

INDOLIZINE DERIVATIVES. II. INDOLIZINES FROM THE PERKIN REACTION
OF 2-PYRIDINECARBALDEHYDE

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The Perkin reaction of 2-pyridinecarbaldehyde (I) gives the indolizines IIIa-f and the pyrrolo[2,1,5-cd]indolizine IVa. In the presence of active methylene compounds the indolizines IIIg-n are formed.

The Perkin reaction of 2-pyridinecarbaldehyde (I) apparently fails to give 3-(2-pyridyl)-acrylic acid (IIa) (1). However, species related to IIa were suggested to be intermediates in the formation of pyrrolo[2,1,5-cd]indolizines in the acylative cyclization of I with unsaturated carbonyl compounds (2). In the present paper it is shown that the Perkin reaction - or more correctly, the acylative cyclization - of I offers a new one-step route to indolizine derivatives. The yields vary from low to good.

When I is heated (130°C) with an excess of Ac₂O and KOAc, the content of the reaction flask immediately turns black. If the reaction is stopped after 30min, the excess of Ac₂O decomposed with water, and the precipitated, ether soluble tar fractionated by column chromatography (Silica gel Woelm/benzene), three indolizine derivatives are obtained: The first is 3-indolizinyll acetate (IIIa) showing a carbonyl absorption at 1780cm⁻¹, in ir, and an AB-quartet, δ6.28 (1-H) and δ6.52 (2-H), J = 4Hz, in pmr (3). The second is the known 1-(3-indolizinyll)-ethanone (IIIb), which on

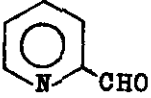
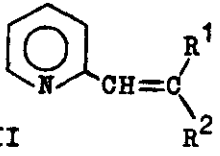
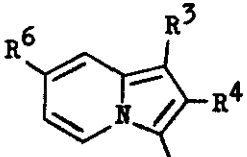

acid hydrolysis gives the parent indolizine (4). The third is 1-(2-methyl-1-pyrrolo [2,1,5-cd]indoliziny1)-ethanone (IVa), which can also be prepared by the acylative cyclization of I with 3-pentene-2-one (2).

The acid IIA (from the Doebner reaction), which would be the expected Perkin product, gives on treatment with Ac_2O and KOAc similarly IIIa, IIIb and IVa. In neat Ac_2O IIA yields the anhydride IIB. With a shorter reaction time (5-15min) only IIIa and IIIb are formed from either I or IIA, while IIIa is absent from the reaction mixture after longer periods than 1h. The $\text{Ac}_2\text{O}/\text{KOAc}$ treatment of IIIa gives IVa, whereas the reaction in the presence of ethyl acetoacetate gives ethyl 2-methyl-1-pyrrolo [2,1,5-cd]-indolizinecarboxylate (IVb). This clearly suggests that IIIa is an intermediate in the formation of IVa from I or IIA.

With $(\text{EtCO})_2\text{O}$ and KOCOEt the analogous indolizines IIIc and IIIId are formed, but the main product is 1-(3-(2-pyridyl)-2-methyl-1-indoliziny1)-1-propanone (IIIe), 5-H at δ 8.69 and 8-H at δ 8.36.

The Perkin reaction of I and phenylacetic acid affords only 2-phenyl-3-indoliziny1 acetate (IIIf) in $\text{Ac}_2\text{O}/\text{KOAc}$.

The Perkin reaction of I in the presence of other compounds containing active methylene groups was also studied. With ethyl acetoacetate I gives ethyl 3-methyl-2-indolizinecarboxylate (IIIg) (5), the 1-acetoxy (IIIh) and 7-C(Ac) $_2$ CO $_2$ Et (IIIi), 8-H at δ 7.25 (br. s), derivatives of this. The cyclization of the expected Perkin product, ethyl 2-(2-pyridyl)-methylene-3-oxobutyrate (IIc), with $\text{Ac}_2\text{O}/\text{KOAc}$ or $\text{Ac}_2\text{O}/\text{KOAc}/\text{CH}_2\text{AcCO}_2\text{Et}$ yields mixtures of IIIg and IIIh or IIIg and IIIi, respectively.

I		II		III		IV	
							
III	R ³	R ⁴	R ⁵	R ⁶	mp. °C	Yield %	From
a	H	H	OAc	H	20	15	t) IIIa
b	H	H	Ac	H	34	8	u) I or IIa
c	H	Me	COEt	H	-	10	v) I and
d	H	Me	COEt	H	-	6	3-pentene-
e	COEt	Me	2-pyridyl	H	147	54	2-one
f	H	Ph	OAc	H	118	27	w) IIa
g	H	COEt	Me	H	48	41	x) IIc
h	OAc	COEt	Me	H	118	61	y) IIId
i	H	COEt	Me	C(Ac) ₂ COEt	77	69	x)
j	H	Ac	Me	H	73	38	
k	OAc	Ac	Me	H	93	66	y)
l	H	Ac	Me	C(Ac) ₃	-	69	y)
m	H	COEt	CH ₂ COEt	H	80	20	
n	CH(COEt) ₂	COEt	Me	H	71	72	

At 100°C IIIh or IIIi is the major product, at 130°C IIIg. Differing from the acid IIa, the ketoester IIc forms indolizines without KOAc when heated in mere Ac₂O or in Ac₂O/CH₂AcCOEt.

The aldehyde I with pentane-2,4-dione or IIId alone furnishes the analogous products IIIj (5), IIIk and IIIl. Diethyl acetone-dicarboxylate gives, besides ethyl 2-ethoxycarbonyl-3-indolizine-

acetate (III_m), the decarboxylated product III_g. Diethyl 2-ethoxy-carbonyl-3-methyl-1-indolizinemalonate (III_n) is the only indolizine isolated from the Perkin reaction between I and diethyl malonate.

The indolizines III_a, III_c, III_f, III_g, III_j, III_m, IV_a and IV_b are reduced ones, as compared to I, the indolizines III_b and III_d even doubly reduced. As the yields never exceeded 50%, some kind a disproportionation mechanism may be involved (6,7). All attempts to find oxidized species in the reaction mixtures have failed as yet. Products, other than the indolizines described above, were those arising from the self condensation of Ac₂O or acylation of active methylene compounds (8).

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