# THE NMR SPECTRA AND CONFORMATIONS OF THE PHTHALIDEISOQUINOLINES

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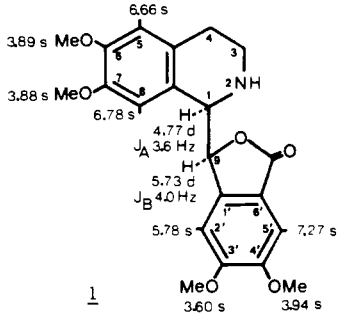
ABSTRACT.—A reconsideration of the nmr spectra of phthalideisoquinolines, including noe studies, has established that conformations **1A** and **2A** are favored for the erythro and the threo norphthalideisoquinolines, respectively; while conformations **1A** and **4A** predominate for the erythro and threo phthalideisoquinolines, respectively.

In conjunction with a new synthetic route to the phthalideisoquinolines, we had occasion some eight years ago to carry out an nmr study, at 60 MHz, of some of these compounds and their analogs. As a result, conclusions were reached concerning the most stable conformations for the *erythro*-nor and *threo*-norphthalideisoquinolines, as well as for their erythro and threo homologues, based mainly on nmr chemical shifts (1). Recently, however, with the advent of the better resolution offered by FT nmr spectroscopy at 200 MHz, we reinvestigated this rather complex problem, assisted also by a series of nmr nuclear Overhauser enhancement (noe) studies. In one instance, out of the four cases originally considered, our new conclusions are at variance with the old. Additionally, our present conclusions also differ in some aspects from recently published data on two phthalideisoquinolines (2) obtained through the use of a 90 MHz FT nmr spectrometer, but without the added advantage of noe experiments.[2]

(±)-*Erythro*-NORPHTHALIDEISOQUINOLINE **1**

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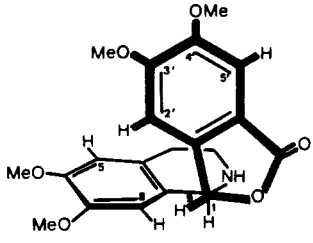


1A

TABLE 1. Nmr chemical shift ($\delta$) and noe data for compound **1**.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-8 (6.78) | H-2' | (5.78) | 4.1 |
| | H-9 | (5.73) | 39.6 |
| | H-1 | (4.77) | 8.3 |
| | C-2 $OCH_3$ | (3.88) | 8.6 |
| H-2' (5.78) | C-3' $OCH_3$ | (3.60) | 8.6 |
| H-9 (5.73) | H-8 | (6.78) | 20.8 |
| | H-1 | (4.77) | 7.3 |
| H-1 (4.77) | H-8 | (6.78) | 9.1 |
| | H-9 | (5.73) | 11.4 |

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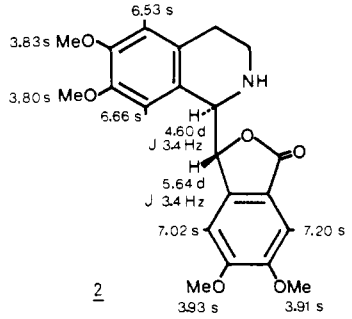
[2]The phthalideisoquinolines studied at 90 MHz correspond to our compounds **3** and **4**.

It will be noted first that H-2' appears upfield at δ5.78 since as indicated in preferred conformation **1A** it is shielded by ring A. The same argument applies to the C-3' methoxyl which also appears upfield at δ3.60. Significantly, irradiation of H-2' (δ5.78) leads to an 8.6% noe of this methoxyl signal (table 1). As required by the close proximity of H-1 with H-9 in expression **1A**, irradiation of H-8 (δ6.78) gives a 39.6% noe of H-9. Our conformational conclusions here are identical with those reached by us originally (1).

(±)-*Threo*-NORPHTHALIDEISOQUINOLINE **2**.

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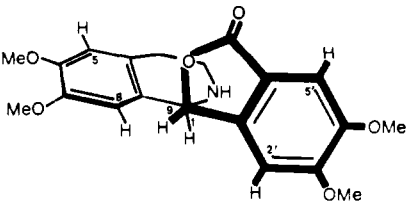


