

THE ALKALOIDS OF *CHONDODENDRON TOXICOFERUM*

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Abstract—Three tertiary bisbenzylisoquinoline alkaloids have been isolated from *Chondodendron toxicoferum* (Wedd.) Kruk. et Mold. These are (–)-curine (I), isochondodendrine (II), and a new base, toxicoferine (III). Spectral and chemical evidence indicate that toxicoferine is a 1:1 molecular complex of (–)-curine and the previously unknown (–)-tubocurine (VII).

INTRODUCTION

A NUMBER of species of the genus *Chondodendron* (Menispermaceae) have been used by the Amazonian Indians in the compounding of curare preparations.¹ All of the species hitherto investigated phytochemically have been found to contain bisbenzylisoquinoline alkaloids.² We now report the results of a study of the tertiary alkaloids of *Chondodendron toxicoferum* (Wedd.) Kruk. et Mold.

Three alkaloids were isolated in crystalline form from the phenolic base fraction of *C. toxicoferum*. The first two were the well-known bisbenzylisoquinoline alkaloids, (–)-curine (chondodendrine, I) and isochondodendrine (II). The third base, toxicoferine (III), did not correspond in its physical properties to any known bisbenzylisoquinoline alkaloid. It was clearly isomeric with and very closely related to (–)-curine (I), since the mass spectra of I and III were superimposable. Furthermore, the u.v. spectra of I and III were identical and their i.r. spectra were very similar. On the other hand, toxicoferine (III) has a much higher m.p. (286°) than that (213°) of curine (I), and III is also much less soluble in organic solvents.

The relationship between I and III was clarified by the conversion of III into its *O,O*-diethyl derivative (IV), followed by the sodium and ammonia cleavage of the latter to give (–)-*N*-methylcoclaurine (V) and racemic *O,O*-diethyl-*N*-methylcoclaurine (VI). It follows that toxicoferine (III) must be a 1:1 molecular complex of (–)-curine (I) and its diastereomer, (–)-tubocurine (VII). This observation marks the first detection of either enantiomer of tubocurine as a naturally occurring alkaloid. (+)-Tubocurine (VIII) was prepared recently by the thiophenoxide ion demethylation of its naturally occurring dimethochloride, (+)-tubocurarine chloride.³ We propose that the name (–)-toxicoferine be retained for the

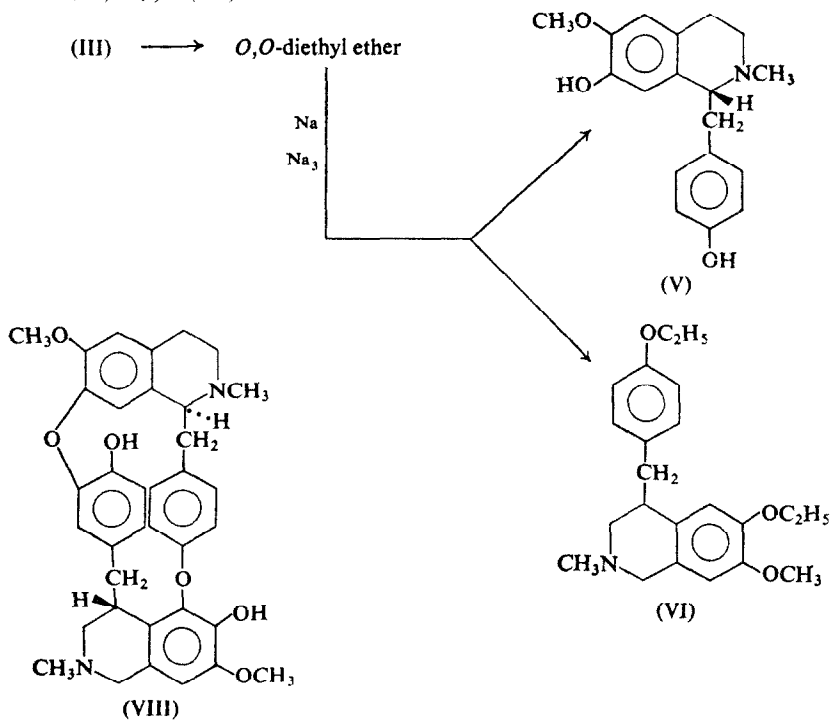
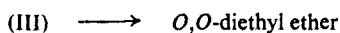
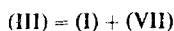
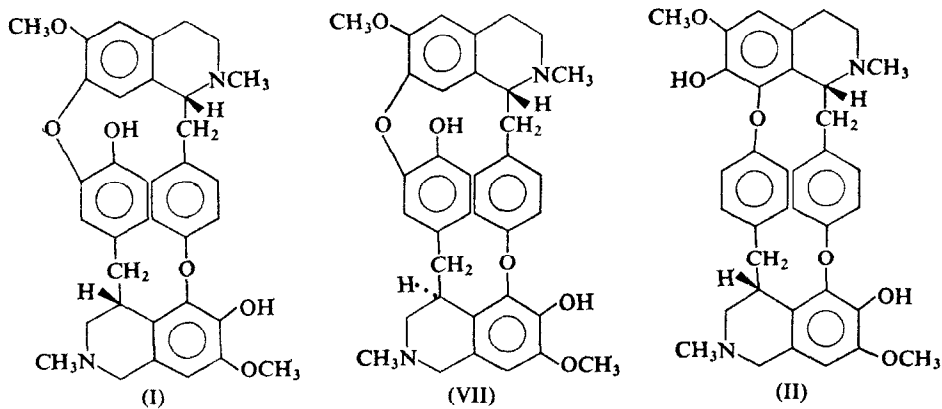
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¹ B. A. KRUKOFF and H. M. MOLDENKE, *Brittonia* 3, 6 (1938).

