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SYNTHESIS OF dl-CYCLEANINE

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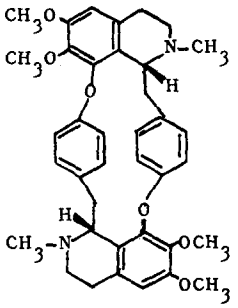
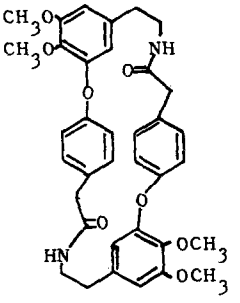
Cycleanine (O,O-dimethylisochondodendrine), a bisbenzylisoquinoline alkaloid, was first isolated from Cyclea insularis (Makino) Diels and Stephania cepharantha Hayata by Kondo et al.[1] in 1937, and was proved to have an exceptionally symmetrical structure involving two diphenyl ether linkages (formula I).[1]-[3] The synthetic approaches to this alkaloid, however, had remained unsuccessful.



I



II

We now wish to report the synthesis of dl-cycleanine

through Bischler-Napieralski cyclization of the cyclobisamide (II).

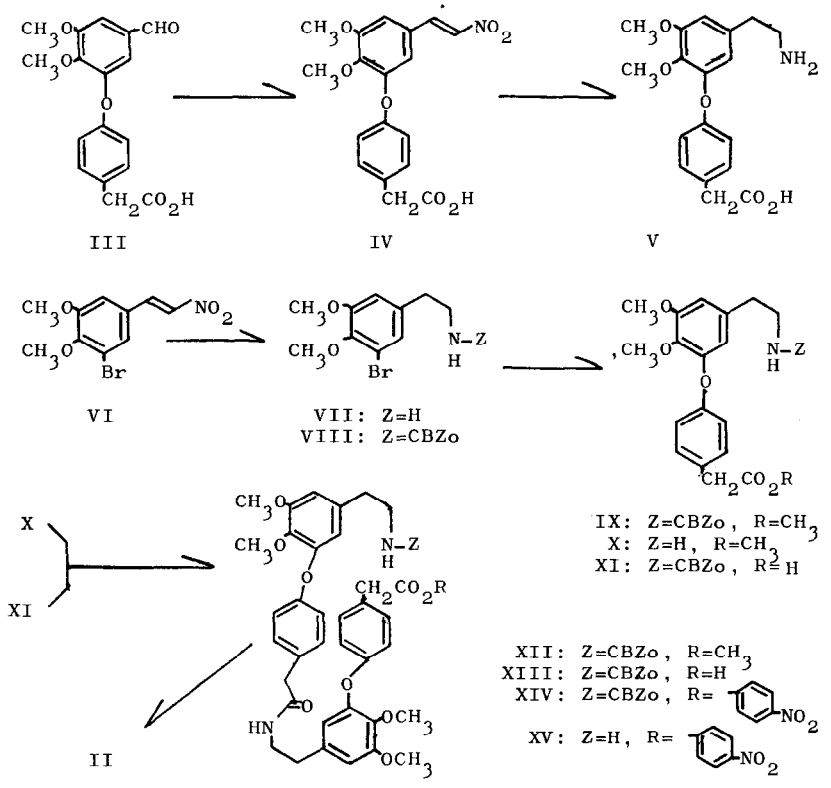
The Ullmann condensation catalysed by cupric oxide[4] between 5-bromoveratraldehyde acetal and methyl p-hydroxyphenylacetate followed by removal of the protective groups afforded the carboxymethyldiphenyl ether carboxaldehyde (III),[4] which was condensed with nitromethane to give the nitrostyrene (IV) as yellow cubes, m.p. 131°. Catalytic hydrogenation of IV over platinum oxide in acetic acid gave the amino acid (V) as colorless microcrystalline, m.p. 225°.

