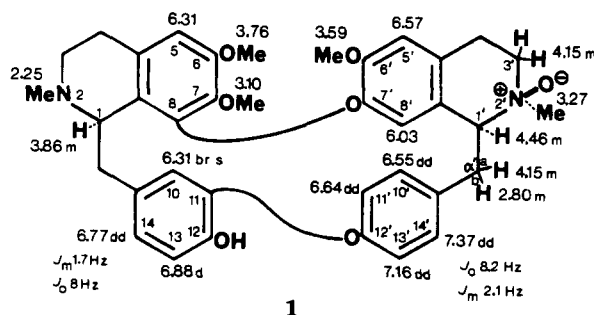


BERBAMINE 2'- β -N-OXIDE, A NEW BISBENZYLISOQUINOLINE
FROM *BERBERIS BRANDISIANA*S. FAZAL HUSSAIN,¹ M. TARIQ SIDDIQUI,¹ LAJBER KHAN,¹ ALAN J. FREYER,
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Berberis brandisiana Ahrendt (Berberidaceae) is a shrub that grows in northern Pakistan. A study of the alkaloidal contents of its aerial parts has resulted in the isolation of the new bisbenzylisoquinoline (+)-berbamine 2'- β -N-oxide (**1**), C₃₇N₄O₇.

sembles in its general features the spectrum for berbamine (**1**). Notable divergences, however, were the chemical shifts of the 2'-N-methyl group and the aliphatic H- α' , H-1', and H-3'. It is known that the 2-N-methyl (or 2'-N-methyl) signal of a bisbenzylisoquino-



1

The mass spectrum of the alkaloid shows molecular ion m/z 624 of medium intensity (38%). This is accompanied by two strong peaks, m/z 608 (100%) and m/z 198 (97%). The m/z 608 peak is due to loss of an oxygen atom from the molecular ion. The m/z 198 peak corresponds to the doubly charged upper half of the m/z 608 species.

Inasmuch as the net loss of one oxygen in the mass spectrum is diagnostic of an N-oxide, our alkaloid was reduced with zinc in HCl to afford the known (+)-berbamine.

The 360 MHz (CDCl₃) nmr spectrum of berbamine 2'- β -N-oxide has been summarized around expression **1**. It re-

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line N-oxide belonging to the same 8-7', 11-12' series as berbamine undergoes a downfield shift of 0.3-0.4 ppm when H-1 (or H-1') lies on the same side as the N-oxide oxygen, while a larger shift of 0.7-0.9 ppm is observed when H-1 (or H-1') is on the side opposite the N-oxide oxygen (1,2). In the specific instance of berbamine 2'- β -N-oxide (**1**), the 2'-N-methyl signal is at δ 3.27 whereas it falls at δ 2.57 in berbamine itself. The downfield shift of 0.7 ppm thus argues in favor of a β -N-oxide configuration in which H-1' and the N-oxide oxygen are *anti* to each other.

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the corresponding absorption in berbamine is at δ 3.85. This $\Delta \delta$ 0.61 ppm thus corroborates the 2'- β -N-oxide arrangement.

To confirm the above stereochemical conclusion, an nmr nOe analysis was performed on berbamine 2'- β -N-oxide (**1**), the results of which are given in the Experimental. A significant feature of this analysis is the reciprocating enhancements between the 2'-N-methyl (δ 3.27) and the H-1' (δ 4.46) signals, so that these hydrogens must be in a *syn* relationship.

Known alkaloids presently found in *B. brandisiana* are the isoquinolone thalifoline, the tetrahydrobenzylisoquinoline (+)-reticuline, the aporphines (+)-apoglaziovine and (+)-isoboldine, the protoberberinium salts berberine and palmatine, and the bisbenzylisoquinolines (+)-isotetrandrine, (+)-berbamine, and (+)-penduline. It should be noted that while the bisbenzylisoquinolines of *Berberis* species usually possess the *R,S'* configuration, as in (+)-isotetrandrine, (+)-berbamine, and (+)-berbamine 2'- β -N-oxide (**1**), (+)-penduline is unusual in that it incorporates the *S,S'* stereochemistry.

EXPERIMENTAL

PLANT MATERIAL.—The aerial parts of *B. brandisiana* (7 kg., dry) were collected in the Ushu valley of Swat in Northern Pakistan. A plant specimen was deposited in the National Herbarium in Islamabad.

EXTRACTION AND ISOLATION.—Extraction of the powdered plant was with cold EtOH. The dried alcoholic extract was taken up in 5% HCl, filtered, and the filtrate basified with NH_4OH . The mixture was extracted exhaustively with CHCl_3 to supply an alkaloidal fraction. This fraction (30 g), which also contained some lignans, was placed on a silica gel column (2 kg, 70-230 mesh) filled with CHCl_3 . Elution was with CHCl_3 and then with CHCl_3 gradually enriched with MeOH. Major alkaloids found were berberine, palmatine, and (+)-berbamine. Minor alkaloids were thalifoline, (+)-reticuline, (+)-apoglaziovine, (+)-isoboldine, (+)-isotetrandrine, and (+)-berbamine 2'- β -N-oxide (**1**) (12 mg). Known alkaloids were identified spectrally or by comparison with authentic samples.

(+)-BERBAMINE 2'- β -N-OXIDE (1**).**—Amorphous, m/z 624 (M^+ , $\text{C}_{37}\text{H}_{40}\text{N}_2\text{O}_7$) (38), 608 (100), 594 (29), 396 (80), 382 (61), 206 (12), 198 (97), 175 (52); λ max (MeOH) 234 sh, 282 nm ($\log \epsilon$ 4.55, 4.04); $[\alpha]_D^{+14}$ (c 0.08, MeOH). Significant nmr nOe's are 2'-NMe to H-1', 4%; H-1' to 2'-NMe, 3%; H-1' to H-8', 10%; 2'-NMe to H- α' a, 4%; H- α' b to H-14', 5%; H- α' b to H-8', 10%; H-1 to 2-NMe, 1.5%; 2-NMe to H-1, 7%; H-1 to H-10, 5%.

REDUCTION OF **1.**—N-oxide **1** (4 mg) was stirred at room temperature for 2 h with powdered zinc (20 mg) and 10% HCl (5 ml). Work-up provided (+)-berbamine (2 mg).

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