

## SYNTHESIS OF NOVEL 7,7'-BIS-6a,7-DEHYDRONORAPORPHINES

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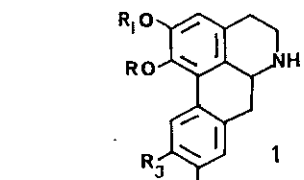
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**Abstract**— New dimers, (±)-bisdehydroanonaine **5a**, (±)-bisdehydroxylophine **5c**, (±)-bisdehydronornantenine **5d** and (±)-7-dehydroxylopinyl-7'-dehydronornantenine **8**, and the previously described (±)-urabaine **5b**, were prepared from dehydroxylophine **3c** and known dehydronoraporphines **3a**, **3b**, and **3d** *via* dimerization at the  $\beta$ -carbon of cyclic secondary enamines.

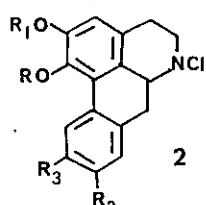
In the last few years, a number of 7,7'-bis-6a,7-dehydroaporphines have been isolated from different Annonaceous plants in our laboratory <sup>1-3</sup>. These compounds, named bipowine, bipowinone<sup>1</sup>, urabaine, *N*-methylurabaine, *N,N'*-dimethylurabaine **2**, and 7,7'-bisdehydroanonaine<sup>3</sup>, are the first representatives of a new class of dimeric alkaloids. Related substances have been reported as oxidation products of 6a,7-dehydroaporphines, using iodine<sup>4</sup> or mercuric nitrate or acetate<sup>5</sup>.

Previously described methods for the preparation of 6a,7-dehydronoraporphines involve photochemical oxidation of noraporphines<sup>6</sup> and total synthesis<sup>7-9</sup>. We have now found that oxidation of noraporphines by *N*-chlorosuccinimide and sodium ethoxide leads to monomeric 6a,7-dehydronoraporphines and their 7,7'-dimers<sup>1</sup>. Thus this previously undescribed dimerization at the  $\beta$ -carbon of a cyclic secondary enamine allowed us to synthesize several dimers from 6a,7-dehydroxylophine **3c** and the known monomers **3a**, **3b** and **3d**. The new dimers were (±)-7,7'-bis-6a,7-dehydroanonaine **5a**, (±)-7,7'-bis-6a,7-dehydroxylophine **5c**, (±)-7,7'-bis-6a,7-dehydronornantenine **5d**, and the asymmetrical (±)-7-dehydroxylopinyl-7'-dehydronornantenine **8**; the previously isolated (±)-urabaine **5b** was also prepared.

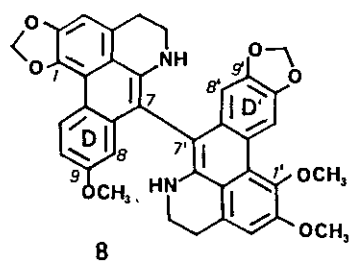
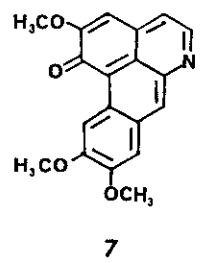
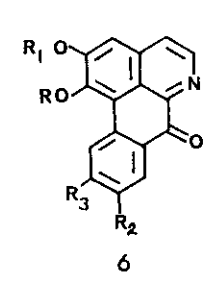
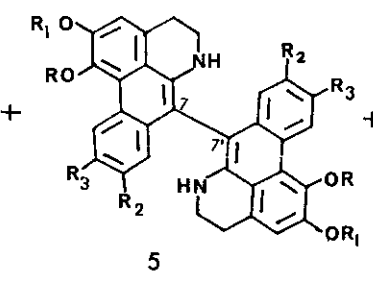
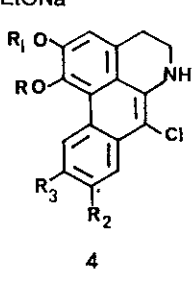
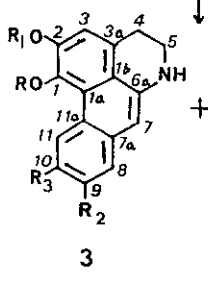
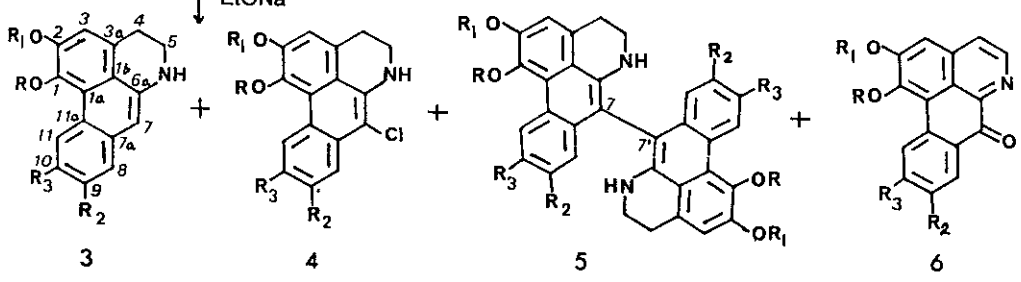
Reaction of the noraporphine **1** with *N*-chlorosuccinimide produced the chloramine **2** (yield 95%) which, when treated with sodium ethoxide at 70 °C, afforded a mixture containing dehydronoraporphine **3** (23-46%), 7-chlorodehydronoraporphine **4** (3-6%), 7,7'-bisdehydronoraporphine **5** (1-16%) and oxoaporphine **6** (12-21%). The dehydronoraporphine **3** was converted in turn into the corresponding dimer **5** (20-60%) and the oxoaporphine **6** (30%), by passing air through a solution of **3** in a mixture of



