SYNTHESIS OF INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS VIA [3 + 2] CYCLOADDITION OF NITRONES

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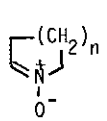
A series of the alkaloids possessing the indolizidine and quinolizidine nuclei have been synthesized by utilizing [3 + 2] nitrone cycloaddition.

A convenient general synthesis of the pentacyclic phenanthridine alkaloids, (±)-tylophorine and (±)-cryptopleurine, and their seco bases, (±)-septicine and (±)-julandine, has been achieved. The key step of this synthesis is 1,3-dipolar cycloaddition reaction of the nitrones (1, n = 1, 2) with 3,4-dimethoxystyrene, affording the isoxazolidines 2. After reductive N-O bond cleavage, these compounds 2 were led to the alkaloids via intramolecular aldol reaction and photocyclization.

Next, the synthesis of 1-aza-3-(4-methoxyphenyl)bicyclo[4,3,0]nonan-4-one (3), key intermediate to (±)-ipalbidine, has been examined. 1,3-Dipolar cycloaddition of the nitrone 1 (n = 1) with p-methoxyallylbenzene proceeded highly regio- and stereoselectively to give the trans-hexahydropyrroloisoxazole (4), which was converted into compound 3 by five steps involving intramolecular cyclization by aldol reaction of the N-formylketone.

Finally, new Lithraceae alkaloids, (±)-lasubine I and (±)-subcosine I, which possess the cis-fused quinolizidine ring system, have been synthesized. A crucial step involves [3 + 2] cycloaddition of 1-(3,4-dimethoxyphenyl)butadiene with the nitrone 1 (n = 2), yielding the E and Z isomers of 2-(3,4-dimethoxystyryl)-2,3,3a,-4,5,6-hexahydropyrrolo[1,2-b]isoxazole favoring the exo adduct in each case. On treatment with hydrogen chloride followed by hydrogenation, the E isomer underwent in situ cyclization to furnish (±)-lasubine I. The lithium salt of lasubine I was treated with 3,4-dimethoxycinnamic anhydride in the presence of 4-(dimethylamino)-pyridine to afford (±)-subcosine I.



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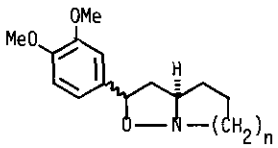

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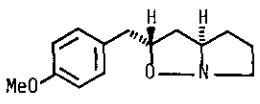

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