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Indolizine Derivatives. V.* The Perkin Reaction of 2-Pyridinecarbaldehyde. Disproportionation of 3-(2-Pyridyl)acrylic Acid

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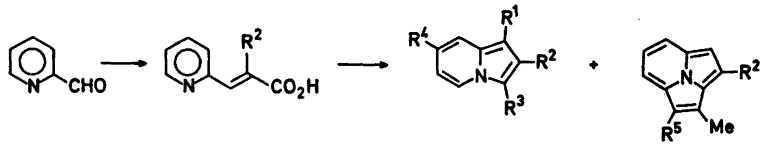
The Perkin reaction of 2-pyridinecarbaldehyde with acetic anhydride/potassium acetate, propionic anhydride/potassium propionate, or acetic anhydride/potassium acetate in the presence of phenylacetic acid gives indolizines and pyrrolo[2,1,5-*cd*]indolizines *via* disproportionation of the normal Perkin reaction products. The mechanisms of these and related reactions are discussed.

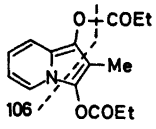
The anticipated 3-(2-pyridyl)acrylic acids (*2*) cannot be isolated from the Perkin reaction of 2-pyridinecarbaldehyde (*1*); instead, indolizine derivatives are formed *via* the normal Perkin reaction products, 3-(2-pyridyl)acrylic anhydrides, as was briefly reported recently.[1] Thus, with acetic anhydride/potassium acetate, compound *1* afforded the indolizines *3a* and *3b* [2] and the pyrrolo[2,1,5-*cd*]indolizine *4a*;[1] with propionic anhydride/potassium propionate the analogous indolizines *3c* and *3d*,[3,1] further, *3h*, *3i* and *3j* and the pyridylindolizine *3e*;[1] and with acetic anhydride/potassium acetate in the presence of phenylacetic acid *3f* and *3g*.[3,4,1] In the light of further investigations, a possible disproportionation mechanism of 3-(2-pyridyl)acrylic acids (*2*) under the conditions of the Perkin reaction leading to the indolizine derivatives *3* and *4* is discussed. The structures of the new indolizines were unambiguously established from their analyses and spectral

* Part IV; Ref. 10.

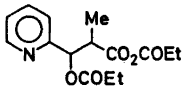


1 *2* *3* *4*

No.	R^2	R^5	No.	R^1	R^2	R^3	R^4
2a	H	–	*3a*	H	H	OAc	H
2b	Me	–	*3b*	H	H	Ac	H
2c	Ph	–	*3c*	H	Me	OCOEt	H
			3d	H	Me	COEt	H
			3e	COEt	Me	2-Pyridyl	H
4a	H	Ac	*3f*	H	Ph	OAc	H
4b	H	COOEt	*3g*	H	Ph	Ac	H
4c	Me	Ac	*3h*	OCOEt	Me	OCOEt	H
			3i	MeCH(OCOEt)	Me	COEt	OCOEt
			3j	H	Me	2-Pyridyl	H
			3k	OCOEt	Me	COEt	MeCH(OCOEt)
			3l	H	Me	Ac	H



3h



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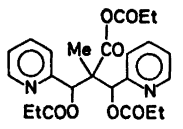

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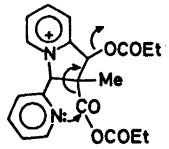


