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STRUCTURE OF CHELERYTHRINE BASE

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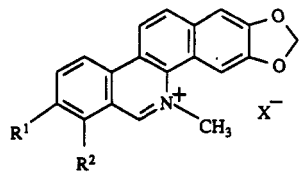
ABSTRACT.—The structure of chelerythrine free base was examined. When chelerythrine chloride [**1b**] was treated with aqueous K_2CO_3 solution, *bis*[6-(5,6-dihydrochelerythrinyl)] ether [**3**] was obtained. An excess of aqueous ammonia under the same conditions yielded *bis*[6-(5,6-dihydrochelerythrinyl)] amine [**4**]. The structures of both derivatives were determined by elemental analysis, ir, 1D and 2D nmr, eims, and cims. The formation of an unstable hydroxy adduct **2a** (pseudobase) was observed in ^{1}H-nmr experiments only.

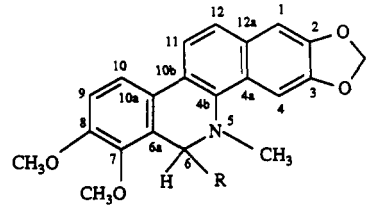
Quaternary benzo[c]phenanthridine alkaloids (QBA) of the sanguinarine group (1–3) are distributed mainly in the plant families Fumariaceae, Papaveraceae, and Rutaceae. In the past two decades, QBA have been studied intensively for their interesting biological activities. Two of the most common members of this group are sanguinarine [**1a**] and chelerythrine [**1b**]. The alkaloid **1a** and its mixture with **1b** were introduced medicinally because of their significant anti-inflammatory, antimicrobial, and antifungal activities (4,5).

Although the structures of the quaternary cations **1a** and **1b** have been well known since 1931 (6,7), the structures of the free bases have apparently not been completely elucidated until now.

A fully aromatized system of a QBA with an iminium bond ($C=N^+$) is a strong chromophore responsible for the intense coloring of all QBA salts. It is known that upon alkalization of aqueous solution of QBA salts, the color disappears with the formation of a white precipitate of a base that goes into solution in non-polar solvents. Because it has been repeatedly shown that the corresponding quaternary hydroxide (represented by **1a, b**; X=OH) cannot exist (2,8), the alkanolamine structure (e.g., **2a**) has been almost universally adopted for this base, although exact proof has been lacking up to now. However, some properties of chelerythrine free base favor the bimolecular structure whose existence was proposed by Gadamer and Stichel (8). Fischer (9) reported the composition of chelerythrine free base as $(C_{21}H_{17}NO_4)_2 \cdot H_2O$, calculated from elemental analysis. This evidently implies a dimeric nature of the compound. The structure of



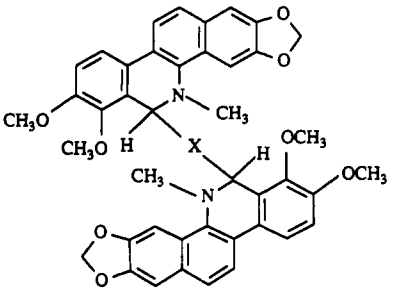
1a $R^1+R^2=OCH_2O$
1b $R^1=R^2=OCH_3$



2a R=OH
2b R=OD
2c R=OCH_3
2d R=OCH_2CH_3
2e R=$OCOCH_3$
2f R=NHD

chelerythrine base was formulated for the first time by Slavík and Slavíková (10) as a dimeric ether **3** without being supported by spectral data.

Our present aim was to elucidate the real structure of a QBA free base, and chelerythrine was chosen as a typical representative of this alkaloid group for the purposes of this study.



3 X=O
4 X=NH

RESULTS AND DISCUSSION

We have observed that the composition of chelerythrine free base liberated from aqueous solutions of **1b** depends on the alkalizing agent. Two different products were obtained depending on whether K_2CO_3 or NH_3 was used.

Chelerythrine chloride [**1b**], when treated with K_2CO_3 followed by crystallization of the product from Et_2O, gave *bis*[6-(5,6-dihydrochelerythrinyl)] ether [**3**]. The mp of compound **3** was in agreement with data published for "chelerythrine base" (9,11,12). Elemental analysis proved the composition to be $C_{42}H_{36}N_2O_9$, consistent with literature data (9,12). The ir spectrum of **3** showed no sign of a hydroxy group.