NCS



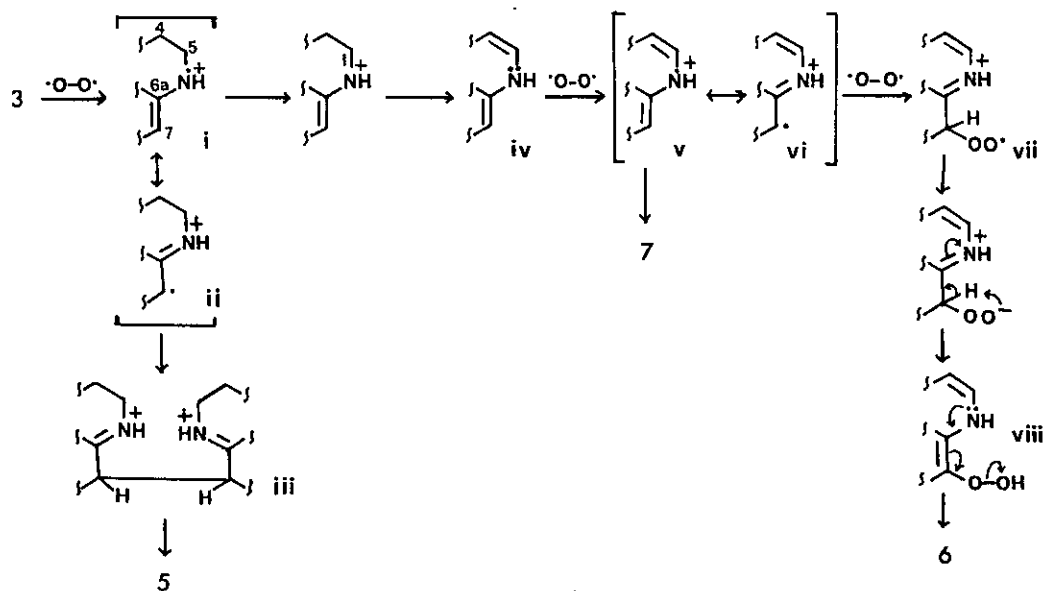
EtONa



- Anonaine 1a :  $R, R_1=CH_2, R_2=R_3=H$
- Nornuciferine 1b :  $R=R_1=CH_3, R_2=R_3=H$
- Xylopinine 1c :  $R, R_1=CH_2, R_2=OCH_3, R_3=H$
- Nornantenine 1d :  $R=R_1=CH_3, R_2, R_3=OCH_2O$
- Norglaucine 1e :  $R=R_1=CH_3, R_2=R_3=OCH_3$
- Wilsonirine 1f :  $R=H, R_1=CH_3, R_2=R_3=OCH_3$

dichloromethane and methanol. By heating with sodium ethoxide, 3 formed an unidentified water-soluble red product and gave only trace of oxidized compounds, except in the case of dehydronorglaucine 3e, which dimerized very smoothly<sup>1</sup>.

