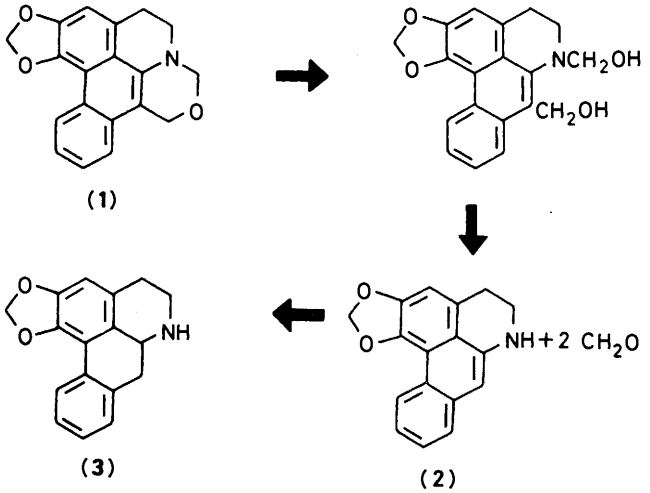
A Biomimetic Synthesis of the Novel 6,7-Oxazine Ring-fused Dehydroaporphine Alkaloid Duguenaine

George R. Lenz* and Francis J. Koszyk
Department of Medicinal Chemistry, Searle Research and Development, Division of G.D. Searle & Co., 4901 Searle Parkway, Skokie, Illinois 60077

A biomimetically patterned synthesis of the novel oxazine-fused dehydronoraporphine alkaloid, duguenaine, which proceeds in three steps from an isoquinoline enamide has been developed. The reactions leading to the natural product are general and yield equivalent structures with more highly substituted dehydronoraporphines.

Approximately three hundred aporphine alkaloids have been isolated and identified from natural sources.[1,2] The vast majority of these have differing substitution patterns on the aromatic ring and degrees of substitution and oxidation of the amino nitrogen. In the last few years, as isolation procedures have improved, new types of aporphines have been discovered. These have included 6a,7-dehydroaporphines, as well as aporphines characterized by hydroxy, methoxy, and even methyl[3] substitution at position 7. Recently, a new type of highly functionalized aporphine, duguenaine (**1**), has been isolated from the bark of *Duguetia calycina* Benoist.[4] This alkaloid contains an oxazine ring fused across the 6,7-positions of a dehydronoraporphine. In this report, we present a biomimetically patterned synthesis of this interesting aporphine, as well as of some related analogues containing higher degrees of substitution.

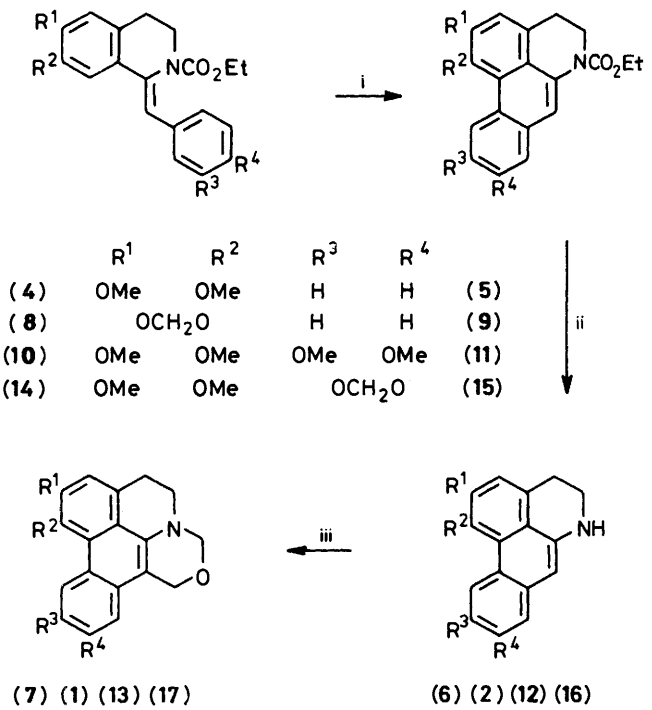


(1) (3) (2)

Scheme 1.

