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NEW SYNTHETIC ESTERS OF DELPHISINE AND NEOLINE

Samir A. Ross† and S. William Pelletier*
Institute for Natural Products Research and the School of Chemical Sciences,
The University of Georgia, Athens, Georgia 30602, USA

Abstract - Delphisine 1-benzoate (3), delphisine 1-(3,4,5-trimethoxybenzoate) (4), delphisine 1-(para-nitrobenzoate) (5), delphisine 1-(ortho-methoxybenzoate) (6), delphisine 1-(para-methoxybenzoate) (7), neoline 1,14-dibenzoate (10), neoline 1,14-dibenzoate-8-acetate (11), neoline 1-(3,4,5-trimethoxybenzoate) (12), neoline 1,14-di(ortho-methoxybenzoate) (13), neoline 1-(3,4,5-trimethoxybenzoate)-14-acetate (14), neoline 1-(para-methoxybenzoate) (15), neoline 1,14-di(para-methoxybenzoate) (16), neoline 1,14-di(3,4,5-trimethoxybenzoate) (17), neoline 1-(para-methoxybenzoate)-14-acetate (18) and neoline 1,14-di(para-nitrobenzoate) (19) are new synthetic esters of delphisine and neoline. The physical and spectral data of these fifteen new compounds are given.

There is a long and fascinating history of the use by various civilizations of species of *Aconitum* and *Delphinium* as sources of poisons and medicinals.[1-6] Various cultures have used *Delphinium* species as pediculicides. Thus both Pliny[1] and Dioscorides[2] noted the effectiveness of crushed seed preparations of the plant *Delphinium staphisagria* L. to kill body lice. *Delphinium* extracts have been employed[1-6] in analgesic balms and also as sedatives, emetics and anthelmintics. The use of *Delphinium* as pediculicides has been shown in a number of cases to be due to diterpenoid alkaloids present in the plant. The pharmacological properties of diterpenoid alkaloids include a broad range of effects, including impairment of the cardiovascular system (hypotension, cardiac arrhythmias), respiratory inhibition, muscular paralysis, and disturbances of the central nervous system.[7]

In connection with another project, a series of synthetic esters of delphisine and neoline was required. This paper records the synthesis and physical and spectral properties of these compounds.

Extraction of the seeds of *D. staphisagria* L., with ligroin yields an alkaloidal fraction of which delphinine[8] is the major component. The mother liquors accumulated during the isolation of a large quantity of delphinine furnished an amorphous fraction from which several alkaloids have been isolated.[9-17] In this paper we report isolation of delphisine (**1**) from that amorphous fraction by adopting a combination of gradient pH separation[18] and vacuum liquid chromatography.[19] Del-

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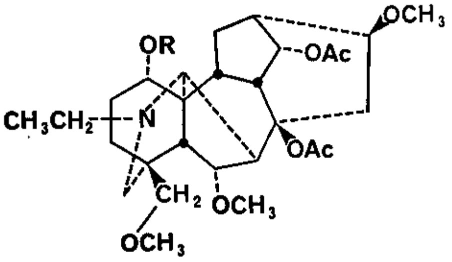
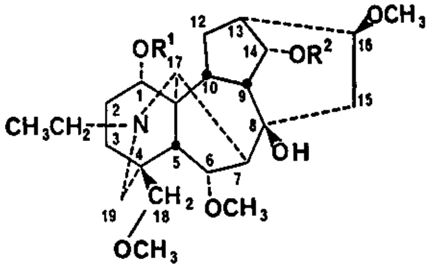
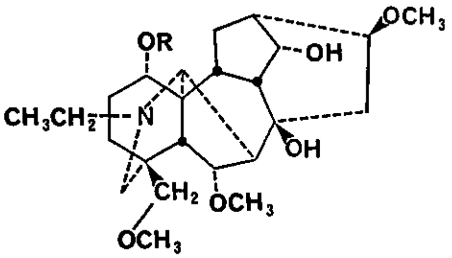
†On leave from the Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt.

