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CONFORMATIONS OF PHTHALIDEISOQUINOLINE SALTS AND *N*-OXIDES

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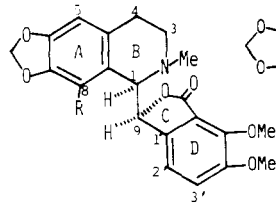
ABSTRACT.—The conformations of two *erythro* bases, (−)-α-narcotine [**1**] and (−)-β-hydrastine [**2**], and two *threo* analogs, (−)-β-narcotine [**3**] and (−)-α-hydrastine [**4**] are compared, together with those of their hydrochloride salts, *N*-metho salts, and *N*-oxides. In most instances, the conformations of the salts and the *N*-oxides are different from those of the free bases.

The classical type phthalideisoquinolines present an interesting problem in conformational analysis, since they may, a priori, adopt any number of different spatial arrangements based upon free rotation about the central C-1 to C-9 axis. The problem has been considered by Shamma and co-workers (1,2) and Kövér and Kerekes (3) who studied a variety of norphthalideisoquinolines and phthalideisoquinolines, all of which were unsubstituted at C-8. It was determined that nor-*erythro* as well as *N*-methylated *erythro* bases prefer to exist in conformation **I**. In the *threo* series, however, conformation **II** is favored for the nor compounds, while **III** predominates in the *N*-methylated analogs.

Because the C-8 oxygenated *erythro* phthalideisoquinoline (−)-α-narcotine [**1**] is used as an antitussive drug in the form of its hydrochloride salt (4,5), we became interested in establishing the favored conformations of (−)-α-narcotine [**1**] and its diastereomer (−)-β-narcotine [**3**], as the free bases and also as the hydrochloride salts. Our studies were then extended to cover the corresponding methiodide salts as well as the *N*-oxides. Inasmuch as the hydrochlorides and *N*-oxides of (−)-β-hydrastine [**2**] and (−)-α-hydrastine [**4**] had not been previously investigated, these were also included in the present study. Hence, of the four bases we considered, two belonged to the *erythro*-series, namely (−)-α-narcotine [**1**] and (−)-β-hydrastine [**2**], while the remaining two, (−)-β-narcotine [**3**] and (−)-α-hydrastine [**4**], incorporated the *threo* stereochemistry.



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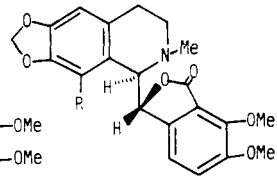

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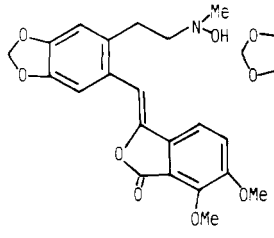

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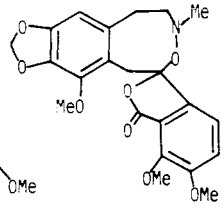

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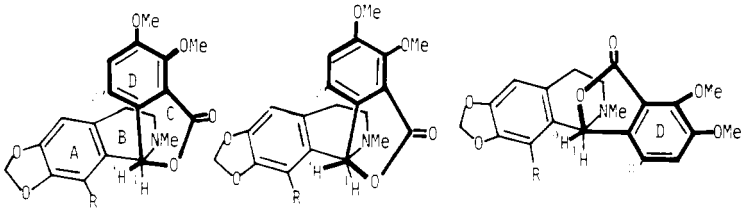
TABLE 1. ^{1}H-nmr Chemical Shifts (in ppm) for N-CH_3, H-1, and H-2′ of the Alkaloids **1–4** in $CDCl_3$

	N-CH_3	H-1	H-2′
(−)-α-Narcotine [**1**]	2.55	4.39	6.08
(−)-β-Hydrastine [**2**][a]	2.55	3.98	6.52
(−)-β-Narcotine [**3**]	2.15	4.21	6.98
(−)-α-Hydrastine [**4**][a]	2.56	4.01	7.30

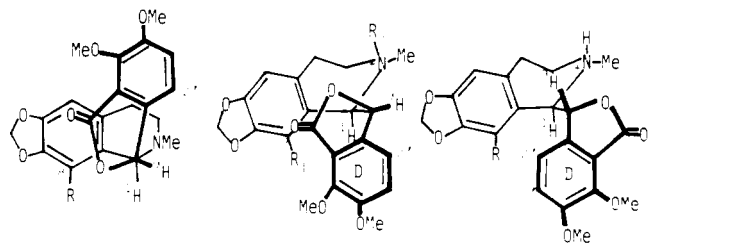
[a]Data in Blaskó *et al.* (1) and Elango *et al.* (2).

