# Cancentrine. III.[1] Dehydroderivatives

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The structures of dehydrocancentrine-A and -B are elucidated by a combination of physical and chemical methods.

Les structures des déhydrocancentrines-A et -B ont été élucidées au moyen de méthodes physiques et chimiques.

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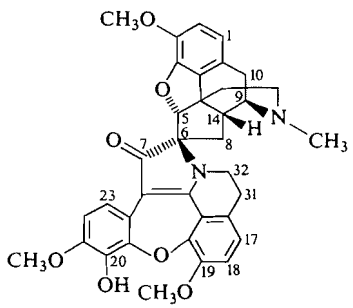
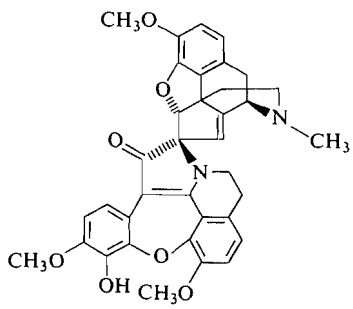
Recently we reported the characterization and structural elucidation of a new dimeric benzylisoquinoline alkaloid, cancentrine (1, 2). Here we describe two new alkaloids, dehydrocancentrine-A (**2**) and dehydrocancentrine-B (**3**), closely related in structure to cancentrine (**1**). Both alkaloids are found in *Dicentra canadensis* (Goldie) Walp. in very small amounts and were separated from cancentrine by chromatography.

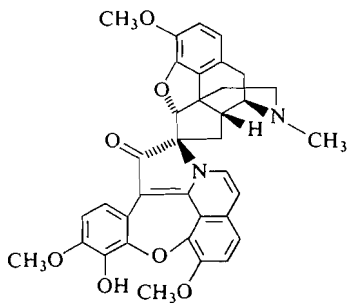
Dehydrocancentrine-B is a red alkaloid with the following u.v. spectrum: $\lambda_{max}^{EtOH}$ 216 (sh), 242, 270 (sh), 310 (sh), 370, 446, 492, and 525 (sh) nm; log $\varepsilon_{max}$ 4.86, 4.78, 4.23, 4.16, 3.90, 4.00, 3.95, and 3.85, respectively. It has i.r. bands at 3450 (OH), 1660 (C=O), and 1630 (C=C) $cm^{-1}$. In its mass spectrum the molecular ion appeared at *m/e* 604 corresponding to an elemental composition of $C_{36}H_{32}N_2O_7$. The fragmentation pattern is very similar to that of cancentrine (2), with the exception that the ions due to the 'cularine' part (moiety A) appear two mass units lower than in the case of cancentrine, indicating that the double bond must be located in the cularine part of the molecule. The only available position is at $C_{31}$—$C_{32}$ and the fragmentation pattern is rationalized accordingly (Scheme 1). Only the formation of the most abundant ions is represented. The elemental compositions in parentheses were determined by high resolution mass spectrometry. Fissions 'a' and 'b' (2) taking place as indicated lead to two fragment ions, one corresponding to the morphine part (moiety B) which fragments further in exactly the same manner as in cancentrine, and the other corresponding to the cularine part, now two mass units lower (at *m/e* 361) than the corresponding ion in cancentrine. Fissions a and b also proceed with H transfer to give an ion at *m/e* 362. Alternatively, fragmentation at 'a' and 'c' with hydrogen transfer from the 'morphine' to the 'cularine' moiety leads to ions at *m/e* 256 and 348, the latter again being two mass units