In the ^{1}H-nmr spectrum of **3** in $CDCl_3$, singlets of a methylenedioxy and methyl groups were recognizable. The singlet exhibited by H-6 at 6.60 ppm was considered a significant feature. Its very deshielded resonance differs from the corresponding H-6 signals of the chelerythrine derivatives that have been described (1, 13–17). Only 5,6-dihydro-6-acetoxychelerythrine [**2e**] has been reported to display the chemical shift of the H-6 proton at 6.55 ppm (18). The deshielded position of the H-6 atom in **3** is probably caused by an anisotropic effect of the second unit of the dimer.

Six aromatic protons were assigned in a ^{1}H-^{1}H-COSY nmr experiment, and chemical shifts of carbon atoms were determined from a ^{13}C-^{1}H-COSY nmr spectrum. The ^{13}C-^{1}H-heterocorrelated spectrum revealed that the chemical shift of the *N*-methyl group was at 3.05 ppm and the C-7 methoxy group displayed an unusually shielded resonance at 2.41 ppm compared to the C-8 methoxy group (3.72 ppm). The most plausible explanation may be an anisotropic effect of the second part of the dimeric molecule. Ten quaternary carbon shifts were assigned on the basis of a selective INEPT nmr experiment applying a value of 7 Hz for the $^3J_{C,H}$ coupling constant. Irradiation of a particular proton enhanced the signal intensity of all carbon atoms three bonds away.

The precipitate separated from the aqueous solution of K_2CO_3 showed an identical ^{1}H-nmr spectrum to the product **3** crystallized from Et_2O.

In the eims, the derivative **3** displayed a peak at *m/z* 711 $[M-1]^+$, which corresponds to an ether α-proton loss. A base peak was observed at *m/z* 348 (quaternary cation **1b**). Another significant peak was at *m/z* 681 (loss of the methoxy group). A $[M-46]^+$ fragment at *m/z* 666 appeared due to loss of the methylenedioxy group. The cation at *m/z*

364 was generated by chelerythrine [**1b**] with the attached oxygen atom $[m/z\ 348+O]^+$. Fragmentation of a monomeric part of the molecule was quite consistent with the published fragmentation scheme of chelerythrine adducts (13). The positive cims of **3** displayed quasi-molecular ions at *m/z* 713 $[M+H]^+$ and at *m/z* 741 $[M+C_2H_5]^+$. In the negative mode, a $[M-H]^-$ ion was observed at *m/z* 711, confirming that the mol wt is indeed 712 daltons. Furthermore, the positive-ion cims spectrum displayed a diagnostic fragment at *m/z* 348 (cation **1b**). The cid ms/ms spectrum of the *m/z* 711 ion in the negative mode showed, as the first intense ion, a fragment at *m/z* 364, corresponding to the anion of the deprotonated **2a**.

Conversion of quaternary chelerythrine chloride [**1b**] *in the alkaline medium* was monitored by nmr spectroscopy. A solution of NaOD in D_2O was added to the solution of **1b** in DMSO-d_6. The ^{1}H-nmr signals of 5,6-dihydro-6-deuteroxychelerythrine [**2b**] (pseudobase deutero analogue) were recorded as: δ 2.59 (*N*-methyl), 3.86, 3.88 (two methoxy groups), and the singlet of the H-6 proton at 5.79 ppm. These chemical shifts are in good agreement with the published nmr data of 5,6-dihydro-6-methoxy(ethoxy)chelerythrine [**2c,d**], where the signals of the H-6 atom were near 5.60 ppm and resonances of both methoxy groups were around 3.90 ppm (1, 13–17). In addition to the adduct **2b**, the resonances of the dimer **3** were observed in the ^{1}H-nmr spectrum. It could be concluded that there are two species in an alkaline aqueous solution of chelerythrine: a primary hydroxy adduct **2a** (pseudobase) and its dimeric condensation product, **3**.

Another experiment carried out in the nmr tube revealed the reactivity of **3** in the presence of D_2O. The dimeric product **3** was thus hydrolyzed and signals of the deuteroxy adduct **2b** were recorded.

