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Indolizine Derivatives. VI.* Indolizines from the Acylative Cyclization of 3-(2-Pyridyl)-2-propen-1-ones and Related Compounds

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3-(2-Pyridyl)-2-propen-1-ones with acetic anhydride/potassium acetate give rise to 1-substituted 2-acetyl-3-methylindolizines. In the presence of ethyl acetoacetate, analogous 2-ethoxycarbonylindolizines are obtained. The reaction using propionic anhydride/potassium propionate gives 4-(2-pyridyl)-2-pyrones, or products requiring a reduction step. 1-(2-Pyridyl)-2-propen-1-ones in neat acetic anhydride cyclize to 1-acetoxyindolizines. The reactions of some related compounds were also studied. The mechanisms are discussed.

It has been established that the Perkin reaction of 2-pyridinecarbaldehyde, as well as 3-(2-pyridyl)acrylic acid and 2-(2-pyridyl)methylene-1,3-dicarbonyl compounds under the conditions of the Perkin reaction, give rise to indolizine derivatives.[1,2] A logical extension of this is to treat (2-pyridyl)propenones in the same way with boiling acetic anhydride/potassium acetate. Thus, the present paper deals with the acylative cyclization of 3-(2-pyridyl)-2-propen-1-ones and related compounds as a novel synthetic route to indolizines.[3]

RESULTS

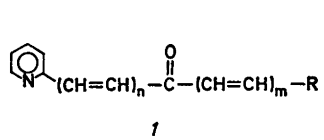
When the pyridylpropenone *1a* (Table 1) was heated with an excess of acetic anhydride/potassium acetate for 2 h, the indolizine *2a* was obtained in *ca.* 80 % yield. Its elemental formula $C_{21}H_{19}NO_3$, supported by the parent peak in the mass spectrum, $m/e = 333$ corresponds to a condensation of *1a* with 2,4-pentanedione and acetylation. Its NMR spectrum shows that there is no strongly deshielding substituent, such as an acetyl group,[4] at C-1 or C-3 of the heterocyclic ring. Thus, the strong IR absorption at 1665 cm^{-1} is due to the acetyl group at C-2. The other strong peak in the IR spectrum (1750 cm^{-1}) originates from the vinyl acetate group on the C-1 side chain. The mass spectrum fragmentation pathway: M − 42 ($CH_2=C=O$) − 105 (PhCO) to give the base peak ($m/e = 186$) corresponding to the quinolizinium ion [5] *3a* is very typical. Similarly, the pyridylpropenones *1b* and *1c* gave with acetic anhydride/potassium acetate the indolizines *2b* and *2c*, respectively. The mass spectra of *2b* and *2c* both exhibit the base peak $m/e = 186$.

The reaction of the pyridylpropenone *1a* with acetic anhydride/potassium acetate in the presence of ethyl acetoacetate afforded the analogous 2-indolizinecarboxylic esters *2d* and *4b*, both showing in their mass spectra the base peak at $m/e = 216$ corresponding to the ion *3b*. The structure of *2d* is manifested by the similarity of its spectral properties to those of *2a*. The absence of the vinyl acetate peak in the IR spectrum, but instead the peak 1695 − 1670 cm^{-1}, and a two proton singlet at δ 4.64, prove that *4b* carries a free phenacyl group at C-1. The treatment of *4b* with boiling acetic anhydride/potassium acetate gave *2d*. Hydrolysis of *4b* to the acid *4c* and subsequent cyclization of the latter by acetic anhydride afforded the lactone *5* (IR: 1715 cm^{-1}), the structure of which is obvious on the basis of its spectral resemblance to *2d*.

The similar reactions of *1a* and *1b* with propionic anhydride/potassium propionate gave the 2-pyrones *6a* and *6b*, respectively. Their

* Part V; Ref. 2.

Table 1. Compounds *1 – 8*.



