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BULGARAMINE, A NEW INDENOBENZAZEPINE ALKALOID

GEORGI I. YAKIMOV,

Higher Medical Institute, 9002 Varna, Bulgaria

NIKOLA M. MOLLOV,

University of Plovdiv, 4000 Plovdiv, Bulgaria

JOHN E. LEET, HELENE GUINAUDEAU, ALAN J. FREYER, and MAURICE SHAMMA

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

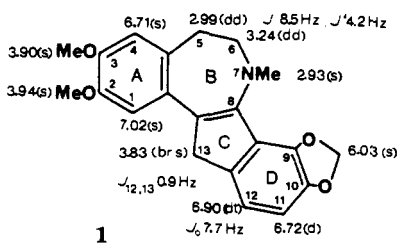
It has been recently recognized that the indenobenzazepines are a distinct group of alkaloids, probably derived biogenetically from the rearrangement of spirobenzylisoquinolines (1). To date, only five naturally occurring indenobenzazepines were known (1-5).

We now wish to describe a new indenobenzazepine, namely the colorless and optically inactive bulgaramine (**1**), $C_{21}H_{21}NO_4$, obtained from Herba Fumaria Officinalis where it is accompanied by O-methylfumarophycine (**2**) (6) and other spirobenzylisoquinolines (7).

Bulgaramine (**1**) shows a complex uv absorption pattern with a strong maximum at 341 nm suggestive of a stilbenoid system (see Experimental section) (8). The mass spectrum exhibits a molecular ion peak *m/z* 351, which is also the base peak.

Substantive evidence for the structure of bulgaramine was derived from the 360 MHz ^{1}H-nmr spectrum in $CDCl_3$, which has been summarized around expression **1**. Salient features of the ^{1}H-nmr spectrum are the broad singlet centered at δ 3.83 and representing the C-13 methylene protons. Long-range coupling obtains between the C-13 protons and H-12. Because H-12 is also split by H-11, it appears at δ 6.90 as a doublet of triplet (J_o=7.7 Hz, $J_{12,13A}$=0.9 Hz, $J_{12,13B}$=0.9 Hz.

An accompanying ^{1}H-nmr nOeds (nuclear Overhauser enhancement difference study) (9), summarized in expression **1a**, provided an interlocking system relating all of the protons in the alkaloid with the exception of those for the ring D methylenedioxy substituent which, as expected, do not show any nOe. The numerical values quoted



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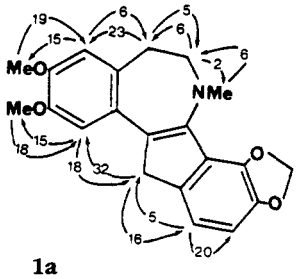
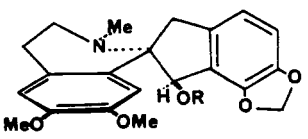
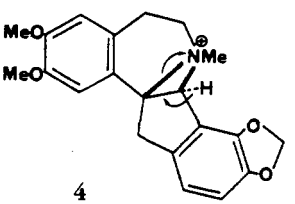


1a



2 R=Ac
3 R=H



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around diagram **1a** represent the apparent nOe percentages actually observed. Irradiation of the δ 3.83 C-13 protons resulted in a 32% nOe of H-1 (δ 7.02), as well as a 16% enhancement of the H-12 absorption (δ 6.90). In turn, irradiation of H-1 caused an 18% increase in the area of the H-13 protons (δ 3.83), as well as a 15% increase of the C-2 methoxyl signal (δ 3.94).

Bulgaramine (**1**) had been previously prepared semisynthetically by the pyrolysis of O-methylfumarophycine (**2**) (10), and our natural and semi-synthetic samples proved to be identical. Several experiments were presently carried out to demonstrate that natural bulgaramine was not derived from the accompanying alkaloid O-methylfumarophycine (**2**) during the isolation process. In one such experiment, O-methylfumarophycine was allowed to stand overnight in 5% HCl at room temperature. No bulgaramine could be detected after work-up. In another experiment, O-methylfumarophycine was kept for several hours at near 90° (water bath). Such heating did not produce any bulgaramine.