Scheme 1 illustrates a retrosynthetic analysis of duguenaine based on its probable biogenesis. The oxazine ring on the alkaloid may be formed from a bis-methylol precursor. The bis-methylol intermediate is the result of the condensation of the naturally occurring dehydroanonaine (**2**)[5] with two equivalents of formaldehyde at positions 6 and 7 in the presence of the electron-rich aromatic rings. The dehydronoraporphine (**2**) is presumed to arise by dehydrogenation of a suitable noraporphine, in this case anonaine (**3**)[1] Dehydronoraporphines have been observed only rarely in nature, while the dehydroaporphines occur much more frequently. Synthetically, only the unsubstituted parent in the dehydronoraporphines has been reported in the literature,[6] while several methods exist for preparing dehydroaporphines by dehydrogenation of aporphines[7] or total synthesis.[8] The total synthesis requires the reduction of a 6-ethoxycarbonyldehydronoraporphine as the last step. This same intermediate will allow ready access to the dehydronoraporphines by hydrolysis and decarboxylation of the carbamate group, although this has not yet been described. The 6-ethoxycarbonyl compounds are readily prepared by oxidative photocyclization of the enamides derived from dihydroisoquinolines.[9,10]

The bis-formaldehyde substitution on the dehydronoraporphine is the crucial step envisaged in the reaction sequence, requiring positions 6 and 7 to undergo selective electrophilic attack in the presence of other electron-rich aromatic rings. However, dehydroaporphines have been shown to be capable of functioning as weak enamines, thus activating position 7 to electrophilic attack.[11-13] We have taken advantage of these observations and concepts to design a biomimetic synthesis of the alkaloid duguenaine starting from a dihydroisoquinoline as shown in Scheme 2.



	R1	R2	R3	R4	
(4)	OMe	OMe	H	H	(5)
(8)	OCH_2O		H	H	(9)
(10)	OMe	OMe	OMe	OMe	(11)
(14)	OMe	OMe	OCH_2O		(15)

(7) (1) (13) (17) (6) (2) (12) (16)

Scheme 2. *Reagents:* i, *hν*, iodine; ii, potassium hydroxide; iii, aqueous formaldehyde

The dimethoxy-substituted enamide (**4**) was used as a model and is readily available from the reaction of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline with ethyl chloroformate and possesses the *Z*-configuration.[14,15] Irradiation of the enamide (**4**) in a mixture of alcohol and tetrahydrofuran (THF), and in the presence of iodine, generates an *E*–*Z*-mixture wherein the *E*-isomer is converted into the 6-ethoxycarbonyldehydronoraporphine (**5**) in 56% yield. The ethoxycarbonyl group in (**5**) was readily removed by refluxing compound (**5**) in alcoholic potassium hydroxide under an inert atmosphere. Quenching the reaction with aqueous citric acid yielded the dehydronoraporphine (**6**) as beautiful off-yellow flakes in 94% yield. These dehydronoraporphines are stable as solids, but discolour rapidly in solution. The oxazine ring was introduced by treating the dehydronoraporphine (**6**) with aqueous formaldehyde for 24 hours to give a 91% isolated yield of the oxazine-fused dehydronoraporphine (**7**). To prepare duguenaine (**1**) itself, the methylenedioxy enamide (**8**) was photocyclized to 6-ethoxycarbonyldehydroanoaine (**9**) in 56% isolated yield. Subsequent saponification and chromatographic isolation yielded the naturally occurring dehydroanonaine (**2**) in 97% yield.[5] Treatment with formaldehyde then gave a 76% yield of duguenaine (**1**) which possessed all of the reported physical properties of the natural product.[4]

