

SYNTHESIS OF dl-CEPHARANTHINE

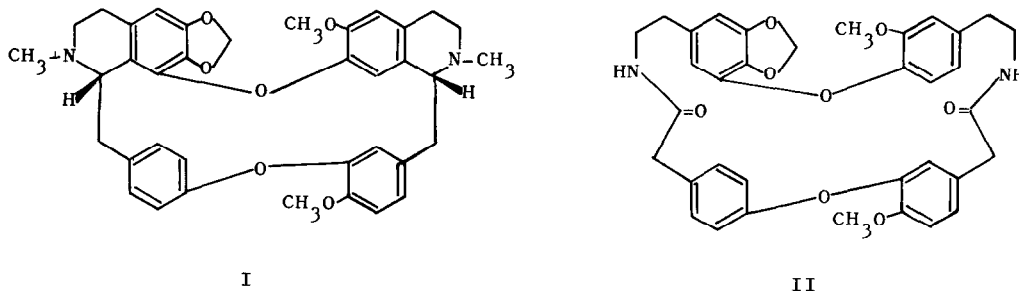
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Cepharanthine (I) is a member of biscoclaurine (bisbenzylisoquinoline) alkaloids, and possesses a unique structural feature with the methylenedioxy group on its tetrahydroisoquinoline nucleus.

Isolation of the base from Stephania cepharantha Hayata and S. Sasaki Hayata (family Menispermaceae) was reported by H. Kondo and his collaborators<sup>1)</sup> and later the structure<sup>2)</sup> and absolute configuration<sup>3)</sup> were fully elucidated, although attempts to synthesize this alkaloid remained ambiguous or unsuccessful<sup>4,5)</sup>. \*

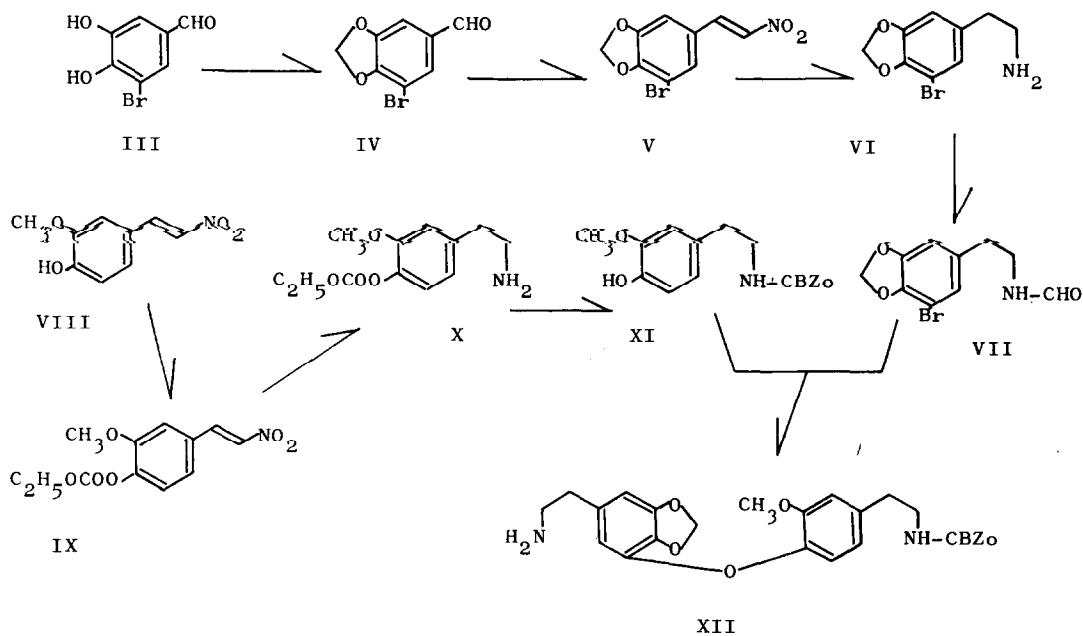
This paper describes the first successful example of the synthesis of dl-cepharanthine, which was achieved through Bischler-Napieralski reaction of cyclobisamide II.



Cyclobisamide II was synthesized by an unambiguous route shown below.