PHTHALIDEISOQUINOLINE FREE BASES.—(−)-α-Narcotine [**1**], which incorporates the same stereochemistry as (−)-β-hydrastine [**2**], exists primarily in conformation **I** in which ring B is a twist half-chair. The H-2′ signal in the ^{1}H-nmr spectrum of (−)-α-narcotine [**1**] is found relatively upfield at 6.08 ppm. This value should be compared with the corresponding chemical shift for (−)-β-hydrastine [**2**] which is 6.52 ppm (Table 1). H-2′ in (−)-α-narcotine [**1**] is more within the shielding zone of ring A than the same hydrogen in (−)-β-hydrastine [**2**] due to a slight distortion of ring B in the former to accommodate the bulky C-1 substituent.

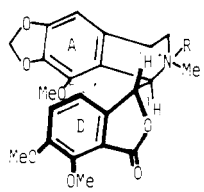
Turning now to (−)-β-narcotine [**3**], which partakes of the *threo*-stereochemistry, we find that this isomer adopts conformation **II** in which the 8-methoxyl and ring C are far apart. Nmr nOe of H-1 results in a 7.9% enhancement of H-2′ (6.98 ppm) so that these hydrogens must be proximate, a requirement fulfilled by conformation **II** but not by **III**. An additional piece of evidence buttressing the assignment of conformation **II** is the large upfield shift (to 2.15 ppm) of the *N*-methyl singlet for (−)-β-narcotine [**3**], whereas the corresponding value for the *erythro* analog (−)-α-narcotine [**1**] is 2.56 ppm



I **I′** **II**



III **IV** **V**



VI

(Table 1). In conformation **II** the *N*-methyl group clearly lies within the shielding zone of ring D and would, therefore, indeed be expected to appear upfield in the nmr spectrum.

The preferred orientation of the *N*-methyl group in free bases was examined by an nOe experiment and by the Bohlmann bands (6). Saturation of the *N*-methyl group at 2.15 ppm in (−)-β-narcotine [**3**] results in a 21.4% enhancement of the H-1 signal at 4.21 ppm. This value is approximately equal to the value (21.7%) for the corresponding proton in (−)-α-narcotine [**1**]. The ir spectrum of (−)-β-narcotine [**3**] shows the Bohlmann band having the apparent molecular absorptivity (7) of 94 at ca. 2800 cm^{-1}, and the ir spectrum of (−)-α-narcotine [**1**] shows Bohlmann band possessing absorptivity of 114 at ca. 2800 cm^{-1}. These data indicate an equatorial orientation of the *N*-methyl group of (−)-β-narcotine [**3**] as well as (−)-α-narcotine [**1**].

It has been stated that the ^{13}C-nmr chemical shifts for C-3 and C-4 may be used in establishing the relative stereochemistry of the classical phthalideisoquinolines (8). Our present results, summarized in Table 2, are at variance with such a conclusion. If one were to look solely at the ^{13}C-nmr data, one would be tempted to conclude that (−)-α-narcotine [**1**] and (−)-α-hydrastine [**4**] possess one kind of stereochemistry, while (−)-β-hydrastine [**3**] and (−)-β-narcotine [**2**] possess another—which is clearly not the case.

TABLE 2. ^{13}C-nmr Chemical Shifts (in ppm) for C-3 and C-4 of the Alkaloids **1–4** in $CDCl_3$

Relative Configuration	Compounds	C-3	C-4
erythro	(−)-α-Narcotine [**1**][a]	50.1	28.1
erythro	(−)-β-Hydrastine [**2**][a]	49.0	26.7
threo	(−)-β-Narcotine [**3**]	49.5	26.5
threo	(−)-α-Hydrastine [**4**]	51.3	29.2

[a]Data in Blaskó *et al.* (1) and Elango *et al.* (2).