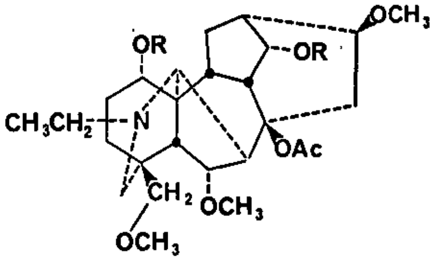




1 R = H
2 R = Ac
3 R = COC_6H_5
4 R = COC_6H_2-3,4,5,$(OCH_3)_3$
5 R = COC_6H_4-4-NO_2
6 R = COC_6H_4-2-OCH_3
7 R = COC_6H_4-4-OCH_3

9 $R^1 = R^2$ = Ac
10 $R^1 = R^2 = COC_6H_5$
13 $R^1 = R^2 = COC_6H_4$-2-OCH_3
14 $R^1 = COC_6H_2$-3,4,5-$(OCH_3)_3$; R^2 = Ac
16 $R^1 = R^2 = COC_6H_4$-4-OCH_3
17 $R^1 = R^2 = COC_6H_2$-3,4,5-$(OCH_3)_3$
18 $R^1 = COC_6H_4$-4-OCH_3; R^2 = Ac
19 $R^1 = R^2 = COC_6H_4$-4-NO_2





8 R = H
12 R = COC_6H_2-3,4,5-$(OCH_3)_3$
15 R = COC_6H_4-4-OCH_3

11 R = COC_6H_5

phisine (**1**) and its hydrolysis product neoline (**8**) were esterified to yield the following new synthetic esters: delphisine 1-benzoate (**3**), delphisine 1-(3,4,5-trimethoxybenzoate) (**4**), delphisine 1-(*para*-nitrobenzoate) (**5**), delphisine 1-(*ortho*-methoxybenzoate) (**6**), delphisine 1-(*para*-methoxybenzoate) (**7**), neoline 1,14-dibenzoate (**10**), neoline 1,14-dibenzoate-8-acetate (**11**), neoline 1-(3,4,5-trimethoxybenzoate) (**12**), neoline 1,14-di(*ortho*-methoxybenzoate) (**13**), neoline 1-(3,4,5-trimethoxybenzoate)-14-acetate (**14**), neoline 1-(*para*-methoxybenzoate) (**15**), neoline 1,14-di(*para*-methoxybenzoate) (**16**), neoline 1,14-di(3,4,5-trimethoxybenzoate) (**17**), neoline 1-(*para*-methoxybenzoate)-14-acetate (**18**) and neoline 1,14-di(*para*-nitrobenzoate) (**19**).

The mps, optical rotations, ir, and ^{13}C nmr data of these new synthetic compounds are given in Tables 1, 2 and 3.

Table 1. Properties of Synthetic Esters

Compound	Melting Point (°C cor.)	Molecular Formula	$[\alpha]_D^{27.5}$ (CHCl$_3$)	IR cm^{-1}		
				OH	C=O	C=C
3	147.5-148.5^{+}	$C_{35}H_{47}NO_9$	zero (c, 0.32)	-	1730, 1708	1597
4	194.5-196.5^{++}	$C_{38}H_{53}NO_{12}$	+4.3 (c, 0.41)	-	1742, 1725, 1702	1583, 1500
5*	Amorphous	$C_{35}H_{46}N_2O_{11}$	+8.1 (c, 0.68)	-	1735, 1727, 1717	1605
6	133-134^{++}	$C_{36}H_{49}NO_{10}$	-1.2 (c, 0.68)	-	1730, 1685	1600, 1580
7	Amorphous	$C_{36}H_{49}NO_{10}$	-1.6 (c, 0.68)	-	1730, 1712, 1705	1603, 1510
10	Amorphous	$C_{38}H_{47}NO_8$	+33.3 (c, 0.35)	3580, 3500	1718, 1712	1600, 1580
11	Amorphous	$C_{40}H_{49}NO_9$	-7.6 (c, 0.43)	-	1730, 1724, 1712	1600, 1583
12	165-167^{+++}	$C_{34}H_{49}NO_{10}$	+12.0 (c, 0.35)	3510	1704	1590, 1505
13	Amorphous	$C_{40}H_{51}NO_{10}$	+33.9 (c, 0.49)	3510	1712, 1697	1600, 1580
14	163-165^{+++}	$C_{36}H_{51}NO_{11}$	+44.3 (c, 0.48)	3500	1740, 1710	1587, 1500
15	Amorphous	$C_{32}H_{45}NO_8$	+13.5 (c, 0.49)	3400-3460	1705	1605, 1510
16	Amorphous	$C_{40}H_{51}NO_{10}$	+30.3 (c, 0.49)	3500	1710, 1705	1605, 1510
17	188.5-190.5^{+++}	$C_{44}H_{59}NO_{44}$	+15.2 (c, 0.29)	3500	1712	1587, 1502
18	Amorphous	$C_{34}H_{47}NO_9$	+49.3 (c, 0.32)	3580	1740, 1710	1605, 1510
19	119-121^{+}	$C_{38}H_{45}N_3O_{12}$	+29.0 (c, 0.57)	3580	1725, 1710	1605

$^{+}$ crystallized from ether; $^{++}$ crystallized from acetone:hexane mixture; $^{+++}$ crystallized from ether:hexane mixture; • the nitro group showed a band at 1526 cm^{-1} in the infrared.