7

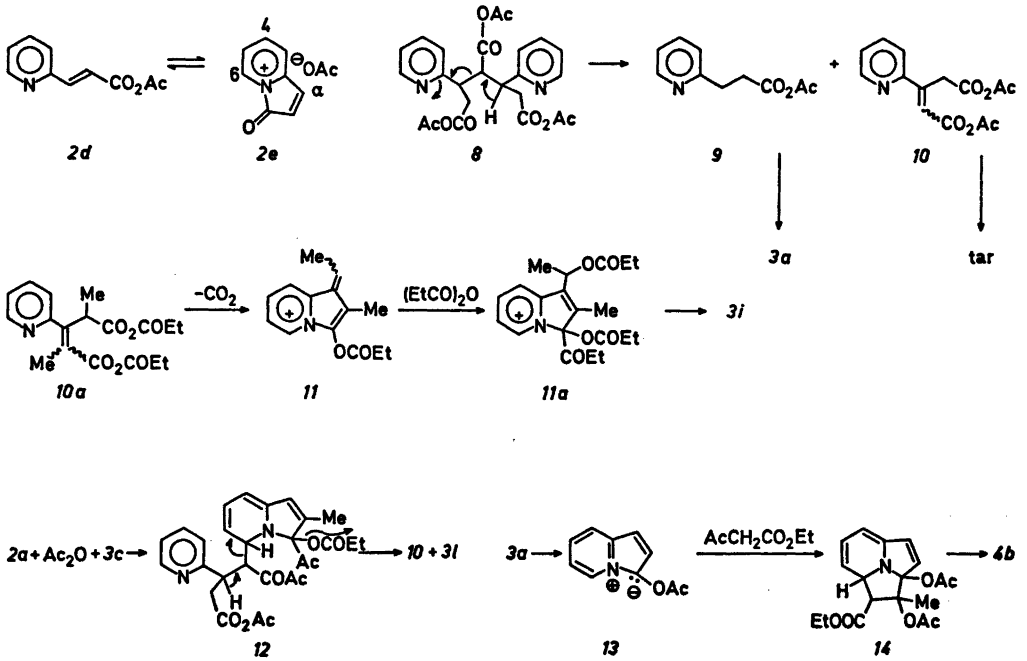
data (UV, IR, NMR, MS)[3,5–7] except *3i*, for which the alternative structure *3k* is possible as well. The structure *3i* is preferred over *3k*, however, because the mass spectrum showed no significant peaks characteristic of the known 1-indolizinyl acylates,[7] for example, the $m/e=$ 106 peak of *3h*.

Formation of indolizines

No change in the oxidation level. The indolizine *3h* is formed if cyclocondensation takes place before the elimination of propionic acid from the acylated aldol *5*. The indolizines *3e* and *3j* can originate from either the dimeric aldol *6*[8] or the cycloaddition product *7*, both routes involving decarboxylation. The indolizine *3j* is readily acylated to give *3e*.

Reduced products. 2-Pyridinecarbaldehyde (*1*) gives with acetic anhydride/potassium acetate the normal Perkin reaction product *2d*, which is susceptible to nucleophilic attack by the enolate anion of acetic anhydride, affording the dimeric addition product *8*.* The latter is cleaved into reduced (*9*) and oxidized (*10*) moieties. The reduced part *9* then cyclizes to the indolizine *3a*. This is in accordance with the facts that 3-(2-pyridyl)acrylic acid (*2a*) (prepared by the Doebner reaction [9]) and 3-(2-pyridyl)propanoic acid also give *3a* when treated with acetic anhydride/potassium acetate.[10]

* The positions 4 and 6 of the pyridine are susceptible to nucleophilic addition as well. Besides, *2d* might also react through its cyclic form *2e*.



Oxidized products. The oxidized part *10* is apparently not able to give any definite molecules, thereby accounting for the complete absence of simple oxidized species in the product mixture; a considerable amount of tar is formed in the Perkin reaction of *1*. In the propionate case, after addition and cleavage steps, the oxidized part *10a* cyclizes to the pyridinium compound *11*. This step involves decarboxylation. The compound *11* then rearranges into the indolizine *3i* through a net addition of propionic anhydride.

Doubly reduced products. Because *2a* gave with acetic anhydride/potassium acetate the same products as *1*, particularly *3b*, it is assumed that also the other doubly reduced products, *3d* and *3g* were formed through the corresponding 3-(2-pyridyl)acrylic anhydrides. They are definitely not formed *via* disproportionation of the corresponding 3-indolizinyl acylates alone. Interestingly, treatment of the indolizine *3c* with acetic anhydride/potassium acetate in the presence of *2a* produced traces of the indolizinylethanone *3l* suggesting that *3l* can be formed through the sequence shown above.