The variety of reaction products observed may be explained by an autoxidation mechanism of the enamine 10, which is probably a free-radical chain process as outlined in Scheme 1. The chloramine 2 may be converted first into an imine, which would then isomerize to a more stable cyclic enamine, forming at the same time the phenanthrene aromatic system of the dehydronoraporphine 3. Alkaloid 3 may produce a radical cation I by transferring one electron of the unshared pair of the nitrogen on an oxygen molecule. Two identical radicals II, the immonium form of I, may couple to produce a dimer III, followed by isomerization into  $\beta,\beta'$ -bisenamine, 7,7'-bis-6a,7-dehydronoraporphine 5. By another way, I may form the 4,5,6a,7- dienamine IV after H<sup>+</sup> transfer at C-5 and isomerization. The very instable IV may be immediately converted into the radical cation V by abstraction of an electron from the nitrogen with oxygen. The immonium radical VI and an oxygen molecule may combine to give the free radical VII, followed by extraction of an electron (the propagation step) and by internal proton transfer at C-7, thus producing  $\beta$ -hydroperoxylenamine VIII. Compound VIII may decompose into an iminoketone, oxoaporphine 6. In the case of the 1-hydroxynoraporphine wilsonirine 1f, V led to pancoridine 7<sup>1</sup> through transfer of H<sup>+</sup> from the phenol.



Scheme 1

The first synthetic example of an asymmetrical 7,7'-dimer, 7-dehydroxylopinyl-7'-dehydronornantenine **8**, was prepared from the mixture of 6a,7-dehydroxylopine **3c** and 6a,7-dehydronornantenine **3d** under the same conditions.

The 7,7'-bisdehydronoraporphines as well as the 7,7'-bisdehydroaporphines<sup>2,4,5</sup> and the 4,7'-bisaporphinoids<sup>11</sup> were the atropisomeric compounds, because rotation about single C-7-C-7' bond is prevented. The atropisomerism of these dimers **5a-5e** appeared in the <sup>1</sup>H nmr spectrum<sup>12</sup> (table 1) by the fact that the protons at C-8, C-8' ( $\delta$  6.52 to 7.13 ppm) and those of methoxyls at C-9, C-9' ( $\delta$  3.5 to 3.6

Table 1. <sup>1</sup>H Nmr spectral data of 6a,7-dehydronoraporphines **3**, their dimers **5**, and the asymmetrical dimer **8**. (CDCl<sub>3</sub>, 250MHz)

Proton	Compounds											
	3a	5a <sup>2</sup>	3b	5b	3c	5c <sup>2</sup>	3d <sup>1</sup>	5d <sup>1</sup>	8	3e <sup>1</sup>	5e <sup>1</sup>	
OCH <sub>3</sub> -1	-	-	3.87	3.94	-	-	3.86	3.96	-	4.00	3.85	3.99
OCH <sub>3</sub> -2	-	-	3.98	4.01	-	-	3.96	4.04	-	4.08	3.92	4.02
OCH <sub>2</sub> O-1,2	6.17	6.30	-	-	6.19	6.32	-	-	6.28	-	-	-
H-3	6.93	7.07	7.02	7.08	6.92	7.04	6.90	7.04	6.99	7.08	6.85	7.02
CH <sub>2</sub> -4 <sup>3</sup>	3.18t	3.25m	3.23t	3.30m	3.21t	3.30m	3.20t	3.24m	3.20m	3.15t	3.22m	
CH <sub>2</sub> -5 <sup>3</sup>	3.43t		3.50t		3.48t		3.44t					3.40t
H-7 <sup>4</sup>	6.57	-	6.73	-	6.56	-	6.55	-	-	-	6.52	-
H-8 <sup>5</sup>	7.50d	7.13d	7.53d	7.13d	6.97d	6.69d	6.96	6.52	6.54d	6.62	6.81	6.61
H-9 <sup>5</sup>	7.39t	7.26t	7.41t	7.22t	-	-	-	-	-	-	-	-
H-10 <sup>5</sup>	7.27t	7.37t	7.31t	7.35t	6.95dd	7.13dd	-	-	6.98dd	-	-	-
H-11 <sup>5</sup>	8.85d	9.07d	9.42d	9.63d	8.08d	9.04d	8.96	9.12	8.98d	9.19	8.95	9.26
OCH <sub>3</sub> -9	-	-	-	-	3.92	3.58	-	-	3.59	-	3.95	3.48
OCH <sub>3</sub> -10	-	-	-	-	-	-	-	-	-	-	3.96	4.02
OCH <sub>2</sub> O-9,10	-	-	-	-	-	-	6.00	5.90	-	{ 5.94d <sup>6</sup>	-	-
										{ 5.96d <sup>6</sup>		
NH		4.05	3.60	4.32	3.80		3.50	3.80			3.10	3.80