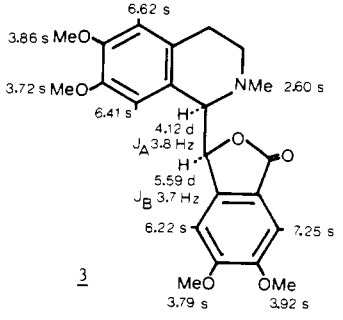

2A

TABLE 2. Nmr chemical shift (δ) and noe data for compound **2**.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-8 (6.66) | H-9 | (5.64) | 14.3 |
| | H-1 | (4.60) | 6.3 |
| | C-2 $OCH_3$ | (3.80) | 4.3 |
| H-5 (6.53) | C-3 $OCH_3$ | (3.83) | 4.8 |
| H-9 (5.64) | H-2' | (7.02) | 4.5 |
| | H-8 | (6.66) | 10.7 |
| | H-1 | (4.60) | 5.4 |
| H-1 (4.60) | H-2' | (7.02) | 5.2 |
| | H-8 | (6.66) | 7.6 |
| | H-9 | (5.64) | 8.9 |

In this instance, it is conformation **2A** which is favored. Irradiation of H-8 (δ6.66) gives a 14.3% noe of H-9, so that these two protons must be proximate. The percent enhancement is larger for H-9 than for H-1 which shows only a value of 6.3, as would be expected from conformation **2A**. Additionally, irradiation of either H-1 (δ4.60) or H-9 (δ5.64) leads to enhancements of the H-2' signal (table 2). Our conformational assignment here is also in accord with that obtained earlier (1).

(±)-ERYTHRO-PHTHALIDEISOQUINOLINE **3**.




3

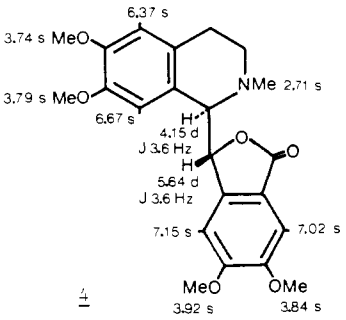
TABLE 3. Nmr chemical shift (δ) and noe data for compound **3**.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-5 (6.62) | C-6 $OCH_3$ | (3.86) | 6.3 |
| H-8 (6.41) | H-9 | (5.59) | 12.5 |
| | H-1 | (4.12) | 10.4 |
| | C-7 $OCH_3$ | (3.72) | 6.6 |
| H-2' (6.22) | H-9 | (5.59) | 3.1 |
| | C-3' $OCH_3$ | (3.79) | 5.6 |
| H-9 (5.59) | H-8 | (6.41) | 10.4 |
| | H-2' | (6.22) | 3.1 |
| | H-1 | (4.12) | 6.7 |
| H-1 (4.12) | H-8 | (6.41) | 10.1 |
| | H-9 | (5.59) | 6.7 |
| | N-$CH_3$ | (2.60) | 2.2 |

Interestingly enough, the *erythro*-phthalideisoquinoline **3** exists in essentially the same conformation **1A** as its *erythro*-norphthalideisoquinoline analog **1**. The absorption for H-2' is located upfield at δ6.22. Irradiation of H-8 (δ6.41) leads to noe's of 12.5% and 10.4% for H-9 and H-1, respectively (table 3). Furthermore, irradiation of H-9 (δ5.59) does not lead to an noe of the *N*-methyl signal.

The above conclusions run counter to our original deductions in which we favored a conformation in which the C/D ring system was turned counterclockwise by about 60° from that indicated in expression **1A** (1). Conformation **1A** for species **3** was also favored in the recently published data gathered through the use of a 90 MHz FT instrument (2).

(±)-THREO-PHTHALIDEISOQUINOLINE **4**.

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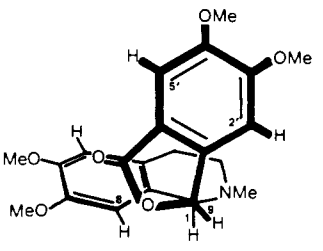



4A

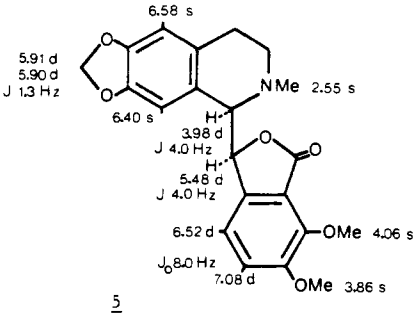
TABLE 4. Nmr chemical shift (δ) and noe data for compound **4**.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-2' (7.15) | H-9 | (5.64) | 6.9 |
| | C-3' $OCH_3$ | (3.92) | 9.4 |
| H-8 (6.67) | H-1 | (4.15) | 21.0 |
| | C-7 $OCH_3$ | (3.79) | 8.9 |
| H-5 (6.34) | C-6 $OCH_3$ | (3.74) | 10.7 |
| H-9 (5.64) | H-2' | (7.15) | 7.8 |
| | H-1 | (4.15) | 17.2 |
| | N-$CH_3$ | (2.71) | 4.0 |
| H-1 (4.15) | H-8 | (6.67) | 26.6 |
| | H-9 | (5.64) | 18.8 |
| | N-$CH_3$ | (2.71) | 4.0 |