Alternatively, the methyl ester (X) of V was synthesized via following route. 3,4-Dimethoxy-5-bromophenethylamine (VII),[5] prepared by the reduction of the nitrostyrene (VI)[5] under Clemmensen condition,[6] was converted to the N-carbobenzoxy (N-CBZo) derivative (VIII), colorless prisms, m.p. 111°, by treatment with carbobenzoxy chloride (CBZo-Cl). The Ullmann condensation catalysed by cupric oxide between VIII and methyl p-hydroxyphenylacetate afforded the product IX as an oily substance. The CBZo group of IX was removed by hydrogenation over palladised charcoal, and the methyl ester (X) was obtained as colorless oil.

Treatment of V with CBZo-Cl in dilute aqueous sodium hydroxide, or alkaline hydrolysis of IX afforded the N-CBZo carboxylic acid (XI) as oil.

Condensation between XI and X with the aid of N,N'-dicyclohexylcarbodiimide (DCCD)[7] in methylene chloride gave a viscous oily amide (XII), which was further converted to the carboxylic acid (XIII) by potassium carbonate treatment. XIII was esteri-

fied by a method similar to that described by Bodanszky and du Vigneaud,[8] and the resulted p-nitrophenyl ester (XIV) was treated with hydrogen bromide-acetic acid to remove the CBZo group. The amine (XV) hydrobromide thus obtained (amorphus mush) was dissolved in dimethylformamide, then submitted to ring closure by adding the solution dropwise to pyridine containing a small amount of triethylamine. The cyclobisamide (II) obtained (overall yield based on XIII 17%) is colorless microcrystalline and decomposes gradually over 280°.



Bischler-Napieralski cyclization of II (1.5 g.) followed by sodium borohydride reduction in methanol afforded a mixture of tetrahydroisoquinolines. Treatment of the product with formalin, then with sodium borohydride yielded the N-methyl derivatives as a mixture which showed several spots on thin layer chromatography.

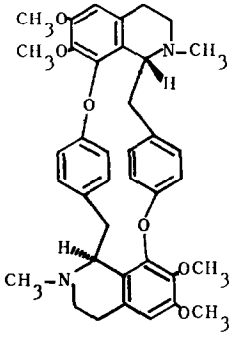
Separation and purification of the products by column chromatography, preparative thin layer chromatography, and fractional recrystallization of the base picrates gave dl-cycleanine together with two other crystalline products (Base A and B).

dl-Cycleanine: Colorless pillars, m.p. 222-225°. Yield 1 mg. The IR spectrum ($CHCl_3$) and thin layer chromatogram wer superimposable on those of natural cycleanine; and in the NMR spectrum, the chemical shifts for O-CH_3 and N-CH_3 groups were completely identical with those of the natural base, though the signals for the other remnant hydrogens were not apparent enoug owing to the small amount available. The mass spectrum of thi base has the same molecular ion peak at m/e 622 and the same fragmentation pattern as natural cycleanine.(9)

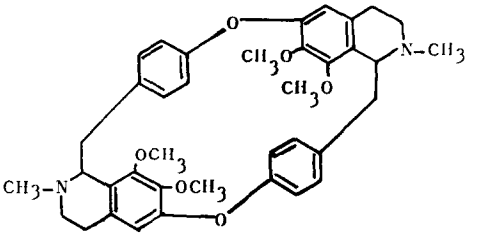
Base A (XVI): Colorless pillars, m.p. 230-233°(decomp.) Yield 3.5 mg. From the IR, NMR, and mass spectral data, Base was confirmed to have the structure XVI, diastereoisomer of the natural base.

Base B (XVII): Colorless pillars, m.p. 210-212°. Yield 29 mg. IR, NMR, and mass spectral data agreed with the formul XVII. On metallic sodium-liquid ammonia treatment, only 1-(4-hydroxybenzyl)-2-methyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquin

line[10] was given almost quantitatively as the bisected product.



XVI



XVII

The homogeneity of the reported compounds was confirmed by NMR spectrometry and thin layer chromatography, and satisfactory elemental analyses were obtained for all crystalline intermediates.

The NMR spectra were taken on a Varian A-60 spectrometer, and the mass spectra were taken with a Hitachi Mass Spectrometer Model RMU-6D equipped with direct inlet system (Model MG-150), chamber voltage 80 eV.

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