

REDUCTIVE DECYANIZATION OF α -AMINO NITRILES WITH NaBH_4
A NEW SYNTHETIC APPROACH TO ISOQUINOLINE- AND INDOLE-ALKALOIDS

Shun-ichi Yamada and Hiroshi Akimoto

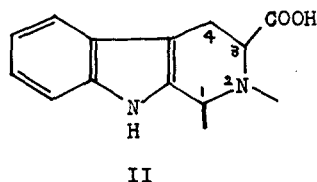
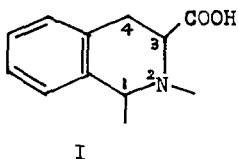
Faculty of Pharmaceutical Sciences, University of Tokyo,

Bunkyo-ku, Tokyo, Japan

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It is well recognized that most isoquinoline- and indole-alkaloids are derived from relatively simple precursors, phenylalanine derivatives and tryptophan, and the decarboxylation of these α -amino acids readily occurs in the course of biogenetic alkaloid syntheses in nature¹⁾.

As to the chemical decarboxylation of α -amino acids, two modifications have been generally performed up to the present time; one is thermal decarboxylation²⁾, the other, oxidative decarboxylation³⁾. The former requires relatively high temperature while the latter often gives complex results. Especially in the decarboxylation of tetrahydroisoquinoline (I) and tetrahydro- β -carboline (II) derivatives, the aromatization of ring systems is usually accompanied under both reaction conditions.^{2a,3)}



The authors have a project to synthesize optically active 1-substituted tetrahydroisoquinoline- and tetrahydro- β -carboline-alkaloids from optically active phenylalanine derivatives and tryptophan. Therefore, the experiment involves selecting the reaction for removing the carboxyl group under milder condition to prevent the aromatization of ring system and racemization at the asymmetric carbon atom of position 1.

The present paper deals with the preliminary experiments for this purpose. An attempt has been carried out to remove the nitrile group of α -amino nitrile prepared from α -amino acid. Decyanization of α -amino nitriles with LiAlH_4 has been already reported⁴⁾, but satisfactory results were obtained only in special cases,^{4c, 4d)} accompanied with the reduction of nitrile group. A milder reducing agent, NaBH_4 , generally inactive for the nitrile group, was employed instead of LiAlH_4 , and the authors succeeded in decyanization of various types of α -amino nitriles(III),(IV) and (V), easily prepared from dehydration of α -amino acid

Table



Runs	Reaction Conditions			Yield % *
	Solvents	Temperature (°C)	Reaction Time (hr.)	
1	Diglyme	60	24	9
2	"	100	24	88 (85)



3	EtOH	35	20	100 (93)
4	Pyridine	60	24	87

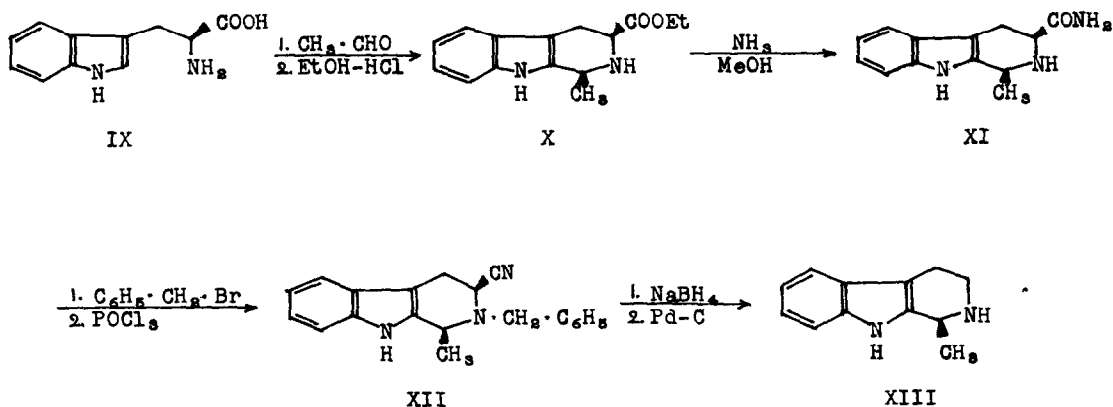


5	EtOH	35	20	97 (92)
6	Pyridine	60	24	81
7	DMF	60	24	73
8	Diglyme	100	24	85 (82)

* By g.l.c. analysis. Numbers in parentheses are isolated yields.

amide derivatives with phosphoroxychloride. The corresponding decyanized amines (VI), (VII) and (VIII), were obtained in good yield as shown in the Table.

Furthermore, to investigate whether or not the racemization occurs under these mild conditions when optically active α -amino acid is employed as a starting material and for the preliminary experiment for alkaloid synthesis, the following reaction was performed.



The carboxamide (XI) [m.p. 144°, $[\alpha]_D^{25} -149^\circ$ (c=0.4, EtOH)] was prepared by aminolysis of optically pure ester (X) [m.p. 116°, $[\alpha]_D^{24} -106^\circ$ (c=0.4, 96%EtOH)] obtained from L-tryptophan (IX) according to the literature⁵⁾. The benzylation of XI with benzyl bromide and sodium bicarbonate in ethanol, followed by dehydration with POCl₃ gave amino nitrile (XII) [m.p. 160-161°, $[\alpha]_D^{25} -12.6^\circ$ (c=1.6, pyridine)]. This compound was decyanized by reduction with NaBH₄ in a mixture of ethanol and pyridine, and subsequent debenylation by catalytic hydrogenation afforded optically active tetrahydroharman, 1-methyl-1,2,3,4-tetrahydro- β -carboline (XIII) [m.p. 177°, $[\alpha]_D^{25} -52^\circ$ (c=2.0, EtOH)].

Optical purity of this compound (XIII) was considered to be pure from the reported value⁶⁾. It has been proven that no racemization occurs at the asymmetric center 1. The absolute configuration at the asymmetric center of (-)-XIII is shown to be (S)-configuration according to the literature^{6a)}. The stereochemistry of X which is the main isomer by the reaction of L-tryptophan and acetaldehyde under the Pictet-Spengler reaction condition is demonstrated

to be 1,3-cis configuration including the absolute configuration as shown in the figure. This conclusion is the same as the proposal by Yoneda⁷⁾.

Stereospecific total syntheses of optically active isoquinoline-, indole- and other alkaloids from optically active amino acids by this reductive decyanization are now in progress in our laboratory.

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