Formation of pyrrolo[2,1,5-*cd*]-indolizines

The indolizine *3a* cyclizes with acetic anhydride/potassium acetate to *4a* and the reaction of *3a* in the presence of ethyl acetoacetate gives *4b*,[1] *via* nucleophilic attack by the anions derived from 2,4-pentanedione (from the self-condensation of acetic anhydride[11]) and ethyl acetoacetate, respectively, on C-5 of the zwitterion *13*. In the propionate case or in the presence of phenylacetic acid the formation of the third ring is prevented owing to the methyl and phenyl substituents, or 3-indolizinyl acylates are attacked at positions other than C-5. When *3c* was treated with acetic anhydride/potassium acetate *4c* was obtained.

An amazing feature of 3-indolizinyl acylates is that they are not acylated at C-1, although 3-alkylindolizines, for example, are easily acylated at this position.[12] The preferred reaction at C-3 (and at C-5) probably explains the absence of 1-acyl derivatives of the compounds *3*.

EXPERIMENTAL

Acid anhydrides contained less than 3 % of the free acid. Potassium acetate and potassium propionate were dried at 110 °C before use. Product mixtures were worked up by hydrolyzing the excess of acid anhydrides with water, extracting into ether and drying on sodium sulfate. Woelm silica was used for dry-column chromatography, and benzene, containing increasing amounts of methylene chloride, was used as eluent. Thin-layer chromatography was carried out using Merck silica gel $HF_{254+366}$ with benzene containing 2 – 5 % of methanol. The solid products were recrystallized from light petroleum (b.p. 40 – 60 °C) if not stated otherwise. Melting points are uncorrected. Elemental analyses were performed by Mrs. A. M. Horko. UV spectra were obtained for solutions in ethanol, IR spectra were obtained for KBr-tablets or liquid films. NMR spectra were measured for solutions in $CDCl_3$ or CCl_4 at 60 MHz. Mass spectra were recorded at 70 eV through the cooperation of Mr. P. Karvonen.

The Perkin reactions of 2-pyridinecarbaldehyde

With Ac_2O/KOAc. 2-Pyridinecarbaldehyde (10.7 g, 0.10 mol), Ac_2O (50 g, 0.5 mol) and KOAc (25 g, 0.25 mol) were refluxed for 0.5 h. After work-up and chromatography the following four compounds were obtained: *3-Indolizinyl acetate*, (*3a*), yield 0.7 g (4 %), m.p. 20 °C. (Found: C 68.85; H 5.10; N 7.75. Calc. for $C_{10}H_9NO_2$: C 68.55; H 5.20; N 8.00). IR, ν_{max} 1775 (s), 1750 (s). ^{1}H NMR: δ 7.52 (1 H, br d, J 7 Hz), 7.21 (1 H, br d, J 9), 6.6 – 6.2 (2 H, m), 6.52 (1 H, d, J 4.3), 6.28 (1 H, d, J 4.3), 2.18 (3 H, s). MS, *m/e* (%): 175 (M^+). *1-(3-Indolizinyl)ethanone*, (*3b*),[2] yield 0.95 g (6 %), m.p. 32 °C. ^{1}H NMR: δ 9.87 (1 H, br d 7), 7.40 (1 H, br d 9), 7.32 (1 H, d 4.7), 7.2 – 6.55 (2 H, m), 6.35 (1 H, br d, J 4.7), 2.46 (3 H, s). MS, *m/e* (%): 159 (M^+, 64), 145 (9), 144 (100), 116 (59), 89 (29), 43 (41). *1-(2-Methyl-1-pyrrolo[2,1,5-cd]-indolizinyl)ethanone*, (*4a*), yield 0.79 g, (4 %), m.p. 79 °C. (Found: C 79.05; H 5.80; N 6.75. Calc. for $C_{13}H_{11}NO$: C 79.15; H 5.60; N 7.10). UV, λ_{max} (log ε): 411 (3.89), 403 (3.86), 395 (sh, 3.77), 313 (3.78), 277 (sh, 3.80), 2.57 (4.23), 240 (4.05). IR, ν_{max}: 1645 (s), 1640 (s), 1630 (s). ^{1}H NMR: δ 8.21 (1 H, dd, J 5.2 and 2.8), 7.90 – 7.70 (2 H, m), 7.60 (1 H, d, J 4.4), 7.24 (1 H, d, J 4.4), 2.95 (3 H, s), 2.72 (3 H, s). MS, *m/e* (%): 197 (M^+, 14), 183 (9), 182 (100), 155 (22), 154 (33), 153 (11). *3-Acetyl-2,6-dimethyl-4H-pyran-4-one*,[11] yield 2.4 g, m.p. 57 °C. When the reaction time was reduced to 10 min, *3a*, 2.6 g (15 %) and *3b*, 1.3 g (8 %), but none of *4a*, were obtained, while *3a* was absent from the product mixture after periods longer than 1 h.