Table 2. ^{13}C NMR Chemical Shifts and Assignments for Delphisine Esters

Carbon	2	3	4	5	6	7
C(1)	77.5	77.7	77.9	78.8	77.3	77.1
C(2)	27.9	28.1	28.1	27.9	27.9	27.9
C(3)	34.4	34.1	34.4	33.6	34.2	34.0
C(4)	38.9 s	38.9 s	38.9 s	38.7 s	38.9 s	38.8 s
C(5)	49.2	49.1	49.1	48.9	48.9	48.8
C(6)	83.4	83.7	83.5	83.3	83.6	83.5
C(7)	49.4	49.1	49.4	49.4	49.2	48.8
C(8)	85.5 s	85.6 s	85.4 s	85.2 s	85.6 s	85.4 s
C(9)	44.2	44.4	44.2	44.2	44.2	44.2
C(10)	38.5	38.4	38.4	38.1	38.3	38.1
C(11)	49.3 s	49.6 s	49.4 s	49.4 s	49.5 s	49.4 s
C(12)	29.4	29.0	29.0	29.1	28.9	28.8
C(13)	44.0	44.1	44.1	43.9	44.1	43.9
C(14)	74.9	75.0	74.9	74.7	75.0	74.9
C(15)	37.6	37.7	37.7	37.6	37.6	37.6
C(16)	83.0	83.3	83.5	83.0	82.9	83.2
C(17)	60.6	61.1	60.8	61.2	61.3	60.9
C(18)	80.0	80.2	80.0	79.9	80.1	80.0
C(19)	54.2	54.3	54.3	54.1	54.1	54.1
N-CH_2	48.5	48.7	48.4	48.5	48.8	48.5
CH_3	13.3	13.6	13.8	13.4	13.4	13.4
C(6)'	58.0	58.1	58.0	58.0	58.0	57.9
C(16)'	56.5	56.5	56.4	56.3	56.3	56.3
C(18)'	59.0	59.1	59.0	58.9	59.1	58.9
C(8)-OC=O	169.4 s	169.5 s	169.4 s	169.3 s	169.4 s	169.3 s
CH_3	22.4	22.4	22.4	22.2	22.4	22.2
C(14)-OC=O	170.7[a] s	170.7 s	170.6 s	170.4 s	170.6	170.4 s
CH_3	21.1[b]	21.2	21.1	20.9	21.1	21.0
C(1)-O-	B	C	D	E	F	G
C=O	170.2[a] s	165.6 s	165.0 s	163.7 s	165.0 s	165.2 s
1'	21.9[b]	131.2 s	126.0 s	136.3 s	120.5 s	123.5 s
2'	-	128.5[a]	106.9	123.5	159.6 s	131.3
3'	-	129.6[a]	153.0 s	130.4	112.3	113.6
4'	-	132.9	142.4 s	150.5 s	131.8	163.3 s
5'	-	129.6[a]	153.0 s	130.4	133.5	113.6
6'	-	128.5[a]	106.9	123.5	120.1	131.3
OCH_3	-	-	56.1	-	55.9	55.3

a and b The assignments may be interchanged in any vertical column.

See Table 3 for meaning of B, C, D, E, F and G.

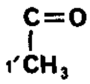
Table 3. ^{13}C NMR Chemical Shifts and Assignments for Neoline Esters