PHTHALIDEISOQUINOLINE HYDROCHLORIDES.—The nmr coupling constant between H-1 and H-9 in the spectrum of (−)-α-narcotine [**1**] hydrochloride is close to 0°. This fact denotes a minor conformational change from **I** to **I′** in going from the free base to the protonated salt. In conformation **I′**, the dihedral angle between H-1 and H-9 is more nearly 90°.

(−)-β-Hydrastine [**2**] hydrochloride exists mostly in conformation **IV** in which the dihedral angle between H-1 and H-9 is also close to 90°, leading to a coupling constant near 0°. The chemical shift of H-2′ falls at lower field (7.55 ppm) than in (−)-α-narcotine [**1**] hydrochloride (7.16 ppm), because in the latter salt which exists in conformation **I′**, H-2′ lies within the ambit of the shielding zone of ring A (Table 3).

On the other hand, the hydrochlorides of (−)-α-hydrastine [**4**] and (−)-β-narcotine [**3**] prefer conformation **V**, an arrangement which had previously never been encountered with the phthalideisoquinolines. Saturation of H-1 in the ^{1}H nmr of (−)-β-narcotine [**3**] having conformation **II**, in which the hydrogens at C-1 and C-9 are gauche, results in a 20.2% enhancement of H-9, while in (−)-β-narcotine [**3**] hydrochloride saturation of H-1 gives only a 2.7% enhancement of H-9 so that these hydrogens must be far apart, a requirement fulfilled by conformation **V**. The dihedral angle between H-1 and H-9 in (−)-α-hydrastine [**4**] hydrochloride is larger than in (−)-β-narcotine [**3**] hydrochloride as indicated by the larger coupling constant for the former (8.0 Hz) as compared to the latter (6.5 Hz). This relatively minor conformational

TABLE 3. ^{1}H-nmr Spectra Data for the Hydrochlorides, *N*-Oxides, and *N*-Methiodide of the Phthalideisoquinolines (**1–4**)[a]

Compound	Preferred Conformation	N-CH_3	O-CH_3		H-1	H-9	OCH_2O		H-5	H-2′	H-3	H-8
1 HCl[b]	**I′**	3.10	3.63 3.94	3.93	5.36	6.14 brd J=1.0	5.92[d]	5.96[d]	6.55	7.16[e]	7.51[e]	
1 HCl[c]	**I′**	3.01	3.45 3.86	3.80	5.28	6.07	5.74	5.84	6.48	7.17 br	7.46[e]	
2 HCl[b]	**IV**	3.16	3.89	3.99	5.13	6.19	5.86[d]	5.88[d]	6.78	7.55[e]	7.60[e]	5.60
2 HCl[c]	**IV**	3.08	3.75	3.89	4.98	6.14	5.71	5.80	6.72	7.40[e]	7.53[e]	5.48
3 HCl[b]	**V**	2.98	3.69 4.07	3.94	4.97 d J=6.5	5.91 d J=6.5	6.0[d]	6.02	6.63	6.60[e]	7.40[e]	
3 HCl[c]	**V**	2.83	3.43 3.88	3.78	4.84 d J=6.5	5.69 d J=6.5	5.80	5.82	6.50	6.44[e]	7.24[e]	
4 HCl[b]	**V**	2.91	3.92	4.03	4.69 d J=8.0	5.90 d J=8.0	6.02[d]	6.05[d]	6.52	6.74 br	7.42[e]	6.89
4 HCl[c]	**V**	2.88	3.85	3.93	4.56 d J=8.0	5.81 d J=8.0	5.95	5.97	6.40	6.66[e]	7.32[e]	6.85
1 *N*-Oxide[b]	**IV**	3.40	3.69 3.95	3.89	5.09	6.14	5.78[d]	5.83[d]	6.44	7.54[e]	7.55[e]	
2 *N*-Oxide[b]	**IV**	3.63	3.87	3.96	4.77	6.31	5.77[d]	5.79[d]	6.68	7.58[e]	7.59[e]	5.36
3 *N*-Oxide[b]	**VI**	3.32	3.54 3.99	3.84	4.76 brd J=5.5	5.77 dd J=5.5, sh	5.84[d]	5.86[d]	6.51	5.98 dd J=8.4, 0.7	7.16[e]	
3 NCH_3I[b]	**VI**	3.19 3.33	3.58 4.01	3.87	5.03 dd J=6.0 1.4	6.10 d J=6.0	5.92[d]	5.94[d]	6.61	5.93 dd J=8.3, 0.8	7.21[e]	