² H.-G. BOIT, *Ergebnisse der Alkaloid-Chemie bis 1960*, Chap XI, Akad.-Verlag, Berlin (1961).

³ M. SHAMMA, N. C. DENO and J. F. REMAR, *Tetrahedron Letters*, 1375 (1966).

molecular complex of I and VII. In view of its ease of isolation and its apparent behavior as a single compound, it will undoubtedly be encountered in future phytochemical investigations.



EXPERIMENTAL

M.p.s are corrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

Plant Material and Crude Tertiary Bases

The woody, climbing stems of *Chondodendron toxicoferum* were collected by Mr. Luis Coelho in a swamp in the Janauari lake area near Manaus, Brazil. The botanical identity of the sample was confirmed by Dr.

Paulo B. Cavalcante (Goeldi museum, Belem) and by Dr. B. A. Krukoff (New York Botanical Garden); a voucher sample (No. 20,910) was deposited at the INPA Herbarium, Manaus. The dried and ground plant material (10.5 kg) was extracted exhaustively with ethanol for 72 hr. The concentrated extract was refluxed for 1 hr with ammoniacal ethyl acetate and the ethyl acetate extract was extracted with 5% aq. H_2SO_4 to remove tertiary bases. The aqueous acid solution was made alkaline with ammonia and extracted with CHCl_3 to give, after solvent evaporation, 5.31 g of crude bases. The residue from the ethyl acetate extraction was dissolved in 5% aq. HOAc. The solution was made alkaline with ammonia and extracted with CHCl_3 to give, after solvent evaporation, 14.89 g of crude bases. Both crude base fractions were identical by TLC and they were combined to give a total of 19.93 g.

Separation and Characterization of the Tertiary Bases

A major aliquot (17.43 g) of the crude bases was dissolved in aq. 5% H_3PO_4 ; neutral tarry products were removed by filtration as well as by ether extraction of the filtrate. The acid solution was made strongly alkaline with 10% aq. NaOH and the mixture was extracted with CHCl_3 ($\times 3$). Evaporation of the dried CHCl_3 extracts gave a complex mixture of non-phenolic bases from which no crystalline components could be obtained on attempted chromatography and crystallization.

