# Nigellimine: A New Isoquinoline Alkaloid from the Seeds of Nigella sativa

Atta-ur-Rahman, Sohail Malik, and Khurshid Zaman

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# NIGELLIMINE: A NEW ISOQUINOLINE ALKALOID FROM THE SEEDS OF *NIGELLA SATIVA*

ATTA-UR-RAHMAN,* SOHAIL MALIK, and KHURSHID ZAMAN

*H.E.J. Research Institute of Chemistry, University of Karachi 75270, Pakistan*

ABSTRACT.—A new isoquinoline alkaloid, nigellimine [**1**], has been isolated as a trace constituent from the seeds of *Nigella sativa*. The structure was assigned on the basis of chemical and spectroscopic studies.

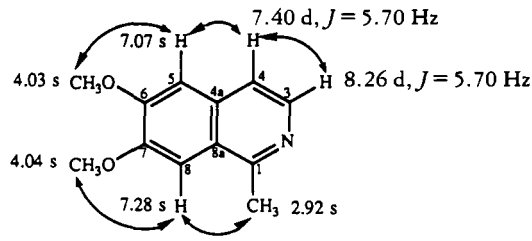
*Nigella sativa* L. (Ranunculaceae) is an herbaceous plant that grows in Mediterranean countries and is also cultivated in Pakistan. The seeds are used as a spice and medicine (1,2). Little work has previously been carried out on its alkaloidal constituents (3–5). As a result of our continuing chemical analysis of the seeds (6,7), we report here the isolation, structure determination, and synthesis of a new isoquinoline alkaloid, nigellimine [**1**]. The structure of nigellimine as 1-methyl-6,7-dimethoxyisoquinoline was confirmed by its synthesis and direct comparison with the synthetic compound (9), as well as by its conversion to nigellimine *N*-oxide which has been earlier isolated from the same seeds (7). The compound was synthesized earlier by Brossi *et al.* (8).

## RESULTS AND DISCUSSION

Nigellimine [**1**], obtained by chromatography of the crude alkaloidal extract of the seeds, showed a uv spectrum characteristic of the isoquinoline system with absorptions at λ max (MeOH) 236, 265, 290 sh, 310, and 324 nm, λ min (MeOH) 262, 305, and 318 nm. Its hrms revealed a molecular ion peak at *m/z* 203.0956 leading to the molecular formula $C_{12}H_{13}NO_2$ (calcd 203.0946). The $^1$H-nmr spectrum ($CDCl_3$, 300 MHz) showed a three-proton singlet at δ 2.92 for the Me group. Two singlets each integrating for three protons resonating at δ 4.03 and 4.04 indicated the presence of two MeO groups attached to the aromatic ring system. The ortho disposition of these two MeO groups was supported by the absence of meta coupling between the two aromatic protons of the benzene moiety. These two protons (H-5 and H-8) appeared as singlets integrating for one proton each at δ 7.07 and 7.28 respectively. Two doublets for two mutually coupled aromatic protons appeared at δ 7.40 and 8.26 ($J$ = 5.70 Hz) and were assigned to H-4 and H-3, respectively, the chemical shifts being consistent with the chemical shifts for protons at these positions in other similar systems (9,10).

The assignment for each proton in the $^1$H-nmr of nigellimine [**1**] was substantiated by carrying out homo-decoupling, COSY-45, and NOESY experiments (11–13), which are summarized in Table 1.

On the basis of the above spectroscopic studies, structure **1** was assigned




**1**

TABLE 1. NOESY Interactions of Nigellimine [**1**].

| δ | δ |
|---|---|
| 2.92 (Me) | 7.28 (8-H) |
| 4.03 (6-MeO) | 7.07 (5-H) |
| 7.07 (5-H) | 4.03 (6-MeO) |
| | 7.40 (4-H) |
| 7.28 (8-H) | 2.92 (Me) |
| | 4.04 (7-MeO) |

to nigellimine (1-methyl-6,7-dimethoxyisoquinoline) (14). Nigellimine [**1**] was synthesized by acetylation of 3,4-dimethoxy-β-phenethylamine with $Ac_2O$/pyridine, followed by cyclizations under Bischler-Napieralski conditions and permanganate oxidation. The synthetic material was found to be spectroscopically and chromatographically identical with nigellimine [**1**]. Its $^{13}C$-nmr spectrum indicated the presence of 12 carbons, and the multiplicity of each carbon was confirmed by carrying out DEPT experiments. Nigellimine [**1**] was converted to its *N*-oxide with *m*-CPBA, and its structure was confirmed by spectroscopic and chromatographic comparison with the isolated nigellimine *N*-oxide (8).

## EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were recorded in glass capillary tubes and are uncorrected. Ir absorption spectra were recorded on a Jasco A-302 spectrophotometer. The spectra were recorded on Shimadzu UV-240 spectrophotometer. Eims were recorded on a Finnigan MAT-312 mass spectrometer connected to PDP 11/34 (DEC) computer system. The nmr spectra were recorded on a Bruker AM-300 NMR spectrometer. All chemicals used were obtained from E. Merck, except for 3,4-dimethoxy-β-phenethylamine which was obtained from Aldrich Chemical Company.