[a]Chemical shifts are shown in ppm (δ_{TMS}=0 ppm) with coupling constant in Hz.
[b]Measured in CD_3OD.
[c]Measured in D_2O.
[d]Doublet J=1.0-1.2 Hz.
[e]Doublet J=8.0-8.5 Hz.

change is simply due to the presence of the 1-methoxyl substituent in (−)-β-narcotine [**3**].

Our nmr measurements were recorded in two different solvents, namely D_2O and CD_3OD, and no significant differences were noticed between these (Table 3).

PHTHALIDEISOQUINOLINE *N*-OXIDES.—The preparation of the *N*-oxides, using *m*-chloroperoxybenzoic acid, was accompanied by the formation of side products **5** and **6** (9). Though the required classical type phthalideisoquinoline *N*-oxides are quite unstable in solution, their nmr spectra could nevertheless still be recorded.

The *N*-oxides of the *erythro* series, i.e., (−)-α-narcotine [**1**] and (−)-β-hydrastine [**2**] prefer to exist in conformation **IV** which is also the conformation of (−)-β-hydrastine [**2**] hydrochloride. In (−)-β-hydrastine [**2**] *N*-oxide, as well as in (−)-β-hydrastine [**2**] hydrochloride, the H-8 singlet is located upfield (5.36 and 5.60 ppm, respectively) due to shielding by ring D (Table 3).

In contrast, (−)-β-narcotine [**3**] *N*-oxide adopts conformation **VI** in which the rings A and D are in close proximity. In the ^{1}H-nmr spectrum of (−)-β-narcotine [**3**] *N*-oxide, H-2′ is found upfield (5.98 ppm) due to shielding by ring A (Table 3).

PHTHALIDEISOQUINOLINE *N*-METHO SALTS.—Just like the *N*-oxide, (−)-β-narcotine [**3**] methiodide adopts conformation **VI**. A twist half-boat conformation for ring B in the methiodide is suggested on the basis of the W coupling (1.4 Hz) between H-1 and H-3. H-2′ is found upfield (5.93 ppm) as a result of shielding by ring A. Saturation of H-1 gives no nOe of H-9 so that these hydrogens are far apart.

In conclusion, it can be stated that the conformations for the salts and the *N*-oxides of the phthalideisoquinolines, except for (−)-α-narcotine [**1**] hydrochloride, differ appreciably from those of the corresponding free bases.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points are uncorrected. Mass spectra were taken with an Hitachi M80 instrument at 75 eV. Ir spectra were recorded on an EPI-G2 (Hitachi) spectrophotometer. ^{13}C- and ^{1}H-nmr spectra were measured with a Varian XL-200 spectrometer operating at 50.3 MHz and 200.06 MHz, respectively, at 24°. The nOe values were obtained from the nOe difference spectra in which the control spectrum with the decoupler off-resonance was subtracted from the spectrum after signal saturation. The solutions were degassed and sealed under vacuum. Tlc and preparative tlc were on Si gel 60 F-254 Merck glass plates.

(−)-α-Narcotine [**1**] and (−)-β-hydrastine [**2**] were commercial samples. (−)-β-Narcotine [**3**] and (−)-α-hydrastine [**4**] were prepared according to the procedure of Marshall *et al.* (10). (−)-β-Narcotine [**3**]: ^{13}C nmr ($CDCl_3$), δ 26.51 (C-4), 45.03 (N-CH_3), 49.54 (C-3), 56.88, 59.12, and 62.32 (3×OCH_3), 61.02 (C-1), 82.97 (C-9), 100.52 (OCH_2O), 102.39 (C-5), 116.62 (C-2′), 118.58 (C-3′), 118.18 (C-1a), 119.60 (C-6′), 131.30 (C-4a), 133.62 (C-7), 139.92 (C-1′), 142.07 (C-8), 147.92 (C-5′), 148.17 (C-6), 152.16 (C-4′).