To determine whether the synthesis could be extended to more highly oxygenated aporphine alkaloids, tetra-substituted derivatives were investigated. The tetramethoxy derivative (**10**) and the dimethoxy methylenedioxy enamide (**14**) were oxidatively photocyclized to the 6-ethoxycarbonyldehydronoraporphines (**11**) and (**15**), respectively, in good yield.[9] The indicated 9,10-oxygenation pattern is in keeping with previous observations in the stilbene–phenanthrene photocyclization.[10] Saponification and hydrolysis under the previously described conditions yielded the dehydronoraporphines (**12**) and (**16**). The crucial reaction in this sequence was again the reaction with aqueous formaldehyde. Both compounds gave exclusively the oxazine-fused dehydronoraporphines (**13**) and (**17**), indicating preferential reaction with the enamine nitrogen and carbon atoms as opposed to the alternative electron-rich aromatic rings. The results of these experiments indicate the generality of oxazine ring formation between formaldehyde and a series of dehydronoraporphines which, incidentally, led to a biomimetic synthesis of the novel dehydroaporphine alkaloid, duguenaine (**1**), in good overall yield starting from an isoquinoline enamide.

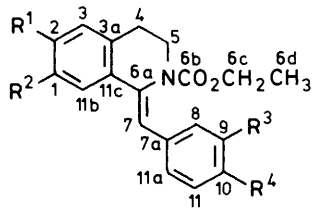
Experimental

General—M.p.s were taken on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. I.r. spectra were recorded in potassium bromide pellets, and u.v.–visible spectra were run in methanol unless otherwise noted. A Varian Associates FT-80 or XL-200 n.m.r. spectrometer was used and the spectra were run in deuteriochloroform using tetramethylsilane as internal standard. Michroanalyses were determined by Searle Laboratories Microanalytical Department under the supervision of Mr. E. Zielinski.

Ethyl 1-*Benzylidene*-6,7-*methylenedioxy*-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (**8**).—A solution of 1-benzyl-6,7-methylenedioxy-3,4-dihydroisoquinoline[16] (20 g, 75 mmol) in chloroform (300 ml) and pyridine (50 ml) was cooled in an ice-bath. Ethyl chloroformate (15 ml) was added dropwise to the stirred solution under nitrogen. After being warmed to room temperature during 6 h, the solution was washed three times with water and dried over anhydrous sodium sulphate. After removal of solvents, the residual oil was dissolved in diethyl ether and scratched to give the *enamide* (**8**) (20 g, 79%), m.p. 136—137.5 °C (Found: C, 71.05; H, 5.6; N, 4.05. $C_{20}H_{19}NO_4$ requires C, 71.20; H, 5.68; N, 4.15%); $\nu_{max.}$ 1 685 cm^{-1}; $\lambda_{max.}$ 228 (ε 22 500 dm^3 mol^{-1} cm^{-1}), 300 (17 200), and 328 nm (19 500); $\lambda_{min.}$ 254 (5 000) and 310 nm (16 500); δ_H 7.25 (6 H, m), 6.71 (1 H, s), 6.57 (1 H, s), 5.92 (2 H, s), 3.75 (4 H, m), 2.87 (2 H. br s), and 0.73 (3 H, br t).

Ethyl 6,7-*Dimethoxy*-1-(3,4-*methylenedioxybenzylidene*)-1,2,3,4-*tetrahydroisoquinoline*-2-*carboxylate* (**14**).—To a solution of 6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)-3,4-dihydroisoquinoline[17] (26.8 g, 82.4 mmol) in dry benzene (400 ml) under nitrogen was added a solution of diethyl pyrocarbonate (13.4 g) in chloroform (50 ml) *via* an addition funnel. After the addition was complete, the solution was stirred for a further 0.5 h and then a few crystals of iodine were added. The solution was refluxed for 45 min to isomerize the *E*–*Z*-isomeric mixture to the *Z*-isomer. The mixture was cooled and washed with dilute aqueous sodium hydrogen sulphite, dried with sodium sulphate, and evaporated to give the crude enamide (**14**). Recrystallization from diethyl ether–methanol gave the *enamide* (**14**) (24.3 g, 74%), m.p. 178—179.5 °C (Found: C, 66.45; H, 5.9; N, 3.3. $C_{22}H_{23}NO_6$ requires C, 66.49; H, 5.83; N, 3.52%); $\nu_{max.}$ 1 690 cm^{-1}; $\lambda_{max.}$ 222 (25 500), 295(sh), 14 000), and 332 nm (25 500); $\lambda_{min.}$ 260 nm (6 000); δ_H 6.5—7.35 (6 H, m), 5.92 (2 H, s), 3.93 (3 H, s), 3.87 (3 H, s), 3.8—4.0 (4 H, m), 2.84 (2 H, br s), and 0.87 (3 H, br s).