The aq. NaOH extract was brought to $\sim \text{pH } 8$ by the addition of NH_4Cl and the mixture was then extracted with CHCl_3 ($\times 3$). Evaporation of the extracts gave the phenolic base mixture as a brown oil. Addition of acetone caused crystallization of (–)-toxicoferin (III, 2.10 g), m.p. 286° . The base was practically insoluble in all common organic solvents. It was recrystallized (m.p. 286°) from a large volume of CHCl_3 -acetone; $[\alpha]_D - 263^\circ$ (1 N HCl in ethanol). The mass spectrum of III indicated a molecular weight of 594; the spectrum was identical in all respects with that of curine (i.e. chondodendrine).⁴

The mother liquor from the crystallization of III was evaporated and the residue was chromatographed on Woelm neutral alumina (grade III, 2×7 cm column). Benzene (125 ml) and benzene- CHCl_3 (9:1) (125 ml) eluted (–)-curine (I), which crystallized from methanol as prisms (3.20 g), m.p. $212-213^\circ$, $[\alpha]_D - 298^\circ$ (ethanol). The material was further identified by direct comparison (i.r., m.m.p.) with an authentic sample. Further elution of the alumina column with benzene- CHCl_3 (1:1) gave, after crystallization from CHCl_3 -methanol, isochondodendrine (II, 0.80 g), m.p. $297-298^\circ$, $[\alpha]_D + 57^\circ$ (pyridine); lit.⁵ m.p. 305° , $[\alpha]_D + 50^\circ$ (pyridine). The material was further identified by direct comparison (i.r., m.m.p.) with an authentic sample.

O,O-Diethyltoxicoferin (IV)

To a solution of Na (0.13 g) in absolute ethanol (13 ml) was added triethylanilinium chloride (1.3 g), toxicoferin (0.060 g), and toluene (5 ml). The ethanol was distilled off and the resulting mixture was heated for 8 hr at $110-120^\circ$. The reaction mixture was acidified with aq. HOAc, steam distilled, and extracted with ether. Basification of the aqueous acidic solution with NaOH, followed by CHCl_3 extraction and evaporation of the dried extract, gave IV (0.042 g) as an amorphous glass. The i.r. spectrum of this material in CHCl_3 differed slightly from that of *O,O*-diethyl-(–)-curine, prepared by the above procedure from (–)-curine; the NMR spectra of both diethyl ethers (in $\text{C}_5\text{D}_5\text{N}$) were identical: 2.80–3.18 τ (9 \times aromatic H), 3.97 (one aromatic H), 6.10 and 6.13 (6 H, $2 \times \text{OCH}_3$), 7.57 and 7.65 (6 H, $2 \times \text{NCH}_3$), 8.74–8.98 (6 H, $2 \times \text{OCH}_2\text{CH}_3$).

Reductive Cleavage of IV

A solution of the diethyl ether IV (0.035 g) in toluene (5 ml) and dry ether (10 ml) was added dropwise to a solution of Na (0.100 g) in liquid NH_3 at $-40 \pm 5^\circ$. Additional Na was added in portions until the solution remained blue. After stirring for 90 min more, the NH_3 was allowed to evaporate overnight. Separation into phenolic and non-phenolic fractions gave fractions showing only one spot each by TLC (silica H, 4:1 CHCl_3 - CH_3OH). The *non-phenolic base* was identified as (±)-*O,O*-diethyl-*N*-methylcoclaurine (VI); $[\alpha]_D 0.0^\circ$ (CH_3OH). Its i.r. spectrum (CHCl_3) and NMR spectrum (CDCl_3) were identical with those of authentic material.⁶ The *phenolic base* was identified as (–)-*N*-methylcoclaurine (V); $[\alpha]_D - 80^\circ$ (CH_3OH). Its i.r. spectrum and NMR spectrum (CDCl_3) were identical with those of the synthetic racemic base.⁶

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⁴ D. C. DEJONGH, S. R. SHRADER and M. P. CAVA, *J. Am. Chem. Soc.* **88**, 1052 (1966).

⁵ M. TOMITA and J. KUNITOMO, *Yakugaku Zasshi* **82**, 741 (1962).

⁶ The NMR spectra of V and VI have been recorded: M. TOMITA, T. SHINGU, K. FUJITANI and H. FURUKAWA, *Chem. Pharm. Bull. (Tokyo)* **13**, 921 (1965).