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AN APPROACH TO THE SYNTHESIS OF RACEMIC O,O'-DIMETHYL ISOCHONDODENDRINE.

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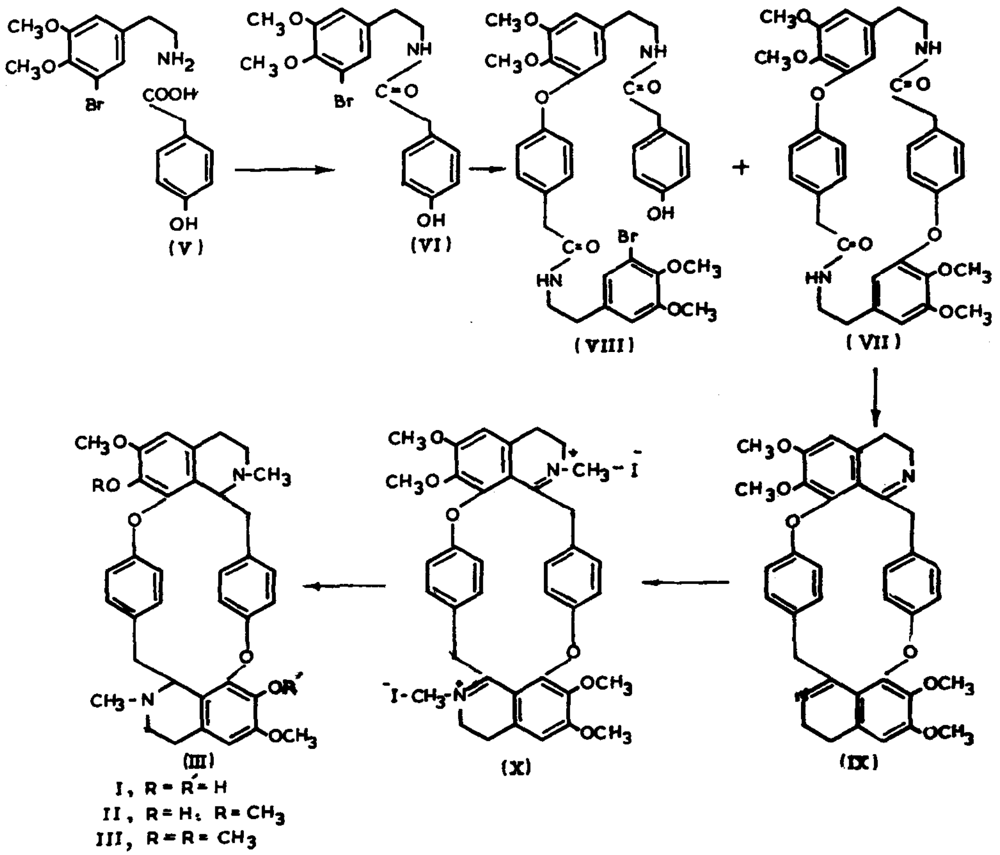
Isochondodendrine (I) is one of the first representatives of curare alkaloid, being isolated in pure state and the structure of which being elucidated (1,2). It belongs to macrocyclic bisbenzyl-isoquinoline alkaloid family with a symmetric molecule containing two phenolic hydroxyls and two tertiary nitrogen atoms. Its Mono-(3) and di-methyl ethers known as norcycleanine (II) and cycleanine (III) were also isolated from plants. The chemical structure of these alkaloids were assigned on the basis of products of degradation (1,2,4), mass spectrometric(5) and proton magnetic resonance (6) examinations. Despite the apparent simplicity of their synthesis by double Ullmann condensation, this reaction was not yet been succeeded (7).

We have used in the present paper the double Ullmann condensation of bromoamide to macrocyclic dipeptide. This on cyclization to bisoxide followed by methylation and reduction can give the alkaloid (III) O,O'-dimethyl isochondodendrine.

The condensation of β-(3,4-dimethoxy-5-bromo-phenyl)-ethylamine (IV) with p-hydroxyphenylacetic acid (V) at 185-90° gave β-(3,4-dimethoxy-5-bromo-phenyl)-ethyl-amide of p- hydroxyphenylacetic acid (VI), colourless crystalline compound, m.p. 116-18° (from isopropanol). Found : C,54.83; H, 5.10; N, 3.26; Br, 20.61, for $C_{18}H_{20}O_4NBr$, requires C, 54.83; H,5.11; N, 3.55; Br, 20.27. Ullmann reaction of its potassium salt afforded the macrocyclic dipeptide (VII), colourless crystalline compound insoluble in alkali, m.p. 114.5-116° (from di-n-butylether or isopropanol). Found : C, 69.02; H, 7.33; N, 4.14, for $C_{36}H_{38}O_8N_2$, requires C, 68.99; H, 6.11; N, 4.47, and uncyclic dipeptide (VIII), amorphous compound soluble in alkali, m.p. 105-108° (def. 60-61°) Found : C, 59.12; H, 5.88; N, 3.8; Br, 11.66, for $C_{36}H_{39}O_8Br$, requires C, 61.10; H, 5.56; N, 3.96; Br, 11.29. Bischler-Napieralski reaction of the cyclic diamide in chloroform with phosphorous oxychloride yielded the bisdihydroisoquinoline base (IX) as a pasty mass pale in colour. By the action of methyl iodide in methanol, the base was converted to dimethiodide (X), a hydroscopic yellow powder, m.p. 153-159° (def. 66-67°). Found C, 51.94; H, 4.72; N, 3.23 for $C_{38}H_{40}O_6N_2I_2$, requires C, 52.18; H, 4.72; N, 3.20.



The reduction of (X) was carried out by zinc dust in dilute acetic acid. The product, a mixture of stereoisomers of (III) (Rf : 0.7; 0.8; 0.9) was separated on paper (Whatman No.1) using BuOH:ACOH:H_2O:63:10:27-developer. Natural cycleanine has Rf = 0.71 ± 0.02. Produced substances are on the study of investigation.

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