Table 1. ^{13}C N.m.r. data (δ/p.p.m.) for the benzylideneisoquinolines[a]

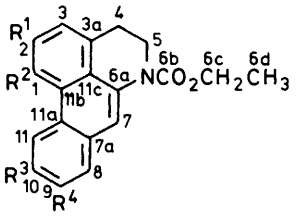


(**4**) $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$
(**8**) $R^1R^2 = OCH_2O$, $R^3 = R^4 = H$
(**10**) $R^1 = R^2 = R^3 = R^4 = OCH_3$
(**14**) $R^1 = R^2 = OCH_3$, $R^3R^4 = OCH_2O$

Carbon	(4)	(8)	(10)	(14)
1	148.0	146.9	148.2	147.7
2	149.6	147.8	149.4	149.1
3	118.8	108.9	111.9	111.6
3a	127.1	129.1	127.4	127.4
4	28.5	28.9	28.5	28.3
5	43.7	43.4	43.7	43.6
6a	133.8	133.8	132.5	132.4
6b	154.3	n.o.	154.6	154.5
6c	61.7	61.6	61.7	61.7
6d	14.0	14.0	14.3	14.1
7	118.1	118.9	118.1	117.9
7a	137.0	136.9	127.4	130.8
8	128.2*	128.2	111.2	108.2
9	128.5*	128.5	148.9*	147.7
10	127.2	127.1	148.4*	146.8
11	n.o.	n.o.	111.2	107.8
11a	n.o.	n.o.	121.5	122.6
11b	106.7	103.6	106.6	106.1
11c	125.5	126.9	123.1	124.5
R^1	56.2	101.2	56.2**	56.0
R^2	55.9		55.9**	55.8
R^3			55.9**	101.0
R^4			56.2**	

[a] Enamide numbering corresponds to aporphine numbering for convenience.
n.o. = signal not observed.
*,** Signal resonances may be interchanged.

Table 2. ^{13}C N.m.r. data for the aporphine esters



(**5**) $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$
(**9**) $R^1R^2 = OCH_2O$, $R^3 = R^4 = H$
(**11**) $R^1 = R^2 = R^3 = R^4 = OCH_3$
(**15**) $R^1 = R^2 = OCH_3$, $R^3R^4 = OCH_2O$

Carbon	(5)	(9)	(11)	(15)
1	146.0	142.4	144.9	145.3
2	151.0	145.2	150.6	150.6
3	112.9	108.7	112.1	112.5
3a	125.9	120.1	125.1	125.6
4	31.1	30.8	31.1	31.3
5	43.3	43.4	43.3	43.4
6a	132.8	132.1*	131.6	131.8
6b	154.8	154.8	154.9	154.9
6c	62.1	62.1	62.0	62.2
6d	14.6	14.6	14.7	14.8
7	118.9	118.1	118.2	119.0
7a	n.o.	133.3*	129.3	129.1
8	125.8	125.5	108.0*	105.5
9	127.8*	127.7	149.3	147.4
10	127.6*	127.7	148.2	147.4
11	126.9*	127.1	108.9*	106.3
11a	128.5	126.3	121.8	123.8
11b	119.9	117.2	119.7	119.8
11c	129.1	n.o.	128.3	129.5
R^1	56.5	101.2	56.5	56.7
R^2	59.9		60.1	60.0
R^3			55.8	101.3
R^4			55.8	

n.o. = signal not observed.
* Signal resonances may be interchanged.

