INDOLIZINE DERIVATIVES. IV. EVIDENCE FOR A DISPROPORTIONATION–DEHYDROGENATION MECHANISM IN THE PERKIN REACTION OF 2-PYRIDINECARBALDEHYDE IN THE PRESENCE OF α,β-UNSATURATED CARBONYL COMPOUNDS TO GIVE 1-ACYLPYRROLO[2,1,5-cd]INDOLIZINES

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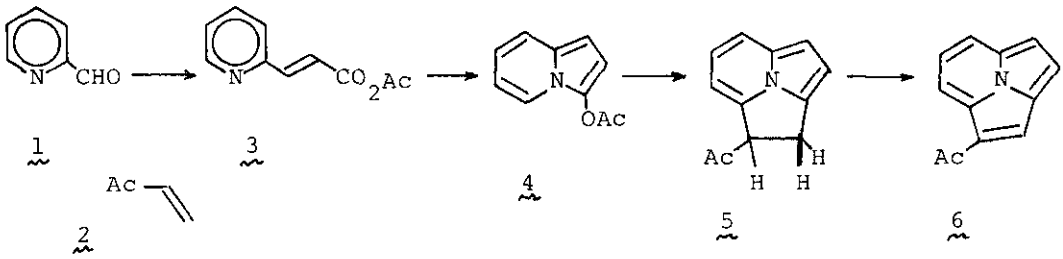
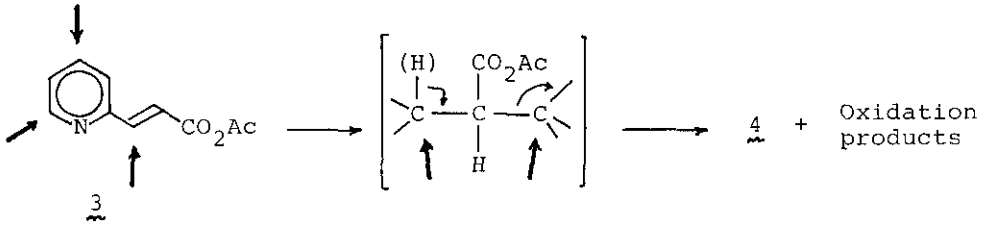
In the Perkin reaction of 2-pyridinecarbaldehyde (1) with 3-buten-2-one (2) and Ac_2O/KOAc the normal Perkin reaction product, acetic 3-(2-pyridyl)acrylic anhydride (3), disproportionates. The reduction products include 3-indolizinyl acetate (4), which with 2 cyclizes to 1-(1,2-dihydro-1-pyrrolo[2,1,5-cd]indolizinyl)ethanone (5). Dehydrogenation of 5 then affords 1-(1-pyrrolo[2,1,5-cd]indolizinyl)ethanone (6).

The synthesis of indolizine derivatives via the Perkin reaction of 2-pyridinecarbaldehyde (1), with several modifications, has been recently reported.[1,2] Further investigations of the minor products and testing of possible intermediates have now implied that the Perkin reaction of 1 in the presence of α,β-unsaturated carbonyl compounds leading to 1-acylpyrrolo[2,1,5-cd]indolizines involves a more complex reaction sequence than suggested before[1].

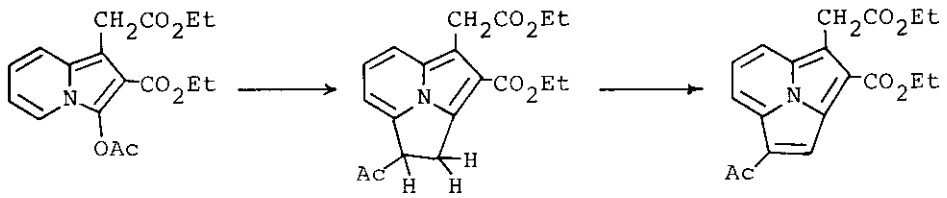
The Perkin reaction of 1 without any α,β-unsaturated carbonyl compounds catalyzed by Ac_2O/KOAc has been shown to give rise to reduced indolizine products through the normal Perkin reaction product, acetic 3-(2-pyridyl)acrylic anhydride (3), including 3-indolizinyl acetate (4),[2] which is also formed by cyclocondensation of 3-(2-pyridyl)propanoic acid (7). Hitherto no oxidized species could be identified.[3]