**1**

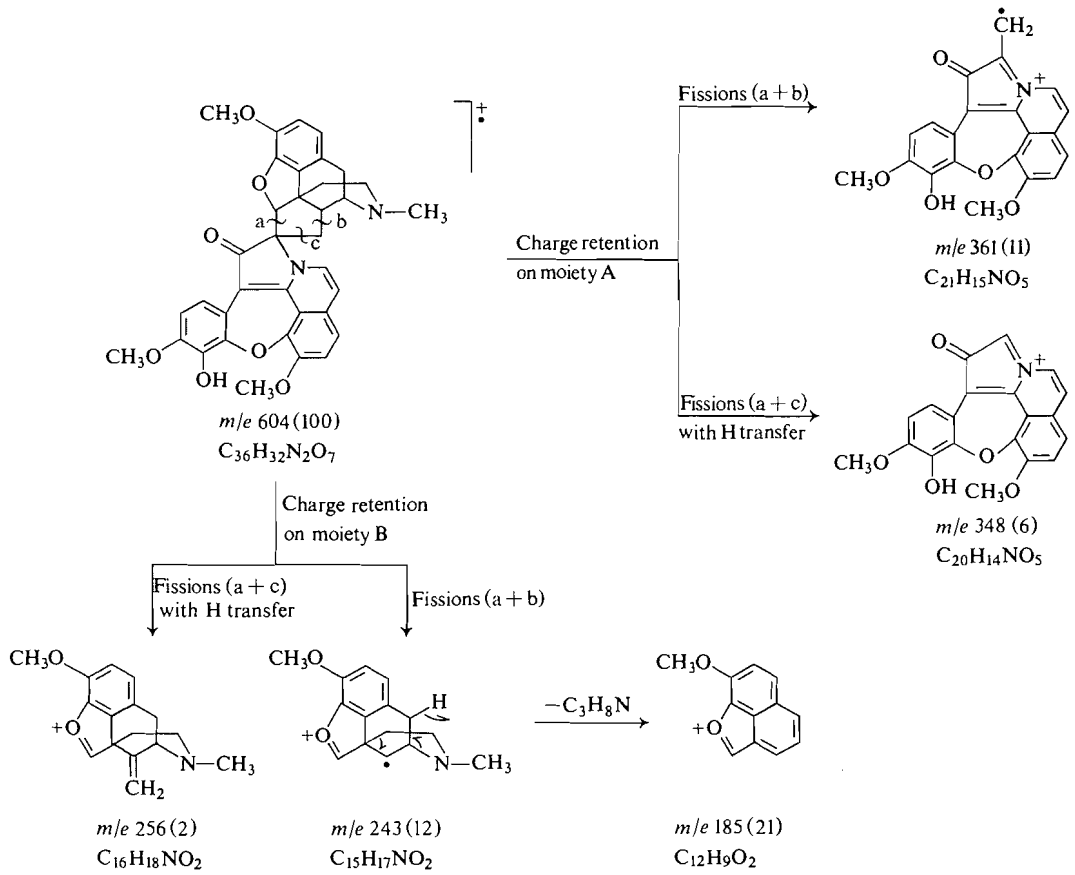


**2**



**3**

[1]For Part II, see ref. 2.

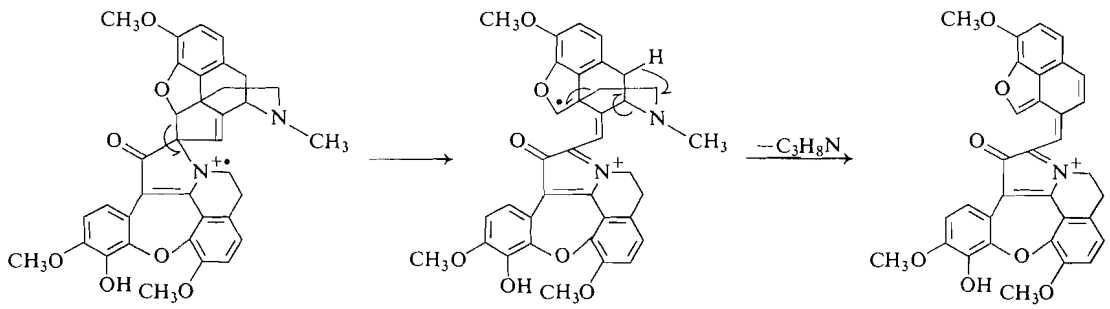



SCHEME 1

lower than the corresponding ion in cancentrine. These ions do not appear to fragment further.