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\* Recently, a synthetic approach to cepharanthine via a route different from ours was reported by T. Kametani *et al.*<sup>6)</sup> though the aimed compound, dl-cepharanthine, was not isolated nor characterized.



Preparation of 5-bromohomopiperonylamine (VI) started with 5-bromopropiocatechuic aldehyde (III) was already described by Erne and Ramirez<sup>7)</sup>, but the modifications adopted by the present authors raised the yield in every step of the reaction sequence.

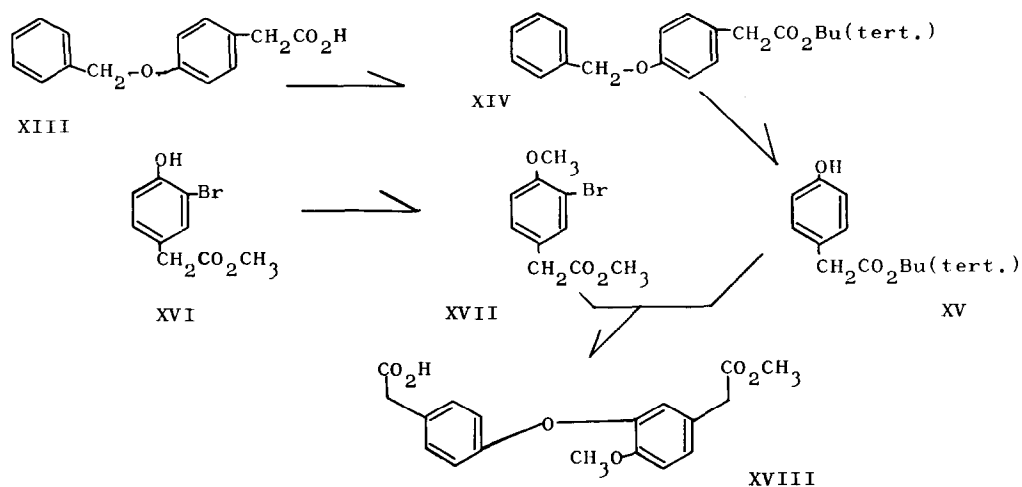
Methylation of III with methylene bromide in dimethylformamide (DMF) was effected under the presence of cupric oxide catalyst<sup>8)</sup>, and the obtained 5-bromopiperonal (yield: 42%) (IV) was condensed with nitromethane in the presence of ammonium acetate in acetic acid to afford the nitrostyrene V (yield: 73%), which was further reduced under Clemmensen condition to the corresponding phenethylamine VI (yield: 68%). N-Formylation of VI with formic acid in decalin gave N-formyl derivative VII (colorless pillars, m.p. 126-7°) in 80% yield.

On the one hand, 3-methoxy-4-hydroxy- $\alpha$ -nitrostyrene (VIII) was treated with ethyl chloroformate in pyridine and the resulted carbethoxy derivative IX (yellow needles, m.p. 126°, yield 89%) was reduced under Clemmensen condi-

tion to the phenethylamine X (oxalate: colorless microcrystalline, m.p. 185-191°, yield: 57%). The carbethoxyamine X was treated with carbobenzoxy chloride to protect the amino function, then the protective group for the phenolic hydroxyl was selectively removed by aqueous sodium bicarbonate treatment. N-Carbobenzoxyhomovanillylamine (XI) was thus obtained as colorless needles, m.p. 73-74° (48% from X).

Ullmann condensation reaction catalysed by cupric oxide between VII and XI followed by the removal of formyl group (hydrochloric acid-methanol) afforded the diphenyl ether XII (pale yellow oily substance) in 27% yield.

Another intermediate for the synthesis of cyclobisamide II, the diphenyl ether diacetic acid mono-ester XVIII was prepared by the following scheme.