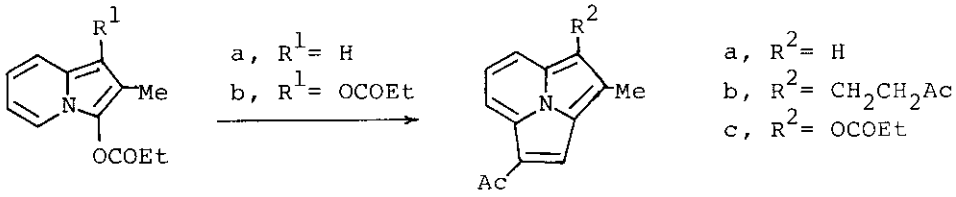
The disproportionation of 3 may be visualized as a nucleophilic attack by the enolate anion of Ac_2O to any of the carbons, marked with fat arrows, of two molecules of 3 simultaneously, and the subsequent redox-cleavage to furnish the reduced indolizine product 4 and oxidations products.



When the indolizine 4 and 3-buten-2-one (2) are heated with Ac_2O (0.5 h, 100 °C), 1-(1-pyrrolo[2,1,5-cd]indolizinyl)ethanone (6)[1] is obtained in a high yield. In this case no dihydro-intermediate, 1-(1,2-dihydro-1-pyrrolo[2,1,5-cd]indolizinyl)ethanone (5), was isolated, but from the reaction of the indolizine 8[4] with 2, if atmospheric oxygen is excluded, the dihydropyrrolo[2,1,5-cd]indolizine 9 is obtained nearly quantitatively.[5] This dihydro-intermadiate is rapidly dehydrogenated to the pyrrolo[2,1,5-cd]indolizine 10 by heating in the presence of air. Further examples of the formation of the pyrrolo[2,1,5-cd]indolizine ring system through 3-indolizinyl acylates are as follows: The indolizines 11a and 11b, prepared from 1 by heating with $(EtCO)_2O$/KOCOEt, are converted into the pyrrolo[2,1,5-cd]-indolizines 12a,b and 12c, respectively, through the action of 2 in Ac_2O (or $(EtCO_2O)$).



8 9 10



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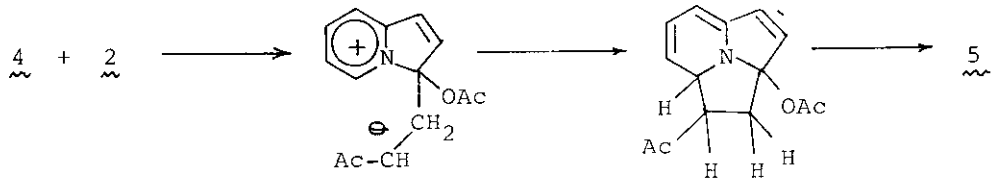
The necessity of the presence of an acid anhydride catalyst in the cyclization of 3-indolizinyl acylates with α,β-unsaturated carbonyl compounds to dihydropyrrolo[2,i,5-cd]indolizines suggests a reaction through ionic species, rather than the concerted [8+2] cycloaddition[6]. The formation of the very probable intermediate 13, from which acetic acid is easily eliminated giving the dihydropyrrolo[2,1,5-cd]indolizine 5, is outlined below:



13

It is now established that the acylative cyclization of 2-pyridinecarbaldehyde (1) with α,β-unsaturated carbonyl compounds to afford 1-acylpyrrolo[2,1,5-cd]indolizines proceeds mainly through the above discussed disproportionation-dehydrogenation steps.

The almost 50 % yields (or even slightly over 50 % for raw products) of 6 from 1 presuppose that other routes, probably such as 3 + 5 ⟶ 4 + 6, leading to 4 or the route suggested earlier[1] may be involved, although they seem to play an unimportant part.

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References and notes:

1. E. Pohjala, Acta Chem. Scand. B., 1974, 28, 582.
2. E. Pohjala, Heterocycles, 1974, 2 585.
3. Instead, from the reaction of 1 with $(EtCO)_2O$/KOCOEt the first example of oxidation products has been isolated. E. Pohjala, Acta Chem. Scand. B., 1975, 2, in press.
4. Prepared by heating diethyl 2-pyridylmethylenemalonate in Ac_2O. Its formation involves migration of one of the ethoxycarbonyl groups. To be published in Acta Chem. Scand. B.
5. All new compounds gave satisfactory analyses and spectra. The nmr spectrum of 9 exhibits a complex ABX-system: δ_A= 3.65, δ_B= 3.75, δ_X= 4.66. $J_{A,X}$= 5 Hz, $J_{B,X}$= 2.7 Hz, $J_{A,B}$= 10 Hz.
6. R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Germany, 1970, p. 83.

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