The ^{13}C nuclear magnetic resonance assignments for these compounds are collected in Table 1.

Ethyl 1,2-*Methylenedioxy*-6a,7-*dehydronoraporphine*-6-*carboxylate* (**9**).—A solution of the enamide (**8**) (1.3 g, 3.85 mmol) in THF (250 ml) and absolute ethanol (150 ml) was irradiated, under argon, in the presence of iodine (0.15 g) with a 450-W medium-pressure mercury arc through a Vycor filter for 9.5 h. Three separate equivalent runs were combined and evaporated. The residue was dissolved in methylene dichloride (250 ml) and the solution was washed with 5% aqueous sodium hydrogen sulphite. The organic phase was dried with sodium sulphate, evaporated to *ca.* 30 ml, and flash chromatographed.[18] Elution with 0.5% ethyl acetate in methylene dichloride yielded a crude cyclized material (2.97 g). Recrystallization from 20% aqueous methanol gave *compound* (**9**) (2.15 g, 54%), m.p. 169—170.5 °C (Found: C, 71.3; H, 5.1; N, 4.15. $C_{20}H_{17}NO_4$ requires C, 71.63; H, 5.11; N, 4.18%); $\nu_{max.}$ 1 675 cm^{-1}; $\lambda_{max.}$ 227 (14 200), 255 (54 600), 287 (9 200), 318 (10 600), 329 (11 000), 357 (3 200), and 376 nm (3 200); $\lambda_{min.}$ 282 (8 400), 296 (4 600), 351 (2 400), and 366 nm (1 800); δ_H 8.97 (1 H, s, 11-H), 7.75 (1 H, s, 7-H), 7.70 (1 H, m), 7.4—7.6 (2 H, m), 6.99 (1 H, s, 3-H), 6.20 (2 H, s), 4.28 (2 H, q), 4.05 (2 H, t), 3.14 (2 H, t), and 1.33 (3 H, t).

Ethyl 1,2-*Dimethoxy*-9,10-*methylenedioxy*-6a,7-*dehydronoraporphine*-6-*carboxylate* (**15**).—The enamide (**14**) (2.94 g, 7.40 mmol) was irradiated in three separate portions and worked up as above. The residue was flash chromatographed using 3% ethyl acetate in methylene dichloride to give *compound* (**15**) (1.36 g, 47%), m.p. 185—187 °C (Found: C, 66.55; H, 5.45; N, 3.4. $C_{22}H_{21}NO_6$ requires C, 66.83; H, 5.35; N, 3.42%); $\nu_{max.}$ 1 690 cm^{-1}; $\lambda_{max.}$ 237sh, (17 600), 262 (47 800), 267 (52 400), 291 (18 000), 318 (11 200), 331 (11 600), 355 (2 600), and 374 nm (2 200); $\lambda_{min.}$ 227 (12 000) and 300 nm (7 000); δ_H 9.07 (1 H, s, 11-H), 7.68 (1 H, s), 7.12 (1 H, s), 7.04 (1 H, s), 6.07 (2 H, s), 4.27 (2 H, q), 4.07 (2 H, t), 4.01 (3 H, s), 3.88 (3 H, s) 3.18 (2 H, t), and 1.33 (3 H, t).

The ^{13}C nuclear magnetic resonance assignments for the 6-carboxylic esters are collected in Table 2.