The *threo*-phthalideisoquinoline **4** prefers conformation **4A** since irradiation of H–9 (δ5.64) does not result in any noe of H–8, but causes instead enhancements of 7.8% and 4.0% of the H–2′ and *N*-methyl signals, respectively (table 4). In a similar vein, irradiation of H–8 gives no noe of H–9, but leads to a 21.0% noe of the H–1 signal. There is also a significant dipole-dipole relaxation interaction between H–1 and H–9 as indicated by the noe values of 17.2% and 18.8% between them (table 4). An interaction of this magnitude is not observed with conformations **1A** and **2A**.

The present assignment does not differ from our original statement concerning the conformation of the *threo*-phthalideisoquinoline **4** (1). It is at odds, however, with the conclusions reached by other researchers who have favored instead a conformation in which rings C/D are turned clockwise by approximately 180° from that represented in expression **4A** (2). Such an alternate conformation would show a substantial noe between H–8 and H–2′ which is not observed. It should also exhibit an noe between H–8 and H–9, which is also not present. A small (4%) but significant noe observed by us is that shown by the *N*-methyl group upon irradiation of H–9 (table 4). Such an interaction would not prevail in the alternate conformation in which H–9 is pointing away from the N-methyl group. Additionally, the strong relaxation interaction between H–1 and H–9 (table 4) is more in keeping with conformation **4A** than the alternate arrangement. It should also be pointed out that H–5′ in species **4** is found upfield at δ7.02 and H–2′ relatively downfield at δ7.15. The chemical shift for H–5′ can be explained since it lies within the shielding zone of ring A.

(−)-β-Hydrastine (**5**).

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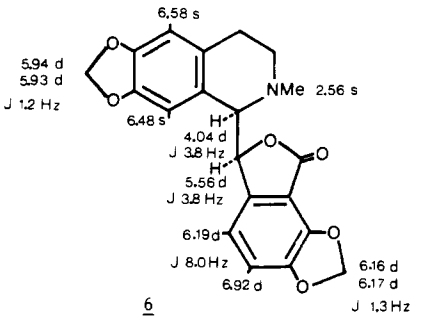


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Table 5. Nmr chemical shift (δ) and noe data for compound **5**.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H–8 (6.40) | H–9 | (5.48) | 23.0 |
| | H–1 | (3.98) | 14.2 |
| H–9 (5.48) | H–2′ | (6.52) | 6.3 |
| | H–8 | (6.40) | 31.3 |
| | H–1 | (3.98) | 11.6 |
| H–1 (3.98) | H–8 | (6.40) | 27.0 |
| | H–9 | (5.48) | 14.5 |
| | N–$CH_3$ | (2.55) | 3.5 |

The base (−)-β-hydrastine (**5**), which belongs to the erythro series, exists primarily in a conformation similar to **1A**. The absorption for H–2′ is found characteristically upfield at δ6.52. Furthermore, irradiation of H–8 (δ6.40) results in 23.0% and 14.2% noe's of H–9 (δ5.48) and H–1 (δ3.98), respectively (table 5). Irradiation of H–9 does not effect an noe of the *N*-methyl signal.

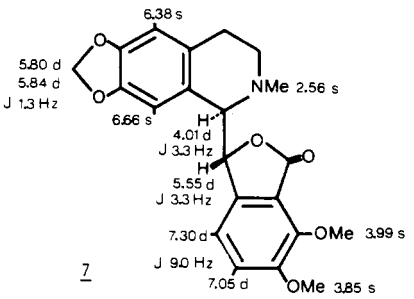
(−)-Bicuculline (6).

Table 6. Nmr chemical shift (δ) and noe data for compound 6.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-8 (6.48) | H-9 | (5.56) | 18.8 |
| | H-1 | (4.04) | 13.3 |
| H-9 (5.56) | H-2' | (6.19) | 2.0 |
| | H-8 | (6.48) | 25.0 |
| | H-1 | (4.04) | 10.9 |
| H-1 (4.04) | H-8 | (6.48) | 17.5 |
| | H-9 | (5.56) | 11.7 |
| | N-$CH_3$ | (2.56) | 2.1 |

The erythro alkaloid (−)-bicuculline (6) possesses the same stereochemistry as (−)-β-hydrastine (5), and the general features of its nmr spectrum (table 6) resemble those for 5. (−)-Bicuculline exists in a conformation similar to 1A, and irradiation of H-8 (δ6.48) leads to enhancements in the signals for H-9 (δ5.56) and H-1 (δ4.04) of 18.8% and 13.3%, respectively (table 6).

