

SYNTHESIS OF 2,3,9,10-TETRAOXYGENATED PROTOBERBERINE ALKALOID,
TETRAHYDROPALMATINE

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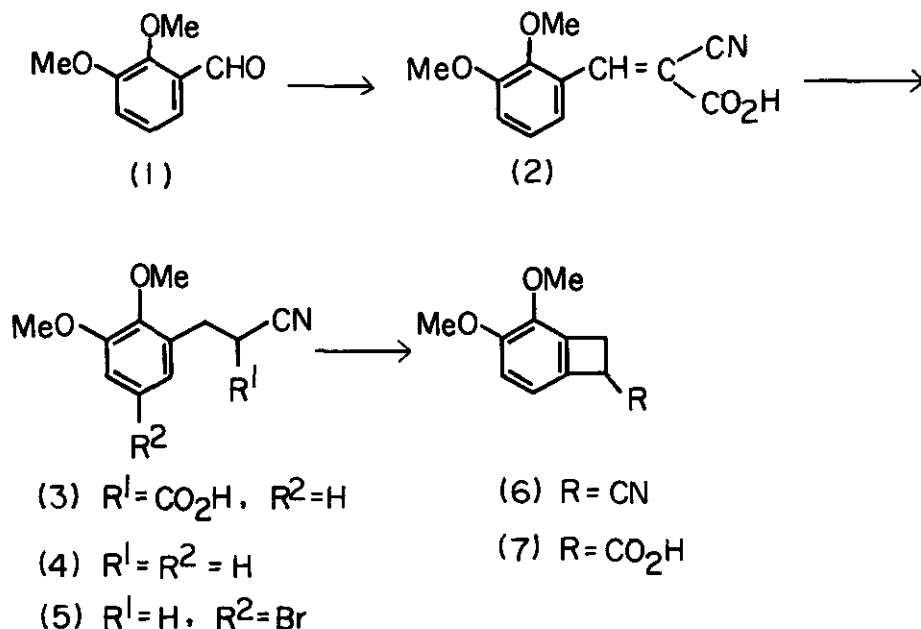
Abstract — Tetrahydropalmatine (15) was synthesized from the 3,4-dihydroisoquinoline derivative (13) by thermal electrocyclic reaction and subsequent reduction. An intermolecular Diels-Alder type reaction of the benzocyclobutene (6) with the 3,4-dihydroisoquinoline afforded the 13-cyanoprotoberberine (9) regioselectively.

Recently we have reported the synthesis of several protoberberine alkaloids by means of retro mass spectral synthesis¹. However, the products synthesized so far had namely 10,11-oxygenated pattern in their D-ring. It is therefore of interest to investigate the further application of the above strategy for the synthesis of 2,3,9,10-oxygenated protoberberine alkaloids, which are also distributed in nature widely.

The requisite benzocyclobutene (6) was synthesized as follows. The cinnamic acid derivative (2), prepared from the aldehyde (1) and cyanoacetic acid by Knoevenagel condensation, was reduced with sodium borohydride to give the dihydrocinnamic acid (3). Decarboxylation of (3) in dimethylacetamide, and subsequent bromination of the cyanide (4) gave rise to the bromide (5) in good yield. The benzocyclobutene (6) was prepared from the bromide (5) by the known procedure developed by Bunnett² via benzyne intermediate in 62% yield.