A similar mechanism probably occurs when bases of QBA are crystallized from alcohol or alcohol containing solvents and form 6-alkoxy adducts of the **2c,d** type (10, 19–23). These derivatives, also called pseudoalcoholates, are sometimes erroneously considered natural substances (1) regardless of the fact that even in weakly acidic media, such as plant tissues, they immediately eliminate a molecule of alcohol yielding the quaternary cation. Therefore, these compounds cannot exist in plants and are evidently artifacts.

Treatment of chelerythrine chloride [**1b**] with excess aqueous NH_3 and crystallization from Et_2O yielded *bis*[6-(5,6-dihydrochelerythrinyl)] amine [**4**]. The melting point of **4** was found to be 268–270° [lit. 263–264° (9)], but we sometimes observed a higher value around 280° (10,24). Elemental analysis of compound **4** proved the composition to be $C_{42}H_{37}N_3O_8$. Following structural considerations, the third nitrogen atom is evidently the atom which connects both parts of the dimeric molecule. This connection is probably formed by the nucleophilic attack of NH_3 on the iminium bond in chelerythrine followed by dimerization. The ir spectrum of compound **4** showed a significant band at 3310 cm^{-1} with low intensity corresponding to the N-H group of secondary amines.

The values of the chemical shifts of the hydrogen and carbon atoms in $CDCl_3$ are very similar or identical with those of product **3**. The only significant difference is in the position of the signals of H-6 and C-6. Here again the signal of the C-7 methoxy group appeared in the shielded region (2.58 ppm) compared to the second methoxy group (3.72 ppm). However, we were not able to identify the signal of the hydrogen atom of the NH group in the ^{1}H-nmr spectrum.

The ^{1}H-nmr spectrum of compound **4** in DMSO-d_6 is very interesting. The signal of the hydrogen atom H-6 appeared as a doublet at 5.85 ppm with J=6.3 Hz. We propose that there is a coupling with NH over three bonds by H-(C-6)-N-H. After

addition of D_2O to the sample of **4** in $CDCl_3$ some new singlets appeared which were assigned to pseudobase **2b**: δ 2.72 (NMe), 3.94, 4.00 (2×OMe), 6.02 (H-6); to dimer **3**: δ 3.05 (NMe), 2.43, 3.72 (2×OMe), 6.60 (H-6); and to 6-amino adduct **2f**: δ 2.71 (NMe), 3.90, 3.92 (2×OMe).

While a single compound [**4**] was obtained by crystallization from Et_2O, the precipitate from aqueous NH_3 was a mixture of **3** and **4**. The ^{1}H-nmr spectrum of this crude material in $CDCl_3$ showed unequivocally a mixture of compounds **3** and **4** in a 1:3 ratio. The experiment proved the simultaneous formation of both basic forms as a result of the competition of the two nucleophiles present in aqueous NH_3. This is in good agreement with previous work in which a mixture of two unidentified products was obtained from chelerythrine chloride [**1b**] after treatment with NH_3 (25).

The eims spectrum of compound **4** displayed a weak molecular ion (0.1%) and a very intense ion at *m/z* 348 (formula **1b**). The fragments important for the proof of the structure appeared at *m/z* 680 (corresponding to a loss of the methoxy group $[M-31]^+$) and at *m/z* 665 (a loss of the methylenedioxy group $[M-46]^+$). The peak at *m/z* 405 corresponds to the fragment consisting of one half of the dimeric molecule (*m/z* 348) +15 (the NH bridge) +42 (fragment -CH=N-CH_3 from the other half of the dimer). The peaks at *m/z* 363 and 364 correspond to the mass of dihydrochelerythrine with NH and NH_2 at C-6, respectively. The base peak at *m/z* 348 results from the most stable fragment, aromatic quaternary cation **1b**. The fragments of the monomeric part at *m/z* 333, 318, 304, 290, 275, 247, and 232 are in good agreement with the published data for 6-substituted derivatives of dihydrochelerythrine (1,13,25). They are formed by the stepwise loss of methyl, carbonyl, and formyl groups.

In the positive ci mode, a doublet at *m/z* 711 $[M]^+$ and 712 $[M+H]^+$ appeared, the second being more intense than expected for the isotopic peak of *m/z* 711. This is in agreement with the molecular weight of 711 daltons. Furthermore, the ms/ms fragment ion spectrum of the *m/z* 712 ion yielded an intense fragment at *m/z* 363 (30% of the base peak), corresponding to structure **1b** with an additional 6-NH_2 group.

