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BIOGENETIC-TYPE THREE-STEP SYNTHESIS OF WITHASOMNINE[*1]

Tadamasa Onaka

ITSUU Laboratory, Tamagawa 2-28-10, Setagaya-ku, Tokyo, Japan

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The roots of Withania somnifera DUNAL (Solanaceae) indigenous to the Western India and Hindustan are sold in the bazars of South India for drug purposes, and used as a tonic and an aphrodisiac.[1)]

Power and Salway[2)] published their pioneering work on the alkaloidal constituent of the roots and described the isolation of a crystalline base (colorless glistening leaflets, mp 116°) upon treatment of amorphous crude base with aq. KOH. The base formed a picrate of silky yellow needles, mp 171°. Schwarting et al.[3)] studied the alkaloids of this roots extensively and obtained nine alkaloids in a pure state. These alkaloids are tropine, pseudotropine, 3-tropyl tigloate, choline, cuscohygrine, dl-isopelletierine, two new alkaloids, anaferine and anhygrine, and one minor alkaloid (hydrochloride, mp 115-7° under vacuum), whose constitution remained uncertain.

More recently, Schröter, Neumann, and Katritzky[4)] reported their investigation of a base named withasomnine, mp 117-8° (hydrochloride, mp 115-7°[*2]; picrate, mp 170-3°), isolated from the roots of Withania somnifera which seems to be identical to Power's base and also to the unidentified alkaloid of Schwarting,[*3] and they proposed the structure of 4-phenyl-1,5-trimethylene-pyrazole (I) for the alkaloid on the basis of its IR, UV, NMR, MS, and pKa data.

In view of the fact that withasomnine possesses an unusual pyrazole nucleus, which has not hitherto been encountered[4)] in the alkaloid realm, it will be worth while to speculate how withasomnine is produced in the plant and especially what the origin of the pyrazole ring would be. Here, we propose a biogenetic hypothesis that withasomnine (I) is constructed from Δ^1-pyrroline (V) and phenylalanine (II) (Chart 1), considering that other alkaloids of the roots of Withania somnifera seem to originate from Δ^1-pyrroline[5)] (V).

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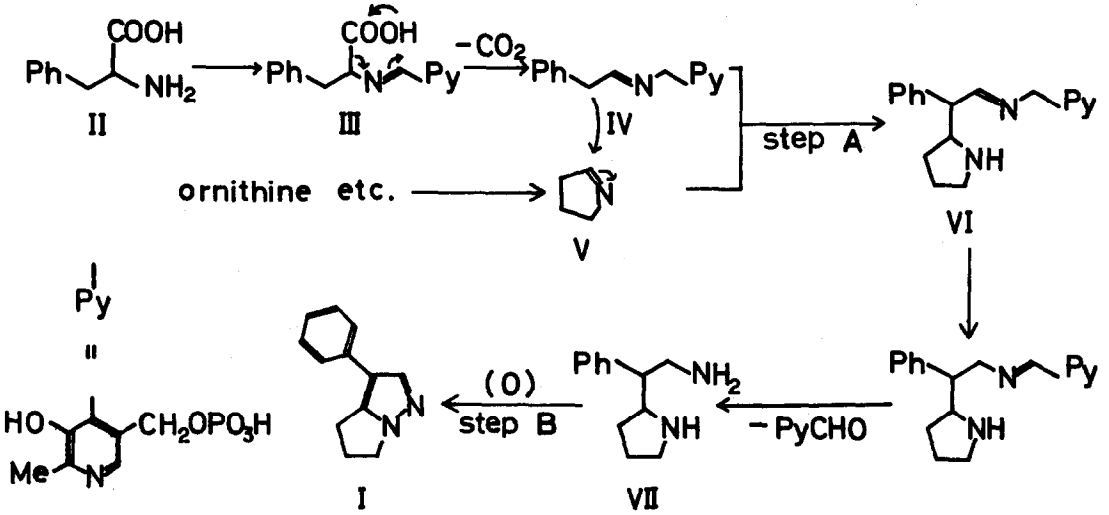
*2 Dr. Neumann informed us in his letter that this hydrochloride easily decomposed under vacuum to the free base and the true melting point of this compound was 190-6°. Our own observation confirmed this and the melting point of synthetic withasomnine hydrochloride was 192-4°, with partial sintering from 137°.

*3 In his recent personal communication, Prof. Schwarting kindly informed us their confirmation of the identity of this alkaloid with withasomnine.

Chart 1.



In the present communication, we wish to report the synthesis of withasomnine along these biogenetic sequences that may provide a synthetic proof for the biogenetic hypothesis (Chart 1) and also for the structure (I) of withasomnine.

