PL 13

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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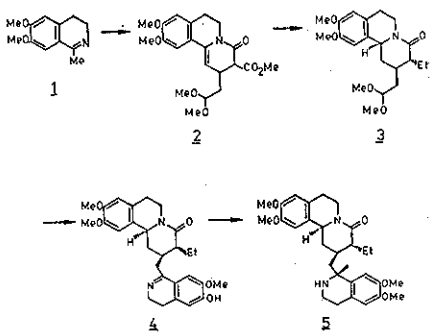
More than ten years ago, we had achieved a total synthesis of many types of isoquinoline alkaloids by an application of Bischler-Napieralski (for example, reticuline), Pictet-Spengler (scoulerine), Pomeranz-Fritsch (cularine), Ullmann reactions (isoliensinine), phenolic cyclization (petaline) and so 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

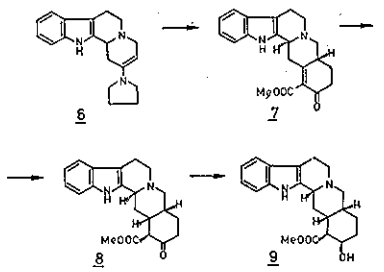


ethyl iodine and sodium hydride, followed by catalytic hydrogenation on Adams catalyst and then decarboethoxylation furnished stereoselectively the saturated lactom (**3**), which on hydrolysis and reduction on lithium aluminium hydride gave the known (±)-dihydroprotoemetine, thus confirming the stereochemistry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



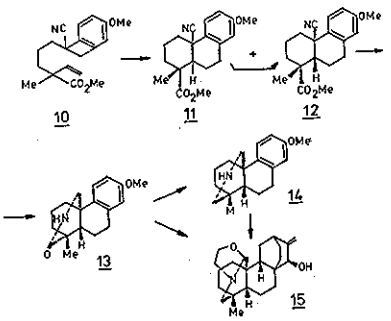
6 7 8 9

2. Total Syntheses by Benzocyclobutene Method[3]

Previously we have shown that the benzocyclobutenes having an olefinic system at the appropriate position is transformed regio- and stereoselectively into perhydrophenanthrene derivatives through o-quinodimethanes by an intramolecular ($4_\pi + 2_\pi$)-cycloaddition. This type of pericyclic reaction was applied for a synthesis of diterpene alkaloids, atisine, garryine and veatchine as follows.

The condensation of 1-cyano-4-methoxybenzocyclobutene with methyl 4-iodo-1-methyl-1-vinylvalerate, prepared from methyl methylacetoacetate, in the presence of sodium hydride furnished the tri-substituted benzocyclobutene (**10**), whose thermolysis over 230° afforded regioselectively the hydrophenanthrene (**11**) and 10aβ-epimer (**12**). The former was converted into the latter (**12**) by oxidation with chromic acid, followed by bromination, dehydrobromination and hydrogenation. The structure of **12** was easily confirmed by conversion into the known 1α-carboxy-1,2,3,4,4aα, 9, 10-10aβ-octahydro-7-methoxy-1β-methylphenanthrene by a reductive decyanation with lithium in liq. ammonia.

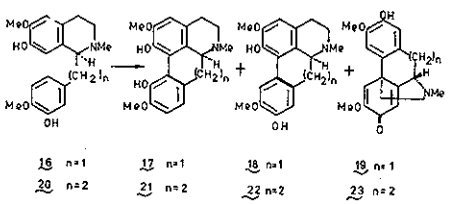
Catalytic reduction of **12** gave the lactam **13** which has been correlated with atisine (**15**) by Wiesner. Moreover, the lactam was reduced with lithium aluminium hydride to afford 16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (**14**). This compound was transformed into (±)-atisine (**15**), (±)-garryine and (±)-veatchine by Nagata.



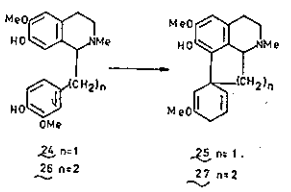
10 11 12 13 14 15

3. Total Syntheses by Enzymic Model Oxidation[4]

Nature provides a splendid method of analysis for developing synthetic routes, which we call biogenesis. Many types of isoquinoline alkaloids have been synthesized along this biogenetic line by a number of group. The laccase and tyrosinase, which have been known as catalysts for phenol oxidation in Nature, involve copper ion and oxygen. In connection with our interest in alkaloid synthesis, we studied phenol oxidation with a mixture of cuprous chloride and molecular oxygen in pyridine as an enzymic model.



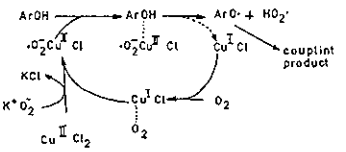
16 n=1, 20 n=2 | 17 n=1, 21 n=2 | 18 n=1, 22 n=2 | 19 n=1, 23 n=2



24 n=1, 26 n=2 | 25 n=1, 27 n=2

Phenol oxidation of (±)-reticuline (**16**) perchlorate with the above system gave (±)-corytuberine (**17**), (±)-isoboldine (**18**) and pallidine (**19**). Racemic homoreticuline (**20**) hydrochloride yielded **21**, **22** and **23** under the same conditions. (±)-Orientalinone (**25**) and (±)-kreysiginone (**27**) were also synthesized from the corresponding 1-benzyl- and 1-phenethylisoquinolines (**24** and **26**). Oxidation with cupric chloride and potassium superoxide in pyridine also gave rise to similar results.

Mechanism of the oxidations by these reagents is suggested as follows.



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