Carbon	9	10	11	12	13	14	15	16	17	18	19
C(1)	77.7	78.1	77.7	78.9	77.1[a]	78.4	78.4	77.6	78.2	77.7	79.3
C(2)	27.5	27.9	27.9	27.6	27.7	27.9	27.6	27.9	28.7	27.9	27.8
C(3)	34.4	34.2	34.0	34.8	34.4	34.6	34.8	34.2	34.7	34.3	34.0
C(4)	39.0 s	39.1 s	38.9 s	39.2 s	39.0 s	39.1 s	39.0 s	39.1 s	39.2 s	39.1 s	39.0 s
C(5)	49.8	49.8	49.1	50.6	49.8	50.1	50.6	49.8	50.0	49.8	49.4
C(6)	82.3	82.8	83.3	82.3	82.6	82.6	82.4	82.8	82.5	82.7	82.6
C(7)	53.5	53.7	49.3	52.5	53.2	53.3	52.6	53.6	52.6	53.3	54.3
C(8)	73.1 s	73.7 s	85.5 s	72.4 s	72.8 s	73.4 s	72.5 s	73.7 s	73.6 s	73.5 s	73.6 s
C(9)	46.7	44.7	44.4	48.5	47.4	46.9	48.7	46.8	46.6	46.9	46.2
C(10)	35.5	36.5	38.5	37.8	36.0	35.7	37.8	36.6	39.2	35.6	36.4
C(11)	49.0 s	49.4 s	49.5 s	49.1 s	49.3 s	49.3 s	49.3 s	49.4 s	49.4 s	49.4 s	49.4 s
C(12)	28.9	28.8	28.7	27.9	28.9	28.9	27.9	28.8	28.7	28.8	28.8
C(13)	43.9	46.7	43.6	45.1	44.1	44.3	45.1	44.7	44.8	44.4	44.5
C(14)	76.3	76.6	75.1	75.0	77.8[a]	76.5	75.2	76.3	76.0	76.7	77.1
C(15)	41.1	41.3	37.8	39.2	40.9	41.4	39.3	41.4	41.0	41.3	41.1
C(16)	81.9	82.2	83.3	82.3	81.9	82.4	82.1	82.2	82.5	82.1	82.0
C(17)	60.8	61.3	61.1	60.8	61.3	60.8	61.3	61.3	60.8	61.1	61.5
C(18)	80.2	80.4	80.0	80.4	80.4	80.4	80.6	80.4	80.2	80.5	80.2
C(19)	54.2	54.4	54.1	54.6	54.3	54.6	54.4	54.4	54.0	54.4	54.3
N-CH_2	48.5	48.7	48.6	48.4	48.7	48.3	48.6	48.7	48.4	48.7	48.8
CH_3	13.4	13.7	13.4	14.0	13.5	13.9	13.9	13.7	13.8	13.7	13.7
C(6)'	57.4	57.8	57.8	57.4	57.4	57.6	57.4	57.6	57.7	57.6	57.7
C(16)'	55.9	55.9	56.4	56.4	55.8	56.1	56.4	55.9	56.1	56.1	56.1
C(18)'	58.9	59.2	59.0	59.2	59.0	59.1	59.2	59.2	59.1	59.1	59.1
C(8)-OC=O	-	-	169.6 s	-	-	-	-	-	-	-	-
CH_3	-	-	21.5	-	-	-	-	-	-	-	-
C(1)-O-	B	C	C	D	F	D	G	G	D	G	E
C=O	170.1 s	165.6 s	165.5 s	165.2 s	165.0 s	165.2 s	165.5 s	165.4 s	165.2 s	165.4 s	163.9 s
1'	21.8	131.3 s	131.1 s	126.2 s	120.5 s	126.2 s	123.8 s	123.8 s	126.1 s	123.7 s	136.4 s
2'	-	128.5	128.4	106.7	159.4 s	107.0	131.4	131.5	106.9	131.4	123.6
3'	-	129.5	129.6	153.0 s	112.1	153.0 s	113.7	113.7	153.1 s	113.7	130.5
4'	-	132.8	132.8	142.2 s	131.6	142.2 s	163.3 s	163.3 s	142.3 s	163.3 s	150.4 s
5'	-	129.5	129.6	153.0 s	133.8	153.0 s	113.7	113.7	153.1 s	113.7	130.5
6'	-	128.5	128.4	106.7	119.9	107.0	131.3	131.5	106.9	131.4	123.6
OCH_3	-	-	-	56.1	55.6	56.1	55.4	55.4	56.1	55.4	-
C(14)-O-	B	C	C	-	F	B	-	G	D	B	E
C=O	170.4 s	166.3 s	166.0 s	-	165.4 s	170.2 s	-	165.4 s	165.7 s	170.2 s	164.5 s
1'	21.0	130.4 s	130.3 s	-	119.1 s	21.2	-	122.7 s	125.3 s	21.2	135.9 s
2'	-	128.5	128.4	-	158.4 s	-	-	131.5	107.1	-	123.5
3'	-	129.5	129.6	-	111.9	-	-	113.7	153.1 s	-	130.7
4'	-	132.8	132.8	-	131.6	-	-	163.3 s	142.3 s	-	150.6 s

Table 3. Continued

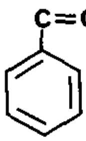
Carbon	9	10	11	12	13	14	15	16	17	18	19
5'	-	129.5	129.6	-	133.1	-	-	113.7	153.1 s	-	130.7
6'	-	128.5	128.4	-	119.9	-	-	131.5	107.1	-	123.5
OCH_3	-	-	-	-	55.6	-	-	55.4	56.1	-	-

a and b The assignments may be interchanged in any vertical column.



