A NOVEL AND FACILE ROUTE TO THE PRECURSORS OF ALKALOIDS SYNTHESIS OF LACTAM-FUSED HETEROCYCLES

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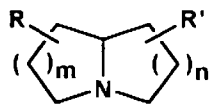
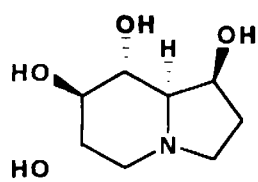
Abstract: Heterocyclic enamines 7 reacted smoothly with ethyl propiolate to give cis-adducts 8 which underwent cyclization on treatment with sodium ethoxide to yield 2-pyridone-fused heterocycles 6. Synthesis of 2-pyrrolidone-fused heterocyclic compound 9 from enamine and ethyl bromoacetate was also achieved.

Pyrrolizidines, indolizidines and quinolizidines, characterized by the presence of heterobicyclic ring 1, consist a large part of naturally occuring alkaloids and they have already attracted considerable interest because of their remarkable biological properties (1-4). Recently, a great deal of attention has been given to the polyhydroxylated alkaloids such as castanospermine 2 (5), swainsonine 3 (6), hadinecine 4 (7) and their derivatives have potent activity as glycosidase inhibitors (8), thereby exhibiting anti-viral, anti-HIV, anti-cancer, and anti-inflammatory activities (5-7). Much efforts have been focused on the investigation of the structure-activity relationships of the polyhydroxylated alkaloidal compounds, giving rise to the synthesis of many of their derivatives for biological evaluation (9). Here, we wish to report a novel and convenient route to the synthesis of 2-pyridone- and 2-pyrrolidone-fused heterocycles, the general and potential precursors of alkaloidal derivatives with and without polyhydroxy groups.



1 : **m, n** = 1, 2



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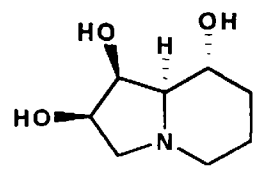

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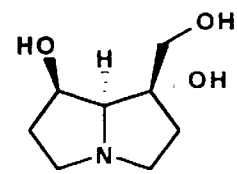

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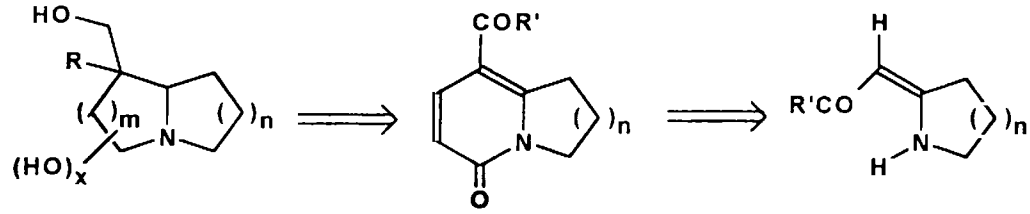
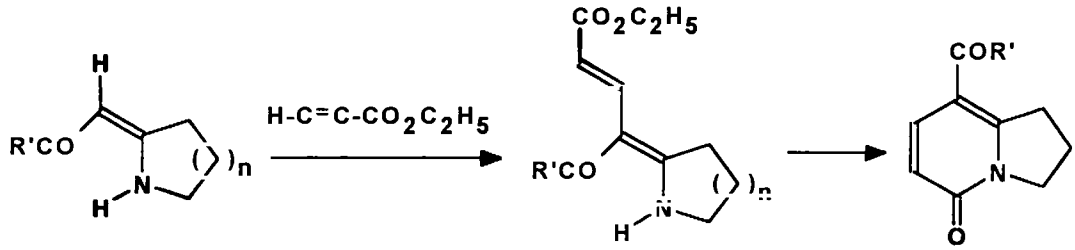
We envisaged that alkaloidal compounds 5 might be synthesized from δ-lactam-fused heterocyclic derivatives 6 by various routes. A further retrosynthetic analysis of 6 led to the heterocyclic enamine intermediates 7 (Scheme 1).



5 : R = H, OH 6 7

Scheme 1.