1,2-*Dimethoxy*-6a,7-*dehydronoraporphine* (**6**) (*Dehydronornuciferine*).—Potassium hydroxide (3 g) was dissolved on being heated under argon in absolute ethanol (100 ml). The resultant solution was cooled, the carbamate (**5**) (1.00 g, 2.85 mmol) added, and the solution was then brought back to reflux for 18 h under argon. The solution was then cooled and a solution of citric acid (3 g) in distilled water (50 ml) was added slowly using an addition funnel. The *dehydronoraporphine* (**6**) crystallized as off-yellow flakes (750 mg, 94%), m.p. 149.5—150.5 °C (Found: C, 77.15, H, 6.15; N, 4.95. $C_{18}H_{17}NO_2$ requires C, 77.40; H, 6.13, N, 5.01%); $\nu_{max.}$ 3 380, 3 370, 3 280, and 1 625 cm^{-1}; $\lambda_{max.}$ 252 (44 200), 261 (41 300), 293 (6 200), 326 (11 900), and 380 nm (2 500); $\lambda_{min.}$ 224 (13 500), 288 (5 800), and 309 nm (5 800); δ_H 9.42 (1 H, m, 11-H), 7.15—7.65 (3 H, m), 7.02 (1 H, s, 3-H), 6.62 (1 H, s, 7-H), 4.00 (3 H, s), 3.89 (3 H, s), 3.47 (2 H, m), and 3.22 (2 H, m).

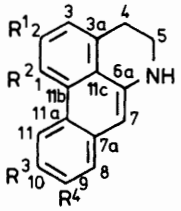
1,2-*Methylenedioxy*-6a,7-*dehydronoraporphine* (2) (*Dehydroanonaine*).—In the same manner as for the preparation of compound (**6**), 6-ethoxycarbonyldehydroanonaine (**9**) (1.0 g, 2.98 mmol) was saponified with potassium hydroxide to give dehydroanonaine (**2**) (720 mg, 97%), m.p. 135—136 °C (methanol–methylene dichloride) (Found: C, 77.65; H, 4.95; N, 5.25. Calc. for $C_{17}H_{13}NO_2$ C, 77.55; H, 4.98; N, 5.32%); $\nu_{max.}$ 3 380 and 1 635 cm^{-1}; $\lambda_{max.}$ 253 (48 900), 258 (50 000), 332 (13 600), and 380 nm (7 100); $\lambda_{min.}$ 230 (17 100) and 289 nm (4 200); δ_H 8.87 (1 H, dd, *J* 7 and 2 Hz, 11-H), 7.2—7.6 (3 H, m), 6.94 (1 H, s, 3-H), 6.56 (1 H, s, 7-H), 6.18 (2 H, s), 3.45 (2 H, distorted t), and 3.17 (2 H, distorted t).

1,2,9,10-*Tetramethoxy*-6a,7-*dehydronoraporphine* (**12**) (*Dehydronorglaucine*).—In the same manner as for compound (**6**), 6-ethoxycarbonyldehydronorglaucine (**11**) (826 mg, 2.10 mmol) was saponified with potassium hydroxide. The crude precipitate was flash chromatographed using 7% ethyl acetate in methylene dichloride to yield dehydronorglaucine* (**12**) (610 mg, 86%), m.p. 180—183 °C (diethyl ether containing a little methanol) (Found: C, 70.5; H, 6.15; N, 4.5. $C_{20}H_{21}NO_4$ requires C, 70.48; H, 6.24; N, 4.13%); $\nu_{max.}$ 3 380, 3 240, and 1 630 cm^{-1}; $\lambda_{max.}$ 242 (sh, 28 300), 260 (47 200), 270 (43 400), 335 (10 800), and 381 nm (3 300); $\lambda_{min.}$ 226 (15 100), and 305 nm (5 300); δ_H 9.07 (1 H, s, 11-H), 6.97 (1 H, s), 6.92 (1 H, s), 6.58 (1 H, s), 4.01 (6 H, s), 3.98 (3 H, s), 3.90 (3 H, s), 3.40 (2 H, m), and 3.20 (2 H, m).