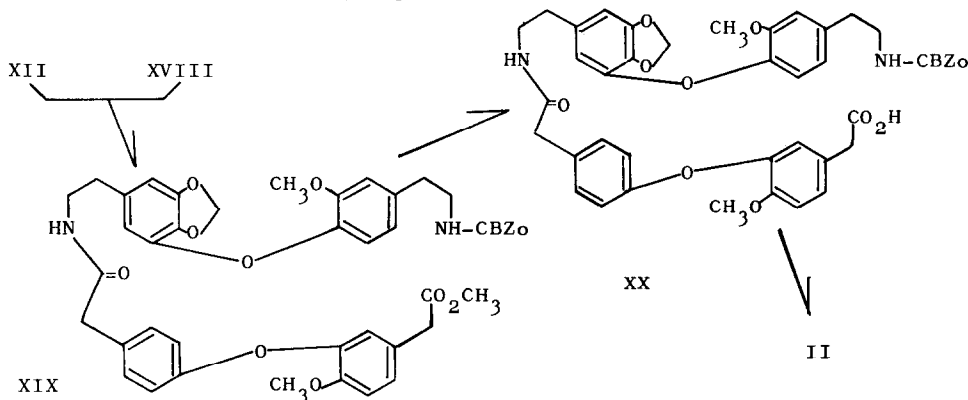


p-Benzyloxyphenylacetic acid (XIII) was converted to the tert. butyl ester XIV in 81% yield (yellowish oil) by phosphoryl chloride-pyridine method<sup>9)</sup>, and the ester XIV was in turn debenzylated by hydrogenolysis over palladised charcoal to give the hydroxy ester XV (colorless pillars, m.p. 96-97°, yield: 95%). Methyl 3-bromo-4-methoxyphenylacetate<sup>10)</sup> (XVII) was prepared by methylation of the corresponding phenolic methyl ester XVI<sup>10)</sup> with dimethyl sulfate and potassium carbonate in DMF; the yield was 88%.

CuO catalysed Ullmann condensation between the hydroxy ester XV and bromo

ester XVII followed by the selective removal of tert. butyl group using *p*-toluene sulfonic acid in benzene yielded the half ester XVIII (colorless needles, m.p. 114-6°, yield: 13%).

Condensation of the amine XII and the carboxylic acid XVIII with the aid of dicyclohexylcarbodiimide in methylene chloride gave the amide XIX (pale yellow oil) in 70% yield, and the resulted amide XIX was hydrolysed by aq. sodium carbonate to the corresponding carboxylic acid XX (pale yellow oil, yield: 90%). The cyclization of XX to the cyclobisamide II was effected in 43% yield by *p*-nitrophenyl ester method similar to that developed by the present authors in the synthesis of *dl*-cycleanine<sup>11)</sup>. The cyclobisamide was obtained as colorless needles, m.p. 232-4°.



Bischler-Napieralski reaction of the cyclobisamide II (700 mg.) with phosphoryl chloride in chloroform gave a mixture of 3,4-dihydroisoquinolines which showed two distinct spots on thin layer chromatography (TLC). This mixture was hydrogenated over platinum catalyst to avoid the ready oxidation with atmospheric oxygen, and the product was treated with formalin and sodium borohydride to afford a mixture of *N*-methyltetrahydroisoquinolines. The mixture showed four distinct spots on TLC (Silica Gel G acc. to Stahl, methanol).

Differences in the composition of the product mixture by the reducing agents were examined using the Bischler-Napieralski cyclization products from each 100 mg. of II. Zinc-sulfuric acid method<sup>12)</sup> gave no substantial diffe-

rence on TLC comparison, but sodium borohydride reduction was found to show a detectable difference in relative ratio of the spots in density, which was understood as ascribable to the stereoselectivity of the reducing agent<sup>12)</sup>.

The reaction products by the above three different method were combined, and separation and purification into four species of bases (Base A, B, C, and D in order of decreasing R<sub>f</sub> values on TLC) were performed utilizing preparative TLC on silicic acid and column chromatography on alumina. The R<sub>f</sub> value of Base C was identical with that of natural cepharanthine.

Among these bases finally obtained, Base C (amorph., 3.5 mg.) gave superimposable spectra with natural cepharanthine on IR (CHCl<sub>3</sub>) and NMR (CDCl<sub>3</sub>) measurements, and thus was proved to be dl-cepharanthine (XXI).

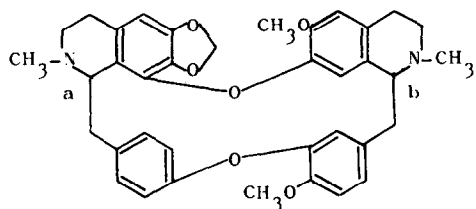
Base D (amorph., 3.0 mg.) was concluded to be the diastereoisomer (XXII) of dl-cepharanthine on the basis of IR, NMR, and mass spectral comparisons with the natural base.