From all the experiments described above it can be concluded that the chelerythrine free base is either *bis*[6-(5,6-dihydrochelerythrinyl)] ether [**3**] or *bis*[6-(5,6-dihydrochelerythrinyl)] amine [**4**], according to the method of their preparation. Both compounds in the presence of acids (even weak ones) immediately form the quaternary salt **1b**.

Nmr spectral experiments proved the formation of 5,6-dihydro-6-hydroxychelerythrine **2a** (pseudobase, alkanolamine) as a primary product in alkaline media. However, **2a** is an unstable species and cannot be isolated as a discrete compound under the usual conditions. In solution, it dimerizes, forming the derivative **3**, which can be isolated as a relatively stable crystalline substance.

The mother liquors, after crystallization of **3** and **4** from Et_2O, afforded some other crystalline substances. These products have considerably lower mps and different nmr spectra. They were missing when bases were precipitated from H_2O. These compounds have not been identified yet but are being investigated.

It seems that the aforementioned properties are common for all QBA of the sanguinarine group (10). Our partial and unpublished results indicate that *bis*[6-(5,6-dihydrosanguinarinyl)] ether can be obtained by the same procedure as for **3**. Elemental analysis proved the composition $C_{40}H_{28}N_2O_9$ and eims gave peaks at *m/z* 679 $[M-1]^+$ (0.1), 648 (0.3), 647 (0.05), 633 (0.5), 332 (100), 317 (95).

The formation of dimeric derivatives is an intrinsic property of benzophenanthridine alkaloids. The structures of dimers containing -CH_2COCH_2- and -HC(CHO)- bridges connecting the principal parts have already been published (1,26,27).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on a Mettler FP51 apparatus and are uncorrected. Ir spectra were measured with a Perkin-Elmer 783 spectrophotometer. ^{1}H-, ^{13}C-, and 2D nmr spectra were recorded on Tesla BS 587A and Varian VXR 300 instruments, with δ values reported in ppm downfield relative to TMS as internal standard. Mass spectra were obtained using a Finnigan-MAT TSQ70 instrument operated in the electron impact (70 eV) mode, and in the ci mode using a CH_4/N_2O mixture as the ionizing gas. Tandem mass spectrometry was performed using Xe as collision gas at a pressure of 0.8 mTorr with a collision offset voltage of 10 V. Elemental analysis was performed on a Perkin-Elmer 2400 instrument. Chelerythrine chloride [**1b**] was isolated from plant material (*Dicranostigma lactucoides* Hook. f. et Thoms) as described previously (28). Et_2O was entirely free of EtOH. Nujol for ir measurements was dried over Na.

Chelerythrine chloride [**1b**].—Yellow needles; mp 209–210°; ir (KBr) ν max 3380 (br, crystallized H_2O), 2920, 2900, 2820, 1640 (C=N$^+$), 1615, 1600, 1575, 1545, 1475, 1450, 1360, 1325, 1280, 1250, 1100, 1035 (C-O-C), 975, 925, 870, 825 cm^{-1}; ^{1}H nmr (80 MHz, DMSO-d_6) δ 4.12, 4.22 (3H each, 2×s, 2×OMe), 5.01 (3H, s, NMe), 6.32 (2H, s, OCH_2O), 7.72 (1H, s, H-1), 8.27 (1H, s, H-4), 8.25 (1H, d, J=9 Hz, H-9), 8.29 (1H, d, J=9 Hz, H-12), 8.77 (2H, d, J=9 Hz, H-10, H-11), 10.04 (1H, s, H-6); fabms *m/z* [M]$^+$ 348 (100), 333 (9), 318 (6), 307 (4), 290 (5), 167 (3), 154 (37), 136 (35), 124 (5).