1,2-*Dimethoxy*-9,10-*methylenedioxy*-6a,7-*dehydronoraporphine* (**16**) (*Dehydronornantenine*).—In the same manner as for

* 6,6a-Dehydronorglaucine has been reported to occur in nature (K. H. B. Duchevska, A. Orahovats, and N. M. Mollov, *Dokl. Bolg. Akad. Nauk.*, 1973, **26**, 899). This compound would not be expected to have this structure but would exist as 6a,7-dehydronorglaucine. However, the reported empirical formula and the n.m.r. spectrum (both from ref. 1) are inconsistent with the dehydronorglaucine structure (**12**) and the structure of the naturally isolated alkaloid remains unknown.

Table 3. N.m.r. data for the noraporphines

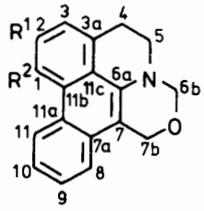


(**2**) $R^1R^2 = OCH_2O$, $R^3 = R^4 = H$
(**6**) $R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$
(**12**) $R^1 = R^2 = R^3 = R^4 = OCH_3$

Carbon	(2)	(6)	(12)
1	141.9	145.9	144.5
2	145.2	151.4	150.8
3	107.5	111.8	110.7
3a	118.2	125.0	125.3
4	30.7	31.1	31.3
5	41.1	41.6	41.3
6a	141.8	141.6	140.4
7	102.1	103.2	102.8
7a	133.9	134.8	130.1
8	125.0	125.7	105.7
9	127.0*	128.0	149.2
10	122.1	122.7	145.7
11	126.9*	126.9	109.1
11a	123.5	125.9	117.8
11b	117.3	118.6	118.5
11c	127.5	129.7	129.9
R^1	100.9	56.4	56.3*
R^2		59.8	59.9
R^3			55.6*
R^4			55.7*

* Signals can be interchanged.

Table 4. ^{13}C N.m.r. data for duguenaine and its dimethoxy analogue



(**1**) $R^1R^2 = OCH_2O$
(**7**) $R^1 = R^2 = OCH_3$

Carbon	(1)	(7)
1	142.0	145.9
2	145.2	151.3
3	107.9	112.1
3a	123.5	124.9
4	30.0	30.3
5	44.9	44.8
6a	130.5*	130.8
6b	80.9	81.1
7	106.1	106.7
7a	137.3	137.2
7b	66.7	66.9
8	123.1	123.4
9	127.5	128.4
10	119.6	119.9
11	127.1	127.2
11a	127.2	128.4
11b	117.6	117.9
11c	130.0*	128.1
R^1	101.0	56.5
R^2		59.8

* Signals can be interchanged.

compound (**6**), 6-ethoxycarbonyldehydronornantenine (**15**) (813 mg, 2.06 mmol) was saponified with potassium hydroxide. The resultant crude light green alkaloid was flash chromatographed using 3% ethyl acetate in methylene dichloride to yield the light yellow dehydronornantenine (**16**) (588 mg, 88%), m.p. 208.5—209.5 °C (acetone–water) (Found: C, 70.2, H, 5.05; N, 4.2. $C_{19}H_{17}NO_4$ requires C, 70.58; H, 5.30; N, 4.33%); $\nu_{max.}$ 3 355 and 1 635 cm^{-1}; $\lambda_{max.}$ 240sh, (26 900), 260 (45 400), 294 (13 500), 335 (10 600), and 382 nm (3 500); $\lambda_{min.}$ 225 (16 100) and 309 nm (6 100); δ_H 8.95 (1 H, 2, 11-H), 6.96 (1 H, s), 6.91 (1 H, s), 6.55 (1 H, s), 5.99 (2 H, s), 3.99 (3 H, s), 3.88 (3 H, s), 3.45 (2 H, m), and 3.19 (2 H, m).

The ^{13}C nuclear magnetic resonance assignments for the dehydronoraporphines are collected in Table 3.