$C{=}O$ / $1'CH_3$

B



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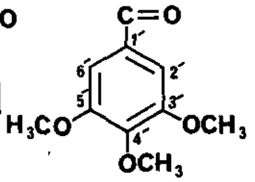

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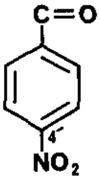

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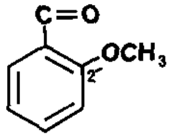

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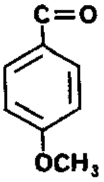

G

EXPERIMENTAL

Melting points are corrected and were taken on a Thomas-Kofler hot stage equipped with a microscope and a polarizer. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter. Infrared spectra were taken on a Perkin-Elmer model 1420 spectrophotometer. ^1H and ^{13}C nmr spectra were recorded on JEOL FT models FX-60 and FX-90Q spectrometers in $CDCl_3$. Mass spectra were determined on a Finnegan *Quadrupole 4023 instrument*. For chromatographic separations on a chromatotron[20,21] rotors were coated with a 1 mm thick layer of aluminum oxide 60 GF-254 neutral (type E, EM reagents, cat. no. 1092); for column, aluminum oxide *neutral, activity* 3 (Woelm, cat. no. 04511) and for vlc[19], silica gel HR (EM reagents, cat. no. 7744).

Isolation of Delphisine (1) from Delphinium Staphisagria — About 41.49 g of the amorphous fraction of the mother liquors of ***Delphinium staphisagria*** was fractionated into 5 groups by gradient pH extraction[18]. *Group* 3 (*pH* 4.5, 8.31g) was chromatographed (vlc)[19] on silica gel. Elution was performed with hexane-$CHCl_3$ in a manner of increasing polarity. Fractions eluted with hexane-$CHCl_3$ (60:40) and hexane-$CHCl_3$ (40:60) were combined (6.54 g), *and crystallized from* acetone-hexane mixture several times to give 5.277 g of delphisine (1), mp 123-125°C. Delphisine was identified by the tlc behavior, mp, mmp, ir, proton and ^{13}C-nmr spectra.

Acetylation of Delphisine (1) — Five ml of a mixture of acetic anhydride and pyridine (1:1) was added to 103.6 mg of 1 and left overnight. *Twenty-five ml of* iced water was added and the reaction mixture was rendered alkaline with $NaHCO_3$. The mixture was extracted with 4 x 25 ml of $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and *evaporated in vacuo* to give 110.0 mg of residue which was crystallized from ether to give 70 mg of delphisine 1-acetate (2), mp 147.5-149.5°C. Delphisine 1-acetate (2) was identified by its tlc behavior *and mp, ir, mass, proton and* ^{13}C-nmr spectra.

Conversion of Delphisine (1) to Delphisine 1-Benzoate (3) — Two ml of benzoyl chloride was added to 100 mg of 1 in 5 ml of pyridine and the solution was kept in refrigerator for 3 days. Thirty-five ml of iced water was added and the reaction mixture was rendered alkaline with $NaHCO_3$. The mixture was extracted with 4 x 30 ml of $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated *in vacuo.* The residue was purified on an alumina rotor of a chromatotron[20,21] to give 66 mg residue which was crystallized from ether to give 45 mg of **3**. For mp, ir, and carbon-13 nmr data see tables 1 and 2; mass: M^+, m/z 625(0.02%), 610(0.1%), 566 (M^+ -59, 1.3%), 504 (M^+ $-OCOC_6H_5$, 38%), 444(20%), 105 (COC_6H_5, 93%), 58(55%), 43(100%); ^{1}H-nmr: δ 1.20 (3H, t, J = 7Hz, $N-CH_2-CH_3$), 1.98 and 2.02 (3H each, s, $OCOCH_3$), 3.21, 3.27 and 3.30 (3H each, s, OCH_3), 7.53-7.05 (5H, m).

Conversion of Delphisine (1) to Delphisine 1-(3,4,5-Trimethoxybenzoate) (4), Delphisine 1-(*para*-Nitrobenzoate) (5), Delphisine 1-(*ortho*-Methoxybenzoate) (6), and Delphisine 1-(*para*-Methoxybenzoate) (7) — Three-hundred mg of 3,4,5-trimethoxybenzoyl chloride and 0.5 ml of pyridine was added to 123 mg of 1 in 5 ml of dry benzene and the solution was stirred at room temperature for 24 h. Then the reaction solution was filtered through a small column of alumina. The filtrate was purified on an alumina rotor of a chromatotron[20,21] to give 138 mg of residue which was crystallized from acetone-hexane mixture to give 126 mg of **4**. For mp, ir, and carbon-13 nmr data see tables 1 and 2; mass: 656 (M^+ -59, 0.1%), 596(0.2%), 504 (M^+ $-OCOC_6H_2(OCH_3)_3$, 10%), 444(10%), 212 (8%), 195 ($COC_6H_2(OCH_3)_3$, 51%), 60(18%), 43(100%); ^{1}H-nmr: δ 1.14 (3H, t, J = 7Hz, $N-CH_2-CH_3$), 1.93 and 1.97 (3H each, s, $OCOCH_3$), 3.15, 3.21 and 3.24 (3H each, s, OCH_3), 3.85 (9H, s, 3 x aromatic-OCH_3), 7.24 (2H,s).