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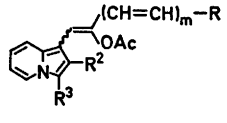

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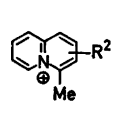

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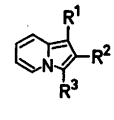

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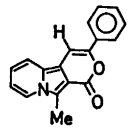

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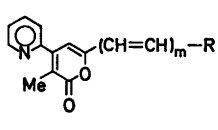

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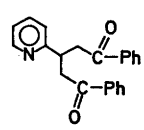

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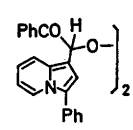

8

Compound No.	n	m	R	R^2	R^3	Compound No.	R^1	R^2	R^3
1a	1	0	Ph			*4a*	CH_2COPh	Ac	Me
1b	1	1	Ph			*4b*	CH_2COPh	CO_2Et	Me
1c	1	0	Me			*4c*	CH_2COPh	CO_2H	Me
1d	0	1	Ph			*4d*	OAc	H	Ph
1e	1	0	OEt			*4e*	CH_2COPh	H	Ph
2a		0	Ph	Ac	Me	*4f*	H	H	Me
2b		1	Ph	Ac	Me	*4g*	COEt	H	Me
2c		0	Me	Ac	Me	*4h*	OAc	Me	Me
2d		0	Ph	CO_2Et	Me	*4i*	CH_2CO_2Et	Ac	Me
2e		0	Ph	H	Ph				
3a				Ac					
3b				CO_2Et					
6a		0	Ph						
6b		1	Ph						

structures are evident on the basis of the spectra, that is, they are 2-pyrones (IR, 1710 – 1680 cm^{-1}) carrying methyl, 2-pyridyl and phenyl (styryl) groups (NMR) at the denoted positions (MS, for example, *6a*: M – PhCO – CO). These pyrones are oxidized products. No reduced species were detected, whereas from the reaction of *1c* with propionic anhydride/potassium propionate the reduction products *4f* and *4g* (NMR, H-8 at δ 8.14), but no oxidized species, were isolated.

One example of the compounds *1*, where $n = 0$, was examined. When *1d* was refluxed with acetic anhydride alone, the indolizine *4d* was obtained in good yield. Its structure is easily obtained from the spectra; that is, it is an indolizine with an acetoxy group (IR, 1760 cm^{-1}) at C-1 (MS, for example, $m/e = 106$[2]) and a phenyl group at C-3 (NMR, H-5 at δ 8.00).

Interestingly, the compound *7* is cyclized with acetic anhydride/potassium acetate to a mixture of the indolizines *2e* and *4e* if worked under nitrogen atmosphere. When exposed to air the indolizine *4e* changes into a compound $C_{44}H_{32}N_2O_4$ for which the structure *8* (without stereochemistry) was proposed (MS, 20 eV, *m/e*, for example, 652, 634, 620, 618 which are very weak, and 310, base peak; NMR, a singlet at δ 6.14 instead of δ 4.16 in *4e* with half the intensity; IR, 1670 cm^{-1}). Use of the aldol derivatives of *1a* (*9a*) and *1c* (*9b*) did not cause any change among the products, while 4-hydroxy-3-methyl-4-(2-pyridyl)-2-butanone (*9c*) is known to yield the indolizine *4h* on cyclization.[4] The methyl substituent of *9c* has therefore a profound effect on the course of reaction.

Ethyl 3-(2-pyridyl)acrylate (*1e*) gave with acetic anhydride/potassium acetate the indolizine *4i*, the structure of which is obvious on the basis of the spectral data.

DISCUSSION

Stereochemistry of the indolizines 2

According to NMR studies, the indolizines *2a*, *2b* and *2d* each consisted of a single isomer, whereas *2c* was a mixture of both geometric isomers. Experiments with molecular models indicated that the *Z*-isomers (the aromatic rings in *trans*-relation) of *2a* and *2d* are sterically less hindered than the corresponding *E*-isomers. According to this and the spectral (particularly NMR) resemblance to compound *5*, the configuration of *2a* and *2d* is assumed to be *Z*. Similarly, the double bond adjacent to the indolizine ring of *2b* possesses *Z*-configuration, whereas the geometry of the other double bond (next to the phenyl group) is *E* (NMR: $J = 16$ Hz). A comparison of the NMR spectra of the two isomers of *2c* reveals great differences. For example, one of the isomers (*2c'*) exhibits the allylic methyl signal higher (δ 1.87) and the acetoxy methyl signal lower (δ 2.17) than the other (*2c''*), at δ 2.13 and δ 1.82, respectively. Assuming that the C-2 acetyl group lies almost in the plane (IR: 1660 cm^{-1}) and the C-1 double bond is twisted out of the ring plane, the acetoxy methyl group of the *Z*-isomer and the allylic methyl group of the *E*-isomer are strongly shielded by the aromatic ring. This leads to assignment of *2c'* as the *E*-isomer and of *2c''* as the *Z*-isomer. The δ value of the vinyl hydrogen of *2c'* is estimated by means of additive shielding increments [6] to be *ca.* 0.25 ppm greater than that of *2c''*. The observed difference of *ca.* 0.15 pmm (δ $H_{vinyl}(2c') = 6.27$, δ $H_{vinyl}(2c'') = 6.14$) is in accordance with the assessed configurations.