HYDROCHLORIDES.—The alkaloids were dissolved in MeOH containing 2-3 drops of HCl. After 10 min, the solvent was removed in vacuo, and the residue was crystallized from Me_2CO; (−)-α-narcotine HCl, mp 192-203° (dec); (−)-β-hydrastine HCl, amorphous colorless powder; (−)-β-narcotine HCl, amorphous yellow powder; (−)-α-hydrastine HCl, mp 215-230° (dec).

PREPARATION OF (−)-α-NARCOTINE *N*-OXIDE.—(−)-α-Narcotine [**1**] (940 mg) was dissolved in $CHCl_3$ (30 ml), and *m*-chloroperoxybenzoic acid (570 mg) was added over 1 h. The solution was washed with 1% NaOH and then with H_2O. The organic layer was dried, and the solvent was evaporated. The residue was subjected to preparative tlc ($CHCl_3$-MeOH, 9:1) to give two products, **5** (154 mg), mp 227-230° [lit. (9) 228-229°]; ms *m/z* (rel. int.) 429 (M^+, 8), 370 (100); cims *m/z* 430 ($M^+ + 1$); ^{1}H nmr δ 2.72 (3H, s, N-CH_3), 3.26 and 3.94 (each 1H, d, J=14 Hz, Ar-CH_2-C<), 3.62, 3.89, and 4.14 (each 3H, s, 3×OCH_3), 5.93 and 5.97 (each 1H, d, J=1.5 Hz, OCH_2O), 6.39 and 7.07 (each 1H, d, J=8 Hz, 2×ArH), 6.49 (1H, s, ArH) and (−)-α-narcotine [**2**] *N*-oxide (116 mg), mp 120-122°; ms *m/z* (rel. int.) 429 (M^+, 7), 370 (100), 220 (52); cims *m/z* 430 ($M^+ + 1$).

PREPARATION OF (−)-β-HYDRASTINE *N*-OXIDE.—(−)-β-Hydrastine [**2**] (2.74 g) was dissolved in $CHCl_3$ (100 ml), and *m*-chloroperoxybenzoic acid (1.85 g) was added over 1 h. Work-up as above gave two products, **6** (2.18 g), mp 195-197° [lit. (9), 194-196°]; ms *m/z* 399 (M^+, 5), 383 (19), 340 (100), 190 (36), 188 (47); cims *m/z* 400 ($M^+ + 1$); ^1H nmr ($CDCl_3$) δ 2.74 (3H, s, N-CH_3), 3.97 and 4.18 (each 3H, s, 2×OCH_3), 6.0 (2H, s, OCH_2O), 6.55 (1H, s, C=CH), 6.74 and 7.74 (each 1H, s, 2×ArH), 7.26 and 7.43 (each 1H, d, J=8.0 Hz, 2×ArH) and (−)-β-hydrastine [**2**] *N*-oxide, amorphous (37 mg); ms *m/z* (rel. int.) 399 (M^+, 2), 340 (17), 190 (100); cims *m/z* 400 ($M^+ + 1$), which was converted to **6** after repeated recrystallization.

PREPARATION OF (−)-β-NARCOTINE *N*-OXIDE.—(−)-β-Narcotine [**3**] (1 g) was dissolved in $CHCl_3$ (30 ml), and *m*-chloroperoxybenzoic acid (580 mg) was added over 1 h. The solution was allowed to stand at room temperature overnight. Work-up gave **5** (150 mg), mp 222-224° and (−)-β-narcotine [**3**] *N*-oxide, amorphous (44 mg); ms *m/z* 429 (M^+, 2), 381 (18), 370 (12), 220 (100); cims *m/z* 430 ($M^+ + 1$).

PREPARATION OF (−)-β-NARCOTINE METHIODIDE.—(−)-β-Narcotine [**3**] (300 mg) was dissolved in $CHCl_3$ (20 ml), and MeOH (30 ml) and MeI (4 ml) were added. The solution was allowed to stand at room temperature overnight. The solvent was evaporated in vacuo, and the residue was crystallized from Me_2CO to give (−)-β-narcotine [**3**] methiodide (325 mg), mp 209-210° (dec); *Anal.* calcd for $C_{23}H_{26}NO_7I$: C, 49.74; H, 4.72; N, 2.52. Found: C, 49.83; H, 4.72; N, 2.44.

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