1: 90 MHz. 2: CDCl<sub>3</sub> + 5% CD<sub>3</sub>OD. 3: J = 5 Hz. 4: Disappeared by addition of D<sub>2</sub>O or CD<sub>3</sub>OD.

5: J<sub>b</sub> = 8 Hz, J<sub>m</sub> = 2.5 Hz 6: J = 1 Hz.

ppm) produced signals at unusually high field, shielded about 0.4 ppm and 0.3 ppm respectively in comparison to the corresponding monomers **3a-3e** ( $\delta$  6.81 to 7.53 ppm and  $\delta$  3.92 to 3.95 ppm). Consequently, it appeared that they were located in the field of the anisotropic effect of D and D' cycles. On the other hand, the feature of the four protons of the methylenes at C-4 and C-5 allowed also to distinguish between the dehydronoraporphine monomers and their 7,7'-dimers. Thus two triplets were found at about  $\delta$  3.2 ppm and  $\delta$  3.4 to 3.5 ppm in the monomers and multiplets centered around  $\delta$  3.25 ppm in the 7,7'-dimers.

Determination of the specific optical rotation of the naturally occurring 7,7'- and 4,7'-dimers<sup>1,2,11</sup> was often quite difficult: solutions are strongly coloured due to the instability of these compounds and their  $[\alpha]_D$  values are particularly low<sup>3</sup>.

Also noteworthy are the high reactivity and the presence of tautomerism of 6a,7-dehydronoraporphine **3** demonstrated in the <sup>1</sup>H nmr spectrum, which showed instantaneous and reversible deuterium exchange of the C-7 proton and NH. Thus, one proton singlet near by  $\delta$  6.55 ppm (doublet of C-7 at  $\delta$  102 ppm of in the <sup>13</sup>C nmr spectrum) in CDCl<sub>3</sub> disappeared by addition of D<sub>2</sub>O or CD<sub>3</sub>OD. Contrary, the dehydroaporphines, *N*-methyl derivatives, did not exchange deuterium under the same conditions, but incorporation of deuterium at C-7 occurred slowly, reaching a maximum after 32 hours and only partially (30%) in CF<sub>3</sub>COOD by acid-catalyzed reaction<sup>13</sup>.

Glaucine, the *N*-methylated derivative of **1e**, reacted with *N*-bromosuccinimide to give 28% yield of 7-bromo-6a,7-dehydroglaucine and 10% 6a,7-dehydroglaucine as previously reported<sup>14</sup>. Nuciferine, however, did not react with *N*-chlorosuccinimide under the above mentioned conditions. The intermediate dienamine **iv** could not be detected, but such dienamines derived from 6a,7-dehydroaporphines were more stable than **iv** and have been prepared by electrochemical oxidation<sup>15</sup> and photooxidation<sup>16</sup>. 6a,7-Dehydronuciferine, *N*-methylated **3b**, was more stable toward oxygen under similar conditions without catalyst and light<sup>17</sup>. In the presence of mercuric nitrate, 6a,7-dehydroaporphines reacted to produce the corresponding 7,7'-dimers<sup>2,5</sup>, but 6a,7-dehydroxylophine **3c** was oxidized further to an oxoaporphine, lanuginosine **6c**. The intermediate **III** could not be isolated, but a related dimeric immonium salt has been obtained from an aporphine through oxidation with iodine<sup>4</sup>. Thus, it is interesting to point out that important differences of reactivity are found between 6a,7-dehydronoraporphines and their *N*-methyl derivatives, the 6a,7-dehydroaporphines, concerning oxidation with air.