The stereochemistry of *2e* is believed to be *Z*, analogously to the other compounds *2*. The absence of a C-2 substituent allows the acetoxy group of *2e* to be situated in the plane of the molecule, and the acetoxy methyl hydrogens appear *ca.* 0.4 ppm downfield relative to those in the other compounds *2*, owing to a larger deshielding by the aromatic rings.

Formation of the indolizines 2

The formation of the indolizines *2* from the pyridylpropenones *1* may be explained as a Michael-addition of 2,4-pentanedione or an equivalent self-condensation product of acetic anhydride [2] to give the addition products, which then cyclize to the corresponding indolizines *4*. Acetylation of the C-1 side chain ketone of *4* furnishes the indolizines *2*.

Owing to the methyl substituent the readiness of the addition compound of *1* and a possible self-condensation product of propionic anhydride to cyclize to an indolizine is reduced. Alternatively, the preferred formation of 2-pyrones arises from the notably higher refluxing temperature needed for propionic anhydride than acetic anhydride, enabling propionic anhydride to attack the pyridylpropenone. Both routes involve a dehydrogenation step. The formation of the reduced indolizine products in the reaction of *1c* with propionic anhydride/potassium propionate probably follows the disproportionation routes suggested before [2] for some analogous reactions.

EXPERIMENTAL

Instruments and chromatographic procedures have been described earlier.[2] Elemental analyses (C, H, N) were carried out by Mrs. A. M. Horko. Mass spectra were obtained through the cooperation of Mr. P. Karvonen.

Preparation of pyridylketones

1-Phenyl-3-(2-pyridyl)-2-propen-1-one (*1a*), *3-phenyl-1-(2-pyridyl)-2-propen-1-one* (*1d*), *1,5-diphenyl-3-(2-pyridyl)-1,5-pentanedione*(*7*) and *3-hydroxy-1-phenyl-3-(2-pyridyl)-1-propanone* (*9a*),[7] *4-hydroxy-4-(2-pyridyl)-2-butanone* (*9b*),[8] and *ethyl 3-(2-pyridyl)acrylate* (*1e*) [9] were prepared as described in the literature.

1-(2-Pyridyl)-5-phenyl-1,4-pentadien-3-one (*1b*). 2-Pyridinecarbaldehyde (10.7 g, 0.10 mol), benzylideneacetone (14.6 g, 0.10 mol), MeOH (100 ml), H_2O (100 ml) and $Ca(OH)_2$ (0.5 g) were heated at 60 °C for 1.5 h. After cooling, addition of water, extraction with ether and drying over Na_2SO_4 gave a dark sticky product mixture, from which *1b* was separated by CC (silica, benzene as eluent), yield 9.6 g (41 %), m.p. (light petroleum, b.p. 40 – 60 °C) 83 °C. Anal. $C_{16}H_{13}NO$.

4-(2-Pyridyl)-3-buten-2-one (*1c*). 2-Pyridinecarbaldehyde (10.7 g, 0.10 mol), AcMe (50 ml), H_2O (100 ml) and $Ca(OH)_2$ were refluxed for 1 h to produce after extraction with $CHCl_3$ and drying (Na_2SO_4) rather pure *1c*, as an oil,[8] accompanied by self-condensation products of acetone (< 5 %, NMR, TLC). Yield 10.1 g. This pyridylpropenone was used without further purifications.

Cyclizations of pyridylketones

General procedure. The pyridylketone with an excess of Ac_2O/KOAc or $(EtCO)_2O$/KOCOEt was refluxed for 1 to 2 h. After cooling, the black product mass was decomposed with water. The product was extracted with ether, neutralized ($NaHCO_3$) and dried (Na_2SO_4). After evaporation, the dark residue was fractionated, when necessary, by CC and purified by recrystallization. LP refers to light petroleum, b.p. 40 – 60 °C.

