr Chemical Shifts and Assignments for Lycoctonine Esters and Ethers

Carbon	4	5	6	7	8	9	10	11	12
1	84.1	84.0	83.9	83.9	83.8	83.9	83.9	84.3	84.4
2	26.2	26.1	26.1	26.1	25.9	26.0	25.9	26.3	26.3
3	32.3	32.0	32.2	32.2	31.8	31.9	31.8	32.6	32.6
4	37.7 s	37.6 s	37.6 s	37.7 s	37.1 s	37.2 s	37.2 s	38.3 s	38.2 s
5	43.4	43.3	43.3	43.4	43.1	43.3	43.2	43.3	43.3
6	91.0	90.9	91.0	91.0	90.7	90.8	90.7	90.7	90.6
7	88.6 s	88.5 s	88.6 s	88.6 s	88.3 s	88.4 s	88.4 s	88.4 s	88.4 s
8	77.6 s	77.5 s	77.4 s	77.5 s	77.3 s	77.1 s	77.3 s	77.6 s	77.5 s
9	50.5	50.5	50.7	50.5	50.2	50.4	50.3	49.8	49.7
10	38.3	38.1	38.1	38.1	37.9	38.0	38.0	38.1	38.2
11	49.1 s	49.1 s	49.1 s	49.1 s	48.8 s	48.9 s	48.9 s	49.0 s	48.9 s
12	28.8	28.7	28.7	28.7	28.8	29.0	28.8	28.8	28.8
13	46.3	46.3	46.1	46.3	46.0	46.1	46.0	46.1	46.1
14	84.1	84.0	83.8	83.9	83.8	83.9	83.9	84.1	84.1
15	33.7	33.6	33.9	33.7	34.1	34.2	34.1	33.6	33.6
16	82.6	82.6	82.6	82.6	82.5	82.6	82.5	82.6	82.6
17	64.5	64.5	64.5	64.5	64.4	64.5	64.5	64.8	64.8
18	69.1	69.4	70.5	69.7	68.8	68.9	68.8	73.2	75.7
19	52.6	52.5	52.4	52.5	52.3	52.4	52.5	52.9	52.9
N-CH_2	51.0	50.9	50.9	50.9	50.8	50.9	50.8	51.1	51.1
CH_3	14.1	14.0	14.0	14.0	14.0	14.0	13.9	14.1	14.2
1'	55.7	55.7	55.7	55.7	55.6	55.7	55.6	55.7	55.7
6'	57.8	57.8	57.8	57.8	57.6	57.7	57.6	57.4	57.2
14'	58.1	58.0	58.2	58.1	57.8	57.7	57.8	57.8	57.8
16'	56.3	56.2	56.3	56.1	56.1	56.3	56.1	56.3	56.3
C(18)-O-	C	D	E	F	G	H	I	J	K
CO	166.1 s	166.2 s	164.4 s	166.0 s					-
1'	122.4 s	119.8 s	135.3 s	124.9 s					66.7
2'	131.6	159.2 s	123.7	107.1					15.0
3'	113.8	112.1	130.6	153.1 s					
4'	163.7	131.6	150.7 s	149.6 s					
5'	113.8	133.7	130.6	153.1 s					
6'	131.6	120.2	123.7	107.1					
OCH_3	55.5	55.7	-	56.3					

^{13}C nmr shifts for R of **8**: 173.4(CO), 31.8(C-1'), 29.2 and 29.5(C-2'–C-15'), 22.6(C-16'), 14.0(C-17').
^{13}C nmr shifts for R of **9**: 173.6(CO), 31.8(C-1'), 29.2 and 29.5(C-2'–C-10'), 22.6(C-11'), 14.0(C-12').
^{13}C nmr shifts for R of **10**: 173.4, 130.1, 129.8, 128.0, 127.7, 31.3, 29.4, 29.0, 27.0, 25.5, 24.8, 22.4, 13.9.
^{13}C nmr shifts for R of **11**: 75.5(CH_2), 127.0 s(C-1'), 128.1(C-2' & 6'), 127.1(C-3', 5', 8' & 12'), 137.1 s (C-4'), 140.7 s (C-7'), 128.8(C-10', 11', 9').

B C D E F G H I J K



Preparation of 13-Benzoyldelphinine (**2**): – One ml of benzoyl chloride was added to 32 mg of delphinine in 5 ml of dry benzene and 0.5 ml of pyridine. The solution was kept at room temperature for one day. Usual work up and subsequent purification on a Chromatotron (silica gel; solvent: gradent with $CHCl_3$–ethanol) furnished 35 mg of **2**; $[\alpha]^{21}$ +12.1° (c, 0.51, $CHCl_3$); ir (Nujol): 1718 cm^{-1} (CO); ^1H nmr ($CDCl_3$, 90 MHz): δ 1.32 (3H, s, $OCOCH_3$), 2.23 (3H, s, *N*-CH_3), 3.18, 3.23, 3.26, 3.53 (3H each, s, 4 X OCH_3), 4.91 (1H, d, J = 6 Hz, C(14)-β-H), 7.30–8.20 (10 H, m); for ^{13}C nmr data see Table 1; mass m/z: 672 (M^+ -31, 0.3), 630(1), 583(5), 570(9), 568(41), 540(4), 508(14), 105(100).