Bulgaramine (**1**) occupies a central position in the biogenetic scheme linking the spirobenzylisoquinolines with the indenobenzazepines. It has been suggested that the ketonic spirobenzylisoquinoline alkaloid parfumidine is reduced in the plant to the alcohol fumaricine (**3**), which can supply the aziridinium cation **4** (1). Proton loss from **4** with fission of the aziridinium ring provides bulgaramine (**1**). Oxidation and aromatization of **1** would then lead to lahoramine, and indeed a very similar scheme has been duplicated in vitro (1). Besides O-methylfumarophicine (**2**), both parfumidine and fumaricine (**3**) occur in Herba Fumaria Officinalis (7). The isolation of bulgaramine (**1**) as a natural product thus lends further credence to the thesis that indenobenzazepines are derived biogenetically from spirobenzylisoquinolines. Characteristically, bulgaramine bears a methylenedioxy substituent in the bottom ring, as do all known spirobenzylisoquinoline and indenobenzazepine alkaloids.

EXPERIMENTAL

PLANT MATERIAL.—Herba Fumaria Officinalis is a commercial medicinal mixture of several *Fumaria* species (Fumariaceae) growing in Bulgaria. The material was purchased from the Bulgarian state enterprise Bilcocoop.

EXTRACTION AND ISOLATION.—Cold MeOH extraction of the dried powder (5.38 kg), was followed by further extraction of the MeOH soluble portion with cold 5% HCl. Work-up of the alkaloidal mixture, including chromatography over silica gel, supplied 675 mg of bulgaramine (**1**).

BULGARAMINE.—Mp 209° (EtOH); λ max (MeOH) 227, 260, 341 nm (log ε 4.14, 3.98, 4.23); λ max (MeOH+H^+) 224 sh, 238, 302 sh, 331 nm (log ε 3.98, 4.07, 4.01, 4.18); ms *m/z* 351 (M^+, 100), 336 (65), 320 (4), 306 (3), 293 (8), 276 (3), 207 (3), 176 (5).

ACKNOWLEDGMENTS

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LITERATURE CITED

1. G. Blaskó, S.F. Hussain, A.J. Freyer, and M. Shamma, *Tetrahedron Lett.*, **22**, 3127 (1981).
2. N. Murugesan, G. Blaskó, R.D. Minard, and M. Shamma, *Tetrahedron Lett.*, **22**, 3131 (1981).
3. G. Blaskó, N. Murugesan, S.F. Hussain, R.D. Minard, M. Shamma, B. Sener, and M. Tanker, *Tetrahedron Lett.*, **22**, 3135 (1981).
4. G. Blaskó, N. Murugesan, A.J. Freyer, D.J. Gula, B. Sener, and M. Shamma, *Tetrahedron Lett.*, **22**, 3139 (1981).
5. G. Blaskó, N. Murugesan, A.J. Freyer, R.D. Minard, and M. Shamma, *Tetrahedron Lett.*, **22**, 3143 (1981).
6. B. Gözler, M. Shamma, H.G. Kiryakov, G. Yakimov, and N. Mollov, *J. Nat. Prod.*, **46**, 433 (1983).
7. R.M. Preisner and M. Shamma, *J. Nat. Prod.*, **43**, 305 (1980).
8. A.I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," New York: Macmillan Co., 1964, p. 99.
9. L.D. Hall and J.K.M. Sanders, *J. Am. Chem. Soc.*, **102**, 5703 (1980).
10. N.M. Mollov and G.I. Yakimov, *Compt. Rend. Acad. Bulg. Sci.*, **24**, 1325 (1971).

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