1a with Ac_2O/KOAc. *1a* (2.09 g, 0.010 mol), Ac_2O (20 ml) and KOAc (10 g) gave *(Z)-2-(2-acetyl-3-methyl-1-indolizinyl)-1-phenyl-vinyl acetate* (*2a*), yield 2.64 g (79 %), m.p. (MeOH) 128 °C. Anal. $C_{21}H_{19}NO_3$. UV (log ε): 394 (3.64), 331 (3.73), 267 (sh, 399), 250.5 (4.23), 231 (sh, 4.04). ^{1}H NMR: δ 7.70 – 7.15 (7 H, m), 7.03 (1 H, s), 6.90 – 6.35 (2 H, m), 2.58 (3 H, s), 2.54 (3 H, s), 1.95 (3 H, s). MS, *m/e* (%): 333 (M^+, 30), 291 (21), 290 (24), 274 (30), 262 (17), 249 (24), 187 (15), 186 (100).

1b with Ac_2O/KOAc. *1b* (2.35 g, 0.010 mol), Ac_2O (20 ml), and KOAc (10 g) gave *(1Z,3E)-1-(2-acetyl-3-methyl-1-indolizinyl)-4-phenyl-2-buta-1,3-dienyl acetate* (*2b*), yield 2.91 g (81 %), m.p. (EtOH) 201 °C. Anal. $C_{23}H_{21}NO_3$.

1c with Ac_2O/KOAc. *1c* (14.7 g, 0.010 mol), Ac_2O (20 ml) and KOAc (10 g) gave *1-(2-acetyl-3-methyl-1-indolizinyl)-2-propenyl acetate* (*2c*) as an oil, yield 1.68 g (62 %). Fractionation by CC afforded the oily *E-2c* (*2c'*), ^{1}H NMR: δ 6.27 (1 H, q 0.9 Hz), 2.64 (3 H, s), 2.46 (3 H, s), 2.17 (3 H, s), 1.87 (3 H, d 0.9 Hz) and *Z-2c* (*2c''*), m.p. (LP) 64 °C. Anal. $C_{16}H_{17}NO_3$. IR: 1750 (s), 1740 (s), 1660 (s). ^{1}H NMR: δ 6.14 (1 H, q 1.2 Hz), 2.53 (3 H, s), 2.43 (3 H, s), 2.13 (3 H, d 1.2 Hz), 1.82 (3 H, s).

1a with Ac_2O/KOAc in the presence of ethyl acetoacetate. *1a* (2.09 g, 0.010 mol), Ac_2O (30 ml), KOAc (15 g) and $AcCH_2CO_2Et$ (1.95 g, 0.015 mol) gave similarly after chromatographic purification *(Z)-2-(2-ethoxycarbonyl-3-methyl-1-indolizinyl)-1-phenyl-vinyl acetate* (*2d*), yield 0.76 g (21 %), m.p. (LP) 113 °C. Anal. $C_{22}H_{21}NO_4$. IR: 1755 (s), 1685 (s), 1680 (s); *ethyl 1-phenacyl-3-methyl-2-indolizinecarboxylate* (*4b*), yield 1.57 g (49 %), m.p. (benzene/LP) 146 °C. Anal. $C_{20}H_{19}NO_3$. IR: 1690 – 1670 (s); and *2a*, 0.23 g (7 %).

Treatment of *4b* with an excess of Ac_2O/KOAc gave *2d* in a good yield. Hydrolysis of *4b* (3.2 g, 0.010 mol) with H_2O/MeOH/NaOH (100 ml/50 ml/2 g) afforded after acidification *1-phenacyl-3-methyl-2-indolizinecarboxylic acid* (*4c*), yield 1.75 g (60 %), m.p. (AcOEt/LP) 190 °C. Anal. $C_{18}H_{15}NO_3$. Heating this acid (1.46 g, 0.005 mol) with Ac_2O (10 ml) afforded *10-methyl-3-phenyl-1H-pyrano[4,3-a]indolizine-1-one* (*5*), yield 1.07 g (85 %), m.p. 140 °C. Anal. $C_{18}H_{13}NO_2$. MS, *m/e* (%): 275 (M^+).