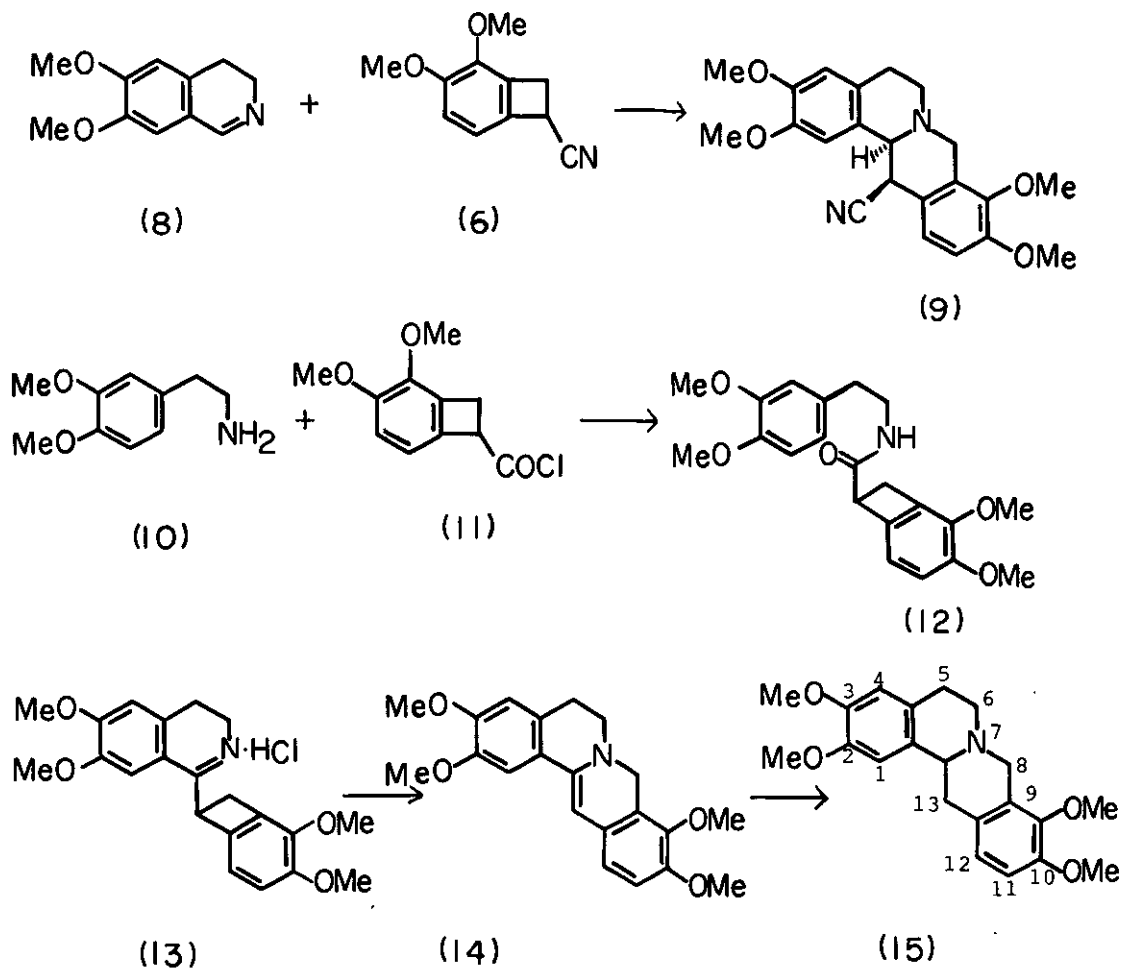
Firstly, an intermolecular cycloaddition reaction of (6) with the 3,4-dihydroisoquinoline derivative (8) was carried out in refluxing *o*-dichlorobenzene to give the 13-cyanoprotoberberine (9) (mp 191-193°C) regioselectively, in 52% yield, whose spectroscopic data were consistent with its structure. This result suggested that

Scheme 1



the reactivity of 1-cyano-3,4-dimethoxybenzocyclobutene (6) was similar to that of 1-cyano-4,5-dimethoxybenzocyclobutene, whose reaction with (8) afforded 13-cyano-2,3,8,9-tetramethoxyprotoberberine³. In order to synthesize a naturally occurring 2,3,9,10-tetramethoxyprotoberberine, the acid (7) derived from the cyanide (6) by hydrolysis was treated with oxalyl chloride to give the acid chloride (11), which without purification was condensed with the amine (10) to yield the amide (12) in 92% yield. Bischler-Napieralski reaction of (12) gave the 3,4-dihydroisoquinoline hydrochloride (13). Heating (13) at 160°C followed by subsequent sodium borohydride reduction furnished, via (14), tetrahydropalmatine (15) which was identical with an authentic specimen⁴. Thus, the facile synthesis of 2,3,9,10-tetramethoxyprotoberberine, such as tetrahydropalmatine (15), was achieved by utilizing the benzocyclobutene (6) as a useful starting material, and this method should be applicable to the synthesis of various types of protoberberine alkaloids bearing 9,10-oxygenated pattern in their D-ring.

Scheme 2



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3. T. Kametani, K. Ogasawara, and T. Takahashi, *Tetrahedron*, 1973, **29**, 73.
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Received, 22nd February, 1984