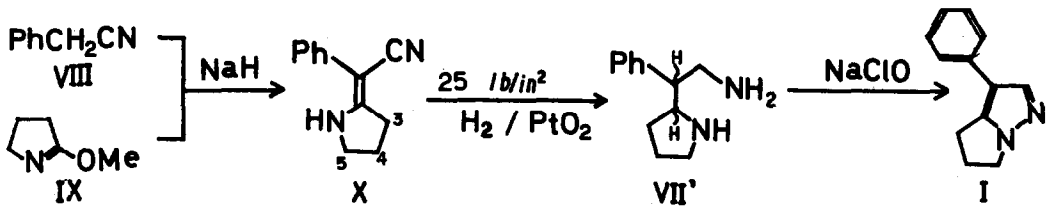
The above biosynthetic hypothesis gives important hints for the laboratory synthesis of withasomnine: (1) The carbon skeleton of withasomnine is advantageously composed by the condensation of pyrrolidine moiety and phenethylamine residue (step A in Chart 1) and (2) the pyrazole ring may be formed by the oxidative cyclization of 1,3-diamine (step B in Chart 1), which also constitutes a new synthetic approach to the pyrazole ring systems.

In the actual synthesis, we chose benzyl cyanide (VIII) as a laboratory variant of biosynthetic intermediate (IV) with an anticipation to trace the naturally occuring condensation process (step A of Chart 1). As the other component, the biogenetical intermediate Δ^1-pyrroline (V) itself may as well be used. We, however, have taken advantage of O-methylbutyrolactim (IX) which can conveniently be obtained from pyrrolidone.[6]

Reaction of O-methylbutyrolactims with reactive methylene compounds has been utilized by Eschenmoser in his synthetic approach to corrin skeleton.[7] Very recently Oishi and Ban have further developed this reaction.[8]

Reaction of O-methylbutyrolactim (IX) with benzyl cyanide (VIII) in benzene or tetrahydrofuran with sodium hydride as a condensation reagent at reflux temperature for 20 hr provided a condensation product (X) in 53% yield, as colorless plates (from MeOH), mp 120-1°; Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.06; H, 6.57; N, 15.48 ; IR ν(KBr): 3320 (NH), 2950 and 2860 (CH), 2213 (CN), 1594 (arom), 760 and 700 (arom. CH).; NMR δ ($CDCl_3$): 7.5-7.1 (5H, m; arom. H), 5.70 (1H, br. s; NH), 3.53 (2H, t, J=7 cps; $C_5\underline{H}$ of pyrrolidine ring), 2.96 (2H, t, J=8 cps; $C_3\underline{H}$ of pyrrolidine ring), 2.4-1.8 (2H, br. quintet, J=7 cps; $C_4\underline{H}$ of pyrrolidine ring). This step corresponds to the condensation process A of the suggested natural route (Chart 1).

Chart 2.



The condensation product (X) was then converted into the assumed biosynthetical intermediate diamine (VII) by hydrogenation over PtO_2 at 25 lb/in^2 in EtOH-HCl solution. The diamine (VII') thus obtained as a diastereomeric mixture was too polar to be purified through alumina column and the crude reduction product was submitted to subsequent oxidation without further purification.

Although various means may be envisaged for nonenzymic chemical simulation of biosynthetic oxidative coupling of the diamine (VII) (step B in Chart 1), we chose the hypochlorite which seemed to react as a laboratory variant of biochemical oxidant of amines.[9] When an excess of aqueous solution of sodium hypochlorite was added to the H_2O-MeOH solution of the diamine (VII'), an instantaneous formation of water-insoluble materials was observed. After extraction with ether and purification through chromatography, the reaction mixture afforded a compound of mp 116-7° (colorless plates from petroleum ether) as a sole crystalline product (yield, 7.5% from X). Its elemental analysis was consistent with $C_{12}H_{12}N_2$ (Anal. Calcd.: C, 78.28; H, 6.57; N, 15.21. Found: C, 77.89; H, 6.67; N, 15.08), and its IR and NMR spectra were in good agreement with the recorded spectra of withasomnine.[4] Mixed melting point determination and IR spectrum comparison with natural withasomnine, kindly provided by Dr. Neumann of Halle/Saale, ensured the identity of the natural and synthesized specimens.*4 Melting point of the picrate (171-3°) of synthesized withasomnine also corresponded well with the reported melting point for withasomnine picrate (170-3°).[2,4] IR spectrum of the synthesized withasomnine hydrochloride was identical with that of the hydrochloride of Schwarting's unknown alkaloid "XI"[3] which was recently identified with withasomnine.*3

*4 After our synthesis was completed, Prof. Katritzky and Dr. Neumann kindly informed us that an independent synthesis of withasomnine had been accomplished by Dr. Schröter. Prof. K. Tsuda, the honorary regional editor, also kindly suggested us, after this communication was submitted for publication, that a synthesis of withasomnine had been completed by the research group in Fujisawa Pharm. Co. and that it would be advisable to identify both of synthesized withasomnine. Our withasomnine was proved to be identical (IR and mixed mp determination) with the specimen prepared in an entirely different way by Dr. A. Morimoto and his coworkers of Fujisawa Pharm. Co. (see accompanied paper).

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