ISOLATION OF NIGELLIMINE.—The plant material (seeds) was identified by Prof. S.I. Ali, Botany Department of Karachi University where the voucher specimen is deposited. The seeds (20 kg) were soaked in EtOH (35 liters), crushed, and filtered. The EtOH was evaporated, and the residue was defatted with $Et_2O$ which was basified with concentrated $NH_3$ to pH 9 and extracted with $CHCl_3$, dried with $Na_2SO_4$ (anyhydrous), filtered, and evaporated to dryness (2.45 g). This mixture was subjected to cc on Si gel 60. Elution with increasing polarities of $CHCl_3$ and EtOAc resulted in a number of fractions. The fraction obtained with 75% $CHCl_3$/25% EtOAc was subjected to preparative tlc using 0.2 mm Si gel (GF-254) precoated plates with petroleum ether (40°–60°)-EtOAc (3:7) as a solvent system. The major alkaloid **1** ($R_f$ 0.29) was separated and crystallized with $Et_2O$-EtOAc (3:1). The alkaloid thus obtained (2.7 mg, $1.35 \times 10^{-3}$% yield) was found to be optically inactive.

*Nigellimine* [**1**].—$C_{12}H_{13}NO_2$: mp 118–119° [$Et_2O$-EtOAc (3:1)]; uv λ max (MeOH) 236, 265, 290 sh, 310, 324 nm, λ min (MeOH) 262, 305, 318 nm; ir ν max ($CHCl_3$) 2900, 2845 (C-H), 1705 (C=N), 1604 (C=C), 1155, 1008 (C-O), 857 $cm^{-1}$ (aromatic C-H); ms (%) $[M]^+$ *m/z* 203 (100), 188 (18), 172 (3), 160 (31), 145 (8), 131 (6), 130 (7), 117 (15), 101 (7); hrms 203.0956 calcd 203.0946 ($C_{12}H_{13}NO_2$); $^{13}C$ nmr ($CD_3OD$) δ 21.39 (1-Me), 56.47 (6-OMe), 56.53 (7-OMe), 105.01 (C-8), 106.50 (C-5), 120.12 (C-4), 124.38 (C-8α), 134.64 (C-4α), 139.49 (C-3), 151.80 (C-7), 154.83 (C-6), 156.62 (C-1).

SYNTHESIS OF NIGELLIMINE [**1**] AND ITS *N*-OXIDE.—3,4-Dimethoxy β-phenethylamine (2.148 g) was treated with a mixture of $Ac_2O$ (6.480 g) and anhydrous $C_5H_5N$ (2.440 g), warmed for about 10 min, and left for 24 h. Evaporation afforded a crystalline material which was washed first with *n*-hexane and then with $Et_2O$ to afford the pure crystalline *N*-acetylated product (2.407 g, 90.96% yield). The *N*-acetylated product (0.827 g) was dissolved in dry $C_6H_6$ (8.0 ml). $POCl_3$ (25 ml) was added slowly in 3 portions, and the mixture was kept at room temperature for 30 min, refluxed for 5 h, allowed to stand overnight at room temperature, and basified with $NH_4OH$ (pH 9.0). The precipitates were filtered and extracted with EtOAc (3 × 200 ml), dried with anhydrous $Na_2SO_4$, filtered, and concentrated. Addition of $Et_2O$ to this concentrate, filtration of the $Et_2O$-soluble portion, and concentration afforded yellow crystals of pure 3,4-dihydronigellimine (0.745 g, 98.02% yield).

The 3,4-dihydronigellimine (0.050 g) was dissolved in $C_5H_5N$ (15 ml), and aqueous $KMnO_4$ solution (1.30 g in 60 ml $H_2O$) was added; the mixture was refluxed for 1 h and filtered. The filterate was concentrated by evaporation in vacuo, and the solution was basified with 10% $NH_4OH$ and extracted with EtOAc (3 × 120 ml), dried with anhydrous $Na_2SO_4$, filtered, and concentrated to afford a light yellow compound which was crystallized with $Et_2O$-EtOAc (3:1). The crystals were washed with *n*-hexane and finally with $Et_2O$-EtOAc (1:1). This afforded whitish crystals of nigellimine [**1**] (0.041 g, 83.67% yield).

OXIDATION OF NIGELLIMINE [1] TO NIGELLIMINE *N*-OXIDE.—Nigellimine [1] (0.030 gm) was dissolved in $CH_2Cl_2$, and pure *m*-CPBA (0.020 g) was added gradually at 0–5°. The solution thus obtained was passed through a basic $Al_2O_3$ column (100–200 mesh) ($Al_2O_3$-to-material ratio, 30:1). Elution with $CHCl_3$-MeOH (9.5:0.5) resulted in the isolation of pure amorphous nigellimine *N*-oxide (0.027 gm, 84.37% yield).

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