## EXPERIMENTAL

All melting points were uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra ( $\delta$  ppm) were measured on a Varian HA-90, a Brüker 250 MHz or a Varian CFT20 in  $\text{CDCl}_3$  using TMS as internal standard. Uv spectra were recorded with a Philips Unicam SP1800 and mass spectra were determined with a Varian MAT311. Spectral data of known aporphines and aporphinoids are described in<sup>18</sup>.

*Oxidation of anonaine 1a.*— A solution of **1a** (107 mg, 0.4 mmol) and *N*-chlorosuccinimide (46 mg, 0.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 ml) was stirred for 30 min at room temperature. The mixture was washed with water and dried over  $\text{Na}_2\text{SO}_4$  and solvent removed *in vacuo* at maximum 30°C. The solution of residue in EtOH (20 ml) containing Na (9.2 mg, 0.4 mmol) was heated for 10 min at 70°C under nitrogen. After evaporation of EtOH the reaction mixture was dissolved in water, taken up into  $\text{CH}_2\text{Cl}_2$  and worked up as usual. The chromatography on silica gel of the residue eluted with 0.2% MeOH in  $\text{CH}_2\text{Cl}_2$  afforded fraction 1: 4 mg **4a** (4.1% yield), fraction 2: 4 mg **5a** (4.6%), fraction 3: 20 mg **3a** (23%), fraction 4: 12 mg unidentified, fraction 5: 10 mg liriodenine **6a** (12%) and fraction 6: 20 mg **1a** unreacted.

7-Chloro-6a,7-dehydroanonaine **4a**.— Amorphous.  $\text{C}_{17}\text{H}_{12}\text{ClNO}_2$ . Ms  $m/z$  (%): 299 ( $\text{M}^+$  +2, 35), 298 ( $\text{M}^+$  +1, 27), 297 ( $\text{M}^+$ , 100). Uv  $\lambda_{\text{max}}$  MeOH nm (log  $\epsilon$ ): 212 (3.64), 253 (4.13), 261sh (4.12), 326 (3.43), 397 (3.13).  $^1\text{H}$  nmr,  $\text{CDCl}_3$ , 250 MHz: 3.22 (2H, t,  $J = 5$  Hz,  $\text{CH}_2$ -4), 3.55 (2H, t,  $J = 5$  Hz,  $\text{CH}_2$ -5), 3.60 (NH), 6.22 (2H, s,  $\text{OCH}_2\text{O}$ ), 6.99 (1H, s, C-3 H), 8.05 (1H, d, C-8 H), 7.57 (1H, t, C-9 H), 7.37 (1H, t, C-10 H), 8.94 (1H, d, C-11 H),  $J_{\text{O}} = 8$  Hz.

(±)-7,7'-Bis-6a,7-dehydroanonaine **5a**.— Amorphous.  $\text{C}_{34}\text{H}_{24}\text{N}_2\text{O}_4$ . Ms  $m/z$ : 525 ( $\text{M}^+$  +1, 12), 263 ( $\text{M}^+$ /2 +1, 16), 43 (100). Uv  $\lambda_{\text{max}}$  MeOH nm (log  $\epsilon$ ): 214 (3.78), 252sh (4.14), 260 (4.14), 328 (3.25), 380 (3.17); MeOH+HCl: 214, 252, 260, 288, 328, 372, 390.

6a,7-Dehydroanonaine **3a**.— Mp 125 - 128°C (acetone) (lit. 8: 135 - 6°C). Ms  $m/z$ : 263 ( $\text{M}^+$ , 100), 248 (17), 232 (12).

*Oxidation of normuciferine 1b.*— 200 mg **1b** were treated in the same manner as **1a** to give 5 mg **4b** (3% yield), 56 mg **3b** (28%), 2 mg **5b** (1%) and 25 mg lysicamine **6b** (13%).