The same above procedure was carried out (using the corresponding acid chloride in each case) to prepare (5) (129 mg), (6) (123 mg), and (7) (129 mg) with characteristics as listed below:

Delphisine 1-(*para*-Nitrobenzoate) (5) — ^{1}H-nmr: δ 1.17 (3H, t, J = 7Hz, $N-CH_2-CH_3$), 1.95 and 1.98 (3H each, s, $OCOCH_3$), 3.17, 3.24 and 3.26 (3H each, s, OCH_3), 7.9-8.52 (4H, m); for ir and ^{13}C nmr data see tables 1 and 2; mass: m/z 611 (M^+ -59, 11%), 579(5%), 551(15%), 504 (M^+ $-OCOC_6H_4NO_2$, 10%), 444(8%), 150(11%), 43(100%).

Delphisine 1-(*ortho*-Methoxybenzoate) (6) — ^{1}H-nmr: δ 1.12 (3H, t, J = 7Hz, $N-CH_2-CH_3$) 1.96 and 2.00 (3H each, s, $OCOCH_3$), 3.19, 3.25, 3.28 and 3.90 (3H each, s, OCH_3), 7.10-7.97 (4H, m); for mp, ir and ^{13}C nmr data see tables 1 and 2; mass: m/z 655 (M^+, 0.01%), 596 (M^+ -59, 1%), 504 (M^+ $-OCOC_6H_4OCH_3$, 33%), 444(15%), 152(4%), 135(100%), 43(99%).

Delphisine 1-(*para*-Methoxybenzoate) (7) — ^{1}H-nmr: δ 1.15 (3H, t, J = 7Hz, $N-CH_2-CH_3$), 1.94 and 1.98 (3H each, s, $OCOCH_3$), 3.18, 3.22, 3.25 and 3.82 (3H each, s, OCH_3), 6.89 and 7.96 (2H each, dd, J = 9Hz, J = 2Hz); for ir and ^{13}C nmr data see tables 1 and 2; mass: m/z 596 (M^+ -59, 0.4%), 504 (M^+ $-OCOC_6H_4OCH_3$, 20%), 444(15%), 152(10%), 135(90%), 58(25%), 43(100%).

Hydrolysis of Delphisine (1) — Hydrolysis of 734 mg of 1 in 5% methanolic KOH solution gave 610 mg of residue which was crystallized from ether to give 578 mg of neoline (**8**), mp 158-160°C. Neoline was identified by tlc behavior and its mp, mmp, ir, proton and ^{13}C-nmr spectra.

Acetylation of Neoline (8) — Five ml of a mixture of acetic anhydride and pyridine (1:1) was added to 90 mg of **8** and left overnight. The reaction was worked up to give 105 mg of a residue which was purified on an alumina rotor of a chromatotron to give 101 mg of neoline 1,14-diacetate (**9**); $[\alpha]^{28}_{D}$ +31.7° (c, 0.61, $CHCl_3$); ir (nujol): 3580-3460 cm^{-1}(OH), 1738 and 1728 cm^{-1} (C=O); ^1H-nmr: δ 1.06 (3H, t, J = 7Hz, $N\text{-}CH_2\text{-}CH_3$), 1.99 and 2.00 (3H each, s, OCH_3), 3.20, 3.26 and 3.29 (3H each, s, OCH_3), 4.10 (1H, dd, J_1 ~ 1Hz, J_2 = 7Hz, C(6)-β-H), 4.75 (1H, dd, J_1 = J_2 = 4.5Hz, C(14)-β-H); mass: m/z 521 (M^+, 0.1%), 506 (M^+ $-CH_3$, 0.4%), 504 (M^+ -OH, 0.3%), 490 (M^+ $-OCH_3$, 0.2%), 463(0.5%), 462(1.7%), 85(28%), 71(36%), 58(68%), 43(100%); for ^{13}C-nmr data see table 3.