The IR, NMR, and mass spectral data of Base A (amorph., 25 mg.) and B (amorph., 36 mg.) pointed out that these bases are diastereoisomeric each to each, with the same planar structure not other than XXIII. The formation of isomers of this type with the undesirable direction of isoquinoline ring closure was already exemplified by the present authors<sup>11)</sup>.

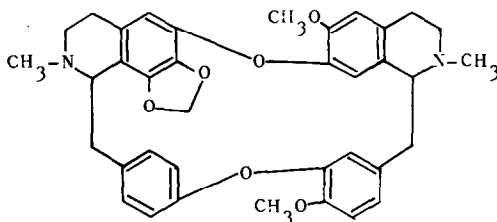
A comparison of chemical shift data of these final products is drawn below.

( $\tau$  values in CDCl<sub>3</sub>, TMS internal standard.)

	-O-CH <sub>2</sub> -O-		-O-CH <sub>3</sub>	-N-CH <sub>3</sub>	
Base A (XIII)	3.96, d., J=1.5 cps	4.09, d., J=1.5 cps	6.08, 6.12	7.37, 7.67	
Base B (XIII)	4.16, s.,		6.10, 6.12	7.38, 7.70	
Base C ( <u>dl</u> -cepha ranthine)	4.42, d., J=1 cps	4.46, d., J=1 cps	6.11, 6.33	7.35, 7.43	identical with natural cepharanthine
Base D (XXII)	4.42, d., J=1 cps	4.56, d., J=1 cps	6.03, 6.50	7.40, 7.45	



XXI (a=S, b=R), (a=R, b=S)  
dl pair (=dl-cepharanthine)



XXIII

XXII (a=S, b=S), (a=R, b=R)  
dl pair

Homogeneity of all compounds were checked by NMR spectrometry at 60 Mc., and satisfactory elemental analyses were obtained for all crystalline compounds.

#### REFERENCES

- H. Kondo, Y. Yamamoto, I. Keimatsu, Yakugaku Zasshi, 54, 620(1934).  
H. Kondo, M. Tomita, M. Satomi, T. Ikeda, ibid., 58, 920(1938).  
H. Kondo, M. Tomita, ibid., 59, 542(1939).
- H. Kondo, I. Keimatsu, Yakugaku Zasshi, 55, 121, 894(1935); 58, 906(1938); Ber., 71, 2553(1938).  
M. Tomita, Y. Sasaki, Chem. Pharm. Bull. (Tokyo), 1, 105(1953); 2, 89, 375(1954); 3, 178,250(1955).
- J. Kunitomo, Yakugaku Zasshi, 82, 981(1962).
- H. Kondo, H. Kataoka, et al., Ann. Rep. ITSUU Lab., 1, 15(1950); 2, 7,11, 13(1951); 3, 10,15(1952); 4, 20(1953); 5, 5(1954); 6, 9(1955).
- W. M. Whaley, C. N. Robinson, J. Org. Chem., 19, 1029(1954).
- A paper read by T. Kametani et al. at the monthly meeting of the Tohoku Branch, the Pharmaceutical Society of Japan (July 16th, 1966).  
cf. Yakugaku Kenkyu, 37(9), 281(1966).
- M. Erne, F. Ramirez, Helv. Chim. Acta, 33, 912(1950).
- M. Tomita, K. Fujitani, Y. Aoyagi, Chem. Pharm. Bull. (Tokyo), 13, 1341 (1965).
- E. Taschner, J. Biernat, B. Rzeszotarska, C. Wasielewski, Ann., 646, 123 (1961).
- H. Kondo, S. Uyeo, Yakugaku Zasshi, 53, 557(1933).
- M. Tomita, K. Fujitani, Y. Aoyagi, Tetrahedron Letters, No 35, 4243(1966).
- H. Furukawa, Yakugaku Zasshi, 86, 253(1966).  
Y. Watanabe, H. Furukawa, M. Kurita, ibid., 86, 257(1966).