With $(EtCO)_2O$/KOCOEt. 2-Pyridinecarbaldehyde (21.4 g, 0.2 mol) was added to the hot mixture of $(EtCO)_2O$ (130 g, 1.0 mol) and KOCOEt (55 g, 0.5 mol) at once and boiled for 0.5 h. Work-up and chromatography gave: *2-Methyl-3-indolizinyl propionate, (3c)*, yield 4.0 g (10 %), m.p. 33 °C. (Found: C 70.65; H 6.20; N 6.75. Calc. for $C_{12}H_{13}NO_2$: C 70.90; H 6.45; N 6.90). UV, λ_{max} (log ε): 3.72 (sh, 2.94), 353 (sh, 3.30), 344 (3.33), 292 (3.49), 281 (3.51), 272 (3.48), 243 (sh, 4.31), 232 (4.44). IR, ν_{max}: 1765 (s). ^{1}H NMR: δ 7.21 (1 H, br d, J 7), 7.08 (1 H, br d, J 9), 6.07 (1 H, br s), 2.49 (2 H, q, J 7.5), 2.12 (3 H, dd, J 0.4 and 0.1), 1.18 (3 H, t, J 7.5). *1-(2-Methyl-3-indolizinyl)-1-propanone, (3d)*,[3] yield 2.3 g (6 %), m.p. 48 °C. ^{1}H NMR identical with that given in Ref. 3, particularly, H-5 at δ 9.92 (br d, J 7). *2-Methyl-3-(2-pyridyl)-indolizine, (3j)*, yield 0.2 g (1 %), as liquid. (Found C 80.75; H 5.60; N 13.45. Calc. for $C_{14}H_{12}N_2$: C 80.75; H 5.80; N 13.45). ^{1}H NMR: δ 9.26 (1 H, br d, J 7), 8.53 (1 H, br d, J 5), 7.9 – 6.15 (6 H, m), 6.20 (1 H, br s), 2.48 (3 H, s). *2-Methyl-1,3-indolizinediyl dipropionate, (3h)*, yield 1.6 g (3 %), m.p. 104 °C. (Found: C 65.80; H 6.00; N 5.20. Calc. for $C_{15}H_{17}NO_4$: C 65.45; H 6.20; N 5.10). UV similar to that of *3c*. IR, ν_{max}: 1765 (s), 1745 (s), 1740 (s). MS, *m/e* (%): 275 (M^+, 10), 219 (16), 190 (10), 163 (49), 162 (100), 106 (19). *1-[2-Methyl-7-propionyloxy-1-(1-propionyloxy-1-ethyl)-3-indolizinyl]-1-propanone, (3i)*, yield 1.4 g (2 %), m.p. 99 °C. (Found: C 66.85; H 6.95; N 3.95. Calc. for $C_{20}H_{25}NO_5$: C 66.85; H 7.00; N 3.90). UV, λ_{max} (log ε): 408 (sh, 2.69), 360 (4.00), 349 (sh, 3.94), 267 (4.21), 263 (sh, 4.18), 253 (sh, 3.99), 244 (sh, 3.93), 228 (4.14). IR, ν_{max} 1745 (s), 1730 (s). ^{1}H NMR: δ 9.92 (1 H, br d 7), 7.01 (1 H, br s), 6.71 (1 H, br d 7), 5.76 (1 H, q 6), 2.82 (2 H, q 7), 2.67 (2 H, q 7), 2.35 (3 H, s), 2.33 (2 H, q 7), 1.56 (3 H, d 6), 1.34 (3 H, t 7), 1.22 (3 H, t 7), 1.00 (3 H, t 7). MS, *m/e* (%): 359 (M^+, 16), 304 (22), 303 (100), 302 (45), 274 (12), 231 (14), 230 (46), 229 (32), 228 (22), 203 (15), 202 (20), 174 (19), 118 (9), 104 (20). *1-[2-Methyl-3-(2-pyridyl)-1-indolizinyl]-1-propanone, (3e)*, yield 7.0 g (27 %), m.p. (EtOH) 147 °C. (Found: C 77.45; H 5.95; N 10.55. Calc. for $C_{17}H_{16}N_2O$: C 77.25; H 6.10; N 10.60). UV, λ_{max} (log ε): 370 (sh, 3.79), 352 (sh, 4.01), 338 (4.06), 325 (4.04), 270 (4.15), 265 (sh, 4.09), 231 (4.20). IR, ν_{max}: 1620 (s), 1610 (s). ^{1}H NMR: δ 8.75 (1 H, br d 5), 8.69 (1 H, br d 7), 8.36 (1 H, br d 9), 2.60 (3 H, s), +EtCO. MS, *m/e* (%): 264 (M^+, 37), 246 (8), 236 (19), 235 (100).