(−)-α-Hydrastine (7).

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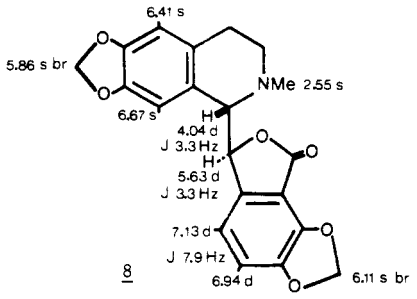


8

Table 7. Nmr chemical shift (δ) and noe data for compound 7.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-8 (6.66) | H-9 | (5.55) | 3.8 |
| | H-1 | (4.01) | 8.4 |
| H-9 (5.55) | H-2' | (7.30) | 2.5 |
| | H-8 | (6.66) | 6.3 |
| | H-1 | (4.01) | 7.9 |
| | N-$CH_3$ | (2.56) | 1.0 |
| H-1 (4.01) | H-8 | (6.66) | 15.0 |
| | H-9 | (5.55) | 7.5 |
| | N-$CH_3$ | (2.56) | 1.4 |

(−)-α-Hydrastine (7), which possesses the threo stereochemistry, exists preferentially in a 4A type configuration. H-2' is found downfield at δ7.30. This chemical shift value is close to that for the corresponding proton in *threo*-phthalideisoquinoline (4), which is at δ7.15. Irradiation of H-9 (δ5.55) effects enhancements of the H-1 (δ4.01), H-2' (δ7.30), and the *N*-methyl protons (δ2.56) signals of 7.9%, 2.5% and 1.0%, respectively (table 7).

(+)-ADLUMIDINE (**8**).

TABLE 8. Nmr chemical shift ($\delta$) and noe data for compound **8**.

| Proton irradiated | Proton observed | | Percent area increase |
|---|---|---|---|
| H-8 (6.67) | H-9 | (5.63) | 8.3 |
| | H-1 | (4.04) | 15.1 |
| H-9 (5.63) | H-2' | (7.13) | 4.2 |
| | H-8 | (6.67) | 14.3 |
| | H-1 | (4.04) | 10.9 |
| | N-$CH_3$ | (2.55) | 2.1 |
| H-1 (4.04) | H-8 | (6.67) | 31.7 |
| | H-9 | (5.63) | 15.6 |
| | N-$CH_3$ | (2.55) | 2.2 |

(+)-Adlumidine (**8**) is a threo phthalideisoquinoline alkaloid existing predominantly in a conformation which is enantiomeric with **4A**. Significantly, H-2' lies downfield at $\delta$7.13. Irradiation of H-9 results in area increases of 10.9%, 4.2%, and 2.1%, for the H-1 ($\delta$4.04), H-2' ($\delta$7.13), and *N*-methyl ($\delta$2.55) signals, respectively (table 8).

## CONCLUSIONS

Erythro phthalideisoquinolines prefer to exist in the relative configuration denoted by stereo expression **1A**, regardless of whether *N*-2 is secondary or *N*-methylated. In the threo series, however, relative conformation **2A** is favored for the nor compounds, while **4A** predominates in the *N*-methyl compounds. The chemical shift of H-8 is a good criterion for differentiating between the threo and erythro series of *N*-methylated phthalideisoquinoline alkaloids. In the erythro series, this proton appears usually between $\delta$6.4 and 6.5. But it is found further downfield in the threo series, around $\delta$6.66. It is also worth pointing out that a conformation in which aromatic rings A and D are on the same side and eclipse each other is never favored due to the large steric interaction that would prevail in such an arrangement.

## EXPERIMENTAL

Nmr data were collected on a Bruker WP-200 MHz Supercon FT spectrometer in deuteriochloroform solution with TMS as internal standard. The noe experiments were carried out by FT noe difference spectroscopy, which allows even enhancements as low as 0.5% to be observed. Noe's were obtained by use of the phase alternating pulses sequence. Four readings were acquired with the decoupler set exactly on a given resonance, and four readings with the decoupler off-resonance were then subtracted. This procedure was repeated until adequate signal to noice ratio was achieved. An equilibration time of 16 sec was used, which corresponds to at least 10 times $T_1$. A diffusion pump was used to degas.

The racemic phthalideisoquinolines **1–4** are derived from the readily available papaverine (**1**). The alkaloids (−)-$\beta$-hydrastine, (−)-$\alpha$-hydrastine, (−)-bicuculline, and (+)-adlumidine are from our alkaloid collection.

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