1a with $(EtCO)_2O$/KOCOEt. *1a* (2.09, 0.010 mol), $(EtCO)_2O$ (25 ml) and KOCOEt (15 g) gave *3-methyl-6-phenyl-4-(2-pyridyl)-2H-pyran-2-one* (*6a*), yield 1.10 g (42 %), m.p. (LP) 136 °C Anal. $C_{17}H_{13}NO_2$. UV, (log ε): 336 (3.96), 265 (3.98), 253 (sh, 4.04), 248 (4.12), 240 (sh, 4.01), 231 (sh, 3.90). ^{1}H NMR: δ 8.64 (1 H, broad d 5), 6.78 (1 H, s), 2.10 (3 H, s). MS, *m/e* (%): 263 (M^+, 79), 236 (17), 235 (100), 234 (23), 206 (32), 158 (28), 130 (64), 105 (17).

1b with $(EtCO)_2O$/KOCOEt. *1b* (2.35 g, 0.010 mol), $(EtCO)_2O$ (25 ml) and KOCOEt (15 g) gave *3-methyl-6-styryl-4-(2-pyridyl)-2H-pyran-2-one* (*6b*), yield 1.16 g, (40 %), m.p. (LP) 167 °C. Anal. $C_{19}H_{15}NO_2$.

1c with $(EtCO)_2O$/KOCOEt. *1c* (1.47 g, 0.010 mol), $(EtCO)_2O$ (25 ml), KOCOEt (15 g) gave after chromatographic purification *3-methylindolizine* (*4f*)[5] as liquid and *1-(3-methyl-1-indolizinyl)ethanone* (*4g*),[5] m.p. (LP) 83 °C. Treatment of *4f* with $(EtCO)_2O$/KOCOEt afforded *4g*. The total yield of *4f* and *4g* was *ca.* 20 %.

1d with Ac_2O. *1d* (2.09 g, 0.010 mol) in 25 ml of Ac_2O was refluxed for 0.5 h. After evaporation of the excess of Ac_2O *in vacuo* and recrystallization *3-phenyl-1-indolizinyl acetate* (*4d*) was obtained, yield 1.96 g (78 %), m.p. (LP) 51 °C. Anal. $C_{16}H_{13}NO_2$. MS, *m/e* (%): 251 (M^+, 24), 210 (12), 209 (100), 208 (21), 180 (11), 106 (15).

7 with Ac_2O/KOAc. *7* (3.29 g, 0.010 mol), Ac_2O (25 ml) and KOAc (10 g) were refluxed for 3 h to produce *(Z)-2-(3-phenyl-1-indolizinyl)-1-phenyl-1-vinyl acetate* (*e*), yield 1.63 g (46 %), m.p. (LP/benzene) 200 °C. Anal. $C_{24}H_{19}NO_2$. UV, (log ε): 359 (sh, 4.36), 346 (4.41). IR: 1745 (s), 1640 (m). ^{1}H NMR: δ 8.10 (1 H, broad d 7), 7.08 (1 H, s), 7.02 (1 H, s), 2.38 (3 H, s). MS, *m/e* (%): 353 (M^+, 67), 312 (20), 311 (93), 310 (98), 282 (47), 207 (26), 206 (100), 205 (25), 204 (44) ,120 (52), 119 (53), 105 (21), 103 (25); and *1,1'-diphenyl-2,2'-di(3-phenyl-1-indolizinyl)-2,2'-dioxyethanone* (*8*), yield 0.68 g (21 %), m.p. ($CHCl_3$) 242 °C. Anal. $C_{44}H_{32}N_2O_4$. A similar reaction of *7* under nitrogen and with added AcOH (10 ml) afforded *1-phenyl-2-(3-phenyl-1-indolizinyl)ethanone* (*4e*) as liquid, yield *ca.* 2.2 g (70%). IR: 1680 (s). MS, *m/e* (%): 311 (M^+, 11), 207 (13), 206 (100). During attempted crystallizations *4e* was oxidized to *8*.

9a with Ac_2O/KOAc. *9a* (2.27 g, 0.010 mol), Ac_2O (30 ml) and KOAc (15 g) gave *2a* in 75 % yield.

9b with Ac_2O/KOAc. *9b* (1.65 g, 0.010 mol), Ac_2O/KOAc (30 ml/15 g) gave *2c* in 55 % yield.

1e with Ac_2OKOAc. *1e* (1.77 g, 0.010 mol), Ac_2O/KOAc (20 ml/10 g) gave *ethyl 2-acetyl-3-methyl-1-indolizinylacetate* (*4i*), yield 1.55 g (60 %), m.p. (LP) 107 °C. Anal. $C_{15}H_{17}NO_3$. IR: 1720 (s), 1640 (s). ^{1}H NMR: δ 3.88 (2 H, s).

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