With Ac_2O/KOAc in the presence of phenylacetic acid. 2-Pyridinecarbaldehyde (10.7 g, 0.10 mol), Ac_2O (50 g, 0.5 mol), KOAc (25 g, 0.25 mol) and phenylacetic acid (13.6 g, 0.10 mol) were boiled for 0.5 h. Work-up and chromatography gave: *2-Phenyl-3-indolizinyl acetate, (3f)*, yield 6.8 g (27 %), m.p. (MeOH) 118 °C. (Found: C 76.25; H 5.25; N 5.35. Calc. for $C_{16}H_{13}NO_2$: C 76.45; H 5.20; N 5.55). UV, λ_{max} (log ε): 384 (sh, 3.54), 365 (3.65), 352 (3.69), 307 (sh, 3.62), 294 (sh, 3.88), 284 (sh, 3.99), 252 (4.68). IR, ν_{max}: 1770 (s), 1765 (s). ^{1}H NMR: δ 7.80 – 7.20 (7 H, m), 6.80 – 6.45 (2 H, m), 6.64 (1 H, s), 2.39 (3 H, s). MS, *m/e* (%): 251 (M^+, 9), 210 (16), 209 (100), 208 (65), 181 (13), 180 (76). *1-(2-Phenyl-3-indolizinyl)ethanone, (3g)*,[3,4] yield 1.2 g, (5 %), m.p. 65 °C. ^{1}H NMR: δ 10.02 (1 H, br d, J 7), 7.36 (5 H, s), 6.36 (1 H, s), 1.95 (3 H, s).

Disproportionation of 3-(2-pyridyl)acrylic acid (2a). 2a[9] (7.5 g, 0.05 mol), Ac_2O (50 g, 0.5 mol), KOAc (25 g, 0.25 mol) were refluxed for 0.5 h producing *3a, 3b* and *4a* in 15, 9 and 4 % yields, resp. In neat Ac_2O *2a* gave 90 % of acetic 3-(2-pyridyl)acrylic anhydride, *(2d)*, m.p. 68 °C. (Found: C 62.60; H 4.50; N 7.65. Calc. for $C_{10}H_9NO_3$: C 62.80; H 4.75; N 7.65). IR, ν_{max}: 1790 (s), 1725 (s), 1625 (s). MS, *m/e* (%): 191 (M^+, –) 148 (57), 132 (100).