bis[*6-(5,6-Dihydrochelerythrinyl)*] *ether* [**3**].—Chelerythrine chloride [**1b**] (59 mg) was dissolved in H_2O and the solution was made alkaline with a saturated solution of K_2CO_3. The precipitate was extracted with Et_2O. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The solution was allowed to stand at room temperature. After two days, colorless crystals were collected and dried *in vacuo* (28 mg): mp 256–258°; ir (nujol) ν max 1600 (aromatic C=C), 1495, 1405, 1280, 1235, 1195, 1165, 1140, 1105, 1080, 1035 (C-O-C), 1015, 970, 940, 890, 860, 845, 820 cm^{-1}; ^{1}H- and ^{13}C-nmr data ($CDCl_3$), see Table 1; ^{13}H nmr (80 MHz, DMSO-d_6) δ 2.98 (3H, s, NMe), 2.36, 3.67 (3H each, 2×s, 2×OMe), 6.21, 6.24 (2H, OCH_2O), 6.41 (1H, s, H-6), 6.98–7.86 (6H, m, aromatic H); eims *m/z* [M−1]$^+$ 711 (0.3), 682 (0.1), 681 (0.4), 666 (0.2), 665 (0.5), 578 (0.07), 522 (0.1), 478 (0.1), 382 (0.3), 380 (1.3), 364 (3), 348 (100), 333 (66), 318 (13), 304 (5), 290 (31), 275 (7), 232 (7), 217 (6), 188 (6), 166 (6); cims (positive-ion) *m/z* [M+1]$^+$ 713 (0.9), 433 (0.7), 378 (6), 362 (9), 350 (64), 348 (100), 333 (25); cims (negative-ion) *m/z* [M−H]$^-$ 711 (4), 681 (8), 364 (33) 346 (53), 336 (100); *anal.*, calcd for $C_{42}H_{36}N_2O_9$, C 70.77, H 5.09, N 3.93; found, C 70.58, H 4.92, N 3.83.

From the mother liquor, 33 mg of an unidentified substance with a mp of 111–113° crystallized.

bis[*6-(5,6-Dihydrochelerythrinyl)*] *amine* [**4**].—Chelerythrine chloride [**1b**] (53 mg) was dissolved in H_2O and the solution was made alkaline with a concentrated solution of NH_3. The precipitate formed was extracted with Et_2O. The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to yield colorless crystals, with the product dried *in vacuo* (27 mg): mp 268–270°; ir (nujol) ν max 3310 (NH), 1595 (aromatic C=C), 1495, 1285, 1265, 1235, 1195, 1165, 1140, 1075, 1035 (C-O-C), 1020, 980, 935, 890, 865, 840, 815 cm^{-1}; ^{1}H- and ^{13}C-nmr data ($CDCl_3$), see Table 1; ^{1}H nmr (80 MHz, DMSO-d_6) δ 3.34 (3H, s, NMe), 2.81, 3.67 (3H each, 2×s, 2×OMe), 5.85 (1H, d, J=6.3 Hz, H-6), 6.20, 6.24 (2H, OCH_2O), 7.37 (1H, s, H-1), 7.88 (1H, s, H-4), 6.96 (1H, d, J=8.2 Hz, H-9), 7.52 (1H, d, J=8.2 Hz, H-12), 7.55 (1H, d, J=8.2 Hz, H-10), 7.76 (1H, d, J=8.2 Hz, H-11); ^{13}C nmr (50 MHz, DMSO-d_6) δ 40.85 (NMe), 55.55, 59.46 (2×OMe), 63.59 (C-6), 101.23 (OCH_2O), 100.29, 104.26, 112.26, 118.65, 119.76, 123.11 (6×C-H aromatic), 122.53, 124.43, 127.01, 130.77, 138.73, 145.03, 147.09, 147.64, 151.58 (10×C q); eims *m/z* [M]$^+$ 711 (0.1), 680 (0.06), 665 (0.1), 405 (0.7), 364 (8), 348 (100), 333 (47), 318 (14), 304 (8), 290 (31), 275 (13), 265 (9), 247 (3), 232 (7), 217 (5), 188 (6), 166 (8); cims (positive ion) [M+1]$^+$ 712 (5), [M]$^+$ 711 (7), 393 (19), 365 (20), 348 (36), 279 (26), 214 (95), 89 (100); *anal.* calcd for $C_{42}H_{37}N_3O_8$, C 70.87, H 5.24, N 5.90; found, C 70.62, H 5.28, N 5.93.

From the mother liquor, 22 mg of an unidentified substance with a mp of 124–125° crystallized.

REACTION OF CHELERYTHRINE CHLORIDE [**1b**] WITH NaOD.—Chelerythrine chloride [**1b**] (4.8 mg; 12 μmol) was dissolved in DMSO-d_6 and a 30% solution of NaOD in D_2O (10 μl; ca. 350 μmol) was added. The ^{1}H-nmr spectrum was recorded at 60° and showed a mixture of derivatives **2b** and **3** in a ratio of 4:1.

