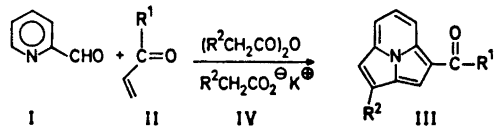
Indolizine Derivatives. I. A Novel One-step Synthesis of Pyrrolo[2,1,5-*cd*]-indolizines. The Mechanism of the Acylative Cyclization of 2-Pyridine-carbaldehyde and Unsaturated Carbonyl Compounds

ESKO POHJALA

Department of Chemistry, Helsinki University of Technology, SF-02150 Otaniemi, Finland

Some fifteen years ago practical syntheses of many pyrrolo[2,1,5-*cd*]indolizine derivatives starting from indolizines [1] were developed. Later, the preparation of pyrrolo[2,1,5-*cd*]-indolizines from pyrrolizines,[2] alkylpyridines,[3] and pyridineacrylates [4] have been reported. The overall yields based on commercial starting materials were seldom better than moderate.

As shown in this paper, the acylative cyclization between the readily available 2-pyridine-carbaldehyde (I) and an α,β-unsaturated carbonyl compounds such as II seems to provide a new, convenient route to 1-acyl-substituted pyrrolo[2,1,5-*cd*]indolizines (III).



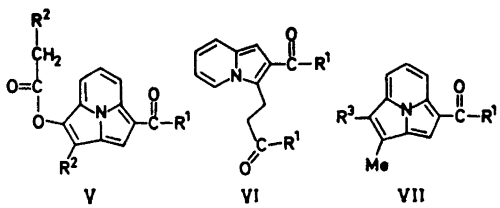
I II IV III

R^1 = Me, Ph, MeO
R^2 = H, Me

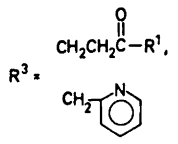
In a typical procedure I and IIa, Ac_2O and KOAc (rather arbitrary mol ratios 2:3:20:10, respectively) are refluxed for 15 min. After a standard work-up* the product IIIa is freed of coloured by-products, best by benzene elution over alumina or silica. The yield is 60 – 70 %.

In order to study the scope and mechanism of this peculiar cyclization reaction, other unsaturated carbonyl compounds were used in place of IIa. Similar cyclizations in a propionate system were examined. The results are shown in Table 1.

The structures of the cyclization products are in accord with analyses and spectral data. The nature and sites of the substituents in pyrrolo[2,1,5-*cd*]indolizines are easily determined by NMR-spectroscopy.[4] The substitution



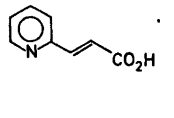
V VI VII



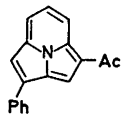
pattern in the resulting pyrrolo[2,1,5-*cd*]indolizines, that is, the acyl group at C-1 and the methyl group (when R^2 = Me) at C-3, verifies that C-1 and C-2 must originate from the α- and β-carbons of II, respectively, and C-2a and C-3 from the 1- and 2-carbons of IV, respectively.

The reaction may be visualized (Scheme 1) as beginning with a Perkin reaction to give the bicyclic intermediate VIII, followed by nucleophilic addition of the anion IX to furnish the intermediate X, which then rearranges into the tricyclic intermediate XI. The aromatization completes the reaction. In the propionate case, besides III, V is also formed, probably owing to steric factors. The propionyloxy group at C-4 originates from the aldol intermediate VIII'. A molecule of hydrogen is then lost from the subsequent intermediate XI'.

