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Synthesis of Uncommon Heterocyclic Systems : Pyrano- and [1]Benzopyrano[3,2-f]indolizines

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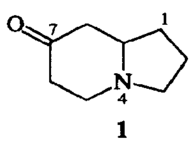
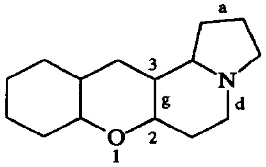
Abstract : Isolation of the morpholine enamine of indolizidin-7-one as a pure regioisomer allowed the synthesis of 3,4,5,7,8,9,9a,10-octahydro-2H-pyrano[3,2-f]indolizines and gave an entry into a new heterocyclic series, the 6H-[1]benzopyrano[3,2-f]indolizines.

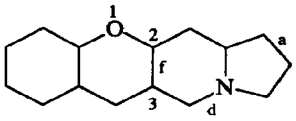
In the field of our studies of condensed C_5O-C_5N heterocycles[1], we took an interest in the morpholine enamine of indolizidin-7-one **1**[2,3]. According to the Δ^6 or Δ^7 position of its double bond, this enamine could lead to different modes of annulation, giving access either to the *Elaeocarpus* alkaloid skeleton[4] or to the nearly unknown pyrano[3,2-f]indolizine derivatives[5,6].



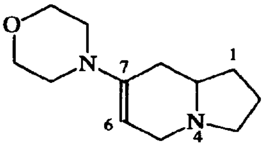
1



[2,3-g] *Elaeocarpus* alkaloids



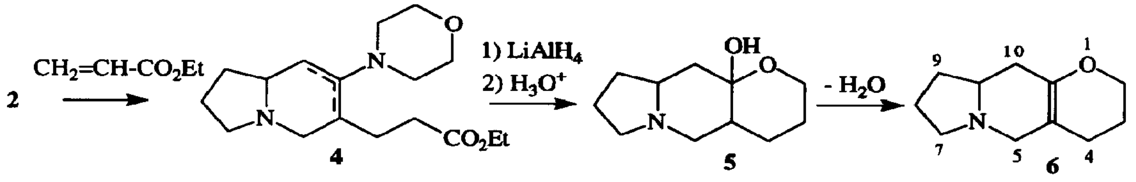
[3,2-f]



2

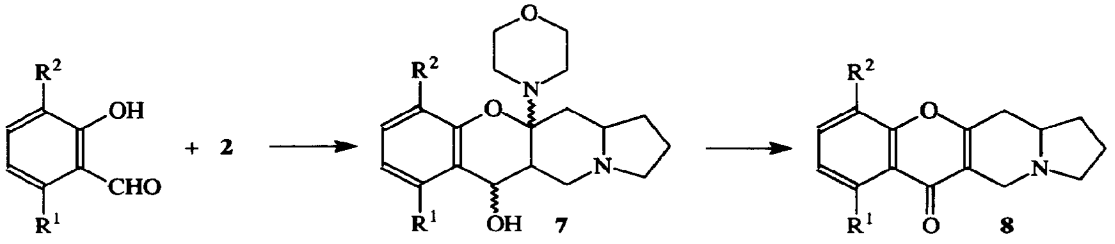
We have prepared the morpholine enamine of indolizidin-7-one according to the general method of Stork[7]. By distillation, the expected enamine was isolated in a 90 % yield, as a viscous oil which progressively crystallized. The ^{13}C NMR spectrum (100 MHz, $CDCl_3$) showed that the distilled product was a mixture of the two regioisomers, one of which being highly predominant (95 %). By a single recrystallization from petroleum ether the predominant isomer **2**[8,9] was isolated in a 70 % yield based on the starting indolizidinone.

In order to prepare the title compounds[8] we extended to this enamine the strategy we have previously devised for the synthesis of 2H-pyrano[3,2-c]pyridine derivatives from the morpholine enamine of 1-benzylpiperidin-4-one[10,11].



The condensation of the enamine **2** with ethyl acrylate in refluxing ethanol yielded the alkylated product **4**, isolated by distillation (in a nearly quantitative yield taking in account the recovered enamine) as a mixture (2/3, 1/3) of the Δ^6 and Δ^7 isomers. Upon $LiAlH_4$ reduction followed by acidic hydrolysis of the enamine group this mixture was converted to an unique ketoalcohol which cyclized to the hemiketal **5** crystallizing in a 64 % yield. IR and ^{13}C NMR studies showed that in solution the compound **5** is a mixture of two diastereoisomeric hemiketals in equilibrium with a small amount of the open ketoalcohol. The azeotropic dehydration in toluene of the hemiketal **5** in the presence of *p*-toluenesulfonic acid afforded in a 72 % yield 3,4,5,7,8,9,9a,10-octahydro-2H-pyrano[3,2-f]indolizine **6** which represents the simplest compound ever reported in this series.

The access to the hitherto unknown [1]benzopyrano[3,2-f]indolizine series was realized as described below according to a method that we have used for the synthesis of 2-azaxanthone[11] and which is reminiscent of Paquette's synthesis of chromones[12,13].



$R^1 = R^2 = H$

$R^1 = CH_3$; $R^2 = H, Cl, Br$

The condensation of various salicylaldehydes with the enamine **2** during 3 days at room temperature gave very good yields of the adducts **7** (80-91 %). These latter were oxidized by the Sarett's reagent in methylene chloride solution affording the indolizinochromones **8** in moderate yields (18-31 %) owing to a competitive opening of the dihydropyran ring.

Nevertheless the products **8** are representatives of a new series of fused heterocycles which differ from the *Elaeocarpus* alkaloids by the linear mode of annulation of their pyrrolidine ring.

References and notes

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