Duguenaine (**1**).—To a magnetically stirred solution of dehydroanonaine (**2**) (501 mg, 2.00 mmol) in dioxane (20 ml) under nitrogen was added 37% aqueous formaldehyde (5 ml). After 24 h at room temperature, the solution was poured into water and extracted with methylene dichloride (4 × 50 ml) in four portions. The combined extracts were dried with sodium sulphate and evaporated. The residue was crystallized from methylene dichloride and methanol to yield duguenaine (**1**) (461 mg, 76%), m.p. 165.5—167 °C (lit.,[4] 168—170 °C).

Similarly prepared from dehydronornuciferine (**6**) (504 mg, 1.80 mmol) was the *oxazine analogue* (**7**) (525 mg, 91%), m.p. 132—135 °C (from methanol) (Found: C, 74.65; H, 5.9; N, 4.3. $C_{20}H_{19}NO_3$ requires C, 74.75; H, 5.96; N, 4.36%; $\lambda_{max.}$ 255 (39 000), 263 (39 000), 327 (11 400), and 380 nm (2 500); $\lambda_{min.}$ 226 (15 200), 259 (30 600), and 295 nm (4 800); δ_H 9.53 (1 H, m, 11-H), 7.40 (3 H, m), 7.02 (1 H, s, 3-H), 5.22 (2 H, s, NCH_2O), 4.69 (2 H, s, CH_2O), 3.99 (3 H, s), 3.87 (3 H, s), and 3.21 (4 H, s, CH_2CH_2N).

Prepared from dehydronorglaucine (**12**) (405 mg, 1.19 mmol) was the *oxazine analogue* (**13**) (390 mg, 86%) with isolation by flash chromatography (7% ethyl acetate in methylene dichloride), m.p. 199.5—202 °C (from methylene dichloride and ethanol) (Found: C, 68.9; H, 6.1; N, 3.6. $C_{22}H_{23}NO_5$ requires C, 69.28; H, 6.08; N, 3.67%); $\lambda_{max.}$(methylene dichloride) 264 (45 200), 274 (42 900), 339 (11 900), 384 nm (3 500); $\lambda_{min.}$ 306 nm (4 800); δ_H 9.18 (1 H, s, 11-H), 6.97 (1 H, s), 6.69 (1 H, s), 5.18 (2 H, s, NCH_2O), 4.67 (2 H, s, CH_2O), 4.02 (3 H, s), 3.98 (6 H, s), 3.87 (3 H, s), 3.24 (4 H, s, CH_2CH_2N).

Dehydronornantenine (**16**) (401 mg, 1.24 mmol) was treated with aqueous formaldehyde analogously to compound (**6**) to yield the 1,2-*dimethoxy*-9,10-*methylenedioxy analogue* (**17**) of duguenaine (324 mg, 72%) after flash chromatography using 3% ethyl acetate in methylene dichloride, m.p. 206—207.5 °C (Found: C, 69.2; H, 5.1; N, 3.8. $C_{21}H_{19}NO_5$ requires C, 69.03, H, 5.24; N, 3.83%); $\lambda_{max.}$ (methylene dichloride) 264 (46 300), 296sh (15 300), 339 (13 000), and 386 nm (3 000); $\lambda_{min.}$ 310 nm (600); δ_H 9.07 (1 H, s, 11-H), 6.96 (1 H, s), 6.76 (1 H, s), 6.02 (2 H, s, OCH_2O), 5.12 (2 H, s, NCH_2O), 4.67 (2 H, s, CCH_2O), 3.98 (3 H, s), 3.84 (3 H, s), 3.24 (4 H, s, CH_2CH_2N).

The ^{13}C nuclear magnetic resonance assignments for duguenaine and its dimethoxy analogue are collected in Table 4. The lack of sufficient solubility of the tetrasubstituted analogues in chloroform or dimethyl sulphoxide precluded our obtaining their ^{13}C n.m.r. spectrum.

Acknowledgements

The authors thank Messrs. Chi Min Woo and Clifford Dorn for the preparation of starting materials.

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Received 30*th September* 1983; *Paper* 3/1722