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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 Ac_2O and KOAc, the content of the reaction flask immediately turns black. If the reaction is stopped after 30min, the excess of Ac_2O 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-indolizinyl 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-indolizinyl)-ethanone (IIIb), which on

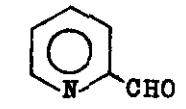
acid hydrolysis gives the parent indolizine (4). The third is 1-(2-methyl-1-pyrrolo[2,1,5-cd]indolizinyl)-ethanone (IVa), which can also be prepared by the acylative cyclization of I with 3-pentene-2-one (2).

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 Ac_2O/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.

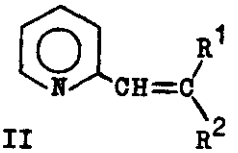
With $(EtCO)_2O$ and KOCOEt the analogous indolizines IIIc and IIId are formed, but the main product is 1-(3-(2-pyridyl)-2-methyl-1-indolizinyl)-1-propanone (IIIe), 5-H at δ8.69 and 8-H at δ8.36.

The Perkin reaction of I and phenylacetic acid affords only 2-phenyl-3-indolizinyl acetate (IIIf) in Ac_2O/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-$C(Ac)_2CO_2Et$ (IIIi), 8-H at δ7.25 (br. s), derivatives of this. The cyclization of the expected Perkin product, ethyl 2-(2-pyridyl)-methylene-3-oxo-butyrate (IIc), with Ac_2O/KOAc or Ac_2O/KOAc/CH_2AcCO_2Et yields mixtures of IIIg and IIIh or IIIg and IIIi, respectively.

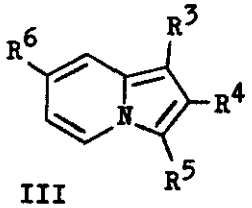


I

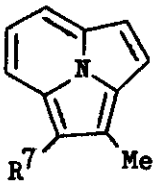


II

II	R^1	R^2
a	H	COOH
b	H	COOAc
c	Ac	COOEt
d	Ac	Ac



III



IV

IV	R^7	mp.°C	Yield %	
a	Ac	79	11	t)
			4	u)
			52	v)
b	COOEt	64	21	t)
			12	w)

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	OCOEt	H	-	10	v)	I and 3-pentene-2-one
d	H	Me	COEt	H	-	6		
e	COEt	Me	2-pyridyl	H	147	54	w)	IIa
f	H	Ph	OAc	H	118	27	x)	IIc
g	H	COOEt	Me	H	48	41	y)	IId
h	OAc	COOEt	Me	H	118	61	x)	
i	H	COOEt	Me	$C(Ac)_2COOEt$	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	COOEt	CH_2COOEt	H	80	20		
n	$CH(COOEt)_2$	COOEt	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 Ac_2O or in $Ac_2O/CH_2AcCOOEt$.

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

acetate (IIIm), the decarboxylated product IIIg. Diethyl 2-ethoxycarbonyl-3-methyl-1-indolizinemalonate (IIIn) is the only indolizine isolated from the Perkin reaction between I and diethyl malonate.

The indolizines IIIa, IIIc, IIIf, IIIg, IIIj, IIIm, IVa and IVb are reduced ones, as compared to I, the indolizines IIIb and IIId even doubly reduced. As the yields never exceeded 50%, some kind a disproportionation mechanism may be involved (6,7). All attemps 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 Ac_2O or acylation of active methylene compounds (8).

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