Preparation and some reactions of heterocyclic enamines are known (10). In the presence of a strong base such as sodium hydride (NaH) or lithium diisopropylamide (LDA), nitrile- and ester-substituted heterocyclic enamines act as a Michael base to undergo alkylation and cyclization reactions with ethyl acrylate and ethyl bromoacetate, respectively (11, 12). Recent investigation (13) on the synthesis and reactions of *exo*-cyclic secondary enamines 7 conducted by us, however, has revealed that the heterocyclic enamines 7 are good nucleophiles and they show greater reactivity toward electron-deficient reagent under neutral conditions. The reaction between 7 and acetylenecarboxylic acid ester, therefore, could yield the fused heterocycles 6.



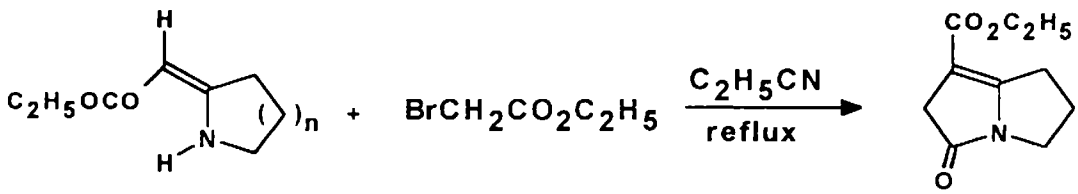
7a-f 8a-f 6a-f

6 - 8	a	b	c	d	e	f
n	1	2	3	1	2	3
R'	OC_2H_5	OC_2H_5	OC_2H_5	CH_3	CH_3	CH_3

In refluxing ethanol, ester-substituted heterocyclic enamines 7a-c react smoothly with ethyl propiolate to give *cis*-addition products 8a-c in excellent yields. The reaction of acetyl-substituted analogues 7d-f is found to take place similarly, but with slow rate and in low yields. Prolonged reaction time causes cyclization of 8d-f spontaneously with the formation of fused heterocyclic products 6d-f in satisfactory yields. In the case of ester-substituted heterocyclic enamines 7a-c, however, only a tiny amount of condensed heterocycles 6a-c is detected. The outcome of the experiments is consistent with the anticipation regarding with the reactivity between two kinds of enamines. Since the signals corresponding to both the vinyl protons and the β-carbon atoms of the ester-substituted heterocyclic enamines 7a-c shift more upfieldly than those of acetyl-substituted analogues 7d-f in ^1H- and ^{13}C-NMR spectra, the delocalization of the lone pair electrons of the nitrogen atom

in the former appears stronger than that in the later, leading to increase of enaminic reactivity and decrease of nucleophilicity of the secondary amino group in such ambident conjugation system. The *E*-configuration of the ethylene moiety in compounds 8 is indicated by ^{1}H-NMR spectra that shows the coupling constant of *ca.* 15 Hz. Strong intramolecular hydrogen bonding, demonstrated by the downfield shift of the amino proton in ^{1}H-NMR spectra, suggests *Z*-arrangement of the enamine double bond. Lactam-fused heterocyclic products 6a-f are obtained almost quantitatively on the treatment of intermediates 8 with a catalytic amount of sodium ethoxide in refluxing ethanol. Transformation of 8 into 6 proceeds *via* isomerization and cyclocondensation sequences. Compounds 6 can also be synthesized directly from enamines 7 and ethyl propiolate in a single operation simply by adding sodium ethoxide as a catalyst to the reaction mixture after consumption of the starting materials 7 monitored by TLC.

To examine the reactivity of heterocyclic enamines toward alkyl halides, the reaction between 7c and ethyl bromoacetate is performed. Under neutral conditions, 7c indeed undergoes substitution and consecutive cyclization reactions with ethyl bromoacetate to afford 2-pyrrolidone-fused heterocyclic product 9.



7c n = 3 9 n = 3

In conclusion, we provide a novel and facile method for the synthesis 2-pyridone- and 2-pyrrolidone-fused heterocyclic compounds.

Both the reactions of other heterocyclic enamines with ethyl bromoacetate and the syntheses of alkaloidal derivatives through lactam-fused heterocyclic intermediates are under investigation.

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