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RECENT DEVELOPMENTS IN 1,2-AZOLES CHEMISTRY

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The physical and chemical data show that 1,2-azoles are heteroaromatic systems. Numerous substitution reactions in their rings and side chains are well known. Double bond addition reactions in the azoles nuclei are less typical.

The bond strength between the heteroatoms diminishes in the row of 1,2-azoles: pyrazole) isothiazole) isoxazole. The lability of the N-O bond in the isoxazole ring is responsible for essential differences of this heterocycle behavior in the destruction reactions under the electron impact, UV light, bases action and during the catalytic hydrogenation. Syntheses of different classes of acyclic, carbocyclic and heterocyclic compounds have been developed on the basis of the two latter reactions.

PL 14

TOTAL SYNTHESIS OF HETEROCYCLIC NATURAL PRODUCTS

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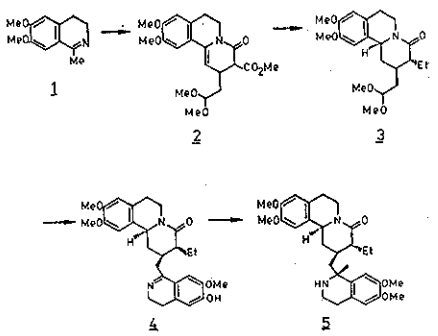
More than ten years ago, we had achieved a total synthesis of many types of isoquinoline alkaloids by an application of Bischler-Napieralski (for example, reticuline), Pictet-Spengler (scoulerine), Pomeranz-Fritsch (cularine), Ullmann reactions (isoliensinine), phenolic cyclization (petaline) and so on as the key reactions. Later, we divided the method of analysis for designing synthetic approaches into three groups; the first one is step-wise synthesis (phenol oxidation, Pschorr reaction, photo-Pschorr reaction, photolysis, benzyne reaction, nitrene reaction and enamine method), the second one Retro-Mass Spectral Synthesis (benzocyclobutene method and iminoketene method) and the third biomimetic synthesis (chemical oxidation, enzymic oxidation, and enzymic model oxidation), and a number of natural products such as alkaloids (morphine), terpenes (garryine) and steroids (estradiol) have been synthesized by these methods. Thus, we wish to discuss a total synthesis of several alkaloids using enamine method (emetine **5** and yohimbine **9**), benzocyclobutene method (atisine **15**) and enzymic model oxidation [oporphines **17** and **18**, morphinandienone **19**, proaporphine (**25**) and homoproaporphine (**27**) alkaloids].

1. Total Syntheses by Enamine Method

1.1. **Emetine**[1]: It is well known that 3,4 dihydro-1-methylisoquinolines show the reactivity as an enamine. On this fact, we have accomplished a stereoselective synthesis of (±)-emetine (**5**) from 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline **1** through a shorter way than any other reported procedures. Treatment of **1** with dimethyl 3-methoxyallylidenemalonate gave, in 85% yield, the benzo[a]quinolizin-4-one (**2**), whose ethylation with



ethyl iodine and sodium hydride, followed by catalytic hydrogenation on Adams catalyst and then decarboethoxylation furnished stereoselectively the saturated lactom (**3**), which on hydrolysis and reduction on lithium aluminium hydride gave the known (±)-dihydroprotoemetine, thus confirming the stereochemistry of **3**.

Mannich reaction of **3** with 3-hydroxy-4-methoxyphenethylamine in the presence of hydrochloric acid afforded the (±)-oxocephaeline (**4**) as a major product, which was transformed into (±)-emetine (**5**) by methylation and reduction.

1.2. **Yohimbine**[2]: The use of enamines with their low basicity and high nucleophilicity often produces good yields in annelation reactions with vinyl ketones in those cases, whose reaction with the corresponding carbonyl compounds failed. By using this special reactivity of enamines, (±)-yohimbine (**9**) was synthesized in this laboratory.

The pyrrolidine enamine (**6**) of the indolo[2,3-a]quinolizin-2-one was treated with methyl 3-oxo-4-pentenoate gave dehydroyohimbinone (**7**), which was reduced on 30% palladium carbon to afford stereoselectively yohimbinone (**8**). Finally, **8** was convertet into (±)-yohimbine (**9**) by sodium borohydride reduction, thus achieving a total synthesis of (±)-yohimbine by the shortest pathway.