Preparation of 13-*O*-Methyldelphinine (**3**): – To 100 mg of delphinine in 15 ml of CH_2Cl_2 was added 60 mg of proton sponge [1,8-bis(dimethylamino)naphthalene] and 70 mg of trimethyloxonium tetrafluoroborate and the mixture was stirred at room temperature for 5 days. Ice water (30 ml) was added and the reaction was rendered alkaline with solid $NaHCO_3$. The mixture was extracted with 4 x 30 ml of $CHCl_3$. The combined extracts were evaporated and the residue was purified by ptlc (alumina; solvent: hexane–ether 1:1) to give 28 mg of **3**; $[\alpha]^{24}$ +14.8° (c, 0.21, $CHCl_3$); ir (Nujol): 1715 cm^{-1} (CO); ^1H nmr ($CDCl_3$, 90 MHz): δ 1.18 (3H, s, C(8)-$OCOCH_3$), 2.33 (3H, s, *N*-CH_3), 3.13, 3.28, 3.30, 3.40, 3.54 (3H each, s, 5 X OCH_3), 5.11 (1H, d, J = 5.9 Hz, C(14)-β-H), 7.39–8.16 (5H, m); for ^{13}C nmr data see Table 1; mass m/z: 613(M^+, $C_{34}H_{47}NO_9$, 0.2), 585(3), 584(12), 582(51), 553(3), 524(6), 522(24), 508(2), 105(100), 43(64).

Conversion of Lycoctonine to 18-*p*-Anisoyllycoctonine (**4**), 18-*o*-Anisoyllycoctonine (**5**), 18-*p*-Nitrobenzoyllycoctonine (**6**), 18-(3,4,5-trimethoxybenzoyl)lycoctonine (**7**), 18-Stearoyllycoctonine (**8**), 18-Lauroyllycoctonine (**9**), 18-Linoleoyllycoctonine (**10**): – To 35 mg of lycoctonine in 4 ml of pyridine was added 10 mg of *p*-dimethylaminopyridine and 100 mg of *p*-anisoyl chloride and the solution was kept at room temperature for 4 days. Ice water (20 ml) was added and the reaction mixture was rendered alkaline with solid $NaHCO_3$. *The mixture was extracted with 3 x 20 ml of* $CHCl_3$. *The combined extracts were evaporated in vacuo* and the residue (66 mg) was purified by ptlc (alumina; solvent: ether–ethanol 95:5) to give 31.2 mg of **4**; $[\alpha]^{23}$ +55.0° (c, 0.2, $CHCl_3$); ^1H nmr ($CDCl_3$ at 90 MHz): δ 1.06 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 3.25, 3.34, 3.36, 3.41, 3.86 (3H, each s, 5 X OCH_3), 6.94 and 7.97 (2H each, d, J = 9 Hz); for ^{13}C nmr data see Table 2; mass m/z: 601(M^+, $C_{33}H_{47}NO_9$, 1), 587(10), 572(13), 570(46), 135(100).

The same above procedure was carried out (using the corresponding acid chloride in each case, except for **10** where the corresponding anhydride was used) to prepare **5** (27.1 mg), **6**(37.2 mg), **7**(35.5 mg), **8**(60.2 mg), **9**(55 mg), and **10**(42.5 mg) with characteristics as listed below.

18-*o*-Anisoyllycoctonine (**5**): – $[\alpha]^{23}$ +32° (c, 0.34, $CHCl_3$); ^1H nmr ($CDCl_3$): δ 1.03 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 3.18, 3.26, 3.31, 3.33, 3.90 (3H each, s, 5 X OCH_3), 6.73–7.70 (4H, m); for ^{13}C nmr data see Table 2; mass m/z: 601(M^+, $C_{33}H_{47}NO_9$, 1), 586(8), 570(44), 135(100).

18-*p*-Nitrobenzoyllycoctonine (**6**): – $[\alpha]^{25}$ +47.3° (c, 0.22, $CHCl_3$); ^1H nmr ($CDCl_3$): δ 1.03 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 3.25, 3.33, 3.36, 3.41 (3H each, s, 4 X OCH_3), 8.10–8.40 (4H, m); for ^{13}C nmr data see Table 2; mass m/z: 616(M^+, $C_{32}H_{44}N_2O_{10}$, 1), 601(13), 587(14), 585(62), 583(18), 150(35), 40(100).