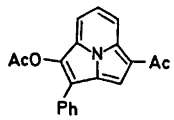
The mechanism is supported by the following findings: Pyridineacrylic acid XII, prepared by the Doebner reaction, reacts as well, yielding with IIa only IIIa in any acylate system. The



XII



XIII



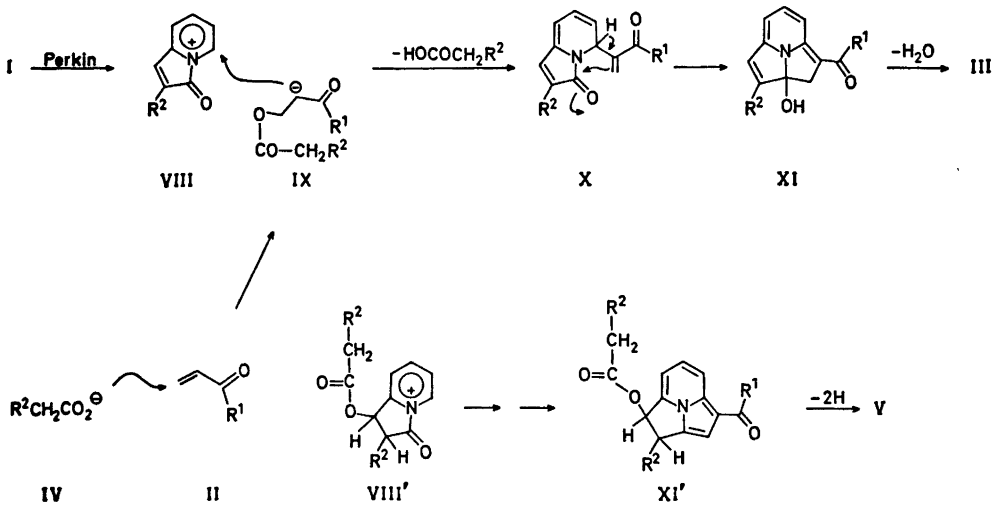
XIV

reaction between I, IIa, and phenylacetic acid gives the compounds XIII and XIV (the phenyl group at C-3). If $KOCOCH_2R^2$ is omitted, neither II nor XII gives rise to pyrrolo[2,1,5-*cd*]indolizines. In mere $(R^2CH_2CO)_2O$ I and the

* The cooled acylating mixture is stirred with water untill acetic anhydride has disappeared. The product is extracted into ether, washed and dried.

Table 1.

	R^1	R^2	Products	(%) of III	Ref.
a	Me	H	IIIa	60–70	(1)
b	Me	Me	IIIb, Vb VIIb	~50	
c	Ph	H	IIIc, VIc	~40	
d	Ph	Me	IIId, Vd, VId, VIId	~20	
e	OMe	H	IIIe	~15	(1)
f	Benzalacetone		None		



Scheme 1.

unsaturated ketones II yield the indolizine VI as the sole product, whereas I and the unsaturated ester IIe do not react at all. Irrespective of the amount of added $KOCOCH_2R^2$, I and IIc always form some indolizine VIc, presumably because the enolate anion IXc is able to compete with an anhydride anion in the first condensation step. Owing to electronic effects, benzalacetone (IIf) does not give sufficiently of the corresponding anion IXf, hence no Xf, which could lead to IIIf.

This mechanism explains the decreasing cyclization tendency IIa > IIc > IIe > IIf; the more II is inclined to form IX, the higher is the reactivity, and makes allowance for the need of a salt catalyst also after the Perkin step.

The author thanks Prof. J. Gripenberg and Dr. T. Hase for their critical comments, and The Finnish Academy for a research grant.

1. Windgassen, R. J., Saunders, W. H. and Boekelheide, V. *J. Amer. Chem. Soc. 81* (1959) 1459; Galbraith, A., Small, T., Barnes, R. A. and Boekelheide, V. *Ibid. 83* (1961) 453.
2. Jessep, M. A. and Leaver, D. *Chem. Commun.* (1970) 790; Johnson, D. and Jones, G. *J. Chem. Soc. Perkin Trans. 1* (1972) 2517.
3. Acheson, R. M. and Robinson, D. A. *J. Chem. Soc. C.* (1968) 1633.
4. Acheson, R. M. and Woollard, J. M. *J. Chem. Soc. C.* (1971) 3296.

Received February 1, 1974.