7-Chloro-6a,7-dehydronormuciferine **4b**.— Amorphous.  $\text{C}_{18}\text{H}_{16}\text{ClNO}_2$ . Ms  $m/z$ : 315 ( $\text{M}^+$  +2, 23), 314 ( $\text{M}^+$  +1, 11), 313 ( $\text{M}^+$ , 99), 279 (9), 263 (45), 254 (100), 235 (51), 220 (23). Uv  $\lambda_{\text{max}}$  MeOH nm (log  $\epsilon$ ): 212 (3.61), 255 (4.13), 262 (4.13), 327 (3.24), 395 (2.88).  $^1\text{H}$  nmr,  $\text{CDCl}_3$ , 250 MHz: 3.22 (2H, t,  $J = 5$  Hz,  $\text{CH}_2$ -4), 3.54 (2H, t,  $J = 5$  Hz,  $\text{CH}_2$ -5), 3.85 (3H, s,  $\text{OCH}_3$ -1), 3.97 (3H, s,  $\text{OCH}_3$ -2), 4.10 (NH), 7.02 (1H, s, C-3 H), 8.05 (1H, d, C-8 H), 7.53 (1H, t, C-9 H), 7.35 (1H, t, C-10 H), 9.50 (1H, d, C-11 H),  $J_{\text{O}} = 8$  Hz.

6a,7-Dehydronormuciferine **3b**.— Mp 147 - 149°C (acetone) (lit. 8: 149.5 - 150.5°C). Ms  $m/z$ : 279 ( $\text{M}^+$ , 100), 264 (36), 236 (25), 220 (32).

(±)-7,7'-Bis-6a,7-dehydronornuciferine **5b** [= (±)-urabaine].— Amorphous.  $C_{36}H_{32}N_2O_4$ . Ms  $m/z$ : 557 ( $M^+ +1$ , 65), 279 ( $M^+ +1/2$ , 50), 263 (60), 41 (100).  $^1H$  nmr and uv spectra as well as Rf were identical with those of natural urabaine<sup>2</sup>.

*Oxidation of xylopine 1c.*— A similar treatment of **1c** 300 mg afforded **4c** 18 mg (6% yield), **3c** 125 mg (46%), lanuginosine **6c** 60 mg (21%) and **1c** 31 mg unreacted.

7-Chloro-6a,7-dehydroxylopine **4c.**— Mp 131 - 133°C (acetone).  $C_{18}H_{14}ClNO_3$ . Ms (ci -  $NH_3$ )  $m/z$ : 330 ( $M^+ +3$ , 35), 329 ( $M^+ +2$ , 22), 328 ( $M^+ +1$ , 100). Uv  $\lambda_{max}$  MeOH nm (log  $\epsilon$ ): 212 (3.71), 355sh (4.14), 269 (4.16), 290sh (3.36), 336 (3.27), 385 (3.15).  $^1H$  nmr,  $CDCl_3$ , 90MHz: 3.13 (2H, t, J = 5Hz,  $CH_2$ -4), 3.52 (2H, t, J = 5Hz,  $CH_2$ -5), 3.92 (3H, s,  $OCH_3$ -9), 5.00 (NH), 6.14 (2H, s,  $OCH_2O$ ), 6.85 (1H, s, C-3 H), 7.42 (1H, d, C-8 H), 6.95 (1H, dd, C-10 H), 8.79 (1H, d, C-11 H),  $J_O = 9Hz$ ,  $J_m = 2.5Hz$ .

6a,7-Dehydroxylopine **3c.**— Mp 125 - 126°C (acetone).  $C_{18}H_{15}NO_3$ . Ms (ci -  $NH_3$ )  $m/z$ : 294 ( $M^+ +1$ , 100). Uv  $\lambda_{max}$  MeOH nm (log  $\epsilon$ ): 208 (4.14), 244sh (4.14), 258sh (4.18), 267 (4.21), 290sh (3.63), 338 (3.48), 380sh (3.20); MeOH - HCl: 208, 240, 254, 272, 292, 324, 350, 370.  $^{13}C$  nmr ( $CDCl_3$ ): 141.1 (C-1), 117.8(C-1a), 117.4 (C-1b), 142.4 (C-2), 111.9 (C-3), 135.5 (C-3a), 30.7 (C-4), 41.2 (C-5), 145.2 (C-6a), 101.9 (C-7), 127.6 (C-7a), 106.6 (C-8), 158.5 (C-9), 105.8 (C-10), 128.5 (C-11), 127.6 (C-11a), 100.7 ( $OCH_2O$ ), 55.1 ( $OCH_3$ ).