18-(3,4,5-Trimethoxybenzoyl)lycoctonine (**7**): – $[\alpha]^{24}$ +39.0° (c, 0.32, $CHCl_3$); ^1H nmr ($CDCl_3$): δ 1.06 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 3.26, 3.34, 3.40, 3.41 (3H each, s, 4 X OCH_3), 3.91 (9H, s, 3 X OCH_3), 7.27 (2H, s); for ^{13}C nmr data see Table 2; mass m/z: 661 (M^+, $C_{35}H_{51}NO_{11}$, 1), 646(18), 632(21), 630(88), 628(17), 212(14), 195(100).

18-Stearoyllycoctonine (**8**): – $[\alpha]^{26}$ +30.8° (c, 0.51, $CHCl_3$); ir (Nujol): 3450 cm^{-1} (OH), 1732 cm^{-1} (CO); ^1H nmr ($CDCl_3$), 270 MHz): δ 0.83 (3H, t, J = 7 Hz, $CO(CH_2)_{16}$-CH_3), 0.99 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 1.2 (32 H, s, CH_2 groups), 3.20, 3.28, 3.31, 3.35 (3H each, s, 4 X OCH_3); for ^{13}C nmr data see Table 2; mass m/z: 733 (M^+, $C_{43}H_{75}NO_8$, 1), 718(5), 703(37), 700(6), 43(100).

18-Lauroyllycoctonine (**9**): – $[\alpha]^{26}$ +30.3° (c, 0.45, $CHCl_3$); ir (Nujol): 3460 cm^{-1} (OH), 1740 cm^{-1} (CO); ^1H nmr ($CDCl_3$, 270 MHz): δ 0.88 (3H, t, J = 7 Hz, CO-$(CH_2)_{10}$-CH_3), 1.05 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 1.26 (20 H, s, CH_2 groups), 3.25, 3.34, 3.36, 3.41 (3H each, s, 4 X OCH_3); for ^{13}C nmr data see Table 2; mass m/z: 649 (M^+, $C_{37}H_{63}NO_8$, 1), 634(7), 620(10), 618(32), 616(8), 43(100).

18-Linoleoyllycoctonine (**10**): – $[\alpha]^{26}$ +35.3° (c, 0.78, $CHCl_3$); ir (Nujol): 3460 cm^{-1} (OH), 1740 cm^{-1} (CO); ^1H nmr ($CDCl_3$, 270 MHz): δ 0.86 (3H, t, J = 7 Hz, CH-$(CH_2)_4$-CH_3), 1.02 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 1.28 (18 H, s), 2.98 (4H, s), 3.22, 3.31, 3.34, 3.39 (3H each, s, 4 X OCH_3), 5.32 (2H, d, J = 7 Hz), 6.46 (2H, d, J = 7 Hz); for ^{13}C nmr data see Table 2; mass m/z: 729 (M^+, $C_{43}H_{71}NO_8$, 1), 715(12), 714(4), 700(28), 699(56), 698(17), 95(23), 67(100), 55(82), 54(77), 41(93).

Preparation of Lycoctonine 18-*O*-*p*-Phenyl Benzyl Ether (**11**): – A mixture of lycoctonine (55 mg), NaH (180 mg), 4-(chloromethyl)biphenyl (35 mg) and dioxane (5 ml) was refluxed at 110°C under nitrogen for 18 h. The reaction mixture was filtered through a neutral alumina column (5 g) and the filtrate was evaporated to afford 102 mg of residue which was purified on Chromatotron (alumina; solvent: gradient of hexane–ether) to furnish 38.8 mg of **11**; $[\alpha]^{25}$ +36.0° (c, 0.83, $CHCl_3$); ir (Nujol): 3430 cm^{-1} (OH); ^1H nmr ($CDCl_3$, 270 MHz): δ 0.96 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 3.14, 3.26, 3.30, 3.36 (3H each, s, 4 X OCH_3), 3.78 (1H, s), 4.01 (1H, s), 4.42 (2H, m); 7.27–7.52 (9H, m); for ^{13}C nmr data see Table 2; mass m/z 633 (M^+, $C_{38}H_{51}NO_7$, 1), 619(14), 615(1), 603(68), 600(7), 167(100), 152(7).

Preparation of Lycoctonine 18-*O*-Ethyl Ether (**12**): – A mixture of lycoctonine (60 mg), NaH (105 mg), iodoethane (1 ml) and dioxane (4 ml) was stirred at room temperature for 18 h. The reaction mixture was worked up as above to give 26 mg of **12**; ^1H nmr ($CDCl_3$, 270 MHz): δ 1.03 (3H, t, J = 7 Hz, *N*-CH_2-CH_3), 1.16 (3H, t, J = 7 Hz, –CH_2-CH_3), 3.23, 3.33, 3.40, 3.41 (3H each, s, 4 X OCH_3); mass m/z 495 (M^+, $C_{27}H_{45}NO_4$); for ^{13}C nmr data see Table 2.

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