

Alkaloids of *Thalictrum* VI.

Isolation of Obamegine from *Thalictrum rugosum*

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A description is given of the isolation of a phenolic tertiary base from the roots of *T. rugosum* and the identification of this base as obamegine.

THE PRESENCE of magnoflorine and berberine in the roots of *Thalictrum rugosum* Ait. (*T. glaucum* Desf.) has been reported in the previous paper of this series (1). The present report describes the isolation of a phenolic tertiary base from the roots of *T. rugosum* and the identification of this base as obamegine (I).

The tertiary base, m.p. 172° dec., $[\alpha]_D^{25} + 241^\circ$ (chloroform), was obtained in crystalline form from the crude tertiary base fraction referred to in the previous paper (1). The U.V. spectrum suggested a benzenoid nucleus, λ_{max} , 285 m μ , while in the I.R. spectrum 2 hydroxyl peaks were detected, 3450 cm.⁻¹ and 3260 cm.⁻¹. The NMR spectrum indicated the presence of 2 methoxyl and 2 *N*-methyl groups. In addition, the NMR spectrum showed the presence of benzene of crystallization. The molecular formula, C₃₈H₃₈N₂O₆·2C₆H₆, was assigned on the basis of the elemental analysis which also suggested the presence of a benzene adduct.

On treatment of the phenolic base with diazomethane, a product was obtained which possessed 4 methoxyl and 2 *N*-methyl groups thereby verifying that the base contains 2 phenolic hydroxyl groups. Analytical data indicated the phenolic base to be of the berbamine type. Since obamegine (2, 3) has been described as a phenolic base possessing 2 hydroxyl groups and belonging to the berbamine type alkaloids (4), this base was compared with an authentic sample of obamegine.¹

The phenolic base was shown to be identical with obamegine by comparison of I.R. spectra and a mixed melting point determination. Finally, this base and its *O,O*-dimethylether and *O,O*-diethylether gave NMR spectra identical with the NMR spectra of obamegine, *O,O*-dimethyl-obamegine, and *O,O*-diethyl-obamegine.¹

This is the first report of the isolation of obamegine from a *Thalictrum* species. Previously, aromoline (thalicine) was isolated from *Thalictrum thalictroides* D.C. by one of the authors (5-7). Aromoline belongs to the oxyacanthine group of alkaloids. Thus, both the berbamine and oxyacanthine type of alkaloids have been isolated from the genus *Thalictrum*. Both obamegine (I) and aromoline (II) have 2 hydroxyl groups in the 7 and 4' or 4'' positions.

EXPERIMENTAL²

Material.—Roots of *T. rugosum* were obtained from Wayside Gardens, Mentor, Ohio. A minimum of 100 plants are being cultivated in The Ohio State University College of Pharmacy Medicinal Plant Garden. In addition, herbarium specimens have been made and are on file.

Isolation and Identification of Obamegine from *T. Rugosum*.—Milled roots, 6.2 Kg., were extracted with methanol in a continuous extractor until a negative test of the extractant for alkaloid was obtained with Valser's reagent. The methanol extract was concentrated almost to dryness, *in vacuo*, and poured while stirring into warm 5% acetic acid. The insoluble material was extracted repeatedly with 5% acetic acid until a negative test was obtained with Valser's reagent. The acidic solution was freed from acidic and neutral substances by extraction with ether, and then made alkaline with ammonium hydroxide solution and extracted exhaustively with ether to remove ether-soluble bases. The ether solution was extracted with 5% potassium hydroxide to remove the phenolic base. The solution containing the phenolic base was made weakly acidic by adding hydrochloric acid and then basic with ammonium hydroxide solution. The alkaline solution was extracted with benzene which was then dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield 4.8 Gm. of colorless crystalline residue. Repeated recrystallization from benzene gave colorless needles, m.p. 172° dec. $[\alpha]_D^{30} + 241^\circ$ (chloroform), ultraviolet λ_{max} , (ethanol) 285 m μ . The infrared spectrum (chloroform) showed 3450 cm.⁻¹, 3260 cm.⁻¹ (OH). The NMR spectrum (CDCl₃) showed τ 7.60, 7.73 (*N*-methyl), 6.27, 6.36 (*O*-methyl), 2.72 (benzene).

Anal.—Calcd for C₃₈H₃₈N₂O₆·2C₆H₆: C, 76.80; H, 6.66; N, 3.73. Found: C, 76.52; H, 6.59; N, 3.76.

The melting point was not depressed on admixture with an authentic sample of obamegine, m.p. 172° dec. In addition, the infrared spectrum in potassium bromide of the sample was identical with that of an authentic sample of obamegine.

***O,O*-Dimethyl Ether.**—A 0.1-Gm. quantity of the above phenolic base was dissolved in 15 ml. of methanol and added to an ethereal solution of diazomethane which was made from 4.3 Gm. of *p*-tolylsulfonylethylmethyl nitrosamide and 0.8 Gm. of potassium hydroxide in 20 ml. of 96% ethanol. After standing 3 days, the ether and the excess diazomethane were evaporated on a steam bath. The residue was dissolved in 20 ml. of 5% acetic acid solution which was then made basic with aqueous sodium hydroxide and extracted exhaustively with ether. The ether solution was dried

Received October 6, 1965, from the College of Pharmacy, The Ohio State University, Columbus.

Accepted for publication November 16, 1965.