(±)-7,7'-Bis-6a,7-dehydroxylopine **5c.**— Amorphous.  $C_{36}H_{28}N_2O_6$ . Ms (ci -  $NH_3$ )  $m/z$ : 585 ( $M^+ +1$ , 100), 294 (10), 292 (10). Uv  $\lambda_{max}$  MeOH nm (log  $\epsilon$ ): 210 (4.16), 258sh (4.19), 268 (4.21), 330 (3.75), 380sh (3.29).

*Oxidation of nornantenerine 1d.*— Treatment of **1d** 50 mg furnished **3d** 19 mg (38%), **5d** 8 mg (16%) and oxonantenerine **6d** 10 mg (20%).

6a,7-Dehydronornantenerine **3d.**— Mp 204 - 205°C (acetone) (lit.8: 208.5 - 9.5°C). Ms (ci -  $NH_3$ )  $m/z$ : 324 ( $M^+ +1$ , 100).

(±)-7,7'-Bis-6a,7-dehydronornantenerine **5d.**— Mp 285 - 290°C (decomp, acetone).  $C_{36}H_{32}N_2O_8$ . Ms (ci -  $NH_3$ )  $m/z$ : 645 ( $M^+ +1$ , 100), 324 (8), 322 (6). Uv  $\lambda_{max}$  MeOH nm (log  $\epsilon$ ): 212 (3.64), 257 (4.14), 280sh (3.89), 336sh (3.28), 395 (3.16).

*Oxidation of norglaucine 1e.*— cf. lit. 1.

N-Chloronorglaucine **2e.**—  $^1H$  nmr,  $CDCl_3$ , 90MHz: 2.60 - 3.90 (4H, m,  $CH_2$ -4 and  $CH_2$ -7), 3.63 (3H, s,  $OCH_3$ -1), 3.84 (3H, s,  $OCH_3$ ), 3.88 (6H, s, 2  $OCH_3$ ), 4.00 - 4.90 (3H, m,  $CH_2$ -5 and CH-6a), 6.58 (1H, s, C-3 H), 6.72 (1H, s, C-8 H), 8.05 (1H, s, C-11 H).

7-Chloro-6a,7-dehydronorglaucine **4e.**— Amorphous.  $C_{20}H_{20}ClNO_4$ . Ms  $m/z$ : 375 ( $M^+ +2$ , 36), 376 ( $M^+$

+1, 28), 373 ( $M^+$ , 100).  $^1H$  nmr,  $CDCl_3$ , 90MHz: 3.16 (2H, t,  $J = 5$ Hz,  $CH_2-4$ ), 3.51 (2H, t,  $J = 5$ Hz,  $CH_2-5$ ), 3.83 (3H, s,  $OCH_3-1$ ), 3.97, 3.98 and 4.00 (9H; 3s, 3  $OCH_3$ ), 4.60 (NH), 6.92 (1H, s, C-3 H), 7.37 (1H, s, C-8 H), 9.06 (1H, s, C-11 H).

*Dimerization of dehydronoraporphines 3.*— Air was passed through a solution of **3** 10 mg in a mixture of  $CH_2Cl_2$  and MeOH (4/1) 50 ml at room temperature until disappearance of **3** on tlc (7 to 10 days). After evaporation of solvent, the residue was submitted to preparative silicagel tlc ( $CH_2Cl_2/MeOH = 99.7/0.3$ ) and afforded dimer **5** and oxoaporphine **6**. Thus, **3a** gave 30% yield of **5a** and 30% of **6a**, **3b** furnished 60% of **5b** and 30% of **6b**, **3c** produced 20% of **5c** and 30% of **6c**. All the compounds were identified by comparison with authentic samples (ms,  $^1H$  nmr, tlc).

The mixture of **3c** (18 mg) and **3d** (12 mg), treated in the same manner, afforded **5c** (2 mg), **5d** (4 mg) and the asymmetrical dimer **8** (4 mg).

7-(6a,7-Dehydroxylopinyl)-7'-(6'a,7'-dehydonornantenine) **8**.— Amorphous.  $C_{37}H_{30}N_2O_7$ . Ms (ci- $NH_3$ )  $m/z$ : 615 ( $M^++1$ , 100), 324 (5), 322 (5), 294 (18), 292 (10). Uv  $\lambda_{max}$  MeOH nm (log  $\epsilon$ ): 210 (4.13), 260sh (4.15), 269 (4.16), 338 (3.27), 385 (3.15).

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