6-Deuteroxy-5,6-dihydrochelerythrine [**2b**].—^{1}H nmr (80 MHz) δ 2.59 (3H, s, NMe), 3.86, 3.88 (3H each, 2×s, 2×OMe), 5.79 (1H, s, H-6), 6.11 (2H, s, OCH_2O), 7.07–7.90 (6H, m, aromatic H).

TREATMENT OF CHELERYTHRINE CHLORIDE [**1b**] WITH AQUEOUS K_2CO_3.—Chelerythrine chloride [**1b**] (27 mg) was dissolved in H_2O and the solution was made alkaline with a saturated solution of K_2CO_3. The precipitate formed was allowed to stand for 0.5 h at room temperature and then filtered off, washed with H_2O, and dried (22 mg). Mp 257–260°. The ^{1}H-nmr spectrum of this material in $CDCl_3$ was identical with analogous data for **3**.

TABLE 1. ^{1}H- and ^{13}C-Nmr Data of Compounds **3** and **4**.[a]

Position	Compound			
	3		**4**	
	δ ^{1}H	δ ^{13}C	δ ^{1}H	δ ^{13}C
1,1′	7.16 s	104.46	7.15 s	104.33
2,2′		147.47[b]		147.38[c]
3,3′		148.03[b]		147.93[c]
4,4′	7.93 s	100.81	7.99 s	101.00
4a,4′a		126.89		127.74
4b,4′b		138.37		139.42
6,6′	6.61 s	77.42	5.98 s	64.02
6a,6′a		123.22		123.07
7,7′		146.27		145.84
8,8′		152.07		151.94
9,9′	6.84 d (8.7)	112.25	6.79 d (8.7)	111.51
10,10′	7.48 d (8.7)	118.66	7.42 d (8.7)	118.58
10a,10′a		126.11[d]		125.23
10b,10′b		125.47[d]		128.31
11,11′	7.68 d (8.5)	119.79	7.65 d (8.5)	119.80
12,12′	7.44 d (8.5)	123.22	7.42 d (8.5)	123.13
12a,12′a		131.16		131.16
OCH_2O (2,3;2′,3′)	6.11 s	101.09	6.10 s	101.00
NMe, N′Me	3.05 s	40.83	2.91 s	41.00
OMe-7, OMe-7′	2.41 s	60.37	2.58 s	60.31
OMe-8, OMe-8′	3.72 s	55.62	3.72 s	55.59

[a]Recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$; shifts in ppm. Values in parentheses are coupling constants in Hz.

[b–d]Values with the same superscript may be interchanged.

TREATMENT OF CHELERYTHRINE CHLORIDE [**1b**] WITH AQUEOUS NH_3.—Chelerythrine chloride [**1b**] was dissolved in H_2O and the solution was made alkaline with concentrated aqueous NH_3. The precipitate formed was allowed to stand for 1 h at room temperature, then was filtered off, washed with H_2O, and dried *in vacuo*. The ^{1}H-nmr spectrum of this material in $CDCl_3$ showed a mixture of derivatives **3** and **4** in a ratio of 1:3.

TREATMENT OF **3** WITH D_2O.—Compound **3** was dissolved in DMSO-d_6 to which was added a drop of D_2O in an nmr tube. The spectrum was recorded at 70°. In addition to the signals of **3** the signals of 6-deuteroxy-5,6-dihydrochelerythrine [**2b**] appeared.

TREATMENT OF **4** WITH D_2O.—Compound **4** was dissolved in $CDCl_3$ and a drop of D_2O was added in an nmr tube. In addition to the signals of **4**, the resonances of **2b**, **2f**, and **3** appeared (recorded at 80 MHz).

6-Deuteroxy-5,6-dihydrochelerythrine [**2b**].—^{1}H nmr (80 MHz) δ 6.05 (2H, s, OCH_2O), 6.02 (1H, s, H-6), 4.00, 3.94, (3H each, 2×s, 2×OMe), 2.72 (3H, s, NMe).

6-Amino-d-*5,6-dihydrochelerythrine* [**2f**].—^{1}H nmr (80 MHz) δ 6.08 (2H, s, OCH_2O), 3.92, 3.90 (3H each, 2×s, 2×OMe), 2.71 (3H, s, NMe). After 20 days the amount of compound **3** in the mixture increased considerably.

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