Conversion of Neoline (8) to Neoline 1,14-Dibenzoate (10) — One ml of benzoyl chloride was added to 76 mg of **8** in 2 ml of pyridine and the solution was kept in refrigerator for 2 days. The reaction was worked up and the residue was purified on an alumina rotor of a chromatotron[20,21] to give 71 mg of **10**. The ^1H nmr: δ 1.22 (3H, t, J = 7Hz, $N\text{-}CH_2\text{-}CH_3$), 3.09, 3.32 and 3.35 (3H each, s, OCH_3), 7.35-8.13 (10H, m); for ir and carbon-13 nmr data see tables 1 and 3; mass: m/z 630 (M^+ $-CH_3$, 0.02%), 524 (M^+ $-OCOC_6H_5$, 21%), 105(100%), 58(40%), 45(32%).

Acetylation of Neoline 1,14-Dibenzoate (10) — Two ml of acetyl chloride was added to 28 mg of **10** and the resulting solution was stirred at room temperature for 48 h. The mixture was evaporated to dryness *in vacuo*, the residue was treated with 5 ml of Na_2CO_3 solution and then extracted with 3 x 10 ml of $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give 29 mg of neoline 1,14-dibenzoate-8-acetate (**11**); ^1H nmr: δ 1.20 (3H, t, J = 7Hz, $N\text{-}CH_2\text{-}CH_3$), 1.36 (3H, s, $OCOCH_3$), 3.20, 3.26 and 3.28 (3H each, s, OCH_3), 7.35-8.12 (10H, m); for ir and carbon-13 nmr data see tables 1 and 3; mass: m/z 628 (M^+ -59, 0.1%), 566 (M^+ $-OCOC_6H_5$, 3.3%), 506(3.3%), 105(100%), 58(27%), 43(58%).

Reaction of 3,4,5-Trimethoxybenzoyl Chloride with Neoline (8) — Two-hundred mg of 3,4,5-trimethoxybenzoyl chloride and 0.5 ml of pyridine were added to 82 mg of **8** in 10 ml of dry benzene and the solution was stirred at room temperature for 24 h. The reaction was worked up to give 72 mg of neoline 1-(3,4,5-trimethoxybenzoate) (**12**) and 23 mg of neoline 1,14-di(3,4,5-trimethoxybenzoate) (**17**) with characteristics as listed below:

Neoline 1-(3,4,5-Trimethoxybenzoate) (12) — ^1H nmr: δ 1.17 (3H, t, J = 7Hz, $N\text{-}CH_2\text{-}CH_3$), 3.27, 3.30 and 3.31 (3H each, s, OCH_3), 3.88 (6H, s, 2 x aromatic-OCH_3), 3.90 (3H, s, aromatic-OCH_3), 7.27 (2H, s); for mp, ir and carbon-13 nmr data see tables 1 and 3; mass: m/z 420 (M^+ $-OCOC_6H_2(OCH_3)_3$, 48%), 404(5%), 388(4.8%), 212(13%), 195(40%), 71(25%), 58(45%), 45(44%), 43(23%), 40(100%).

Neoline 1,14-Di(3,4,5-trimethoxybenzoate) (17) — ^1H nmr: δ 1.21 (3H, t, J = 7Hz, $N\text{-}CH_2\text{-}CH_3$), 3.16, 3.32 and 3.34 (3H each, s, OCH_3) 3.89 (12H, s, 4 x aromatic-OCH_3), 3.91 (6H, s, 2 x aromatic-OCH_3), 7.31 (4H, s); for mp, ir and carbon-13 nmr data see tables 1 and 3; mass: m/z 614 (M^+ $-OCOC_6H_2(OCH_3)_3$, 2%), 598(0.1%), 212(13%), 195(29%), 71(6%), 44(38%), 43(13%), 40(100%).

Acetylation of Neoline 1-(3,4,5-Trimethoxybenzoate) (12) — Three ml of a mixture of acetic anhydride and pyridine (1:1) was added to 42 mg of **12** and left overnight at room temperature. The reaction mixture was worked up to give 35 mg of neoline 1-(3,4,5-trimethoxybenzoate)-14-acetate (**14**). For mp, ir and carbon-13 nmr data see tables 1 and 3; ^1H nmr: δ 1.17 (3H, t, J = 7Hz, N-CH_2-CH_3), 2.00 (3H, s, $OCOCH_3$), 3.12, 3.29 and 3.33 (3H each, s, OCH_3), 3.88 (9H, s, 3 x aromatic-OCH_3), 7.24 (2H, s); mass: m/z 672 (M^+ -H, 0.02%), 462 (M^+ $-OCOC_6H_2(OCH_3)_3$, 44%), 212(14%), 195(50%), 71(22%), 58(45%), 43(100%), 40(90%).