Cyclocondensation of 3-(2-pyridyl)propanoic acid with Ac_2O/KOAc. 2a[9] (14.9 g, 0.10 mol), 10 %-Pd/C (0.5 g) and ethanol (150 ml) were shaken under hydrogen (1 atm) at room temperature for 12 h. After filtration, evaporation and recrystallization from chloroform 11.2 g (74 %) of *3-(2-pyridyl)propanoic acid*[13] was collected. This saturated acid (1.5 g, 0.01 mol) was heated with Ac_2O (10 ml) and KOAc (5 g) at 100 °C for 15 min to produce *3a*, yield 0.77 g (44 %), but none of *3b*.

Cyclization of 3-indolizinyl acylates with Ac_2O/KOAc

3-Indolizinyl acetate (3a) with Ac_2O/KOAc. 3a (3.5 g, 0.020 mol) was added to the hot mixture of 20 ml Ac_2O and 10 g of KOAc and boiled for 20 min. Work-up and chromatography gave *4a*, yield 0.44 g, (11 %).

3-Indolizinyl acetate (3a) with Ac_2O/KOAc in the presence of ethyl acetoacetate. 3a (3.5 g, 0.020 mol), Ac_2O (20 ml), KOAc (10 g) and ethyl acetoacetate (2.6 g, 0.020 mol) gave *ethyl 2-methyl-1-pyrrolo[2,1,5-cd]indolizine-carboxylate (4b)*, yield 0.95 g, (21 %), m.p. 64 °C. (Found: C 73.90; H 5.85; N 6.00. Calc. for $C_{14}H_{13}NO_2$: C 74.00; H 5.75; N 6.15). UV similar to that of *4a*. IR, ν_{max}: 1690 (s), 1685 (s). ^{1}H NMR similar to that of *4a*, COOEt instead of $COCH_3$. MS, *m/e* (%): 227 (M^+, 69), 199 (22), 198 (23), 182 (100), 155 (40), 154 (52), 153 (34), 73 (37). Starting from *2a* afforded similarly *4b* in 12 % yield.

2-Methyl-3-indolizinyl propionate (3c) with Ac_2O/KOAc. 3c (2.0 g, 0.010 mol) was boiled with Ac_2O (10 ml) and KOAc (5 g) for 15 min. After work-up and chromatography *1-(2,3-dimethyl-1-pyrrolo[2,1,5-cd]indolizinyl)ethanone (4c)* was obtained, yield 0.34 g (16 %), m.p. 70 °C. (Found: C 79.35; H 6.30; N 6.75. Calc. for $C_{14}H_{13}NO$: C 79.60; H 6.20; N 6.65). UV and IR similar to those of *4a*. ^{1}H NMR: δ 2.77

(3 H, d, *J* 1) instead of *δ* 7.24 (1 H, d, *J* 4.4) in *4a*. MS, *m/e* (%): 211 (M^+, 55), 197 (15), 196 (100), 168 (11), 167 (28).

2-Methyl-3-indolizinyl propionate (3c) with Ac_2O/KOAc in the presence of 2a. *3c* (2.0 g, 0.010 mol) and *2a* (1.5 g, 0.010 mol) were treated with Ac_2O (20 ml) and KOAc (10 g). After work-up *ca.* 15 mg of *1-(2-methyl-3-indolizinyl)ethanone (3l)*[3] was collected by means of preparative thin-layer chromatography, m.p. 81 °C. ^1H NMR identical with that given in Ref. 3, particularly, H-5 at *δ* 9.93 (br, d, *J* 7). The product mixture contained several other indolizines, such as *3a*, *3b* and *4a*.

All attempts to cyclize *3a* with $(EtCO)_2O$/KOCOEt failed; *3a* disappeared during prolonged heating.

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