The p.m.r. spectrum confirms this placement of the double bond at $C_{31}$—$C_{32}$. The spectrum displays a sharp singlet at 2.50 $\delta$ (3H) corresponding to one *N*-methyl group, three sharp singlets at 3.84 (3H), 3.90 (3H), and 3.99 $\delta$ (3H) due to the three aromatic methoxyls, a sharp singlet at 4.84 $\delta$ (1H) attributed to the 5$\beta$ proton, and the three aromatic AB systems (6H). A fourth new AB system due to the double bond at $C_{31}$—$C_{32}$ is partly masked by the aromatic hydrogens but one half of it is clearly seen at 6.25 $\delta$ (1H) with a coupling constant $J_{AB} = 7.0$ Hz.

Dehydrocancentrine-A is a yellow alkaloid with the following u.v. spectrum: $\lambda_{max}^{EtOH}$ 216, 269, 296 (sh), and 445 nm; log $\varepsilon_{max}$ 4.77, 4.36, 4.29, and 3.87, respectively. It has i.r. bands at 3440 (OH), 1660 (C=O), and 1620 (C=C) $cm^{-1}$. Its high resolution mass spectrum has a molecular ion at *m/e* 604 corresponding in composition to $C_{36}H_{32}N_2O_7$. The 100 MHz p.m.r. spectrum of dehydrocancentrine-A (in $CDCl_3$) has all the characteristic peaks of cancentrine (2), namely, three aromatic methoxyls at 3.80 (6H) and 3.93 $\delta$ (3H), one *N*-methyl singlet at 2.53 $\delta$ (3H), and six aromatic hydrogens forming three AB systems. There is also a sharp singlet at 5.04 $\delta$ as in the case of cancentrine but integrating for more than one proton. The spectrum was therefore recorded in DMSO-$d_6$ where it showed two sharp singlets at 5.05 and 5.26 $\delta$ integrating for one proton each and attributed to the 5$\beta$ hydrogen and a vinylic hydrogen, respectively. The vinylic proton is not coupled to any other proton in the spectrum and, therefore, the double bond in **2** must be




SCHEME 2

located at $C_9$—$C_{10}$ or $C_8$—$C_{14}$. A double bond at $C_9$—$C_{10}$ would be at a bridgehead position, and therefore the structure of dehydrocancentrine-A is represented as in formula **2**.

This structure is in accord with the fragmentation pattern revealed in the mass spectrum. The only important fragment ion is formed by loss of the nitrogen bridge from the molecular ion giving rise to the ion at *m/e* 546 (Scheme 2). This is typical of the morphine alkaloids (3). The ion at *m/e* 546 has no tendency to fragment further because of its aromatic character. This behavior of **2** is strikingly different from that of cancentrine and its derivatives, and constitutes a good example of how a small structural change in a molecule can have a dramatic effect upon its fragmentation pattern. Both the molecular ion, *m/e* 604, and the fragment ion, *m/e* 546, have homologous ions 14 mass units above and below, apparently resulting from *trans* methylation processes at the high source temperatures required for volatilization of these high molecular weight compounds. Dehydrocancentrine-B behaved similarly but to a lesser degree.

Finally, the position of the hydroxyl group in **2** and **3** was shown to be identical with that in cancentrine by catalytic hydrogenation of the alkaloids to the latter compound. In the case of **2** a small amount of another yellow compound probably the C-14 epimer, was also formed and detected by t.l.c. Dehydrogenation of cancentrine over 5% palladium–charcoal in boiling naphthalene gave *inter alia* **2** and **3** in low yield and only detectable by t.l.c. Since the relative stereochemistry of cancentrine is known (1), these results support the stereochemical assignments made for the alkaloids in structures **2** and **3**.