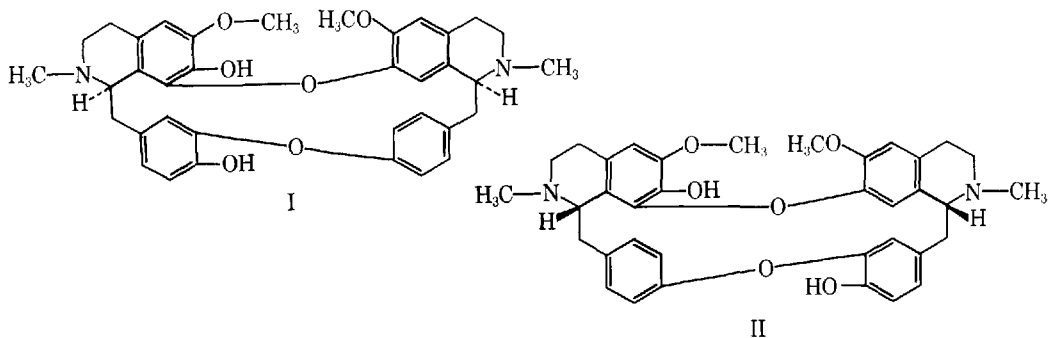
This investigation was supported by grant CA-06028 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

Previous paper: Tomimatsu, T., Gharbo, C. R., and Beal, J. L., *J. Pharm. Sci.*, **54**, 1390(1965).

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¹ The authors thank Dr. M. Tomita and Dr. T. Ibuka, Kyoto University, for an authentic sample of obamegine which was supplied by them, and for the loan of the NMR spectra charts of obamegine, *O,O*-dimethyl-obamegine, and *O,O*-diethyl-obamegine.

² Melting points were determined with a Thomas-Hoover melting point apparatus. Infrared spectra were obtained using a Perkin-Elmer Infracord spectrophotometer, model 237. The NMR spectra were obtained using a Varian Associates 60 mc/galicyclic spectrophotometer. The authors thank Dr. David Dalton, Department of Chemistry, for the NMR interpretations and valuable suggestions.



over anhydrous potassium carbonate and the ether then evaporated on a steam bath. The residue was dissolved in benzene and chromatographed on a column of Woelm, grade 1, neutral alumina (10 Gm., column 1 cm. \times 6 cm.) using benzene as the solvent. A single compound was obtained in the eluate. The NMR data (CDCl_3) indicated τ 7.46, 7.76 (*N*-methyl), 6.12, 6.29, 6.41, and 6.87 (*O*-methyl), and was identified with that of *O,O*-dimethylbamegine.

***O,O*-Diethyl Ether.**—A 0.1-Gm. sample of the phenolic base was dissolved in 10 ml. of methanol and added to an ethereal solution of diazoethane which was made from 7 Gm. of nitrosoethylurea and 40 Gm. of 50% potassium hydroxide solution. After standing 4 days at room temperature, the solution was treated by the usual method and the

residue crystallized from acetone as colorless rosette crystals (0.098 Gm.), m.p. 203–204°. The NMR spectrum (CDCl_3) showed τ values at 7.39, 7.71 (*N*-methyl), 6.22, and 6.40 (*O*-methyl). The NMR spectrum was superimposable with that of known *O,O*-diethylbamegine.

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Tosylation of *N*-Phenyl-*N'*-(3-hydroxypropyl)urea

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Two unexpected products, *N*-phenyl-*N'*-(3-chloropropyl)urea (II) and 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine (III), are formed from the reaction of *p*-toluenesulfonyl chloride and *N*-phenyl-*N'*-(3-hydroxypropyl)urea (I).

AS PART of a program dealing with the synthesis of potential antiradiation drugs, it became necessary to carry out the reaction of *p*-toluenesulfonyl chloride and *N*-phenyl-*N'*-(3-hydroxypropyl)urea (I). The authors have found that this reaction in pyridine solvent gives 2 unexpected products: *N*-phenyl-*N'*-(3-chloropropyl)urea (II) and 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine (III) in total yield of 86%.

Addition at 0–10° of an equivalent of *p*-toluenesulfonyl chloride to the hydroxypropyl urea (I) (prepared from 2 equivalents of phenyl isocyanate with 3-aminopropanol and subsequent basic hydrolysis of the product),¹ followed by acidification gave a white solid. The infrared spectrum of the solid revealed a tosylate ester band at 1340 cm^{-1} (2), and was totally void of tosylate anion absorp-

tion. When dried in a vacuum oven at 55° or allowed to stand at room temperature for 3 days, the solid decomposed. The resulting syrup did not crystallize on cooling, and its infrared spectrum showed intense tosylate anion bands at 1005 and 1020 cm^{-1} (3). When dissolved in a minimum of ethanol and poured into water, a white solid precipitated; its infrared spectrum did not show tosylate anion bands. A sodium fusion of this material revealed the presence of chlorine, and elemental analysis for C, H, N, and Cl agreed with that calculated for *N*-phenyl-*N'*-(3-chloropropyl)urea. The yield was 48%.

The conversion of —OH to —Cl during a tosylation reaction is not unprecedented. Under certain conditions and with phenols bearing nitro groups in the nucleus, an abnormal reaction (4, 5) takes place in which the OH group is replaced by chlorine.

The filtrate from the chloro-urea was made strongly basic with 10% sodium hydroxide, and additional white solid precipitated. Again, the infrared spectrum was void of tosylate anion bands. A sodium fusion for sulfur and chlorine was negative and elemental analysis agreed with that calculated for 2-phenylimino-2,4,5,6-tetrahydro-1,3-oxazine. The yield was 38%.

These observations can be rationalized in the following way. The tosylation reaction gives a mixture of the chloro-urea (II) and *N*-phenyl-

Received September 27, 1965, from the Midwest Research Institute, Kansas City, Mo.

Accepted for publication November 15, 1965.

This work was supported by the Army Medical Research and Development Command, U. S. Department of the Army, under contract DA-49-193-MD-2174.

* Deceased.

¹ The procedure used for the tosylation reaction was essentially that of Marvel and Sekera (1).