Conversion of Neoline (**8**) to Neoline 1,14-Di(*ortho*-methoxybenzoate) (**13**) — About 0.3 ml of *ortho*-anisoyl chloride and 0.3 ml of pyridine were added to 60 mg of **8** in 5 ml of dry benzene and the solution was stirred at room temperature for 24 h. Then the reaction solution was worked up to give 31 mg of **13**. For ir and carbon-13 nmr data see tables 1 and 3. ^1H nmr: δ 1.14(3H, t, J = 7Hz, N-CH_2-CH_3), 3.04, 3.32 and 3.39 (3H each, s, OCH_3), 3.89 and 3.91 (3H each, s, aromatic-OCH_3), 6.89-8.08 (8H, m); mass: m/z 554 (M^+ $-OCOC_6H_4OCH_3$, 3.8%), 538(0.2%), 152(3%), 135(70%), 77(20%), 58(13%), 44(37%), 43(14%), 40(100%).

Conversion of Neoline(**8**) to Neoline 1-(*para*-Methoxybenzoate) (**15**) and Neoline 1,14-Di(*para*-methoxybenzoate) (**16**) — About 0.8 ml of *para*-anisoyl chloride and 0.8 ml of pyridine were added to 137 mg of **8** in 15 ml dry benzene and the mixture was stirred at room temperature for 24 h. The mixture was worked up to give 48 mg of **16** and 59 mg of 15 with characteristics as listed below:

Neoline 1-(*para*-Methoxybenzoate) (**15**) — ^1H nmr: δ 1.19 (3H, t, J = 7Hz, N-CH_2-CH_3), 3.27, 3.31 and 3.32 (3H each, s, OCH_3), 3.86 (3H, s, aromatic-OCH_3), 6.92 and 7.96 (2H each, d, J = 9Hz); for ir and carbon-13 nmr data see tables 1 and 3; mass: m/z 570 (M^+ -H, 0.2%), 556 (M^+ $-CH_3$, 0.1%), 420 (M^+ $-OCOC_6H_4OCH_3$, 75%), 404(5%), 152(21%), 135(100%), 107(21%), 77(35%), 71(37%), 58(66%)), 40(68%).

Neoline 1,14-Di(*para*-methoxybenzoate) (**16**) — ^1H nmr: δ 1.21 (3H, t, J = 7Hz, N-CH_2-CH_3), 3.10, 3.32 and 3.35 (3H each, s, OCH_3), 3.83 and 3.86 (3H each, s, aromatic-OCH_3), 6.88, 6.92, 7.95 and 8.00 (2H each, d, J = 9Hz); for ir and carbon-13 nmr data see tables 1 and 3; mass: m/z 554 (M^+ $-OCOC_6H_4OCH_3$, 8%), 152(7%), 135(96%), 107(11%), 77(15%), 58(18%), 44(42%), 40(100%).

Acetylation of Neoline 1-(*para*-Methoxybenzoate) (**15**) — Five ml of a mixture of acetic anhydride and pyridine (1:1) was added to 26 mg of **15** and left overnight. The reaction mixture was worked up to give 26.3 mg residue which was purified on an alumina rotor of a chromatotron to give 23 mg of neoline 1-(*para*-methoxybenzoate)-14-acetate (**18**). For ir and carbon-13 nmr data see tables 1 and 3; ^1H nmr: δ 1.19 (3H, t, J = 7Hz, N-CH_2-CH_3), 2.02 (3H, s, $OCOCH_3$), 3.14, 3.31 and 3.35 (3h each, s, OCH_3), 3.86 (3H, s, aromatic-OCH_3), 6.91 and 7.98 (2H each, d, J = 9Hz); mass: m/z 462 (M^+ $-OCOC_6H_4OCH_3$, 17%), 152(20%), 135 (68%), 107(12.5%), 77(23%), 71(13%), 58(35%), 44(48%), 43 (100%), 40(45%).

Reaction of *para*-Nitrobenzoyl Chloride with Neoline (**8**) — About 0.4 g of *para*-nitrobenzoyl chloride and 0.5 ml of pyridine were added to 100 mg of **8** in 10 ml of dry benzene and the solution was stirred at room temperature for 6 h. Then the reaction solution was worked up to give 129 mg of neoline 1,14-di(*para*-nitrobenzoate) (**19**). For mp, ir and carbon-13 nmr see tables 1 and 3; ^1H nmr: δ 1.17 (3H, t, J = 7Hz, N-CH_2-CH_3), 3.08, 3.28 and 3.30 (3H each, s, OCH_3), 7.9-8.3 (8H, m); mass: m/z 569 (M^+ $-OCOC_6H_4NO_2$, 11.5%), 553(3.5%), 537(3%), 167(5%), 150 (18%), 104(15%), 65(43%), 45(26%), 44(39%), 40(100%).

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