## Experimental

*Methods*

Melting points were determined on a Fisher Mel-Temp apparatus and are uncorrected. Mass spectra[2] were recorded on a CEC 21-110B double focussing mass spectrometer. For high resolution work, spectra were recorded on plates and accurate mass measurements were made using perfluorokerosene as marker (4). The p.m.r. spectra were recorded using the frequency sweep mode of a Varian HA-100 spectrometer. Samples were dissolved in $CDCl_3$ (unless otherwise specified) using added TMS as the internal locking signal. Chemical shifts were measured relative to TMS using a V315 frequency counter incorporated in the instrument. A Beckmann IR 10 spectrometer was used to record the i.r. spectra and a Coleman-Hitachi EPS-3T spectrometer was used for the u.v. spectra.

*The Purification of Cancentrine and Isolation of Dehydrocancentrine-A and -B*

Crude cancentrine (5) when chromatographed on a t.l.c. plate (silica gel) in benzene–methanol (4:1) proved to be a mixture of several compounds. The major component cancentrine (90%) had a $R_f$ of about 0.35 in the system, while dehydrocancentrine-A ran about 20% faster and dehydrocancentrine-B almost overlapped with cancentrine (*ca.* 2% faster).

Cancentrine (10 g) was chromatographed on a large column of silica gel (85 × 3 cm; 70–325 mesh ASTM; E. Merck) in benzene–methanol, 9:1. The column was eluted slowly over several days and the relevant fractions collected.

The solvents were removed and the residues crystallized from methanol. Dehydrocancentrine-A (40 mg), m.p. 194°. Dehydrocancentrine-B could only be induced to crystallize after repeated chromatography to separate it completely from cancentrine (25 mg), m.p. 206°. The molecular formulae were determined by high resolution mass spectrometry.

Dehydrocancentrine-A: Calcd. for $C_{36}H_{32}N_2O_7$: 604.221. Found: 604.224.

Dehydrocancentrine-B: Calcd. for $C_{36}H_{32}N_2O_7$: 604.221. Found: 604.221.

[2]A complete listing of mass spectral data may be found in the Depository of Unpublished Data, National Science Library, National Research Council, Ottawa, Canada K1A 0S2.

*Hydrogenation of Dehydrocancentrine-A and -B*

Dehydrocancentrine-A (20 mg) in methanol (25 ml) was hydrogenated overnight at room temperature and pressure in the presence of Adams catalyst (10 mg). The solution was filtered and the methanol removed from the filtrate under reduced pressure. A small specimen of the residue when tested by t.l.c. (silica gel; benzene–methanol, 4:1) showed the presence of cancentrine (*ca.* 90%) and another yellow compound (*ca.* 10%) with $R_f$ about half that of cancentrine. The bulk of the crude product was therefore purified by column chromatography and crystallized from $CHCl_3$–MeOH (12 mg), m.p. 235°. The i.r. spectrum of the product and its behavior on t.l.c. were identical with that of cancentrine.

Dehydrocancentrine-B (5 mg) was similarly hydrogenated, in this case, a single product was obtained. Its. i.r. spectrum and t.l.c. behavior were identical with that of cancentrine.

*Dehydrogenation of Cancentrine*

Cancentrine (1 g) was refluxed in naphthalene (5 g) with 5% palladium–charcoal (100 mg) for 3 h. Most of the naphthalene was sublimed out on a steam bath under reduced pressure and a small specimen of the residue was then examined by t.l.c. using the same system as before. It proved to be a very complex mixture containing a large proportion of unchanged cancentrine but the presence of both dehydrocancentrine-A and -B was clearly evident. The bulk of the dehydrogenation product was then chromatographed on a column of silica gel as before and the relevant fractions taken. These fractions when examined by t.l.c. in comparison with authentic samples, confirmed the presence of dehydrocancentrines-A and -B, but it was not possible to obtain these small amounts of material sufficiently pure to induce crystallization.

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